Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Continuous glucose monitoring in pregnant women with type 1 diabetes

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question: what is the clinical and cost effectiveness of continuous glucose monitoring in pregnant women with type 1 diabetes?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of identifying published evidence on the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia. Diabetes mellitus can be classified into the following general categories:

- Type 1 diabetes (due to autoimmune beta-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (due to a progressive loss of beta-cell insulin secretion frequently on the background of insulin resistance)
- Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
- Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation) (EUnetHTA 2018).

Women with diabetes of any kind are at increased risk of morbidity and mortality during pregnancy, and pregnancy outcomes for women with pre-existing diabetes and their infants are poor compared to those for women who do not have diabetes. Miscarriage, pre-eclampsia and preterm labour are more common in women with pre-existing diabetes. Stillbirth, congenital malformations, macrosomia, birth injury, perinatal mortality and postnatal adaptation problems (such as hypoglycaemia) are more common in babies born to women with pre-existing diabetes (NICE 2015a, Jones et al. 2019).

Poor glycaemic control, and in particular hyperglycaemia, is strongly associated with increased risk of abortion or severe congenital malformations in early pregnancy. After 12 weeks gestation, hyperglycaemia also induces fetal hyperinsulinaemia, accelerated growth, and excess adiposity in

animal models and in women with diabetes. Intensified glycaemic control minimises macrosomia and other neonatal complications (Jones et al. 2019).

Based on figures from the 2017/18 Patient Episode Database for Wales (PEDW) dataset (NHS Wales Informatics Service 2018), the number of women in Wales with type 1 diabetes (T1DM) who become pregnant each year is estimated to be 206. This population figure is made up of three separate codes within the 024 pregnancy heading where a hospital admission was recorded. The most numerous code was the exact match for the population: 0240 – pre-existing T1DM (n = 157). In addition to this figure, the unspecified diabetes codes of 0243 (n = 5) and 0249 (n = 44) are included. The total of 206 is lower than those seen in previous years (equivalent estimates for previous years: 2015/16 n = 249; 2016/17 n = 325).

The most well-established method of monitoring blood glucose during pregnancy is to test capillary glucose using a blood glucose meter (self-monitoring of blood glucose, or SMBG). Flash glucose monitoring, whereby glucose levels are measured continuously by a sensor, but results are available only when the sensor is scanned with a reading device, is an alternative method of monitoring blood glucose in people with diabetes.

3. Health technology

Continuous glucose monitoring (CGM) is a method of continuously following glucose levels in the interstitial fluid to improve glycaemic control. The glucose sensors of most CGM systems are inserted subcutaneously and worn externally by the user (Petrie et al. 2017). A number of different CGM systems are available in the UK, as summarised in Table 1. CGM devices can collect data that is visible to the user in real time (here termed "real-time CGM") or not visible in real-time but used retrospectively to determine trends in glucose levels (here termed "retrospective CGM"). In most cases, CGM systems are designed to be used alongside SMBG testing, but the amount of SMBG testing varies according to the CGM system using. Flash glucose monitoring is not covered by this assessment as an intervention but is considered as a comparator.

Table 1. Continuous glucose monitoring systems available in the UK and their indications for use.

Continuous glucose monitoring system	Indications for use
Guardian Connect® Continuous Glucose Monitoring system, Medtronic	For continuous monitoring of glucose levels in the interstitial fluid under the skin, in persons with diabetes mellitus. The Guardian Connect® app (CSS7200): intended for continuous or periodic monitoring of glucose levels in the interstitial fluid under the skin, in persons with diabetes mellitus. The Guardian Connect® app is intended for use with a compatible consumer mobile electronic device. It allows users to track patterns in glucose concentrations and to possibly identify episodes of low and high glucose. The Guardian Connect® app displays alerts if a glucose level reaches, falls below, or rises above set values. Sensor glucose values displayed on the screen are not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a meter blood glucose measurement may be required. Guardian Connect® transmitter (MMT-7821*): for single-patient or multiple-patient use as a component of select Medtronic CGM systems Enlite™ sensor (MMT-7008*): intended for use with Medtronic Diabetes (Medtronic) glucose sensing systems to continuously monitor glucose levels in persons with diabetes.

Continuous glucose monitoring system	Indications for use
	CareLink™ Connect feature: intended to work with the Guardian Connect® CGM system. The CareLink™ Connect feature is intended to provide a secondary display of continuous glucose monitoring on a supported consumer electronic device for users of a Guardian Connect® CGM system and their designated care partners. The CareLink™ Connect feature is not intended to replace the real-time display of continuous glucose monitoring. All therapy decisions should be based on blood glucose measurements obtained from a blood glucose meter. The CareLink™ Connect feature is not intended to analyse or modify the continuous glucose monitoring data that it receives. Nor is it intended to control any function of the continuous glucose monitoring system to which it is connected.
Eversense® Continuous Glucose Monitoring system, Senseonics, Incorporated (marketed by Roche in UK)	The Eversense® CGM System is indicated for continually measuring interstitial fluid glucose levels in adults (18 years and older) with diabetes for the operating life of the sensor. The system is intended to: • aid in the management of diabetes; • provide real-time glucose readings; • provide glucose trend information; provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycaemia) and high blood glucose (hyperglycaemia).Historical data from the system can be interpreted to aid in providing therapy adjustments.These adjustments should be based on patterns and trends seen over time. The system is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices.
Eversense® XL Continuous Glucose Monitoring system, Senseonics, Incorporated (marketed by Roche in UK)	The Eversense® XL CGM System is indicated for continually measuring interstitial fluid glucose levels in adults (18 years and older) with diabetes for the operating life of the sensor. The system is intended to: • aid in the management of diabetes; • provide real-time glucose readings; • provide glucose trend information; • provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycaemia) and high blood glucose (hyperglycaemia). Historical data from the system can be interpreted to aid in providing therapy adjustments. These adjustments should be based on patterns and trends seen over time. The system is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices.
G6® Continuous Glucose Monitoring System, Dexcom	A glucose monitoring system indicated for persons age 2 years and older, designed to replace finger-stick blood glucose (BG) testing for treatment decisions. Interpretation of the Dexcom G6® System results should be based on the glucose trends and several sequential readings over time. The Dexcom G6® System also aids in the detection of episodes of hyperglycaemia and hypoglycaemia, facilitating both acute and long-term therapy adjustments. The Dexcom G6® System is intended for use by patients at home and in healthcare facilities.

4. Current guidelines and guidance

HTW have published Guidance on FreeStyle Libre flash glucose monitoring for the management of type 1 or type 2 diabetes (November 2018). This Guidance states that Freestyle Libre shows promise for detecting and guiding the correction of hypoglycaemia in patients requiring multiple daily insulin dosing for T1DM and T2DM. The current evidence, however, does not support routine adoption. The use of Freestyle Libre may be considered as an alternative to finger-prick self-monitoring of blood glucose in clinical circumstances where multiple testing (eight or more times per day) is required (Health Technology Wales 2018).

The NICE Guideline *Diabetes in pregnancy: management from preconception to the postnatal period* (NG3) includes the following recommendations on CGM (NICE 2015a):

- Do not offer continuous glucose monitoring routinely to pregnant women with diabetes (recommendation 1.3.17).
- Consider continuous glucose monitoring for pregnant women on insulin therapy:
    - who have problematic severe hypoglycaemia (with or without impaired awareness of hypoglycaemia) or
    - who have unstable blood glucose levels (to minimise variability) or
    - to gain information about variability in blood glucose levels (recommendation 1.3.18).
- Ensure that support is available for pregnant women who are using continuous glucose monitoring from a member of the joint diabetes and antenatal care team with expertise in its use (recommendation 1.3.19).

These recommendations were published in 2015 and are under review but the timescales for updating these are not known.

Diabetes UK Position Statement *A Type 1 diabetes technology pathway: consensus statement for the use of technology in Type 1 diabetes* (February 2019) includes a clinical pathway developed in collaboration with NHS England. This pathway recommends use of real-time CGM as an option for people with T1DM where multiple daily injections of insulin as part of optimal standard care (structured education, 4-10 SMBG tests per day, dose optimisation, support from a specialist team and psychological support) does not result in them meeting their personalised glucose target. In pregnant women who meet these criteria, real-time CGM with alarms should be considered as first-line therapy (Choudhary et al. 2019).

5. Evidence search methods

The criteria used to select evidence for the appraisal are outlined in Appendix 1. These criteria were developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts.

Initial exploratory searches identified the existence of two relevant sources of secondary evidence:

- A Rapid Evidence Assessment (REA) by the European Network for Health Technology Assessment (EUnetHTA), assessing the use of CGM in people diabetes mellitus treated with insulin (EUnetHTA 2018)
- A Cochrane Review assessing techniques for monitoring blood glucose during pregnancy for women with pre-existing diabetes (Jones et al. 2019)

Both of these analyses summarised evidence from randomised controlled trials of CGM in pregnant women with T1DM published up to 2018. The suitability of these analyses to inform this appraisal were assessed using the EUnetHTA adaption toolkit: informed by this, information on the technology's use and characteristics was adapted from the EUnetHTA Rapid Evidence Assessment; evidence on clinical effectiveness was adapted from the Cochrane Review. HTW also conducted

supplementary searches to identify any evidence published more recently (last date of search: 16 July 2019).

6. Clinical effectiveness

We identified four randomised controlled trials comparing CGM to current care; these same trials were included in the Cochrane Review by Jones (2019) and no other relevant studies published subsequently were found by our searches. Characteristics of these trials are summarised in Table 2. The Cochrane Review included evidence on all outcomes of interest to this review, and conducted meta-analysis where possible. However, the Cochrane Review included evidence on the use of CGM to manage either T1DM or T2DM in pregnant women: across the four studies identified, 740 women were included in total, 493 of whom had T1DM. Only one trial specifically assessed the population of interest to this review (pregnant women with T1DM). We have therefore conducted subgroup analyses where possible to report outcomes specifically from women with T1DM.

6.1. Clinical outcomes: CGM in addition to standard care vs standard care alone

6.1.1. Maternal outcomes

Maternal outcomes with CGM as an addition to standard care compared to standard care alone are summarised in Table 3**Error! Reference source not found.**. Women who used CGM had statistically significantly better glycaemic control, in terms of the proportion of women who achieved HbA1c of ≤ 6.5% at 34 weeks gestation (one study, 187 patients, risk ratio 1.27, 95% CI 1.00, 1.62) and maternal HbA1c levels at 34 weeks gestation (one study, 187 patients, mean difference -0.18%, 95% CI -0.36, 0.00), although the latter may not represent a clinically meaningful difference (NICE 2015b). The incidence of pre-eclampsia was significantly lower in women who used CGM (two studies, 308 patients, risk ratio 0.40, 95% CI 0.20, 0.80). The incidences of caesarean section and pregnancy-induced hypertension were also numerically lower with CGM but the differences between groups did not reach statistical significance. The results of two studies (334 patients) indicate uncertainty about the effect of CGM on incidence of miscarriage (risk ratio 1.59, 95% CI 0.53, 4.77), possibly due to the low number of events reported (8/168 events with CGM vs 5/166 events with standard care). Quality of life outcomes at 34 weeks gestation were measured in one trial (214 patients) using three different QOL scales. Only one of these reported a statistically significant difference in quality of life between the two interventions (blood glucose monitoring system rating questionnaire: mean difference 4.30, 95% CI 0.73, 7.87, favours CGM).

6.1.2. Neonatal outcomes

Neonatal outcomes in pregnancies where women used CGM in addition to standard care versus standard care along are summarised in Table 4. Evidence from two studies (323 patients) suggest that use of CGM during pregnancy lowers the incidence of neonatal hypoglycaemia (risk ratio 0.64, 95% CI 0.45, 0.91). One study (200 patients) reported lower rates of neonatal intensive care admissions following CGM use during pregnancy (risk ratio 0.63, 95% CI 0.42, 0.93). Other measured outcomes (birthweight, large/small for gestational age, macrosomia, stillbirth/neonatal mortality) were not statistically significantly different between CGM and standard care.

Table 2. RCTs comparing continuous glucose monitoring in addition to standard care to standard care alone

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
Feig et al. (2017) (CONCEPTT)	Randomised controlled trial. 31 centres in Canada, USA and Europe.	Inclusion criteria: • women aged 18–40 years with T1DM for a minimum of 12 months • receiving intensive insulin therapy via multiple daily injections or an insulin pump • pregnant and at 13 weeks and 6 days gestation or less • HbA1c between 6·5–10·0% (48–86 mmol/mol)	Intervention: CGM in addition to capillary glucose monitoring. CGM system used: Guardian REAL-Time or MiniMed Minilink system (both Medtronic). Participants were instructed to use CGM daily, and taught to use insulin dose adjustment algorithms and to make changes to their insulin regimen based on the data from the CGM and capillary glucose monitoring (n =108). Control: SMBG alone (n = 107) Participants in both groups were advised to test capillary glucose levels at least seven times daily.	• Rates of caesarean sections • Risk of pre-term birth • HbA1c values; time in target range • Incidence of maternal hypoglycaemia • Rates of admission to neonatal intensive care, and length of stay in intensive care • Birthweight, including rates of macrosomia • Rates of births that are large for gestational age • Rates of stillbirth • Neonatal morbidity/mortality • Incidence of gestational hypertension • Incidence of pre-eclampsia • Length of infant and maternal hospital stay after delivery • Patient satisfaction • Quality of life • Incidence of neonatal hypoglycaemia	No risks of bias identified.

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
Voormolen et al. (2018) (GlucoMOMS)	Randomised controlled trial 22 centres; 21 in the Netherlands and one in Belgium	Inclusion criteria: • Women with pre-existing diabetes who were pregnant and at a gestational age of less than 16 weeks • Pregnant women with gestational diabetes mellitus requiring insulin therapy before 30 weeks gestational age 300 women recruited; 109 had T1DM.	Intervention: intermittent, retrospective CGM using the iPro2 device (Medtronic) in addition to SMBG. Women were instructed to use the device for 5-7 days every 6 weeks. Glucose profiles were obtained retrospectively, directly after use and evaluated by the local endocrinologist. Insights were discussed with the patient and changes in diet or insulin therapy were advised accordingly. (T1DM, n = 50; total, n = 147) Control: SMBG alone. (T1DM, n = 56; total, n =153) All participants performed SMBG (4-8 times/day; at least fasting, after every meal, at bedtime and, preferably, also before every meal).	• Macrosomia • Pregnancy-induced hypertension • Pre-eclampsia • Caesarean section • Severe hypoglycaemia • Large or extremely large size for gestational age • Birth weight • Neonatal mortality • Birth trauma • Neonatal hypoglycaemia • Neonatal morbidity	It is unclear whether allocation to treatment arms was concealed to trial staff. Only 66% of patients used CGM according to study protocol: a high number of patients refused to use CGM after the first or second time. Not all outcomes listed in the methods were reported in the results: high risk of reporting bias. Not all patients had T1DM. Results were reported separately for the T1DM subgroup for some, but not all, outcomes.

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
Secher et al. (2013)	Randomised controlled trial Single centre, Denmark	Inclusion criteria: • Women with T1DM or T2DM who were pregnant and at a gestational age of less than 14 weeks 154 women recruited; 123 had T1DM (the remainder had T2DM).	Intervention: real time CGM using Guardian Real-time Continuous Glucose Monitoring System with the Sof-Sensor (Medtronic). CGM was used for 6 days at pregnancy visits during 8, 12, 21, 27 and 33 weeks, in addition to routine pregnancy care. Women were also instructed to continue performing SMBG. Hyper/hypoglycaemic alarms were used: alarm limits were flexible, and patients were supported in individual alarm settings. Control: routine pregnancy care with SMBG performed 7 times daily	• Large for gestational age • Neonatal morbidity • Pre-term delivery • Neonatal hypoglycaemia • Miscarriage • Pre-eclampsia	No risks of bias identified. Only forty-nine (64%) women with T1DM or T2DM diabetes used real-time CGM per protocol. Near-continuous real-time CGM use (at least 60% of the time) was only chosen by five (7%) women. Not all patients had T1DM. Results were reported separately for the T1DM subgroup for some, but not all, outcomes.
Murphy et al. (2008)	Randomised controlled trial. Two centres, UK	Inclusion criteria: • T1DMand T2DM pregnant women at 16 weeks' gestation 71 women recruited; 46 had T1DM (the reminder had T2DM)	Intervention: CGM using the CGMS Gold device (Medtronic). The device was worn for 7 days at intervals of 4-6 weeks. Data was downloaded and reviewed retrospectively with the patient at scheduled clinic appointments to identify patterns of hypo- and hyperglycaemia and suggest possible solutions in terms of changes to diet, activity, and insulin dose (n = 38) Control: standard antenatal care (n = 33) In both arms, participants were advised to carry out SMBG at least 7 times per day.	• Maternal HbA1c values/glycaemic control • Birthweight/weight for gestational age • Macrosomia • Miscarriage • Neonatal mortality • Neonatal morbidities • Pre-eclampsia • Mode of delivery	No risks of bias identified. Not all patients had T1DM. Results were not reported separately for the T1DM subgroup. Results from this study have therefore only been included in sensitivity analysis.
CGM: continuous glucose monitoring; SMBG: self monitoring of blood glucose; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus					

Table 3. Continuous glucose monitoring compared to standard care: maternal outcomes

Outcome	Evidence source	Number of studies and patients	Absolute effect	Relative effect [95% CI] (interpretation)	Comments on reliability
Caesarean section	Feig 2017, Secher 2013	Two studies, 325 patients	83/163 events with CGM vs 101/162 events with standard care	Risk Ratio 0.84 [0.71, 1.00] (favours neither intervention)	Borderline statistical significance. Meta-analysis indicates high heterogeneity between studies.
Pre-eclampsia	Feig 2017, Voormolen 2018	Two studies, 308 patients	10/150 events with CGM vs 26/158 events with standard care	Risk Ratio 0.40 [0.20, 0.80] (favours CGM)	Studies used different CGM protocols (one study used RT CGM; one study used retrospective CGM)
Pregnancy-induced hypertension	Feig 2017, Voormolen 2018	Two studies, 308 patients	10/150 events with CGM vs 18/158 events with standard care	Risk Ratio 0.59 [0.28, 1.24] (favours neither intervention)	Studies used different CGM protocols (one study used RT CGM; one study used retrospective CGM). Meta-analysis indicates heterogeneity between studies.
Glycaemic control					
Maternal HbA1c at 34 weeks gestation [%]	Feig 2017	One study, 187 patients	6.35% with CGM vs 6.53% with standard care	Mean Difference -0.18 [-0.36, 0.00] (favours CGM)	HbA1c values missing for 17 patients in CGM arm and 22 patients in control arm. Borderline statistical significance; difference may not be clinically significant (NICE 2015b).
Achieved maternal HbA1c <= 6.5% (48 mmol/mol) at 34 weeks	Feig 2017	One study, 187 patients	63/95 participants with CGM vs 48/92 participants with standard care	Risk Ratio 1.27 [1.00, 1.62] (favours CGM)	HbA1c values missing for 17 patients in CGM arm and 22 patients in control arm.

Outcome	Evidence source	Number of studies and patients	Absolute effect	Relative effect [95% CI] (interpretation)	Comments on reliability
Incidence of miscarriage	Feig 2017, Secher 2013	Two studies, 334 patients	8/168 events with CGM vs 5/166 events with standard care	Risk Ratio 1.59 [0.53, 4.77] (favours neither intervention)	
Quality of life					
Sense of well-being and quality of life (Short form 12, total score at 34 weeks' gestation)	Feig 2017	One study, 214 patients	41.7 with CGM vs 42.4 with standard care	Mean difference -0.70 [-2.50, 1.10] (favours neither intervention)	
Sense of well-being and quality of life (PAID), total score at 34 weeks' gestation)	Feig 2017	One study, 214 patients	17.2 with CGM vs 16.4 with standard care	Mean difference 0.80 [-3.06, 4.66] (favours neither intervention)	
Sense of well-being and quality of life (BGMSRQ, total score at 34 weeks' gestation)	Feig 2017	One study, 214 patients	98.2 with CGM vs 93.9 with standard care	Mean difference 4.30 [0.73, 7.87] (favours CGM)	

BGMSRQ: blood glucose monitoring system rating questionnaire; CGM: continuous glucose monitoring; CI: confidence interval; N/R: not reported; PAID: problem areas in diabetes; RR: risk ratio; QOL: quality of life

Table 4. Continuous glucose monitoring compared to standard care: neonatal outcomes

Outcome	Evidence source	Study and patient characteristics	Absolute effect	Relative effect (interpretation)	Comments
Birthweight [kg]	Feig 2017	One study, 200 patients	Mean 3.55 with CGM vs 3.58 with standard care	Mean difference -0.03 [-0.23, 0.17] (favours neither intervention)	Number assessed is less than number randomised due to pregnancy losses during the trials
Large-for-gestational age	Feig 2017, Secher 2013	Two studies, 323 patients	83/163 events with CGM vs 90/160 events with standard care	Risk ratio 0.99 [0.56, 1.75] (favours neither intervention)	Number assessed is less than number randomised due to pregnancy losses during the trials. Meta-analysis indicates high heterogeneity between studies. Different definitions of LGA were used by the two studies.
Small-for-gestational age	Feig 2017	One study, 202 patients	2/100 events with CGM vs 2/102 events with standard care	Risk ratio 1.02 [0.15, 7.10] (favours neither intervention)	Number assessed is less than number randomised due to pregnancy losses during the trials
Macrosomia	Feig 2017, Voormolen 2018	Two studies, 308 patients	45/150 events with CGM vs 47/158 events with standard care	Risk ratio 1.04 [0.74, 1.47] (favours neither intervention)	Studies used different CGM protocols (one study used RT CGM; one study used retrospective CGM).
Stillbirth	Feig 2017	One study, 211 patients	0/105 events with CGM vs 1/106 events with standard care	Risk ratio 0.34 [0.01, 8.17] (favours neither intervention)	

Outcome	Evidence source	Study and patient characteristics	Absolute effect	Relative effect (interpretation)	Comments
Neonatal mortality	No data available				No outcome data specific to T1DM available. See appendix 3 for outcomes in T1DM and T2DM combined.
Neonatal hypoglycaemia	Feig 2017, Secher 2013	Two studies, 323 patients	36/163 events with CGM vs 55/160 events with standard care	Risk ratio 0.64 [0.45, 0.91] (favours CGM)	
Neonatal intensive care unit admissions	Feig 2017	One study, 200 patients	27/100 events with CGM vs 43/100 events with standard care	Risk ratio 0.63 [0.42, 0.93] (favours CGM)	Number assessed is less than number randomised due to pregnancy losses during the trials
Neonatal intensive care unit length of admission > 24 hours	Feig 2017	One study, 200 patients	27/100 events with CGM vs 43/100 events with standard care	Risk ratio 0.63 [0.42, 0.93] (favours CGM)	Number assessed is less than number randomised due to pregnancy losses during the trials
CI: confidence interval; LGA: Large-for-gestational age ; N/R: not reported; RT-CGM: real-time continuous glucose monitoring; QOL: quality of life					

6.1.3. Sensitivity analysis: clinical outcomes with CGM in women with any pre-existing diabetes

Sections 6.1 and 6.2 include outcome data either from studies that only included women with T1DM, or where outcomes for women with T1DM were reported separately. Evidence on the use of CGM compared to usual care to manage either T1DM or T2DM in pregnant women is also available, some of which has been excluded from this analysis. Appendix 3 summarises a sensitivity analysis conducted to assess the effect of including evidence from any form of pre-existing diabetes on outcomes.

6.2. Clinical outcomes: CGM vs flash glucose monitoring

Searches did not identify any evidence from randomised trials comparing CGM to flash glucose monitoring in pregnant women with T1DM. One non-randomised trial using these two interventions was identified (Kristensen et al. 2019). The design and characteristics of this trial are summarised in Table 5. Clinical outcomes with CGM and flash glucose monitoring reported by Kristensen (2019) are summarised in Table 6. There were no statistically significant differences between the two interventions for any of the maternal or neonatal outcomes reported.

6.3. Ongoing trials

We did not identify any ongoing randomised controlled trials assessing the use of CGM in pregnant women with T1DM.

Table 5. Characteristics of a non-randomised trial comparing continuous glucose monitoring to flash glucose monitoring

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
Kristensen et al. (2019)	Retrospective observational cohort study Two centres, Sweden 2014 to 2017	Women with T1DM who received pregnancy care at either study centre; aged over 18 years and using a CGM device compatible with the internet-based Diasend system. All women received routine clinical care, with antenatal visits every 2 to 4 weeks. N = 186	RT-CGM using Dexcom G4 CGMS (n = 92) Flash glucose monitoring using FreeStyle Libre (Abbott) (n = 94) For both interventions, glucose values were downloaded to the Diasend system on a weekly basis and the results were communicated to a diabetologist or a trained diabetes nurse for adjustment of insulin doses All women were advised to continue SMBG at least twice daily.	• Pre-eclampsia/pregnancy-induced hypertension • Caesarean section • Gestational age • Preterm birth <37 weeks • Birthweight • LGA infant • Macrosomia, defined as birthweight >4500 g • Neonatal hypoglycaemia • NICU admission >24 h	Women received treatment based on personal choice. Maternal characteristics were comparable between groups, with two exceptions: insulin pumps were used more commonly by women with RT-CGM (42% as opposed to 16%) and users of RT-CGM also had a longer duration of diabetes.

NICU: neonatal intensive care unit; RT-CGM; real-time continuous glucose monitoring; SMBG: self-monitoring of blood glucose; T1DM: type 1 diabetes mellitus.

Table 6. Outcomes from a non-randomised trial comparing continuous glucose monitoring to flash glucose monitoring. Adapted from Kristensen et al. (2019)

Outcome	Continuous glucose monitoring (n = 92)	Flash glucose monitoring (n = 94)	*P* value
Pre-eclampsia/pregnancy-induced hypertension, n (%)	15 (16)	19 (20)	0.47
Caesarean section, n (%)	46 (50)	41 (44)	0.38
Gestational age, weeks, median (range)	38 (27–40)	38 (29–40)	0.47
Preterm birth <37 weeks, n (%)	24 (26)	28 (30)	0.57
Birthweight, g, mean ± SD	3812 ± 678	3834 ± 747	0.84
LGA infant, n (%)	48 (52)	50 (53)	0.89
Macrosomia, defined as birthweight >4500 g, n (%)	14 (15)	16 (17)	0.74
Neonatal hypoglycaemia, n (%)	19 (21)	26 (28)	0.27
NICU admission >24 h, n (%)	27 (29)	33 (35)	0.40
LGA: large for gestational age; NICU: neonatal intensive care unit; SD: standard deviation			

7. Economic evaluation

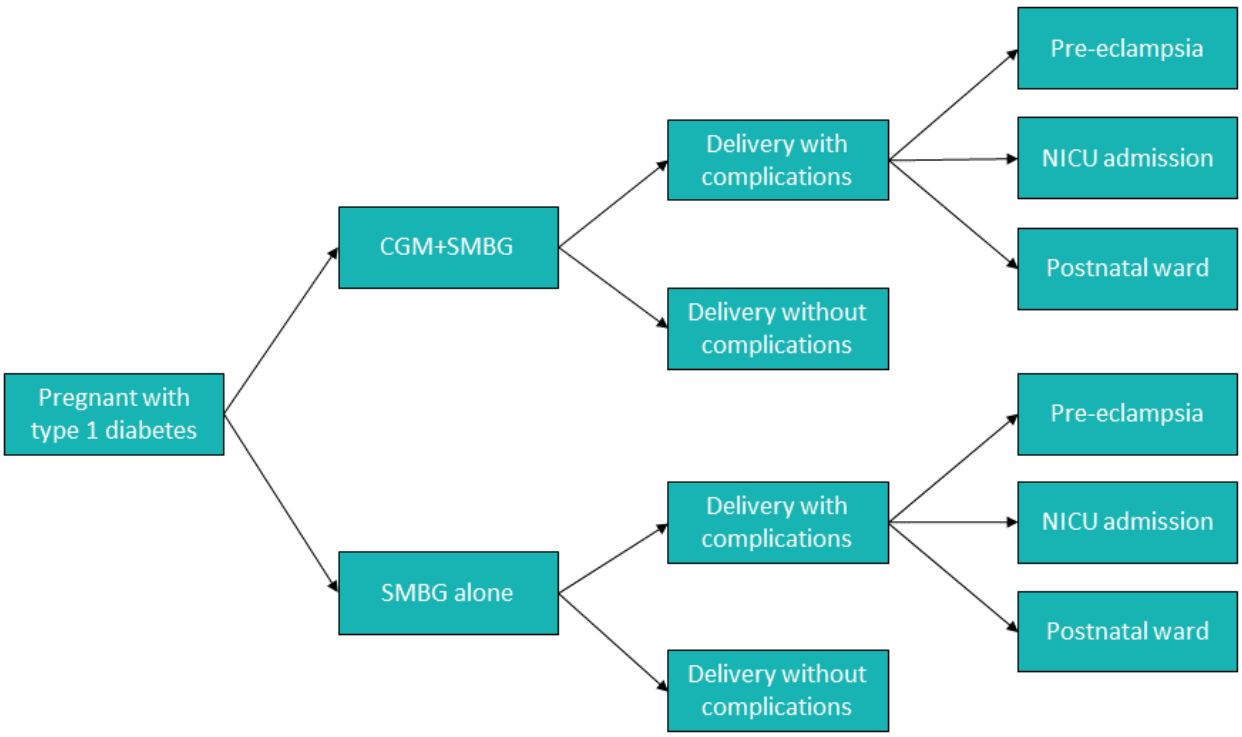
7.1. Existing economic evidence

Murphy et al. (2019) presented an economic impact evaluation based on clinical outcome data from the CONCEPTT trial (detailed in section 6.1). The analysis took the perspective of the UK National Health Service (NHS). The structure of the study follows a clinical quality of life equivalence approach with relative cost savings achieved through a reduction in short term resource use. The evaluation seeks to demonstrate the cost impact of CGM from the 10th week of pregnancy through to delivery. Their findings suggest a reduction in complications which leads to a net saving, GCM + SMBG is estimated to be cost saving when compared to SMBG alone.

7.2. De novo economic evaluation

This de novo modelling adapts the approach taken by Murphy et al. (2019).The analysis takes the form of a cost minimisation analysis within the UK NHS setting, comparing real time CGM +SMBG to SMBG in pregnant women with T1DM. Costs are reported in 2018 GBP, and there is no discounting as the evaluation occurs within a single year.

Whilst there is insufficient evidence to develop a detailed economic evaluation of real-time CGM compared to flash glucose monitoring, a sensitivity analysis with flash glucose monitoring as a comparator has been included (Section 7.6). Figure 1 shows the structural layout of resource related outcomes.



CGM: continuous glucose monitoring; SMBG: self-monitoring of blood glucose; NICU: neonatal intensive care unit

Figure 1. Structural layout of resource related outcomes

According to the findings of Feig et al. (2017), the use of CGM, in addition to SMBG, resulted in an improvement to time in glycaemic target ranges. The improved glycaemic control was associated with changes in a range of neonatal outcomes, reducing the overall number of complications. Murphy et al. (2019) display the range of resource use outcomes collected by the CONCEPTT trial. To align the analysis with that of Murphy et al. (2019) work, the cohort size of 1,441 women was used to populate the model. The relative complication rates are displayed in

Table 7.

Table 7. Complication Rates

Complication outcome	CGM + SMBG	SMBG alone
Proportion admitted to NICU > 24 hours	27%	43%
Mean length of stay NICU (days)	6.6	9.1
Proportion of neonates admitted to NICU who also had a postnatal ward stay	57%	42%
Number of days neonates admitted to NICU also had on a postnatal ward	222	260
Mean duration of postnatal ward care pre- or post NICU admission (days)	4.1	6.4
Mean duration of hospitalisation in neonates not admitted to NICU (days)	3	3
Proportion with pre-eclampsia	9%	18%
CGM: continuous glucose monitoring; SMBG: self-monitoring of blood glucose; NICU: neonatal intensive care unit		

7.3. Cost inputs

The CONCEPTT trial offers an appropriate structure for applying the clinical outcomes to a cost model. The indication, setting and scope in the CONCEPTT trial match that of this analysis. The majority of inputs reported by Murphy et al. (2019) were used in this analysis with one notable exception, NICU costs. Murphy et al. (2019) used a figure of £3,747 for each day in the NICU. This value is cited in the paper as coming from a paediatric population which excluded neonates from their analysis. The nature of NICU stay tends to follow a pathway of admission into a higher dependency NICU followed by additional time in lower dependency NICU. Wales specific data[1] from the maternity dataset (Euroking) was matched with neonatal data (Badgernet) to identify neonatal admissions to NICU. The matched data identified a representative 'NICU day stay' according to dependency. The majority of NICU stay reported was that of high dependency (65.4%) followed by intensive care NICU (34.6%). A weighted average day case for NICU costs £1,105 using the NHS reference costs 2017/18 (ICU: £1,445, High dependency £925).

Intervention costs are calculated over the 28-week duration. A single transmitter is required along with 28 sensor units (1 per week). Following the approach from the CONCEPTT trial, SMBG strips are included at a rate of 4 per day for the CGM + SMBG group and 10 per day for the SMBG only group.

[1] (Consultant in Neonatal Medicine, University Hospital of Wales, Personal communication, 5 September 2019)

Table 8. Unit costs

Resource	Unit cost	Reference
Real time CGM transmitter	£350	Murphy (2019)
Sensor unit	£52.5	Murphy (2019)
Glucose strip	£0.3	BNF (2019)
NICU stay (per day)	£1,105	Weighted average of high dependency and intensive care from NHS Reference costs (2018)
Neonatal (non NICU bed day)	£347	NHS Reference costs (2017/18)
Increase cost of complicated delivery	£1,400	NHS Reference costs (2017/18)
CGM: continuous glucose monitoring; NICU: neonatal intensive care unit; BNF: British National Formulary; NHS: National Health Service		

Comparative costs include the blood glucose testing approach, the delivery and the short-term neonatal process. The clinical evidence captured by the CONCEPTT trial suggests a reduction in complication and significantly lower usage of NICU.

7.4. Results

The updated costs are reported in

Table 9. Costs are reported according to the intervention costs and then each clinical outcome.

Table 9. Comparative costs of interventions

Cost item	CGM with SMBG	SMBG alone	Difference (CGM + SMBG minus SMBG alone)
CGM cost	£2,622,620	-	£2,622,620
SMBG cost	£338,923	£847,308	-£508,385
NICU length of stay cost	£2,837,488	£6,230,689	-£3,393,202
Postnatal ward costs in neonates admitted to NICU	£315,512	£577,951	-£262,439
Postnatal ward costs in non-NICU neonates	£1,095,059	£855,046	£240,013
Delivery complications costs	£181,566	£363,132	-£181,566
Total cost	£7,391,168	£8,874,126	-£1,482,959
CGM: continuous glucose monitoring; SMBG: self-monitoring of blood glucose; NICU: neonatal intensive care unit			

The largest cost driver was the NICU length of stay costs. NICU costs were calculated as the proportion of individuals requiring NICU multiplied by the total number of patients and then

multiplied by the average duration of stay and the NICU cost per day of £1,105. The two NICU costs were therefore (0.27 * 1,441) * (6.6 *£1,105) = £2,837,488 for CGM + SMBG and (0.43 *1,441) *(9.1 * £1,105) = £6,230,689 for SMBG alone.

The cost minimisation approach finds that CGM + SMBG is cost saving when compared to SMBG alone. The cost reduction of £1,482,959 associated with CGM equates to **£1,029** saved per pregnancy. The uncertainty surrounding the NICU attendance and duration are assessed in the sensitivity analysis as the NICU costs represent the largest cost component of the analysis. One aspect omitted from the analysis is that of attending a NICU for less than 24 hours. The omitted resource use is assumed to result in a more conservative estimate of possible cost savings as the CGM + SMBG group exhibited lower rates than SMBG alone.

7.5. Sensitivity analysis

The sensitivity analysis seeks to assess the impact of adjustment in outcomes or assumptions to better characterise the uncertainty within the model. The focus of the sensitivity analysis was that of NICU attendance. A range of one-way sensitivity analyses and threshold analyses re used to assess the robustness of the model to the uncertainty in the inputs. NICU attendance was included in the model as a combination of the two highest severity levels of neonatal critical care.

Substituting alternative dependency levels of neonatal critical care in the place of neonatal critical care day case cost illustrates the impact that NICU cost has on the model outcomes.

The base case intensive care cost of £1,105 was replaced by a range of critical care options. The resulting cost outcomes are reported in Table 10.

Table 10. Sensitivity analysis

Critical care option	HRG day cost	Cost impact (CGM +SMBG minus SMBG alone)	Cost impact per pregnancy
Critical care: Intensive care	£1,445	-£2,537,021	-£1,754
Critical care: High dependency	£925	-930,220	-£624
Critical care: Special care without external carer	£605	£52,427	£37
Critical care: Normal care	£435	£576,665	£400
HRG: healthcare resource group; CGM: continuous glucose monitoring; SMBG: self-monitoring of blood glucose			

A threshold analysis determining the break-even point for the NICU healthcare resource group (HRG) finds that a cost of £622 per day would result in the two approaches costing the same.

7.6. Scenario Analysis

There is currently insufficient evidence to develop a detailed evaluation of CGM + SMBG in comparison to flash glucose monitoring. However, a hypothetical indirect comparison can be estimated according to the current market access position of flash glucose monitoring. Flash

glucose monitoring is currently recommended based on a clinical and cost equivalence to SMBG, where eight SMBG are required daily. CGM + SMBG vs flash glucose can be assessed using a cost minimisation approach, under the assumption that flash glucose monitoring is equal to eight SMBG. CGM + SMBG was found to be cost saving with an estimated cost reduction of £911 per pregnancy. Under the assumption that glucose monitoring devices are used in combination with SMBG. The scenario of CGM + SMBG (four daily) compared to flash glucose monitoring + SMBG (four daily) estimates a cost saving associated with CGM + SMBG of £1,147 per patient.

The uncertainty surrounding the relative risk of attending neonatal intensive care was reported by Feig et al. (2017). The estimate of the odds ratio was reported to be 0.48 with 95% confidence intervals of 0.26-0.86. Assuming a fixed odds of attending neonatal intensive care in the control group, the 95% odds ratio for the intervention group would range between 17% and 40%. Applying this range of values results in a cost saving of between £81 and £1,758 per patient and £116,761 to £2,533,880 for the whole population. Note that while risk of attending neonatal intensive care was varied in this analysis, the disparity in NICU stay duration was maintained.

7.7. Budget impact

The Patent Episode Database for Wales (PEDW) information and statistics report on finished consultant episodes for 2017/18 (NHS Wales Informatics Service 2018) suggests that there were 206 hospital admissions for pre-existing T1DM pregnancies. The budget impact estimate offers a range of plausible adoption levels. A 50% adoption level for the population of 206 patients and savings per patient of £1,029 equates to an overall cost saving of £105,987. The initial intervention cost during pregnancy (intervention cost less comparator cost) equals an increase in spending of £151,121. The per patient cost increase for CGM is £1,467. The range of population estimates and adoption uptake levels result in cost savings between £52,994 and £334,425. Table 11 shows of the budget impact estimates for the overall population at a range of adoption levels.

Table 11. Budget impact estimates according to adoption level

Population Estimate	Adoption Level			
	25%	50%	75%	100%
2015/16 (n=325)	£83,606	£167,213	£250,819	£334,425
2016/17 (n=249)	£64,055	£128,111	£192,166	£256,221
2017/18 (n=206)	£52,994	£105,987	£158,981	£211,974
Average (n=260)	£66,885	£133,770	£200,655	£267,540

8. Organisational issues

Use of CGM will result in potential training needs for both patients and clinical staff, in terms of both initial set-up of devices and their ongoing use. For optimal use, this must cover not just technical aspects of using the device, but also the optimal usage of CGM as a technology to improve diabetes therapy (Petrie et al. 2017). Training and ongoing support is provided by CGM device manufacturers.

Use of CGM requires careful data handling and reporting. Different CGM systems use different formats for display of glucose data, and there are a number of tools available for data display and analysis (Petrie et al. 2017).

9. Patient issues

The evidence review identified one qualitative meta-analysis on the impact of continuous glucose monitoring on life with T1DM (Messer et al. 2018). This did not directly focus on T1DM during pregnancy, and none of the included nine studies focussed on this population specifically. Other factors limiting transferability include the inclusion of three studies on artificial pancreas systems (not covered by this health technology assessment) and the inclusion of children/adolescents, or their parents (156 out of total of 343 individual participants). However, in the absence of any evidence specific to pregnant women with T1DM, a summary of this meta-synthesis is included here.

The metasynthesis identified six themes describing how CGM impacts the lives of users:

Theme 1: Interaction with CGM. This included concerns such as discomfort caused by the sensor or worry about bumping or dislodging the device, and highlighted the pain and discomfort that CGM use can cause. Users reported that they can find CGM alarms either useful or frustrating, depending on their frequency and their perceived utility in specific situations (such as whilst driving or working.

Theme 2: Burden of living with CGM. CGM users experience significant non-physical burdens associated with CGM use including emotional burden, time for CGM, altered sleep and worry about cost. These can exacerbate the emotional burden of diabetes.

Theme 3: Feeling different from others. People with diabetes often feel different from those without diabetes, and CGM can exacerbate these feelings. CGM can make diabetes visible to others, and alter the person's body image.

Theme 4: Feeling empowered. CGM affords users a sense of security about diabetes that is not possible without ongoing monitoring. CGM users describe feeling safer while wearing CGM, which enables them to live with less fear of unexpected hypoglycaemia, and provides reassurance to the wearer (and to spouses and significant others) during daily activities. A sense of independence and personal control may be heightened with CGM use.

Theme 5: Interacting with glucose information. CGM use leads to increased glucose information to contend with, and subthemes include managing the information from CGM, achieving better glucose control, and questioning the reliability of CGM. Managing the extra information on glucose levels provided by CGM can be both helpful and overwhelming.

Theme 6: Impact on relationships. CGM users experience altered relationships with spouses, caregivers and healthcare providers due to CGM use. Subthemes include positive and negative impact on spousal relationships, child-parent relationships and healthcare provider relationships.

10. Conclusions

Evidence from randomised trials exists assessing the clinical effectiveness of CGM in pregnant women with T1DM, used as an adjunct to SMBG, compared to SMBG alone. All of the studies identified used CGM systems produced by Medtronic; some of the older trials used systems that have been superseded and may not be as representative of current clinical practice as newer systems.

Overall, the evidence suggests CGM may offer benefits by improving some maternal (glycaemic control, pre-eclampsia) and neonatal (risk of NICU admission, risk of hypoglycaemia) outcomes. The evidence indicates uncertainty in how CGM affects other outcomes, such as risk of caesarean section, pregnancy-induced hypertension, miscarriage, birthweight and neonatal mortality/stillbirth.

Very limited evidence exists to compare CGM to flash glucose monitoring in pregnant women with T1DM, and the relative effectiveness of these two interventions in this population is therefore uncertain.

CGM, used as an adjunct to SMBG, is associated with a significant reduction in complications and subsequently hospital resources when compared to SMBG alone to a sufficient extent to offset the initial higher intervention cost and offer overall cost savings to the NHS.

11. Contributors

This topic was proposed by Julia Platts, Consultant in Diabetes, Cardiff and Vale University Health Board and National Clinical Lead for Diabetes in Wales.

The HTW staff involved in writing this report were:

- J Washington: conducted literature searches
- D Jarrom: analysed clinical effectiveness data and co-wrote evidence appraisal report
- T Winfield: analysed economics data and co-wrote evidence appraisal report
- A Mironas: quality assurance of evidence appraisal report
- M Prettyjohns: quality assurance of economic analysis

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of experts from the UK provided material and commented on a draft of this report. Their views were documented (available on request) and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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Appendix 1. Selection criteria for including evidence in the review

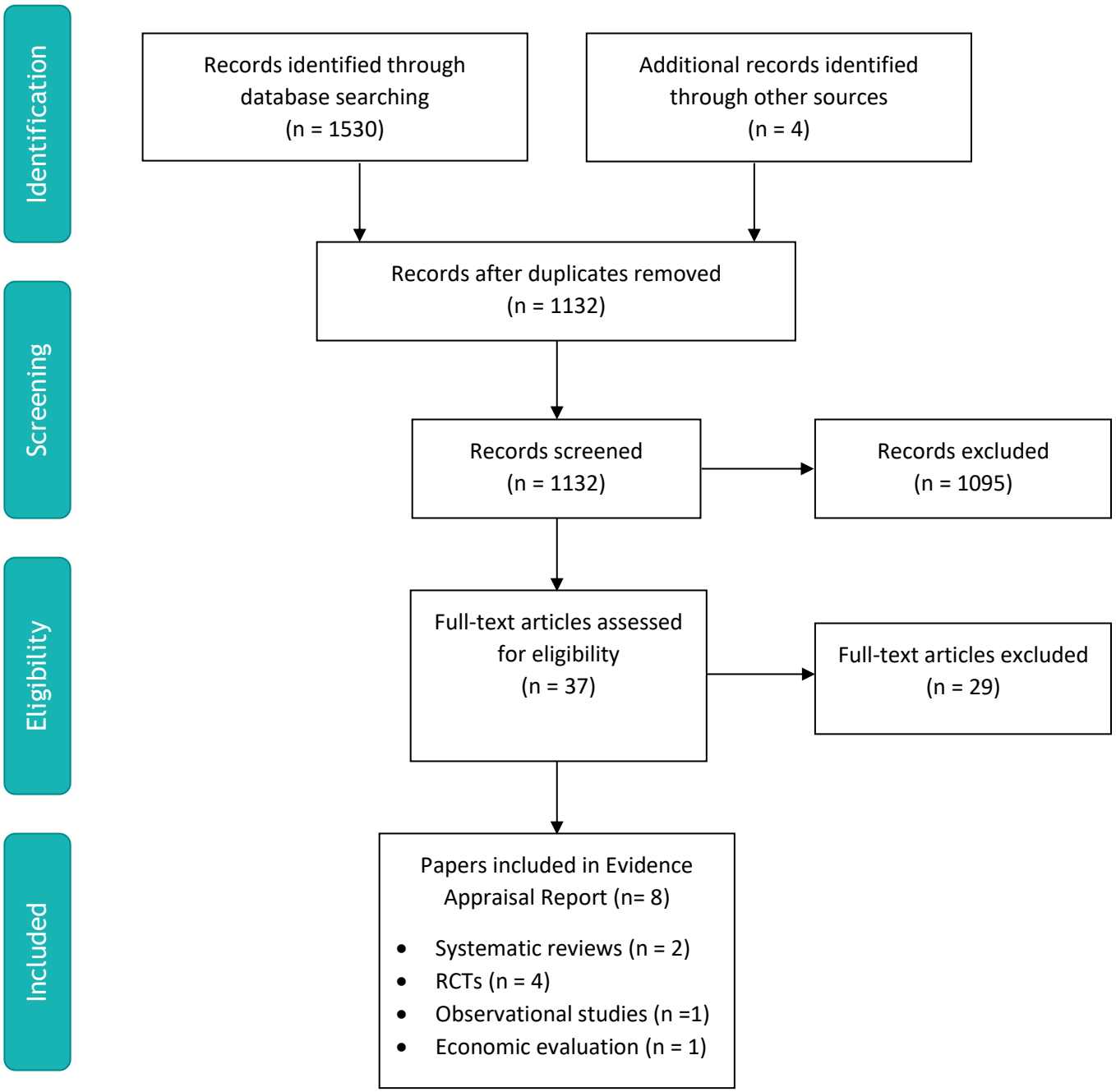
Research Question	What is the clinical and cost effectiveness of continuous glucose monitoring in pregnant women with type 1 diabetes?

	Inclusion criteria	Exclusion criteria
Population	Pregnant women with type 1 diabetes using any background insulin regiment to control their diabetes (insulin pumps, or injections of long- or short-acting insulin).	
Intervention	Continuous glucose monitoring (as an adjunct to, or a replacement for, standard care) We will consider any CGM system (retrospective or real-time) CE-marked and available in the UK, including, but not limited to: • G6® Continuous Glucose Monitoring System, Dexcom • FreeStyle Navigator II® Continuous Glucose Monitoring System (Abbott) • Guardian Connect® Continuous Glucose Monitoring system (Medtronic) • Eversense® Continuous Glucose Monitoring system (Senseonics Incorporated, marketed by Roche in UK) • Eversense® XL Continuous Glucose Monitoring system (Senseonics Incorporated, marketed by Roche in UK)	Flash glucose monitoring Any CGM system for which use in pregnancy is contraindicated (G4® PLATINUM, G5® Mobile, both Dexcom)
Comparison/ Comparators	Standard care; usually capillary blood glucose monitoring/self monitoring of blood glucose. Flash glucose monitoring may also be considered as a comparator, although levels of uptake are not known.	

Outcome measures	Rates of unassisted vaginal birth or caesarean sections, including rates of elective or emergency caesarean where reported Risk of pre-term birth HbA1c values; time in target range (preferred); HbA1c values/time in target range for each trimester where this is reported Incidence of maternal hypoglycaemia Rates of admission to neonatal intensive care /special care baby unit Birthweight, including rates of macrosomia Rates of births that are large for gestational age Rates of miscarriage/stillbirth/neonatal deaths Maternal insulin usage Gestational weight gain Incidence of gestational hypertension Incidence of pre-eclampsia Length of hospital stay after delivery Patient satisfaction Quality of life Incidence of neonatal hyper/hypoglycaemia Incidence of neonatal morbidity Adverse events
Study design	We will include the following clinical evidence in order of priority: • Systematic reviews. • Randomised controlled trials. • Non-randomised trials.

	We will only include evidence for “lower priority” evidence where outcomes are not reported by a “higher priority” source. We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison.
Search limits *dates, language, etc.*	No date limits applied.

Appendix 2 - PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness (last date of search: August 2019)



Appendix 3. Sensitivity analysis of comparative outcomes with CGM in pregnant women with type 1 diabetes, versus outcomes in women with either type 1 or type 2 diabetes

Appendix table 1. Continuous glucose monitoring compared to standard care: maternal outcomes in women with T1DM vs women with T1DM or T2DM. Figures in bold highlight any differences in treatment effect between the two populations.

Outcome	Population	Evidence source	Number of studies and patients	Absolute effect	Relative effect [95% CI] (interpretation)
Caesarean section	T1DM	Feig 2017, Secher 2013	Two studies, 325 patients	83/163 events with CGM vs 101/162 events with standard care	Risk Ratio 0.84 [0.71, 1.00] (favours neither intervention)
	T2DM or T1DM	Feig 2017, Secher 2013, Murphy 2008	Three studies, 427 patients	118/217 events with CGM vs 126/210 events with standard care	Risk Ratio 0.94 [0.75, 1.18] (favours neither intervention)
Pre-eclampsia	T1DM	Feig 2017, Voormolen 2018	Two studies, 308 patients	10/150 events with CGM vs 26/158 events with standard care	**Risk Ratio 0.40 [0.20, 0.80] (favours CGM)**
	T2DM or T1DM	Feig 2017, Voormolen 2018, Secher 2013, Murphy 2008	Four studies, 609 patients	22/306 events with CGM vs 34/303 events with standard care	**Risk Ratio 0.65 [0.39, 1.08] (favours neither intervention)**
Pregnancy-induced hypertension	T1DM	Feig 2017, Voormolen 2018	Two studies, 308 patients	10/150 events with CGM vs 18/158 events with standard care	Risk Ratio 0.59 [0.28, 1.24] (favours neither intervention)
	T2DM or T1DM	Feig 2017, Voormolen 2018	Two studies, 384 patients	18/189 events with CGM vs 28/195 events with standard care	Risk Ratio 0.67 [0.38, 1.16] (favours neither intervention)
Glycaemic control					
Maternal HbA1c at 34 weeks gestation [%]	T1DM	Feig 2017	One study, 187 patients	6.35% with CGM vs 6.53% with standard care	**Mean Difference -0.18 [-0.36, 0.00] (favours CGM)**
	T2DM or T1DM	Feig 2017, Murphy 2008	Two studies, 258 patients	NR	**Mean Difference -0.37 [-0.78, 0.04] (favours neither intervention)**

Outcome	Population	Evidence source	Number of studies and patients	Absolute effect	Relative effect [95% CI] (interpretation)
Achieved maternal HbA1c <= 6.5% (48 mmol/mol) at 34 weeks	T1DM	Feig 2017	One study, 187 patients	63/95 participants with CGM vs 48/92 participants with standard care	Risk Ratio 1.27 [1.00, 1.62] (favours CGM)
	T2DM or T1DM	No extra data available			
Incidence of miscarriage	T1DM	Feig 2017, Secher 2013	Two studies, 334 patients	8/168 events with CGM vs 5/166 events with standard care	Risk Ratio 1.59 [0.53, 4.77] (favours neither intervention)
	T2DM or T1DM	Feig 2017, Secher 2013, Murphy 2008	Three studies, 439 patients	9/225 events with CGM vs 7/214 events with standard care	Risk Ratio 1.24 [0.47, 3.26] (favours neither intervention)
Sense of well-being and quality of life (Short form 12, total score at 34 weeks' gestation)	T1DM	Feig 2017	One study, 214 patients	41.7 with CGM vs 42.4 with standard care	Mean difference -0.70 [-2.50, 1.10] (favours neither intervention)
	T2DM or T1DM	No extra data available			
Sense of well-being and quality of life (PAID), total score at 34 weeks' gestation)	T1DM	Feig 2017	One study, 214 patients	17.2 with CGM vs 16.4 with standard care	Mean difference 0.80 [-3.06, 4.66] (favours neither intervention)
	T2DM or T1DM	No extra data available			
Sense of well-being and quality of life (BGMSRQ, total score at 34 weeks' gestation)	T1DM	Feig 2017	One study, 214 patients	98.2 with CGM vs 93.9 with standard care	Mean difference 4.30 [0.73, 7.87] (favours CGM)
	T2DM or T1DM	No extra data available			

Appendix table 2. Continuous glucose monitoring compared to standard care: neonatal outcomes in women with T1DM vs women with T1DM or T2DM. Figures in bold highlight any differences in treatment effect between the two populations.

Outcome	Population	Evidence source	Study and patient characteristics	Absolute effect	Relative effect (interpretation)
Birthweight [kg]	T1DM	Feig 2017	One study, 200 patients	Mean 3.55 with CGM vs 3.58 with standard care	Mean difference -0.03 [-0.23, 0.17] (favours neither intervention)
	T2DM or T1DM	Feig 2017, Murphy 2008	Two studies, 267 patients	NR	Mean difference -0.13 [-0.38, 0.12] (favours neither intervention)
Large-for-gestational age	T1DM	Feig 2017, Secher 2013	Two studies, 323 patients	83/163 events with CGM vs 90/160 events with standard care	Risk ratio 0.99 [0.56, 1.75] (favours neither intervention)
	T2DM or T1DM	Feig 2017, Secher 2013, Murphy 2008	Three studies, 421 patients	100/216 events with CGM vs 112/205 events with standard care	Risk ratio 0.84 [0.57, 1.26] (favours neither intervention)
Small-for-gestational age	T1DM	Feig 2017	One study, 202 patients	2/100 events with CGM vs 2/102 events with standard care	Risk ratio 1.02 [0.15, 7.10] (favours neither intervention)
	T2DM or T1DM	Feig 2017, Murphy 2008	Two studies, 269 patients	6/137 events with CGM vs 2/132 events with standard care	Risk ratio 2.40 [0.55, 10.51] (favours neither intervention)
Macrosomia	T1DM	Feig 2017, Voormolen 2018	Two studies, 308 patients	45/150 events with CGM vs 47/158 events with standard care	Risk ratio 1.04 [0.74, 1.47] (favours neither intervention)
	T2DM or T1DM	Feig 2017, Voormolen 2018, Murphy 2008	Three studies, 451 patients	69/226 events with CGM vs 78/225 events with standard care	Risk ratio 0.84 [0.61, 1.17] (favours neither intervention)

Outcome	Population	Evidence source	Study and patient characteristics	Absolute effect	Relative effect (interpretation)
Stillbirth	T1DM	Feig 2017	One study, 211 patients	0/105 events with CGM vs 1/106 events with standard care	Risk ratio 0.34 [0.01, 8.17] (favours neither intervention)
	T2DM or T1DM	No extra data available			
Neonatal mortality	T1DM	No data available			
	T2DM or T1DM	Murphy 2008, Voormolen 2018	Two studies, 256 patients	2/130 events with CGM vs 2/126 events with standard care	Risk ratio 0.92 [0.13, 6.37] (favours neither intervention)
Neonatal hypoglycaemia	T1DM	Feig 2017, Secher 2013	Two studies, 323 patients	36/163 events with CGM vs 55/160 events with standard care	Risk ratio 0.64 [0.45, 0.91] (favours CGM)
	T2DM or T1DM	Feig 2017, Secher 2013, Murphy 2008	Three studies, 428 patients	43/220 events with CGM vs 62/208 events with standard care	Risk ratio 0.66 [0.48, 0.93] (favours CGM)
Neonatal intensive care unit admissions	T1DM	Feig 2017	One study, 200 patients	27/100 events with CGM vs 43/100 events with standard care	Risk ratio 0.63 [0.42, 0.93] (favours CGM)
	T2DM or T1DM	No extra data available			
Neonatal intensive care unit length of admission > 24 hours	T1DM	Feig 2017	One study, 200 patients	27/100 events with CGM vs 43/100 events with standard care	Risk ratio 0.63 [0.42, 0.93] (favours CGM)
	T2DM or T1DM	No extra data available			