National Institute for Health and Care Excellence

Final

Diabetes in pregnancy: management from preconception to the postnatal period

[A] Continuous glucose monitoring

NICE guideline NG3

Methods, evidence and recommendations

December 2020

Final

These evidence reviews were developed by the Guidelines Update Team

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1 Glucose monitoring in women with type 1 diabetes who are planning to become pregnant or who are already pregnant

1.1 Review question

In women with type 1 diabetes who are planning to become pregnant or who are already pregnant, what is the most effective method of glucose monitoring to improve maternal and infant outcomes:

- continuous glucose monitoring
- flash glucose monitoring
- intermittent capillary blood glucose monitoring?

1.1.1 Introduction

There are a number of risks associated with pregnancy in women with type 1 diabetes. Such risks can be reduced by managing diabetes, through glucose monitoring, when planning a pregnancy and during the pregnancy. Glucose levels can be monitored using different methods such as intermittent capillary blood glucose monitoring, continuous glucose monitoring (CGM) or flash glucose monitoring. CGM consists of a subcutaneous sensor which measures the glucose levels in the interstitial fluid and sends data to a display device. The user can then analyse the data and respond to changes in real-time or can make changes to insulin delivery, dose or timing based on retrospective data or trends. Flash glucose monitoring also consists of a subcutaneous sensor measuring interstitial fluid glucose. The user can obtain real-time data as well as trends by scanning the sensor with a reader device (including smart phones).

The 2015 NICE guideline on diabetes in pregnancy: management from preconception to the postnatal period states that CGM should not be offered routinely to pregnant women with diabetes. However, CGM can be considered for pregnant women on insulin therapy who have problematic severe hypoglycaemia, who have unstable blood glucose levels or to gain information about variability in blood glucose levels. The topic was reviewed by NICE'S surveillance team and new evidence was identified which prompted a partial update of the guideline. This review aims to determine the clinical and cost effectiveness of different glucose monitoring methods in improving maternal and infant outcomes in women with type 1 diabetes who are planning to become pregnant or who are already pregnant.

1.1.2 Summary of the protocol

PICO Table	
Population	Women with type 1 diabetes who are planning to become pregnant or are pregnant
Intervention	• Continuous glucose monitoring • Flash glucose monitoring • Intermittent capillary blood glucose monitoring
Comparator	Compared to each other
Primary Outcomes	**Maternal outcomes (as defined by author):** • Mode of birth: spontaneous vaginal delivery, instrumental vaginal delivery, caesarean section

PICO Table	

	• Preterm birth (birth before 37 + 0 weeks' gestation; take dichotomous or continuous data)
	• HbA1c (dichotomous or continuous outcome, depending how it is reported)
	• Time spent in target glucose range
	• Hypoglycaemia including:
	  ○ severe hypoglycaemia
	  ○ nocturnal hypoglycaemia
	(dichotomous or continuous outcome, depending how it is reported)
	• Maternal satisfaction- measured using validated questionnaires (e.g. Glucose Monitoring System Satisfaction Survey (GMSS))
	
	Foetal/Neonatal outcomes (as defined by author):
	• Mortality - perinatal and neonatal death (e.g. still birth)
	• Large for gestational age (or however defined in the study, for example, using a customised measure based on gestational age and population norms; dichotomous data preferred)
	• Small for gestational age
	• Neonatal intensive care unit length of stay 24 hours or greater (any term admission)

Secondary outcomes	**Maternal outcomes (as defined by author):**
	• Pregnancy induced hypertension
	• Pre-eclampsia
	• Time in hypoglycaemia
	• Awareness of hypoglycaemia
	• Glycaemic variability
	• Quality of life (continuous) – measured by validated tools (e.g. Short Form 12 (SF-12), Glucose Monitoring System Satisfaction Survey (GMSS), BG Monitoring System Rating Questionnaire (BGMSRQ), Hypoglycaemia Fear Survey- II (HFS-II),
	• Length of hospital stay
	• Adverse events (dichotomous):
	  ○ Diabetic ketoacidosis (DKA)
	  ○ Diabetes related hospitalisation
	  ○ local reaction due to CGM monitor
	  ○ malfunction of CGM monitor
	  ○ Postpartum haemorrhage
	  ○ Uterine rupture
	  ○ serious adverse events
	• Mental health outcomes measured using validated questionnaires (e.g. The Problem Areas in Diabetes (PAID) questionnaire and Diabetes Distress Scale (DSS):
	  ○ Diabetes distress (including fear of hypoglycaemia, daily burden and diabetes burnout)
	  ○ Diabetes related depression and anxiety
	  ○ Body image issues due to diabetes
	  ○ Eating disorders due to diabetes
	
	Foetal/Neonatal outcomes (as defined by author):
	• Length of hospital stay
	• Congenital abnormalities

PICO Table	
	• Foetal growth restriction • Neonatal hypoglycaemia

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and appendix B.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

In this review, the clinical and cost effectiveness of the following glucose monitoring systems were explored:

Continuous glucose monitoring: Consists of a subcutaneous sensor which measures the glucose levels in the interstitial fluid and automatically sends data to a display device (a handheld monitor, smart phone or pump) at 5 -minute intervals. The user can then analyse data and respond to changes in real-time or can make changes to insulin delivery, dose or timing based on retrospective data or trends. CGM models allow users to set alerts for high and low glucose levels, and rapid rate of change of glucose levels. Continuous glucose monitoring can also be referred to as real time continuous glucose monitoring (rt-CGM). In this review the term continuous glucose monitoring (CGM) will be used.

Flash glucose monitoring: Consists of a subcutaneous sensor which continuously measures the glucose levels in the interstitial fluid at 15-minute intervals. The user can obtain real-time data as well as trends by scanning the sensor with a reader device (including smart phones). The information provided gives a glucose level and information regarding the rate of change of glucose levels. Flash glucose monitoring can also be referred to as intermittently scanned CGM (isCGM). In this review, the term flash glucose monitoring will be used.

Intermittent capillary blood glucose monitoring: Conventional self-monitoring of blood glucose (SMBG) through 'finger prick' testing. Alternate sites may also be used for testing such as the palm, the upper forearm, the abdomen, the calf or the thigh, but this is rare.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A total of 5,472 RCTs and systematic reviews and 411 observational studies were identified in the search. After removing duplicate references, 2,745 RCTs and systematic reviews and 303 observational studies were screened at title and abstract stage. 1 additional study was identified from the 2015 NICE guidance on diabetes in pregnancy: management from preconception to the postnatal period. Overall, a total of 3049 studies were screened.

Following title and abstract screening, 54 studies (32 RCTs and systematic reviews and 22 observational studies) were included for full text screening. These studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A). Overall, 3 studies were included (2 RCTs and 1 retrospective cohort study).

The studies included examined the following interventions:

- CGM versus intermittent capillary blood glucose monitoring (2 RCTs)
- CGM versus flash glucose monitoring (1 retrospective cohort study)

No studies were identified which compared flash glucose monitoring with intermittent capillary blood glucose monitoring.

Evidence was identified for the preconception period (women planning to become pregnant) and during pregnancy. One study (Feig 2017) also presented evidence on women who conceived while planning for pregnancy. This evidence was also included in the analysis.

See appendix E for evidence tables and the reference list in section 1.1.13.

1.1.4.2 Excluded studies

Overall, 51 studies (20 RCTs/ systematic reviews and 21 observational studies) were excluded. See appendix K for the list of excluded studies with reasons for their exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Reference	Study type	Population	Intervention	Comparator	Maternal Outcomes	Neonatal Outcomes
Feig 2017	RCT	Women aged 18-40 years with type 1 diabetes for a minimum of 12 months, receiving intensive insulin therapy via multiple daily injections or an insulin pump, who were pregnant or planning pregnancy	Continuous glucose monitoring (CGM)	Intermittent capillary blood glucose monitoring Participants were advised to test capillary glucose levels at least 7 times daily (before and 1-2h after meals and before bed).	• HbA1c (%) • Achieved HbA1c less than or equal to 6.5% (48 mmol/mol) • Achieved HbA1c less than or equal to 7.0% (53 mmol/mol) • Time in target glucose range (%) • Severe hypoglycaemia • Adverse event- Diabetic ketoacidosis • Glucose variability • Pre-eclampsia • Mode of birth - Caesarean section • Preterm birth - <37 weeks • Serious adverse events • Diabetes related hospitalisation • Quality of life - measured using BG monitoring systems rating questionnaire (BGMSRQ) • Quality of life- Hypoglycaemia Fear Survey • Diabetes related distress - measured using the Problem Areas in Diabetes scale (PAID)	• Large for gestational age • Small for gestational age • Neonatal hypoglycaemia • Still birth • Congenital anomaly • Macrosomia • High level neonatal care (NICU) • Pregnancy loss <20 weeks

Reference	Study type	Population	Intervention	Comparator	Maternal Outcomes	Neonatal Outcomes
					• Quality of Life- Short form- 12 (SF-12) • Local reaction due to CGM monitor (skin changes reported during trail)	
Kristensen 2019	Retrospective observational study	Women with type 1 diabetes who received pregnancy care between 2014 and 2017.	Continuous glucose monitoring (CGM)	Flash glucose monitoring	• HbA1c (%) • Pre-eclampsia/ Pregnancy induced hypertension • Mode of birth- Caesarean section • Pre-term birth < 37 weeks	• Large for gestational age - Birthweight >2SD above expected birthweight for gestational age and sex • Macrosomia - birthweight >4500g • Neonatal hypoglycaemia - Plasma glucose <2.6mmol/L >3h after birth • NICU admission >24h
Secher 2013	RCT	All Danish-speaking pregnancy women with pre-gestational diabetes referred to the Centre for Pregnant Women with Diabetes, before 14 completed gestational weeks with one living intrauterine foetus.	Continuous glucose monitoring (CGM) Intermittent real-time CGM (Guardian Real-time Continuous Glucose monitoring system with offered for 6 days at the first pregnancy visit at	Intermittent capillary blood glucose monitoring Participants were asked to monitor plasma glucose for 6 days, including measurements at 3 am, at study visits at	• Pre-eclampsia • Mode of birth - Caesarean section • Preterm birth - < 37 weeks of gestation	• Large for gestational age • Neonatal hypoglycaemia • Severe neonatal hypoglycaemia • Miscarriage

Reference	Study type	Population	Intervention	Comparator	Maternal Outcomes	Neonatal Outcomes
			8 weeks and at 12, 21, 27 and 33 weeks on top of routine pregnancy care.	8,12,21,27 and 33 weeks.		

See appendix E for full evidence tables

1.1.6 Summary of the effectiveness evidence

Continuous glucose monitoring vs. intermittent capillary blood glucose monitoring

Preconception period (women who are planning to become pregnant)

Maternal outcomes at ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%) – MD less than 0 favours CGM					
1 Feig 2017	RCT	88	-0.23 (-0.55, 0.09)	Moderate	Could not differentiate between monitoring systems
Achieved HbA1c target (7.0% (53 mmol/mol) - RR greater than 1 favours CGM					
1 Feig 2017	RCT	88	1.30 (0.87, 1.95)	Moderate	Could not differentiate between monitoring systems
Time spent in glucose target range (%) – whole population – MD less than 0 favours CGM					
1 Feig 2017	RCT	91	5.00 (-0.96, 10.96)	Moderate	Could not differentiate between monitoring systems
Time spent in glucose target range (%) – Insulin pump users – MD less than 0 favours CGM					
1 Feig 2017	RCT	67	4.00 (-2.72, 10.72)	Moderate	Could not differentiate between monitoring systems
Time spent in glucose target range (%) – Multiple daily injection users – MD less than 0 favours CGM					
1 Feig 2017	RCT	24	4.00 (-8.87, 16.87)	Low	Could not differentiate between monitoring systems

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Severe hypoglycaemia – RR less than 1 favours CGM					
1 Feig 2017	RCT	109	1.53 (0.52, 4.54)	Moderate	Could not differentiate between monitoring systems
Serious adverse events – RR less than 1 favours CGM					
1 Feig 2017	RCT	110	2.15 (0.20, 23.04)	Moderate	Could not differentiate between monitoring systems
Adverse event – Diabetic ketoacidosis – RR less than 1 favours CGM					
1 Feig 2017	RCT	109	0.22 (0.01, 4.46)	Moderate	Could not differentiate between monitoring systems
Adverse event- local reaction (skin changes during trial) – RR less than 1 favours CGM					
1 Feig 2017	RCT	109	5.04 (2.07, 12.29)	High	**Intermittent capillary blood glucose favoured**
Quality of life- BGMSRQ- Satisfaction subscale – MD greater than 0 favours CGM					
1 Feig 2017	RCT	110	-1.90 (-4.33, 0.53)	Moderate	Could not differentiate between monitoring systems
Quality of life- BGMSRQ – **Impact subscale-** MD greater than 0 favours CGM					
1 Feig 2017	RCT	110	5.10 (2.31, 7.89)	Moderate	**CGM favoured**
Quality of life- BGMSRQ – Obstruction subscale –MD less than 0 favours CGM					
1 Feig 2017	RCT	110	-2.80 (-4.71, -0.89)	Moderate	**CGM favoured**
Quality of life- HFS-II – Behaviour subscale – MD less than 0 favours CGM					
1 Feig 2017	RCT	110	-0.30 (-3.11, 2.51)	High	Could not differentiate between monitoring systems
Quality of life- HFS-II – Worry subscale - MD less than 0 favours CGM					
1 Feig 2017	RCT	110	-6.80 (-11.62, -1.98)	Moderate	**CGM favoured**
Quality of life- Short form -12 -					
1 Feig 2017	RCT	110	-0.50 (-2.90, 1.90)	Moderate	Could not differentiate between monitoring systems
Diabetes related distress – PAID score -					
1 Feig 2017	RCT	110	1.00 (-4.26, 6.26)	High	Could not differentiate between monitoring systems

During pregnancy

Maternal outcomes at ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%) – MD less than 1 favours CGM					
1 Feig 2017	RCT	187	-0.17 (-0.35, 0.01)	High	Could not differentiate between monitoring systems

Neonatal/ infant outcomes at ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Pregnancy loss/ Miscarriage – RR less than 1 favours CGM					
2 Feig 2017 Secher 2013	RCTs	334	1.59 (0.53, 4.77)	Moderate	Could not differentiate between monitoring systems

Maternal outcomes at > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%) – MD less than 0 favours CGM					
1 Feig 2017	RCT	187	-0.18 (-0.36, 0.00)	High	**CGM favoured**
Achieved HbA1c target (6.5% (48 mmol/mol) - MD greater than 1 favours CGM					
1 Feig 2017	RCT	187	1.27 (1.00, 1.62)	High	**CGM favoured**
Time spent in glucose target range (%) – whole population - MD greater than 0 favours CGM					
1 Feig 2017	RCT	154	7.00 (2.57, 11.43)	Moderate	**CGM favoured**
Time spent in glucose target range (%) – Insulin pump users - MD greater than 0 favours CGM					
1 Feig 2017	RCT	72	4.00 (-2.24, 10.24)	Moderate	Could not differentiate between monitoring systems
Time spent in glucose target range (%) – Multiple daily injection users - MD greater than 0 favours CGM					
1 Feig 2017	RCT	24	8.00 (1.43, 14.57)	Moderate	**CGM favoured**
Severe hypoglycaemia – RR less than 1 favours CGM					
2 Feig 2017 Secher 2013	RCT	304	0.77 (0.42, 1.44)	Moderate	Could not differentiate between monitoring systems

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Serious adverse events – RR less than 1 favours CGM					
1 Feig 2017	RCT	214	1.60 (0.54, 4.73)	Moderate	Could not differentiate between monitoring systems
Adverse event – Diabetic ketoacidosis – RR less than 1 favours CGM					
1 Feig 2017	RCT	207	1.01 (0.14, 7.03)	Moderate	Could not differentiate between monitoring systems
Adverse event- local reaction due to CGM monitor (skin changes during trial) – RR less than 1 favours CGM					
1 Feig 2017	RCT	207	6.18 (3.08, 12.40)	High	**Intermittent capillary blood glucose favoured**
Adverse event- Diabetes related hospitalisation – RR less than 1 favours CGM					
Feig 2017	RCT	207	2.02 (0.38, 10.79)	Moderate	Could not differentiate between monitoring systems
Pre-eclampsia – RR less than 1 favours CGM					
2 Feig 2017, Secher 2013	RCT	325	0.61 (0.32, 1.14)	Moderate	Could not differentiate between monitoring systems
Mode of birth – Caesarean section – RR less than 1 favours CGM					
2 Feig 2017, Secher 2013	RCT	325	0.82 (0.69, 0.99)	High	**CGM favoured**
Preterm birth <37 weeks – RR less than 1 favours CGM					
2 Feig 2017, Secher 2013	RCT	325	0.93 (0.68, 1.26)	Moderate	Could not differentiate between monitoring systems
Quality of life- BGMSRQ- Satisfaction subscale - MD greater than 0 favours CGM					
1 Feig 2017	RCT	214	-0.40, (-2.12, 1.32)	High	Could not differentiate between monitoring systems
Quality of life- BGMSRQ – **Impact subscale -** MD greater than 0 favours CGM					
1 Feig 2017	RCT	214	4.80 (2.98, 6.62)	Moderate	**CGM favoured**
Quality of life- BGMSRQ – Obstruction subscale - MD less than 0 favours CGM					
1 Feig 2017	RCT	214	-1.90 (-3.09, -0.71)	Moderate	**CGM favoured**
Quality of life- HFS-II – Behaviour subscale - MD less than 0 favours CGM					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 Feig 2017	RCT	214	1.00 (-1.06, 3.06)	High	Could not differentiate between monitoring systems
Quality of life- HFS-II – Worry subscale - MD less than 0 favours CGM					
1 Feig 2017	RCT	214	0.80 (-3.01, 4.61)	High	Could not differentiate between monitoring systems
Quality of life- Short form -12 - MD greater than 0 favours CGM					
1 Feig 2017	RCT	214	-0.70 (-2.50, 1.10)	High	Could not differentiate between monitoring systems
Diabetes related distress – PAID score – MD less than 0 favours CGM					
1 Feig 2017	RCT	214	0.80 (-3.06, 4.66)	High	Could not differentiate between monitoring systems

Neonatal/ infant outcomes at >6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Still birth – RR less than 1 favours CGM					
1 Feig 2017	RCT	211	0.34 (0.01, 8.17)	Moderate	Could not differentiate between monitoring systems
Congenital anomaly – RR less than 1 favours CGM					
1 Feig 2017	RCT	211	0.67 (0.11, 3.95)	Moderate	Could not differentiate between monitoring systems
Small for gestational age – RR less than 1 favours CGM					
1 Feig 2017	RCT	200	1.00 (0.14, 6.96)	Moderate	Could not differentiate between monitoring systems
Large for gestational age – RR less than 1 favours CGM					
2 Feig 2017, Secher 2013	RCT	323	0.91 (0.74, 1.11)	Moderate	Could not differentiate between monitoring systems
Macrosomia- RR less than 1 favours CGM					
1 Feig 2017	RCT	200	0.85 (0.11, 1.65)	Moderate	Could not differentiate between monitoring systems
Neonatal hypoglycaemia – RR less than 1 favours CGM					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
2 Feig 2017, Secher 2013	RCT	317	0.67 (0.47, 0.95)	Moderate	**CGM favoured**
Severe neonatal hypoglycaemia – RR less than 1 favours CGM					
1 Secher 2013	RCT	117	0.95 (0.42, 2.16)	Very low	Could not differentiate between monitoring systems
High level neonatal care (NICU) >24 hours – RR less than 1 favours CGM					
1 Feig 2017	RCT	200	0.63(0.42, 0.93)	High	**CGM favoured**

During pregnancy – women who conceived during 24-week planning pregnancy trial

Maternal outcomes at ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%)– MD less than 0 favours CGM					
1 Feig 2017	RCT	24	-0.25 (-0.71, 0.21)	Moderate	Could not differentiate between monitoring systems

Neonatal/ infant outcomes at ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%) – MD less than 0 favours CGM					
1 Feig 2017	RCTs	31	2.43 (0.52, 11.36)	Moderate	Could not differentiate between monitoring systems

Maternal outcomes at > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%)– MD less than 0 favours CGM					
1 Feig 2017	RCT	24	-0.27 (-0.71, 0.17)	Moderate	Could not differentiate between monitoring systems
Achieved HbA1c target (7.0% (53 mmol/mol) before pregnancy and 6.5% (48 mmol/mol after pregnancy) – MD greater than 0 favours CGM					
1 Feig 2017	RCT	24	1.43 (0.70, 2.91)	Moderate	Could not differentiate between monitoring systems
Severe hypoglycaemia – RR less than 1 favours CGM					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 Feig 2017	RCT	30	1.14 (0.18, 7.08)	Moderate	Could not differentiate between monitoring systems
Adverse event – Diabetic ketoacidosis – RR less than 1 favours CGM					
1 Feig 2017	RCT	30	3.40 (0.15, 77.34)	Moderate	Could not differentiate between monitoring systems
Pre-eclampsia – RR less than 1 favours CGM					
1 Feig 2017	RCT	25	0.48 (0.02, 10.84)	Moderate	Could not differentiate between monitoring systems
Mode of birth – Caesarean section – RR less than 1 favours CGM					
1 Feig 2017	RCT	25	0.95 (0.57, 1.59)	Moderate	Could not differentiate between monitoring systems
Preterm birth <37 weeks – RR less than 1 favours CGM					
1 Feig 2017	RCT	25	1.88 (0.66, 5.32)	Moderate	Could not differentiate between monitoring systems

Neonatal/ infant outcomes at >6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Still birth – RR less than 1 favours CGM					
1 Feig 2017	RCT	31	RR not estimable	Low	Not applicable as treatment effect could not be estimated
Congenital anomaly – RR less than 1 favours CGM					
1 Feig 2017	RCT	31	RR not estimable	Low	Not applicable as treatment effect could not be estimated
Small for gestational age – RR less than 1 favours CGM					
1 Feig 2017	RCT	31	RR not estimable	Low	Not applicable as treatment effect could not be estimated
Large for gestational age – RR less than 1 favours CGM					
1 Feig 2017	RCT	25	0.82 (0.45, 1.48)	Moderate	Could not differentiate between monitoring systems
Macrosomia – RR less than 1 favours CGM					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 Feig 2017	RCT	25	0.43 (0.11, 1.66)	Moderate	Could not differentiate between monitoring systems
Neonatal hypoglycaemia – RR less than 1 favours CGM					
1 Feig 2017	RCT	25	1.50 (0.76, 2.95)	Moderate	Could not differentiate between monitoring systems
High level neonatal care (NICU) >24 hours – RR less than 1 favours CGM					
1 Feig 2017	RCT	25	1.75 (0.83, 3.67)	Moderate	Could not differentiate between monitoring systems

Continuous glucose monitoring vs. Flash glucose monitoring

During pregnancy

Maternal outcomes at ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%) - MD less than 0 favours CGM					
1 Kristensen 2019	Retrospective study	186	0.10 (-0.17, 0.37)	Low	Could not differentiate between monitoring systems

Maternal outcomes at > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%) - MD less than 0 favours CGM					
1 Kristensen 2019	Retrospective study	186	0.00 (-0.20, 0.20)	Low	Could not differentiate between monitoring systems
Pre-eclampsia - RR less than 1 favours CGM					
1 Kristensen 2019	Retrospective study	186	0.81 (0.44, 1.49)	Low	Could not differentiate between monitoring systems
Mode of birth – Caesarean section - RR less than 1 favours CGM					
1 Kristensen 2019	Retrospective study	186	1.15 (0.84, 1.56)	Low	Could not differentiate between monitoring systems
Preterm birth <37 weeks - RR less than 1 favours CGM					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 Kristensen 2019	Retrospective study	186	0.88 (0.55, 1.39)	Low	Could not differentiate between monitoring systems

Neonatal/ infant outcomes at > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Large for gestational age - RR less than1 favours CGM					
1 Kristensen 2019	Retrospective study	186	0.98 (0.75, 1.29)	Low	Could not differentiate between monitoring systems
Macrosomia- RR less than 1 favours CGM					
1 Kristensen 2019	Retrospective study	186	0.89 (0.46, 1.72)	Low	Could not differentiate between monitoring systems
Neonatal hypoglycaemia - RR less than 1 favours CGM					
1 Kristensen 2019	Retrospective study	186	0.75 (0.45, 1.25)	Low	Could not differentiate between monitoring systems
NICU admission >24 hours - RR less than 1 favours CGM					
1 Kristensen 2019	Retrospective study	186	0.84 (0.55, 1.27)	Low	Could not differentiate between monitoring systems

See appendix H for full GRADE tables.

1.1.7 Economic evidence

No existing economic evidence was identified for this review question

1.1.7.1 Included studies

A total of 1742 studies were screened.

Following title and abstract screening., 1 study was included for full text screening. 0 studies were included.

1.1.7.2 Excluded studies

1 study was excluded. See appendix L for excluded studies list.

1.1.8 Summary of included economic evidence

As no existing cost-utility models were found the only economic evidence presented is from the original economic model developed for this guideline.

1.1.9 Economic model

An original model was developed to address this review question, a summary table is shown below. Full details of methods and results are available in appendix M.

Applicability & limitations	Other comments	Base-case cost–utility results						Uncertainty
		Intervention	Absolute		Incremental			
			Cost	QALYs	Cost	QALYs	ICER/ NMB	
Original economic model								
Directly applicable with potentially serious limitations	Costs and QALYs associated with NICU admission, caesarean rates downstream caesarean costs and postnatal ward admission. Original decision tree type model built for the review question Uncertainty around a key study led to significant model uncertainty which limited its capacity to inform decision making.	Flash	£7,123	0.0172	-	-	-	**Deterministic:** In order to be associated with the highest net health benefit CGM would have to be associated be roughly 2.5 times the QALY gain from flash, or the cost would need to reduce by around £900. **Probabilistic:** With base case costs CGM was associated with the highest NHB in 13% of cases when a QALY is valued between £20,000 and £30,000.
		CGM	£8,026	0.0162	£903	-0.0010	Dominated	
		SMBG	£8,756	-0.0197	£1,633	-0.0369	Dominated	

1.1.10 Evidence statements

Evidence was also identified for which GRADE could not be applied as the evidence was presented in the form of median and interquartile range. This evidence is presented in Appendix G and summarised narratively here.

Preconception period

Glycaemic variability measures:

- Could not differentiate coefficient of variation at 24 weeks in women using CGM compared to those in the intermittent capillary blood glucose arm.
- Could not differentiate the mean amplitude of glucose excursion at 24 weeks in women using CGM compared to those in the intermittent capillary blood glucose arm.
- The rate of change at 24 weeks was higher in women using CGM s compared to women in the intermittent capillary blood glucose arm.

It should be noted that in this trial (Feig 2017) women in the intermittent capillary blood glucose arm obtained CGM measures using a masked sensor.

Percentage of time spent in glucose range < 3.5 mmol//l:

- Could not differentiate percentage of time spent in glucose range <3.5 mmol/l in women using CGM compared to those in the intermittent capillary blood glucose arm.

During pregnancy

Glycaemic variability measures:

- Could not differentiate the coefficient of variation at 34 weeks in women using CGM compared to those in the intermittent capillary blood glucose arm.
- The mean amplitude of glucose excursion at 34 weeks was lower in women using CGM compared to women in the intermittent capillary blood glucose arm.
- There rate of change at 34 weeks was higher in women using CGM compared to women in the intermittent capillary blood glucose arm.

It should be noted that in this trial (Feig 2017) women in the intermittent capillary blood glucose arm obtained CGM measures using a masked sensor.

Percentage of time spent in glucose range < 3.5 mmol//l:

- Could not differentiate percentage of time spent in glucose range <3.5 mmol/l in women using CGM compared to those in the intermittent capillary blood glucose arm.

HbA1c (%)

- Could not differentiate HbA1c levels at 21 weeks and at 36 weeks in women using CGM compared to those in the intermittent capillary blood glucose arm.

Maternal length of stay (days)

- Could not differentiate maternal length of stay in women using CGM compared to those in the intermittent capillary blood glucose arm.

Infant length of hospital stay (days)

- Infant length of hospital stay was significantly shorter in women using CGM compared to those in the intermittent capillary blood glucose arm.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee noted that maternal outcomes such as time in target glucose range, hypoglycaemia and caesarean sections were important and critical outcomes of interest. The committee also further noted that neonatal outcomes such as large for gestational age and neonatal intensive care unit stay were also important outcomes. The committee had also identified other important outcomes which are listed in the review protocol in appendix A.

1.1.11.2 The quality of the evidence

Overall, 3 studies were included in this review. Two RCTs (Feig 2017 and Secher 2013) compared continuous glucose monitoring (CGM) with intermittent capillary blood glucose monitoring and 1 retrospective cohort study (Kristensen 2019) was identified which compared flash glucose monitoring (also referred to as intermittently scanned continuous glucose monitoring) with CGM. Feig 2017 (CONCEPTT trial) included women who were pregnant as well as women who were planning on becoming pregnant. The study also included evidence for women who were part of the planning pregnancy trial and conceived. Evidence for this population was also included in this review.

Evidence comparing CGM with intermittent capillary blood glucose monitoring started off as high quality but was downgraded through GRADE as several issues were identified pertaining to the quality of this evidence. Firstly, the CONCEPTT trial was judged to be at low risk of bias however Secher 2013 was judged to be at high risk of bias as severe hypoglycaemia and other outcome parameters were analysed per protocol. Furthermore, in the CONCEPTT trial sensor compliance was generally high with 70% of pregnant participants and 77% of participants planning pregnancy using CGM for more than 75% of the time. However, in Secher 2013, only 7% of women (5 participants) used CGM for at least 60% of the time and remaining participants used CGM intermittently. Due to this, the evidence from Secher 2013 was downgraded for indirectness.

Heterogeneity was also identified in the evidence for women who are pregnant. In the meta-analysis for the outcome large for gestational age, very serious heterogeneity was identified (I^2 = 82%). Forest plot for this outcome can be found in appendix F. While both studies had utilised similar definitions for large for gestational age, in the CONCEPTT trial CGM was favoured and in Secher 2013 intermittent capillary blood glucose monitoring was favoured but this finding was not significant. Due to this heterogeneity, the outcome was downgraded for very serious inconsistency in GRADE.

The CONCEPTT trial explored a number of maternal and neonatal outcomes. In this study, participants were either assigned to CGM (Guardian Real-Time of MiniMed Minilink systems) or to intermittent capillary glucose monitoring. To examine direct CGM measures such as time in target glucose range, time above or below range and glycaemic variability measures, participants in the control arm used masked sensors (iPro 2 sensors). By using masked sensors, the study identified that pregnant women using CGM spent more time in the glucose target range compared to women using intermittent capillary glucose monitoring. While this favoured the use of CGM in pregnant women the committee did note that the evidence base on direct CGM measures was small as this evidence could only be obtained from the CONCEPTT trial as Secher 2013 did not utilise masked sensors in the control arm.

The committee highlighted that the overall evidence base was small and ranged in quality, but some significant evidence was identified for important outcomes such as time in target glucose range, caesarean sections and high level neonatal care stay which all favoured the use of CGM in pregnancy. The CONCEPTT trial also demonstrated that use of CGM resulted in few babies born large for gestational age compared to intermittent capillary blood glucose

monitoring. This evidence was graded as high to moderate quality. Additionally, outcomes such as HbA1c, number of women achieving HbA1c target and neonatal hypoglycaemia also favoured the use of CGM. Based on this the committee agreed that CGM could play a role in monitoring women with type 1 diabetes. Therefore, the committee recommended that CGM should be offered to all women with type 1 diabetes to help women achieve pregnancy glucose targets and better neonatal outcomes.

No studies were identified which compared flash with intermittent capillary blood glucose monitoring however, one retrospective cohort study was identified which compared flash with CGM. The study could not differentiate between flash and CGM for important outcomes such as caesarean section, large for gestational age and NICU admissions. The study demonstrated serious risk of bias as there was no correction for selection bias and the study did not take into account confounding factors. The committee further noted that there were baseline differences as women in the real-time CGM arm had longer duration of diabetes and a greater proportion were on insulin pumps compared with women using flash. Additionally, the authors of the paper concluded that while they found no differences in maternal and neonatal outcomes between flash and CGM, the observational design of the study means that firm conclusions cannot be drawn.

Based on the clinical evidence the committee were unable to recommend flash monitoring as first line for pregnant women with type 1 diabetes. Additionally, while evidence was identified for some neonatal outcomes such as large for gestational age, macrosomia, neonatal hypoglycaemia and NICU admissions, the committee highlighted it would be useful to have more evidence on these outcomes as well as other important neonatal outcomes such as still birth. Therefore, the committee drafted a research recommendation to further explore the use of flash.

1.1.11.3 Benefits and harms

Hypoglycaemia may occur more frequently in pregnant women and can result in women developing diabetes related distress which can include fear of hypoglycaemia and diabetes burnout. The CONCEPTT trial could not differentiate between CGM and intermittent capillary blood glucose monitoring for outcomes such as severe hypoglycaemia and quality of life measured using the Problem Areas in Diabetes (PAID) score. However, the committee highlighted that hypoglycaemia is an issue in practice.

The committee further highlighted that compared with flash, CGM includes predictive alert features such as alarms which can alert the user of impending hypoglycaemic and hyperglycaemic episodes. The committee also noted that this is particularly important in women with impaired hypoglycaemic awareness as well as those with problematic nocturnal hypoglycaemia. Based on their clinical expertise, the committee recommended that CGM should be offered to all pregnant women with type 1 diabetes to help them meet their pregnancy blood glucose targets and improve neonatal outcomes.

The committee also highlighted that some CGM monitors are compatible with insulins pumps. This means that CGM can also beneficial in pregnant women on insulin pump therapy as these devices are likely to allow increased time in target glycaemic range and less time in the hypoglycaemic range. By contrast, currently available flash glucose devices are not currently approved for insulin pump compatibility by manufacturers.

While weak evidence was identified which compared flash with CGM, the committee noted that there were circumstances in which flash could be beneficial. Firstly, adverse events such as local reactions can occur during the use of CGM and flash. The CONCEPTT trial identified that more pregnant women using CGM experienced skin changes during the trial, compared with intermittent blood capillary blood glucose monitoring. These skin changes included acute erythema, acute oedema, chronic scabbing, chronic dry skin, chronic hypopigmentation, and chronic hyperpigmentation. The committee highlighted that women

who present with hypersensitivities to CGM may prefer to use flash instead. However, the committee did note that skin reactions can still occur with the adhesive dressing used with flash glucose monitors.

Secondly, the committee noted that some women may already be using flash glucose monitoring prior to pregnancy and may prefer to use it during their pregnancy. Lastly, the committee noted that some women can experience alarm fatigue. This occurs when the user is frequently exposed to alarms and can lead to the user becoming less likely to respond to a true alarm. This can discourage the user from using the device. The committee noted that in these scenarios, women may prefer to use flash instead.

Thirdly, while no evidence was identified comparing flash with intermittent capillary blood glucose monitoring, the committee noted that some women who may find intermittent capillary blood glucose monitoring difficult to manage and this can cause anxiety in patients. In this group, flash glucose monitoring can encourage them to monitor their glucose levels.

Taking all these factors into consideration, the committee drafted a recommendation to state that intermittently scanned CGM (isCGM, commonly referred to as flash) can be offered to women who are unable to use CGM or express a clear preference for it. The committee further noted that discussions should occur between the clinician and patient and the decision should be made based on individual needs.

1.1.11.4 Cost effectiveness and resource use

The committee discussed the economic evidence regarding glucose monitoring in women with type 1 diabetes during pregnancy. No existing cost–utility models were identified so the evidence presented was exclusively from the original economic model developed for this review question.

In the base case the NHS ceiling price of £2,000 was used. A broad range of prices was explored in the sensitivity analyses, and the committee took this into account when considering the model results. Due to the absence of evidence of differences in the modelled outcomes between CGM devices it was assumed that all CGM devices are clinically equivalent.

The committee saw that, in the model's base case, flash is associated with both the lowest overall costs and the highest overall QALYs. SMBG is associated with the highest cost and lowest QALYs in all scenarios; this is because the higher expected costs of delivery (more caesarean sections with SMBG) and neonatal management (more critical care with SMBG) are enough to outweigh the acquisition costs of monitoring devices.

The committee reviewed the results of the probabilistic sensitivity analysis, which show that, while there is a high degree of certainty that flash has a lower overall cost than CGM, any QALY difference between these monitoring methods is much less certain. This is consistent with the lack of significant differences in effectiveness found in the clinical review. There is also a high degree of certainty that SMBG results in the fewest QALYs and has higher net costs than flash and CGM . The committee agreed that this demonstrates that both flash and CGM provide better value for money than SMBG.

Deterministic one-way and two-way analyses were also presented to the committee. Firstly, the relationship between cost and 'process utility' for CGM was explored. Process utility refers to the impact on a person's quality of life that is associated with a mode of management itself (as opposed to the outcomes to which it leads). In the case of glucose monitoring, the committee advised that most people value the convenience of automated monitoring systems over fingerprick testing, and may also derive reassurance from an enhanced ability to keep track of their glucose levels over time. In line with these expectations, there is high-quality evidence that flash provides benefits over SMBG in this area in a way that can be quantified in QALYs. However, there is no such evidence for CGM.

In the absence of direct evidence, the committee agreed it would be reasonable to assume the same level of process utility for CGM as for flash. One potential additional benefit of CGM is that it can provide alarms; however, the committee advised that this feature is not always welcome – some people find it reassuring while some people find it an annoyance. In either event, there is no evidence by which the direct quality of life impact of this feature can be quantified. Therefore, it was important to explore the assumption of equivalence between flash and CGM, in this area, in sensitivity analysis. The committee noted that CGM either needs to become roughly equivalent in cost to flash or be associated with a process utility around 3 times higher than flash for it to be associated with an ICER of £20,000/QALY or better. Although there was no evidence in this population, the committee were concerned about the accuracy of flash. Because of these concerns, the committee noted that pregnant women using flash could perform around 4 finger-pricks for verification per day. Not only would this increase costs, but it would be likely to erode the QALY benefit derived from using flash alone. This means that CGM could be associated with greater process utility.

The relative effectiveness of flash and CGM in reducing the number of caesareans and NICU admissions was also explored. This was another important source of uncertainty, as the model inputs rely on evidence from a retrospective observational study that is certain to be subject to some degree of selection bias. The committee saw evidence demonstrating that, for CGM to be associated with an ICER of £20,000 per QALY or better compared with flash, flash would have to be broadly equivalent to SMBG, in these areas. The committee agreed that it could only be true that flash is only marginally better than SMBG if the findings of the observational study comparing flash and CGM are subject to very high levels of bias. The committee agreed that this was plausible, and that the neonatal outcomes could be linked to time in range which was lower for flash than CGM.

The committee agreed that there are circumstances where CGM offers a clear benefit over flash. Above all, it was keen to emphasise the likely benefits of CGM for women who need predictive alerts. CGM offers alarm functionality whereas flash currently does not. Although there is no evidence about whether CGM and flash are associated with different rates of hypos, in this population, the committee was concerned that using flash monitoring alone could lead to overreliance on the device. This could lead to increased rates of severe hypoglycaemia. Although there is no direct evidence of cost effectiveness in a population at high risk of hypoglycaemia, the committee inferred that CGM is likely to provide reasonable value for money. This is especially true if it leads to a reduction in risk of severe hypoglycaemic episodes for people who need to be warned of an impending episode, as these are associated with a substantial negative impact on the woman and substantial costs to the healthcare system.

Although flash was found to be the most cost-effective option in the economic modelling the committee noted limitations with the model and evidence base which, coupled with their clinical experience and expertise led them recommending CGM over flash.

- First, the committee was concerned that the model relied on very low-quality evidence for flash from a single observational study. While the analysis suggested that flash would need to offer almost no clinical advantage over SMBG for CGM to be the most cost-effective option, the committee was unable to exclude this as a plausible scenario. Additionally, the committee noted that only 2 neonatal outcomes had been available to model (caesarean births and admission to NICU), and differences in other neonatal outcomes could have a large cumulative impact, even if the differences are small. It is likely that differences in maternal glucose control are associated with lifelong impacts, for some babies; the very low quality of the data available for flash make it impossible to rule out such effects.
- Second, committee members were concerned about the accuracy of flash. They noted that, while the very low-quality observational evidence had been unable to demonstrate any difference in neonatal outcomes between women who had used CGM and those who had used flash, it did suggest that CGM is associated with less time below target range.

This could be especially important, as committee members' experience is that flash is least accurate in the hypoglycaemic range. Members who used it in practice stated that they frequently performed verification SMBG checks when flash was suggesting that they were at risk of a hypoglycaemic event. Committee members noted that, if women became over-reliant on a device with no alarm, it could increase their risk of a hypoglycaemic event.

- Finally, the committee noted that women who use flash during pregnancy need to continue multiple finger-pricks per day to verify the blood glucose levels indicated by flash. This has the effect of increasing overall costs and is also likely to attenuate the quality of life benefit associated with flash in the model (which was based on research that contrasted flash and SMBG, without accounting for the fact that some SMBG is still necessary for women using flash).

As all of the uncertainties above were in favour of CGM and the quality of evidence for flash was very low, the committee did not feel confident recommending flash glucose monitoring for women in pregnancy. Therefore, the committee recommended to offer CGM to all women with Type 1 diabetes during pregnancy.

In accordance with the NHS Long-Term Plan, NHS England have committed to funding CGM centrally for pregnant women with type 1 diabetes, removing the opportunity cost of funding CGM locally. There is also ringfenced funding for flash available, although this is only guaranteed until April 2021.

The committee considered the likely resource impact of its recommendations. In the presence of central funding for both flash and CGM there will be no increased cost for either of these devices to local commissioners but there would be future savings (reduced perinatal resource-use).

Due to the potential complications associated with using a new device NICE already recommends that support should be available to help women use devices appropriately. The committee amended the recommendation to emphasise that this support should be available at all times. This is a relatively minor clarification of NICE's existing recommendation, which reflects current best practice.

1.1.11.5 Other factors the committee took into account

Only 1 study (CONCEPTT trial) was identified which included women who were planning on becoming pregnant. This evidence compared CGM with intermittent capillary glucose monitoring. This evidence could not differentiate between the two glucose monitoring systems for important outcomes such as time in target glucose range. Additionally, no evidence was identified which compared flash with CGM in this population. Due to the lack of evidence the committee were unable to make specific recommendations for continuous glucose monitoring in women with type 1 diabetes who are planning to become pregnant but did note that different methods can be utilised such as optimisation of insulin therapy, that can also help achieve glycaemic control in this population.

It should also be noted that there are also existing recommendations that cover preconception planning and care. Recommendations on monitoring blood glucose and ketones in the preconception period (Rec 1.1.12- 1.1.15) state that up to monthly HbA1c measurement should be offered to women with diabetes who are planning to become pregnant. Additionally, a meter for self-monitoring of blood glucose should be offered. If a woman with diabetes planning to become pregnant needs intensification of blood glucose-lowering therapy, advise her to increase the frequency of self-monitoring of blood glucose to include fasting levels and mixture of pre-meal and post-meal levels. Women with type 1 diabetes who are planning to become pregnant should also be offered blood ketone testing strips and a meter to test for ketonaemia. The committee also noted that further research is

necessary for continuous glucose monitoring or flash monitoring in women planning to become pregnant and therefore drafted a research recommendation.

Studies have been conducted which have assessed the accuracy of flash glucose monitoring compared to CGM. While these studies were not conducted in pregnant women with type 1 diabetes, and therefore not reviewed, the committee did highlight that the evidence shows that flash may be less accurate in reporting (or detecting) in low blood glucose levels. The committee highlighted that it is crucial that glucose monitoring is accurate in this population due to consequence associated with poor glycaemic control on both the health of the mother and child. Based on this, the committee recommended that CGM should be offered to all women with type 1 diabetes.

The committee further noted that in pregnant women with diabetes, time in target glucose range is a more reliable measure than HbA1c and international consensus has highlighted that pregnant women should spend more than 70% of their time in target glucose range. The CONCEPTT trial also identified that more women in the CGM arm spent more time in target glucose range and this resulted in better maternal and neonatal outcomes. The study also demonstrated that 5% increments in time in range were associated with better neonatal outcomes.

The committee highlighted that these targets are well understood by clinicians and this can be captured through CGM devices. Therefore, the committee recommended that CGM should be offered to all women but the committee did not make specific recommendations on time in target range, but highlighted that clinicians should discuss this with pregnant women and encourage them to spend more time in their personalised target glucose ranges.

The 2015 recommendations on continuous glucose monitoring focused on all women with diabetes (type 1, type 2 and gestational diabetes). However, the current review question focused on women with type 1 diabetes and new recommendations were drafted for this population. While women on insulin therapy but who do not have type 1 diabetes were outside the remit of the review question, the committee noted that the 2020 update of the guideline needed to cover this group. The committee further noted that the 2015 recommendations needed to be amended as during the development of these recommendations, technologies such as flash glucose monitoring had not been developed. This meant that it was important for the recommendations to specifically identify women who need continuous glucose monitoring.

Based on these discussions, the committee amended existing recommendations to state that continuous glucose monitoring should be considered for pregnant women who are on insulin therapy but do not have type 1 diabetes if they have problematic severe hypoglycaemia (with or without impaired awareness of hypoglycaemia) or they have unstable blood glucose levels that are causing concern despite efforts to optimise glycaemic control. The 2015 recommendation had highlighted that continuous glucose monitoring could be offered to women if it would be useful to gain information about variability in blood glucose levels, but the committee noted that this is a factor that is important for all pregnant women and should not, on its own, be used as a reason for consideration for continuous glucose monitoring. Therefore, this statement was removed from the recommendation.

Glucose monitoring devices allow remote monitoring to be conducted without the need for face-to face contact. The committee highlighted that such support would be beneficial in pregnancy as diabetes in pregnancy can be stressful for women and can cause anxiety. Through remote monitoring, support can be provided throughout pregnancy and can allow optimisation of care.

The committee also noted that along with support, education was vital, particularly on how to use the different glucose monitoring devices. This support and education would also be important in women with language difficulties and as well as those with learning disabilities.

Based on this understanding the committee recommended that for pregnant women using isCGM or continuous glucose monitoring, a member of the joint diabetes and antenatal care team with expertise in these systems should provide education and support. This includes information of sources of out of hours support such as support set up by manufacturers in case there are issues with monitoring systems.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.17 to 1.3.20 and the research recommendations on glucose monitoring for women planning a pregnancy and flash glucose monitoring for pregnant women.

1.1.13 References – included studies

1.1.13.1 Effectiveness

RCTs

Feig, D.S., Donovan, L.E., Corcoy, R. et al. (2017) Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. The Lancet 390(10110): 2347-2359

Secher, A.L., Ringholm, L., Andersen, H.U. et al. (2013) The effect of real-time continuous glucose monitoring in pregnant women with diabetes A randomized controlled trial. Diabetes Care 36(7): 1877-1883

Observational studies

Kristensen, K., Ogge, L.E., Sengpiel, V. et al. (2019) Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. Diabetologia

1.1.13.2 Economic

None

1.1.13.3 Other

Batelino T, Danne T, Bergenstal RM et al. (2019) Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From The International Consensus On Time In Range. Diabetes care 42(8): 1593-1603

Little RR and Rohlfing CL (2013) The Long And Wining Road To Optimal Hba1c Measurement. Clinica chimca acta; international journal for clinical chemistry 418: 63-71

Appendices

Appendix A – Review protocols

Review protocol for glucose monitoring in women with type 1 diabetes who are planning to become pregnant or who are already pregnant

ID	Field	Content
0.	PROSPERO registration number	-
1.	Review title	Glucose monitoring in women with type 1 diabetes who are planning to become pregnant or who are already pregnant
2.	Review question	In women with type 1 diabetes who are planning to become pregnant or who are already pregnant, what is the most effective method of glucose monitoring to improve maternal and infant outcomes: • continuous glucose monitoring • flash glucose monitoring • intermittent capillary blood glucose monitoring?
3.	Objective	To determine the clinical and cost effectiveness of different glucose monitoring methods in improving maternal and infant outcomes in women with type 1 diabetes who are planning to become pregnant or who are already pregnant.
4.	Searches	The following databases will be searched: Clinical searches:

		• Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • DARE • MEDLINE • MEDLINE In Process • MEDLINE ePubs • PsycINFO Economic searches: • Econlit • Embase • HTA • MEDLINE • MEDLINE In Process • MEDLINE ePubs • NHS EED • PsycINFO Searches will be restricted by: • English language • Study designs of RCTs, SRs and observational studies will be applied

		• Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results Other searches: • N/A The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion (depending on publication date). The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Type 1 diabetes in women who are planning to become pregnant or who are already pregnant.
6.	Population	Inclusion: Women with type 1 diabetes who are planning to become pregnant or are pregnant Exclusion: Women with gestational diabetes and women with type 2 diabetes
7.	Intervention	• Continuous glucose monitoring • Flash glucose monitoring • Intermittent capillary blood glucose monitoring Definitions: **Continuous glucose monitoring:** Consists of a subcutaneous sensor which measures the glucose levels in the interstitial fluid and sends data to a display device (a handheld monitor, smart

		phones or pump). The user can then analyse data and respond to changes in real-time or can make changes to insulin delivery, dose or timing based on retrospective data or trends. CGM models allow users to set alerts for high and low glucose levels, and rapid rate of change of glucose levels. **Flash glucose monitoring:** Consists of a subcutaneous sensor which continuously measures the glucose levels in the interstitial fluid. The user can obtain real-time data as well as trends by scanning the sensor with a reader device (including smart phones). The information provided gives a glucose level and information regarding the rate of change of glucose levels. Flash glucose monitoring can also be referred to as intermittently scanned CGM (isCGM). **Intermittent capillary blood glucose monitoring:** Conventional self-monitoring of blood glucose (SMBG) through 'finger prick' testing. Alternate sites may also be used for testing such as the palm, the upper forearm, the abdomen, the calf or the thigh.
8.	Comparator	Compared to each other • **Note:** comparison group should be on the same insulin regimen (e.g. rapid acting, short acting, intermediate, long acting or mixed insulin) as the treatment group. • **Note:** Studies using blinded CGM (masked sensors) alongside intermittent capillary blood glucose monitoring as a control will be considered.
9.	Types of study to be included	• RCTs • Systematic reviews of RCTs

		• If insufficient[1] RCT evidence is identified for individual comparisons, comparative prospective observational studies ○ If no comparative prospective observational studies are identified, comparative retrospective observational studies will be included. **Note:** Comparative observational studies that attempt to assess and adjust for baseline differences (e.g. through propensity matching) or adjust for confounding (e.g. maternal age, smoking and BMI) in multivariable analysis will be used. [1]: This will be assessed for the review. There is no strict definition, but in discussion with the guideline committee we will consider whether we have enough to form the basis for a recommendation.
10.	Other exclusion criteria	• Exclude studies <1-week duration • Non-English language studies • Conference abstracts • Studies which examine retrospective (blinded) glucose monitoring
11.	Context	This review is part of an update of the NICE guideline on diabetes in pregnancy: management from preconception to the postnatal period (NG3). This update covers women with diabetes who are planning a pregnancy or are pregnant. This guideline will also cover all settings where NHS healthcare is provided or commissioned.

12.	Primary outcomes (critical outcomes)	**Maternal outcomes (as defined by author):**
		• Mode of birth: spontaneous vaginal delivery, instrumental vaginal delivery, caesarean section
		• Preterm birth (birth before 37 + 0 weeks' gestation; take dichotomous or continuous data)
		• HbA1c (dichotomous or continuous outcome, depending how it is reported)
		• Time spent in target glucose range
		• Hypoglycaemia including:
		  ○ severe hypoglycaemia
		  ○ nocturnal hypoglycaemia
		(dichotomous or continuous outcome, depending how it is reported)
		• Maternal satisfaction- measured using validated questionnaires (e.g. Glucose Monitoring System Satisfaction Survey (GMSS))
		
		Foetal/Neonatal outcomes (as defined by author):
		• Mortality - perinatal and neonatal death (e.g. still birth)
		• Large for gestational age (or however defined in the study, for example, using a customised measure based on gestational age and population norms; dichotomous data preferred)
		• Small for gestational age
		• Neonatal intensive care unit length of stay 24 hours or greater (any term admission)
		
		Note: Core outcome sets were explored however none were identified for this population.

13.	Secondary outcomes (important outcomes)	**Maternal outcomes (as defined by author):** • Pregnancy induced hypertension • Pre-eclampsia • Time in hypoglycaemia

		• Awareness of hypoglycaemia
		• Glycaemic variability
		• Quality of life (continuous) – measured by validated tools (e.g. Short Form 12 (SF-12), Glucose Monitoring System Satisfaction Survey (GMSS), BG Monitoring System Rating Questionnaire (BGMSRQ), Hypoglycaemia Fear Survey- II (HFS-II),
		• Length of hospital stay
		
		• Adverse events (dichotomous):
		  ○ Diabetic ketoacidosis (DKA)
		  ○ Diabetes related hospitalisation
		  ○ local reaction due to CGM monitor
		  ○ malfunction of CGM monitor
		  ○ Postpartum haemorrhage
		  ○ Uterine rupture
		  ○ serious adverse events
		
		• Mental health outcomes measured using validated questionnaires (e.g. The Problem Areas in Diabetes (PAID) questionnaire and Diabetes Distress Scale (DSS):
		  ○ Diabetes distress (including fear of hypoglycaemia, daily burden and diabetes burnout)
		  ○ Diabetes related depression and anxiety
		  ○ Body image issues due to diabetes
		  ○ Eating disorders due to diabetes
		
		Foetal/Neonatal outcomes (as defined by author):
		• Length of hospital stay
		• Congenital abnormalities
		• Foetal growth restriction

		• Neonatal hypoglycaemia
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Randomised control trials (individuals or cluster) will be assessed using the Cochrane risk of bias tool 2.0. Assessment of observational studies will dependent on study design. Cohort studies will be assessed using the Cochrane ROBINS-1 tool while case-control studies will be assessed using CASP case control checklist.
16.	Strategy for data synthesis	For details please see section 6 of Developing NICE guidelines: the manual Meta-analysis will be conducted where appropriate.

		Evidence will be grouped into the following categories: • Preconception • During pregnancy Furthermore, outcomes in these categories will be grouped into the following time-points: • ≤6 months (or the one nearest to 6 months if multiple time-points are given) • >6 months (or the longest one if multiple time-points are given)
17.	Analysis of sub-groups	Results will be stratified by the following subgroups where possible: • Type of insulin regimen (e.g. rapid acting, short acting, intermediate, long acting or mixed insulin) • Mode of insulin delivery (e.g. multiple daily injections, continuous subcutaneous insulin infusion or insulin pump) • Length of CGM monitoring
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic

		☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	6/12/19		
22.	Anticipated completion date	16/12/20		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☑
		Piloting of the study	☐	☑

		selection process		
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Guideline Updates Team		

		5b Named contact e-mail Diabetesupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)
25.	Review team members	From the Guideline Updates Team: • Dr Caroline Mulvihill • Ms Shreya Shukla • Mr Gabriel Rogers • Mr Thomas Jones • Ms Sarah Glover
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of

		Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10158
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Continuous glucose monitoring, flash glucose monitoring, intermittent capillary blood glucose monitoring, pregnancy, type 1 diabetes, glycaemic control
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing

		☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]
36.	Details of final publication	www.nice.org.uk

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened. As the number of records for screening was relatively small (2746 RCTs/ SRs and 303 observational studies), a stopping criterion was not used when conducting screening. Therefore, all records were screened.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search. If additional studies were identified that were erroneously excluded during the priority screening process, the full database was subsequently screened.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool 2.0. Cohort studies were quality assessed using the ROBINS-I tool. Each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.
- Critical risk of bias (ROBINS-I only) - It is very likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses are less heterogeneous (with $I^2 < 50\%$) the results from these subgroups will be reported using fixed effects models. This may lead to situations where pooled results are reported from random-effects models and subgroup results are reported from fixed-effects models.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence as identified, only pooled results are presented.

In any meta-analyses where some (but not all) of the data came from studies at critical or high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline.

In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 1. For other continuous outcomes not specified in the table below, no MID was defined.

Table 1: Identified MIDs

Outcome	MID	Source *
HbA1c (presented as a percentage or mmol/l)	0.5 percentage points (5.5 mmol/ mol)	Little 2013
Time in range (%)	5% change in time in range	Batelino 2019
*Full reference provided in reference section.		

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For relative risks where no other MID was available, the line of no effect was used.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review makes explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from randomised controlled trials, non-randomised controlled trials and cohort studies were initially rated as high quality while data from other study types were originally rated as low quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 2.

Table 2: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant). If relative risk could not be estimated (due to zero events in both arms), outcome was downgraded for very serious imprecision as effect size could not be calculated. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Summary of evidence is presented in section 1.1.6. This summarises the effect size, quality of evidence and interpretation of the evidence in relation to the significance of the data.

Evidence was also identified for which GRADE could not be applied as the evidence was presented in the form of median and interquartile range. This evidence is presented in Appendix G. This evidence has been summarised narratively in section 1.1.10.

Appendix C - Literature search strategies

Clinical strategies

Database: MEDLINE

Strategy used:

Database: Ovid MEDLINE(R) <1946 to December 17. 2019>

Search Strategy:

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1 exp Diabetes Mellitus/ or Pregnancy in diabetics/ (418724)

2 diabet*.tw. (527500)

3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (1588)

4 lada.tw. (518)

5 (dm1 or iddm or t1d* or dka).tw. (18399)

6 (dm2 or t2d* or mody or niddm).tw. (30227)

7 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (299)

8 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (62)

9 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (88)

10 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (817)

11 (DM adj4 (keto* or acidi* or gastropare*)).tw. (71)

12 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (4068)

13 or/1-12 (593050)

14 Blood Glucose Self-Monitoring/ or Monitoring, Ambulatory/ or Blood Glucose/ (171402)

15 (continu* or flash or real-time or "real time" or realtime).tw. (1047267)

16 14 and 15 (13483)

17 (continu* adj4 glucose adj4 monitor*).tw. (3387)

18 (ambulatory adj4 glucose adj4 monitor*).tw. (45)

19 (CGM or CGMS or CBGM).tw. (2028)

20 Extracellular Fluid/ or Extracellular Space/ (28699)

21 ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw. (26801)

22 IPRO2*.tw. (18)

23 (("real time" or real-time or retrospective*) adj4 (glucose adj4 monitor*)).tw. (329)

24 (RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM").tw. (113)

25 flash.tw. (15315)

26 FGM.tw. (780)

27 glucorx.tw. (2)

28 (medtronic* adj4 (enlight* or veo* or guardian* or envision*)).tw. (58)

29 (Senseonic* adj4 eversense*).tw. (2)

30 (Dexcom* adj4 (G4* or G5* or G6* or 7* or seven*)).tw. (101)

31 (medtrum* adj4 (A6* or TouchCare*)).tw. (1)

32 (freestyle* adj4 navigator*).tw. (43)

33 ((freestyle* adj4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*)).tw. (70)

34 "free style libre*".tw. (3)

35 or/16-34 (78927)

36 13 and 35 (9257)

37 animals/ not humans/ (4622703)

38 36 not 37 (7991)

39 limit 38 to english language (7467)

40 randomized controlled trial.pt. (496527)

41 randomi?ed.mp. (770516)

42 placebo.mp. (190347)

43 or/40-42 (821353)

44 (MEDLINE or pubmed).tw. (151434)

45 systematic review.tw. (109769)

46 systematic review.pt. (117831)

47 meta-analysis.pt. (108624)

48 intervention$.ti. (117766)

49 or/44-48 (355796)

50 43 or 49 (1075015)

51 39 and 50 (1760)

Database: MEDLINE in Process

Strategy used:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to December 17, 2019>

Search Strategy:

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1 exp Diabetes Mellitus/ or Pregnancy in diabetics/ (0)

2 diabet*.tw. (67792)

3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (293)

4 lada.tw. (72)

5 (dm1 or iddm or t1d* or dka).tw. (2511)

6 (dm2 or t2d* or mody or niddm).tw. (6679)

7 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (51)

8 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (5)

9 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (11)

10 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (130)

11 (DM adj4 (keto* or acidi* or gastropare*)).tw. (10)

12 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (913)

13 or/1-12 (68349)

14 Blood Glucose Self-Monitoring/ or Monitoring, Ambulatory/ or Blood Glucose/ (0)

15 (continu* or flash or real-time or "real time" or realtime).tw. (173295)

16 14 and 15 (0)

17 (continu* adj4 glucose adj4 monitor*).tw. (689)

18 (ambulatory adj4 glucose adj4 monitor*).tw. (6)

19 (CGM or CGMS or CBGM).tw. (425)

20 Extracellular Fluid/ or Extracellular Space/ (0)

21 ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw. (2043)

22 IPRO2*.tw. (5)

23 (("real time" or real-time or retrospective*) adj4 (glucose adj4 monitor*)).tw. (66)

24 (RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM").tw. (29)

25 flash.tw. (3635)

26 FGM.tw. (224)

27 glucorx.tw. (1)

28 (medtronic* adj4 (enlight* or veo* or guardian* or envision*)).tw. (4)

29 (Senseonic* adj4 eversense*).tw. (0)

30 (Dexcom* adj4 (G4* or G5* or G6* or 7* or seven*)).tw. (17)

31 (medtrum* adj4 (A6* or TouchCare*)).tw. (0)

32 (freestyle* adj4 navigator*).tw. (5)

33 ((freestyle* adj4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*)).tw. (50)

34 "free style libre*".tw. (0)

35 or/16-34 (6613)

36 13 and 35 (686)

37 animals/ not humans/ (0)

38 36 not 37 (686)

39 limit 38 to english language (679)

40 randomized controlled trial.pt. (276)

41 randomi?ed.mp. (69856)

42 placebo.mp. (17138)

43 or/40-42 (75960)

44 (MEDLINE or pubmed).tw. (33002)

45 systematic review.tw. (27099)

46 systematic review.pt. (555)

47 meta-analysis.pt. (43)

48 intervention$.ti. (19798)

49 or/44-48 (63220)

50 43 or 49 (125188)

51 39 and 50 (120)

Database: MEDLINE in Process
Strategy used:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to December 17, 2019>

Search Strategy:

---

1 exp Diabetes Mellitus/ or Pregnancy in diabetics/ (0)

2 diabet*.tw. (67792)

3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (293)

4 lada.tw. (72)

5 (dm1 or iddm or t1d* or dka).tw. (2511)

6 (dm2 or t2d* or mody or niddm).tw. (6679)

7 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (51)

8 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (5)

9 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (11)

10 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (130)

11 (DM adj4 (keto* or acidi* or gastropare*)).tw. (10)

12 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (913)

13 or/1-12 (68349)

14 Blood Glucose Self-Monitoring/ or Monitoring, Ambulatory/ or Blood Glucose/ (0)

15 (continu* or flash or real-time or "real time" or realtime).tw. (173295)

16 14 and 15 (0)

17 (continu* adj4 glucose adj4 monitor*).tw. (689)

18 (ambulatory adj4 glucose adj4 monitor*).tw. (6)

19 (CGM or CGMS or CBGM).tw. (425)

20 Extracellular Fluid/ or Extracellular Space/ (0)

21 ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw. (2043)

22 IPRO2*.tw. (5)

23 (("real time" or real-time or retrospective*) adj4 (glucose adj4 monitor*)).tw. (66)

24 (RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM").tw. (29)

25 flash.tw. (3635)

26 FGM.tw. (224)

27 glucorx.tw. (1)

28 (medtronic* adj4 (enlight* or veo* or guardian* or envision*)).tw. (4)

29 (Senseonic* adj4 eversense*).tw. (0)

30 (Dexcom* adj4 (G4* or G5* or G6* or 7* or seven*)).tw. (17)

31 (medtrum* adj4 (A6* or TouchCare*)).tw. (0)

32 (freestyle* adj4 navigator*).tw. (5)

33 ((freestyle* adj4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*)).tw. (50)

34 "free style libre*".tw. (0)

35 or/16-34 (6613)

36 13 and 35 (686)

37 animals/ not humans/ (0)

38 36 not 37 (686)

39 limit 38 to english language (679)

40 randomized controlled trial.pt. (276)

41 randomi?ed.mp. (69856)

42 placebo.mp. (17138)

43 or/40-42 (75960)

44 (MEDLINE or pubmed).tw. (33002)

45 systematic review.tw. (27099)

46 systematic review.pt. (555)

47 meta-analysis.pt. (43)

48 intervention$.ti. (19798)

49 or/44-48 (63220)

50 43 or 49 (125188)

51 39 and 50 (120)

Database: MEDLINE epubs
Strategy used: Database: Ovid MEDLINE(R) Epub Ahead of Print <December 17, 2019>

Search Strategy:

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1 exp Diabetes Mellitus/ or Pregnancy in diabetics/ (0)

2 diabet*.tw. (9564)

3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (31)

4 lada.tw. (11)

5 (dm1 or iddm or t1d* or dka).tw. (449)

6 (dm2 or t2d* or mody or niddm).tw. (1016)

7 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (6)

8 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (1)

9 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (2)

10 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (17)

11 (DM adj4 (keto* or acidi* or gastropare*)).tw. (1)

12 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (95)

13 or/1-12 (9637)

14 Blood Glucose Self-Monitoring/ or Monitoring, Ambulatory/ or Blood Glucose/ (0)

15 (continu* or flash or real-time or "real time" or realtime).tw. (20685)

16 14 and 15 (0)

17 (continu* adj4 glucose adj4 monitor*).tw. (182)

18 (ambulatory adj4 glucose adj4 monitor*).tw. (1)

19 (CGM or CGMS or CBGM).tw. (110)

20 Extracellular Fluid/ or Extracellular Space/ (0)

21 ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw. (334)

22 IPRO2*.tw. (3)

23 (("real time" or real-time or retrospective*) adj4 (glucose adj4 monitor*)).tw. (24)

24 (RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM").tw. (13)

25 flash.tw. (233)

26 FGM.tw. (37)

27 glucorx.tw. (0)

28 (medtronic* adj4 (enlight* or veo* or guardian* or envision*)).tw. (1)

29 (Senseonic* adj4 eversense*).tw. (0)

30 (Dexcom* adj4 (G4* or G5* or G6* or 7* or seven*)).tw. (8)

31 (medtrum* adj4 (A6* or TouchCare*)).tw. (0)

32 (freestyle* adj4 navigator*).tw. (0)

33 ((freestyle* adj4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*)).tw. (16)

34 "free style libre*".tw. (1)

35 or/16-34 (787)

36 13 and 35 (188)

37 animals/ not humans/ (0)

38 36 not 37 (188)

39 limit 38 to english language (188)

40 randomized controlled trial.pt. (1)

41 randomi?ed.mp. (12839)

42 placebo.mp. (2993)

43 or/40-42 (13844)

44 (MEDLINE or pubmed).tw. (6628)

45 systematic review.tw. (6353)

46 systematic review.pt. (21)

47 meta-analysis.pt. (20)

48 intervention$.ti. (3899)

49 or/44-48 (13023)

50 43 or 49 (23777)

51 39 and 50 (31)

Database: Embase

Strategy used:

Database: Embase <1974 to 2019 December 17>

Search Strategy:

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1 exp diabetes mellitus/ (917499)

2 diabet*.tw. (894856)

3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (3766)

4 lada.tw. (955)

5 (dm1 or iddm or t1d* or dka).tw. (37421)

6 (dm2 or t2d* or mody or niddm).tw. (66214)

7 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (9942)

8 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (673)

9 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (105)

10 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (160)

11 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (1781)

12 (DM adj4 (keto* or acidi* or gastropare*)).tw. (177)

13 or/1-12 (1088716)

14 blood glucose monitoring/ (24723)

15 glucose blood level/ (240154)

16 glucose level/ (1931)

17 or/14-16 (256858)

18 (continu* or flash or real-time or "real time" or realtime).tw. (835745)

19 17 and 18 (15981)

20 continuous glucose monitoring system/ (977)

21 (continu* adj4 glucose adj4 monitor*).tw. (7750)

22 (ambulatory adj4 glucose adj4 monitor*).tw. (74)

23 (CGM or CGMS or CBGM).tw. (5761)

24 extracellular fluid/ or extracellular space/ (26984)

25 ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw. (34276)

26 IPRO2*.tw. (172)

27 IPRO2*.dv. (64)

28 (("real time" or real-time or retrospective*) adj4 (glucose adj4 monitor*)).tw. (749)

29 (RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM").tw. (318)

30 flash.tw. (23832)

31 FGM.tw. (1291)

32 glucorx.tw. (3)

33 (medtronic* adj4 (enlight* or veo* or guardian* or Envision*)).tw. (181)

34 (enlight* or veo* or guardian*).dv. (583)

35 (Senseonic* adj4 eversense*).tw. (20)

36 eversense*.dv. (23)

37 (Dexcom* adj4 (G4* or G5* or G6* or 7* or seven*)).tw. (459)

38 (G4* or G5* or G6* or G7*).dv. (547)

39 (medtrum* adj4 (A6* or TouchCare*)).tw. (2)

40 (A6* or TouchCare*).dv. (30)

41 (freestyle* adj4 navigator*).tw. (105)

42 navigator*.dv. (411)

43 ((freestyle* adj4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*)).tw. (384)

44 (libre* or FSL-Pro* or "FSL Pro*" or FSLPro*).dv. (175)

45 "free style libre*".tw. (22)

46 or/19-45 (96086)

47 13 and 46 (16297)

48 nonhuman/ not human/ (4518475)

49 47 not 48 (14944)

50 limit 49 to english language (14183)

51 random:.tw. (1481775)

52 placebo:.mp. (444321)

53 double-blind:.tw. (204552)

54 or/51-53 (1732650)

55 (MEDLINE or pubmed).tw. (240336)

56 exp systematic review/ or systematic review.tw. (274012)

57 meta-analysis/ (177146)

58 intervention$.ti. (189404)

59 or/55-58 (615001)

60 54 or 59 (2154368)

61 50 and 60 (2858)

62 limit 61 to (conference abstract or conference paper or "conference review") (1216)

63 61 not 62 (1642)

Database: Cochrane

Strategy used:

Search Name: GU Diabetes Suite_Q1-4 Glucose Monitoring

Date Run: 18/12/2019 17:40:07

Comment:

ID Search Hits

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees 28035

#2 MeSH descriptor: [Pregnancy in Diabetics] this term only 207

#3 (diabet*):ti,ab,kw 87010

#4 ((DM near/4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I))):ti,ab,kw 252

#5 (lada):ti,ab,kw 64

#6 ((dm1 or iddm or t1d* or dka)):ti,ab,kw 3036

#7 ((dm2 or t2d* or mody or niddm)):ti,ab,kw 9530

#8 ((DM near/4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II))):ti,ab,kw 1150

#9 ((DM near/4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw):ti,ab,kw 348

#10 ((DM near/4 onset* near/4 (maturit* or adult* or slow*))):ti,ab,kw 0

#11 ((DM near/4 depend* near/4 (non-insulin* or non insulin* or noninsulin*))):ti,ab,kw 220

#12	((DM near/4 (earl* or sudden onset or juvenile or child*))):ti,ab,kw	250
#13	((DM near/4 (keto* or acidi* or gastropare*))):ti,ab,kw	12
#14	{or #1-#13}	88380
#15	MeSH descriptor: [Blood Glucose Self-Monitoring] this term only	713
#16	MeSH descriptor: [Monitoring, Ambulatory] this term only	539
#17	MeSH descriptor: [Blood Glucose] this term only	15435
#18	{or #15-#17}	16092
#19	((continu* or flash or real-time or "real time" or realtime)):ti,ab,kw	128562
#20	#18 and #19	2038
#21	((continu* near/4 glucose near/4 monitor*)):ti,ab,kw	1930
#22	((ambulatory near/4 glucose near/4 monitor*)):ti,ab,kw	24
#23	((CGM or CGMS or CBGM)):ti,ab,kw	1446
#24	MeSH descriptor: [Extracellular Fluid] this term only	61
#25	MeSH descriptor: [Extracellular Space] this term only	121
#26	(((extracellular* or interstitial* or intercellular*) near/4 (fluid* or space))):ti,ab,kw	861
#27	(IPRO2*):ti,ab,kw	57
#28	((("real time" or real-time or retrospective*) near/4 (glucose near/4 monitor*))):ti,ab,kw	243
#29	((RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM")):ti,ab,kw	97
#30	(flash):ti,ab,kw	1005
#31	(FGM):ti,ab,kw	109
#32	(glucorx):ti,ab,kw	1
#33	((medtronic* near/4 (enlight* or veo* or guardian*))):ti,ab,kw	34
#34	((Senseonic* near/4 eversense*)):ti,ab,kw	5
#35	((Dexcom* near/4 (G4* or G5* or G6* or 7* or seven*))):ti,ab,kw	125
#36	((medtrum* near/4 (A6* or TouchCare*))):ti,ab,kw	3
#37	((freestyle* near/4 navigator*)):ti,ab,kw	21
#38	(((freestyle* near/4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*))):ti,ab,kw	106
#39	"free style libre*"	63
#40	{or #20-#39}	5640
#41	#14 and #40	3139
#42	"conference":pt or (clinicaltrials or trialsearch):so	444510

#43	#41 not #42	1831
#44	"www.who.int":so	126722
#45	#43 not #44	1831

Database: CRD

Strategy used:

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☐	2	MeSH DESCRIPTOR pregnancy in diabetics	21	Delete
☐	3	(DM) AND (("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I))	29	Delete
☐	4	(lada)	1	Delete
☐	5	((dm1 or iddm or t1d* or dka))	53	Delete
☐	6	((dm2 or t2d* or mody or niddm))	83	Delete
☐	7	(DM) AND (("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II))	53	Delete
☐	8	(DM) AND ((autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*))	8	Delete
☐	9	(DM) AND (onset*) AND (maturit* or adult* or slow*)	14	Delete
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☐	12	(DM) AND (keto* or acidi* or gastropare*)	3	Delete
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☐	14	MeSH DESCRIPTOR Blood Glucose Self-Monitoring	112	Delete
☐	15	MeSH DESCRIPTOR Monitoring, Ambulatory	66	Delete
☐	16	MeSH DESCRIPTOR Blood Glucose	496	Delete
☐	17	#14 OR #15 OR #16	605	Delete
☐	18	(continu* or flash or real-time or "real time" or realtime)	6720	Delete
☐	19	#17 AND #18	101	Delete
☐	20	((continu* AND glucose AND monitor*))	96	Delete
☐	21	((ambulatory AND glucose AND monitor*))	26	Delete
☐	22	(CGM or CGMS or CBGM)	20	Delete
☐	23	MeSH DESCRIPTOR Extracellular Fluid	2	Delete
☐	24	MeSH DESCRIPTOR Extracellular Space	0	Delete
☐	25	(extracellular* or interstitial* or intercellular*) AND (fluid* or space)	19	Delete
☐	26	(IPRO2*)	0	Delete
☐	27	("real time" or real-time or realtime or retrospective*) AND (glucose and monitor*)	50	Delete
☐	28	(RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM")	3	Delete
☐	29	(flash)	19	Delete
☐	30	(FGM)	6	Delete

☐	31	(glucorx)	0	Delete
☐	32	(medtronic*) AND (enlight* or veo* or guardian* or envision*)	2	Delete
☐	33	(Senseonic* AND eversense*)	0	Delete
☐	34	(Dexcom*) AND (G4* or G5* or G6* or 7* or seven*)	2	Delete
☐	35	(medtrum*) AND (A6* or TouchCare*)	0	Delete
☐	36	(freestyle* AND navigator*)	1	Delete
☐	37	(freestyle* AND libre*) OR (FSL-Pro* or "FSL Pro*" or FSLPro*)	0	Delete
☐	38	("free style libre*")	0	Delete
☐	39	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	218	Delete
☐	40	#13 AND #39	118	Delete

Database: PsycINFO

Strategy used:

Database: PsycINFO <1806 to December Week 2 2019>

Search Strategy:

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1 exp Diabetes Mellitus/ (8110)

2 diabet*.tw. (30688)

3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (83)

4 lada.tw. (11)

5 (dm1 or iddm or t1d* or dka).tw. (1003)

6 (dm2 or t2d* or mody or niddm).tw. (1594)

7 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (12)

8 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (4)

9 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (4)

10 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (48)

11 (DM adj4 (keto* or acidi* or gastropare*)).tw. (7)

12 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (223)

13 or/1-12 (31446)

14 Blood Sugar/ (1124)

15 (continuous or flash or real-time or "real time" or realtime).tw. (66155)

16 14 and 15 (48)

17 (continu* adj4 glucose adj4 monitor*).tw. (62)

18 (ambulatory adj4 glucose adj4 monitor*).tw. (1)

19 (CGM or CGMS or CBGM).tw. (93)

20 ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw. (1167)

21 IPRO2*.tw. (0)

22 (("real time" or real-time or retrospective*) adj4 (glucose adj4 monitor*)).tw. (6)

23 (RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM").tw. (18)

24 flash.tw. (3576)

25 FGM.tw. (192)

26 glucorx.tw. (0)

27 (medtronic* adj4 (enlight* or veo* or guardian* or Envision*)).tw. (0)

28 (Senseonic* adj4 eversense*).tw. (0)

29 (Dexcom* adj4 (G4* or G5* or G6* or 7* or seven*)).tw. (1)

30 (medtrum* adj4 (A6* or TouchCare*)).tw. (0)

31 (freestyle* adj4 navigator*).tw. (0)

32 ((freestyle* adj4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*)).tw. (13)

33 "free style libre*".tw. (0)

34 or/16-33 (5119)

35 13 and 34 (103)

36 animals/ not humans/ (7208)

37 35 not 36 (103)

38 limit 37 to english language (100)

39 randomized controlled trial.pt. (0)

40 randomi?ed.mp. (80482)

41 placebo.mp. (39596)

42 (MEDLINE or pubmed).tw. (21512)

43 systematic review.tw. (25823)

44 systematic review.pt. (0)

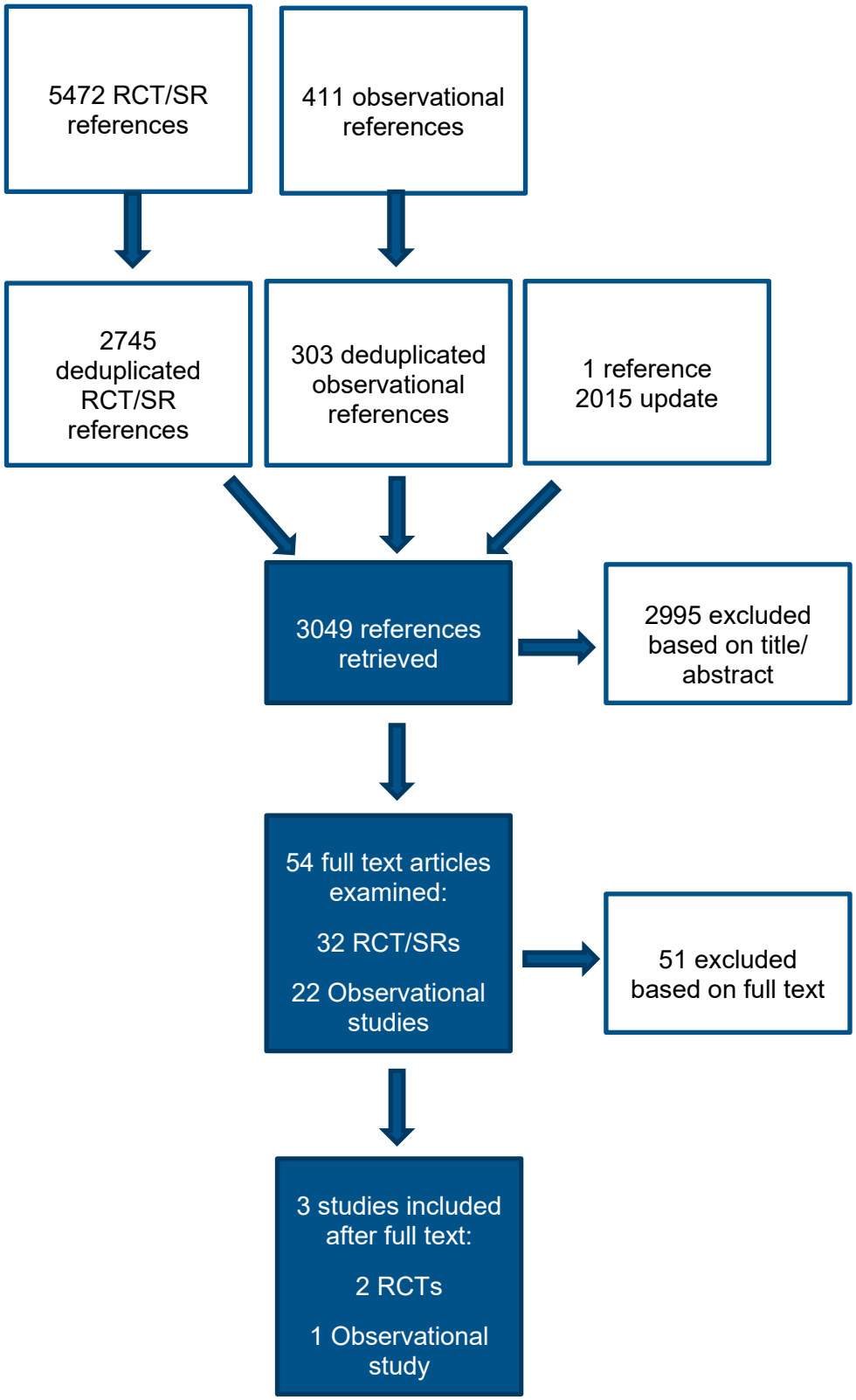
45 meta-analysis.pt. (0)

46 intervention*.ti. (68301)

47 or/39-46 (191173)

48 38 and 47 (15)

Appendix D – Effectiveness evidence study selection



Appendix E – Effectiveness evidence tables

E.1 RCTs

Feig 2017

Feig, 2017

Bibliographic Reference	Feig, D.S.; Donovan, L.E.; Corcoy, R.; Murphy, K.E.; Amiel, S.A.; Hunt, K.F.; Asztalos, E.; Barrett, J.F.R.; Sanchez, J.J.; de Leiva, A.; Hod, M.; Jovanovic, L.; Keely, E.; McManus, R.; Hutton, E.K.; Meek, C.L.; Stewart, Z.A.; Wysocki, T.; O'Brien, R.; Ruedy, K.; Kollman, C.; Tomlinson, G.; Murphy, H.R.; Grisoni, J.; Byrne, C.; Davenport, K.; Neoh, S.; Gougeon, C.; Oldford, C.; Young, C.; Green, L.; Rossi, B.; Rogers, H.; Cleave, B.; Strom, M.; Adelantado, J.M.; Isabel Chico, A.; Tundidor, D.; Malcolm, J.; Henry, K.; Morris, D.; Rayman, G.; Fowler, D.; Mitchell, S.; Rosier, J.; Temple, R.; Turner, J.; Canciani, G.; Hewapathirana, N.; Piper, L.; Kudirka, A.; Watson, M.; Bonomo, M.; Pintaudi, B.; Bertuzzi, F.; Daniela, G.; Mion, E.; Lowe, J.; Halperin, I.; Rogowsky, A.; Adib, S.; Lindsay, R.; Carty, D.; Crawford, I.; Mackenzie, F.; McSorley, T.; Booth, J.; McInnes, N.; Smith, A.; Stanton, I.; Tazzeo, T.; Weisnagel, J.; Mansell, P.; Jones, N.; Babington, G.; Spick, D.; MacDougall, M.; Chilton, S.; Cutts, T.; Perkins, M.; Scott, E.; Endersby, D.; Dover, A.; Dougherty, F.; Johnston, S.; Heller, S.; Novodorsky, P.; Hudson, S.; Nisbet, C.; Ransom, T.; Coolen, J.; Baxendale, D.; Holt, R.; Forbes, J.; Martin, N.; Walbridge, F.; Dunne, F.; Conway, S.; Egan, A.; Kirwin, C.; Maresh, M.; Kearney, G.; Morris, J.; Quinn, S.; Bilous, R.; Mukhtar, R.; Godbout, A.; Daigle, S.; Lubina, A.; Jackson, M.; Paul, E.; Taylor, J.; Houlden, R.; Breen, A.; Banerjee, A.; Brackenridge, A.; Briley, A.; Reid, A.; Singh, C.; Newstead-Angel, J.; Baxter, J.; Philip, S.; Chlost, M.; Murray, L.; Castorino, K.; Frase, D.; Lou, O.; Pragnell, M.; Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial; The Lancet; 2017; vol. 390 (no. 10110); 2347-2359

Study details

Study type	**Randomised controlled trial (RCT)** **Open label, multicentre, multinational, randomised, controlled study two parallel trials: a pregnancy trial and a planning pregnancy trial. Data from both trials will be used.**
Study location	31 hospitals in Canada, England, Scotland, Spain, Italy, Ireland, and the USA.
Study setting	Hospital setting
Study dates	March 25th 2013 to March 22nd 2016
Duration of follow-up	Pregnancy trial:

	Study visits were scheduled at randomisation (≤13 weeks and 6 days' gestation) and 8,12,16,20,24,28,32,34, and 36 weeks' gestation. Planning pregnancy trial: Study visits were scheduled at 4, 8, 12, 16, 20, and 24 weeks after randomisation. Women who conceived during the trial continued in their same randomised group and followed the pregnancy study visit schedule.
Sources of funding	The trial was funded by Juvenile Research Foundation (JDRF) grants. and grants under the JDRF Canadian Clinical Trial Network. Medtronic supplied the CGM sensors and CGM systems at reduced cost. The funders had no role in the trial design, data collection, data analysis, or data interpretation.
Inclusion criteria	Women aged 18-40 years with type 1 diabetes for a minimum of 12 months, receiving intensive insulin therapy via multiple daily injections or an insulin pump, who were pregnant or planning pregnancy Pregnant women were eligible if they had a live singleton fetus confirmed by ultrasound, were at 12 weeks and 6 days' gestation or less, and had HbA1c between 6.5-10.0% (48-86 mmol/mol) Women planning for pregnancy were eligible if they had an HbA1c level between 7.0-10.0% (53-86 mmol/mol) After enrolment, participants has to complete a run-in phase with a masked CGM device (iPro2 Professional CGM, Medtronic, Northridge, CA, USA) before they were eligible for randomisation. In the run-in period, glucose values were recorded but were not visible to the user or clinical team. Eligibility required that participants wear the sensor 6 days, provided at least 96h of glucose values including a minimum of 24h overnight, and obtain at least 4 capillary glucose daily. Participants meeting this criteria were randomised to receive either CGM in addition to capillary glucose monitoring (intervention) or capillary glucose monitoring alone (control)
Exclusion criteria	Regular CGM users and women with severe nephropathy or medical conditions such as psychiatric illness requiring hospitalisation that could prevent them from completing the trail were excluded.
Sample size	325 participants were randomised: 215 pregnant women 110 women planning pregnancy 34 women conceived during the 24-week planning pregnancy trial
Loss to follow-up	Pregnancy trial: 1 withdrew before baseline assessment (intervention arm) 2 withdrew after baseline assessment (intervention arm and control arm) Planning pregnancy trial: 3 withdrew before 20-week study assessment (intervention arm) 1 withdrew before 20-week study assessment (control arm)
Interventions	**Continuous glucose monitoring (CGM)** Participants in the CGM group were provided with a CGM system (Guardian REAL-Time or MiniMed Minilnk system, both Medtronic, Northbridge, CA). They were trained to use the study devices and were instructed to use them daily by their local diabetes or antenatal

	clinical teams. CGM users were advised to verify the accuracy of CGM measurements using their capillary glucose meter before insulin dose adjustment, as per the regulatory labelling instructions. Participants were advised to test capillary glucose levels at least 7 times daily (before and 1-2h after meals and before bed) and given written instructions for how to use capillary or CGM measures for insulin delivery. **Capillary glucose monitoring** Participants in the control group continued their usual method of capillary glucose monitoring. Participants were advised to test capillary glucose levels at least 7 times daily (before and 1-2h after meals and before bed) and given written instructions for how to use capillary or CGM measures for insulin delivery. It should be noted that masked sensor was used in the control group to obtain CGM measures.
Outcome measures	• HbA1c (%) - All HbA1c measurements were done using the tubidimetric inhibition immunoassay for haemodlysed whole blood on the Cobas Integra 700 platform at a central laboratory. • Achieved HbA1c less than or equal to 6.5% (48 mmol/mol) at 34 weeks - Data from pregnancy trial • Time in target glucose range (%) - Glucose target range of 3.5-7.8 mmol/L • Severe hypoglycaemia - Defined as an episode requiring third-party assistance • Adverse event- Diabetic ketoacidosis - Definition not provided. • Glucose variability - coefficient of variation - measures include coefficient of variation, SD (mmol/L), mean amplitude of glucose excursion (mmol/L) and rate of change (mmol/L per h) • Pre-eclampsia • Mode of birth - Caesarean section • Preterm birth - <37 weeks • Large for gestational age - > 90th centile) • Neonatal hypoglycaemia • Serious adverse events • Diabetes related hospitalisation • Still birth • Congenital anomaly • Macrosomia - ≥4000 g • Small for gestational age - < tenth centile • High level neonatal care (NICU) - ≥24 hours • Quality of life - measured using BG monitoring systems rating questionnaire (BGMSRQ) - Data provided for overall score as well as subscales: satisfaction, impact and obstruction • Quality of life- Hypoglycaemia Fear Survey (HFS-II) - Data provided for overall score as well as subscales: behaviour and worry

	• Diabetes related distress - measured using the Problem Areas in Diabetes scale (PAID) • Quality of Life- Short form- 12 (SF-12) • Local reaction due to CGM monitor (skin changes reported during trail) • Acute erythema, acute edema, chronic scabbing, chronic dry skin, chronic hypopigmentation, chronic hyperpigmentation, other • Achieved HbA1c less than or equal to 7.0% (53 mmol/mol) at 24 weeks - Data from planning for pregnancy trial • Maternal length of stay (days) • Percentage of time spent < 3.5 mmol//l

Study arms

Continuous glucose monitoring (CGM) - Pregnancy trial (N = 107) Guardian REAL-Time or MiniMed Minilnk system, both Medtronic, Northbridge, CA
Capillary glucose monitoring- Pregnancy trial (N = 107)
Continuous glucose monitoring (CGM)- Planning pregnancy trial (N = 53) 17 women conceived during the 24 week planning pregnancy trial Guardian REAL-Time or MiniMed Minilnk system, both Medtronic, Northbridge, CA
Capillary glucose monitoring- Planning pregnancy trial (N = 57) 17 women conceived during the 24 week planning pregnancy trial

Characteristics

Arm-level characteristics

	Continuous glucose monitoring (CGM) - Pregnancy trial (N = 107)	Capillary glucose monitoring- Pregnancy trial (N = 107)	Continuous glucose monitoring (CGM)- Planning pregnancy trial (N = 53)	Capillary glucose monitoring- Planning pregnancy trial (N = 57)
Age (years)				
Mean/SD	31.4 (4.5)	31.5 (4.9)	33.5 (3.5)	32.4 (3.6)
Gestation age (Weeks)				
Mean/SD	10.5 (2.2)	11 (2)	NA (empty data)	NA (empty data)
Duration of diabetes				
MedianIQR	17 (6 to 28)	16 (6.6 to 26.4)	18 (6.2 to 30)	19 (9 to 28)
Insulin pump				
n (%)	n = 50 ; % = 46	n = 48 ; % = 45	n = 39 ; % = 74	n = 42 ; % = 74

	Continuous glucose monitoring (CGM) - Pregnancy trial (N = 107)	Capillary glucose monitoring- Pregnancy trial (N = 107)	Continuous glucose monitoring (CGM)- Planning pregnancy trial (N = 53)	Capillary glucose monitoring- Planning pregnancy trial (N = 57)
Automated insulin delivery **Pumps with low glucose suspend features**				
Total number n (%)	103 n = 19 ; % = 18	104 n = 6 ; % = 6	52 n = 6 ; % = 11	57 n = 1 ; % = 2
Insulin injections				
n (%)	n = 58 ; % = 54	n = 59 ; % = 55	n = 14 ; % = 26	n = 15 ; % = 26
Total insulin dose ((U/kg per day))				
Mean/SD	0.69 (0.25)	0.76 (0.31)	0.61 (0.19)	0.61 (0.16)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

Secher 2013

Secher, 2013

Bibliographic Reference	**Secher, A.L.; Ringholm, L.; Andersen, H.U.; Damm, P.; Mathiesen, E.R.; The effect of real-time continuous glucose monitoring in pregnant women with diabetes A randomized controlled trial; Diabetes Care; 2013; vol. 36 (no. 7); 1877-1883**

Study details

Study type	**Randomised controlled trial (RCT)**
Study location	Denmark
Study setting	Hospital Setting
Study dates	15th February 2009 to 15th February 2011
Duration of follow-up	Antenatal visits to clinic at 8, 12, 21, 27, and 33 weeks gestation.
Sources of funding	Authors received financial support from the European Foundation for the Study of Diabetes and LideScan, Rigshospitalet's Research Foundation, the Capital Region of Denmark, the Medical Faculty Foundation of Copenhagen University. Authors also received financial support from the Novo Nordisk Foundation. Medtronic supplied the study with real-time CGM monitors and links and glucose sensors were offered at a reduced price, but had no influence on study design, handling of data, or writing of the manuscript.
Inclusion criteria	All Danish-speaking pregnancy women with pre-gestational diabetes referred to the Centre for Pregnant Women with Diabetes, before 14 completed gestational weeks with one living intrauterine foetus.
Exclusion criteria	Regular CGM users and women with severe nephropathy or medical conditions such as psychiatric illness requiring hospitalisation that could prevent them from completing the trail were excluded. Present use of real-time CGM, severe mental or psychiatric barriers, diabetes nephropathy, or severe concurrent co-morbidity
Sample size	154 women: 123 with type 1 diabetes
Loss to follow-up	5 women were excluded (unclear if women had type 1 or type 2 diabetes)
Interventions	**Continuous glucose monitoring (CGM)** Participants in the intervention arm were offered intermittent real-time CGM (Guardian Real-time Continuous Glucose monitoring system with the Sof-Sensor; Medtronic Minimed, Northbridge, CA) for 6 days at the first pregnancy visit at 8 weeks and at 12, 21, 27 and 33 weeks on top of routine pregnancy care. **Capillary glucose monitoring** Self- monitored plasma glucose measurements were recommended seven times daily (before and 1.5h after each main meal and at bedtime), and diet and insulin doses were adjusted by the women themselves every third day and in collaboration with an experienced diabetologist every second week. For the study purpose, participants were asked to monitor plasmas glucose for 6 days, including measurements at 3 am, at study visits at 8,12,21,27 and 33 weeks. All women were offered free use of blood glucose meter with corresponding test strips.
Outcome measures	• Pre-eclampsia • Mode of birth - Caesarean section • Preterm birth - < 37 weeks of gestation

	• Large for gestational age - Infant birth weight ≥90th centile adjusted for sex and gestational age • Neonatal hypoglycaemia • Severe neonatal hypoglycaemia - 2h plasma glucose <2.5 mmol/L treated with intravenous glucose infusion • Miscarriage - Miscarriage defined as before 22 weeks • HbA1c (%) • Severe hypoglycaemia - defined as self-reported events with symptoms of hypoglycaemia requiring help from another person to actively administer oral carbohydrate or injection of glucose or glucagon in order to restore normal blood glucose level.

Study arms

Continuous glucose monitoring (N = 63) Guardian Real-time Continuous Glucose monitoring system with the Sof-Sensor; Medtronic Minimed, Northbridge, CA. For 6 days at the first pregnancy visit at 8 weeks and at 12, 21, 27 and 33 weeks on top of routine pregnancy care.
intermittent capillary blood glucose monitoring (N = 60) For the study purpose, participants were asked to monitor plasma glucose for 6 days, including measurements at 3 am, at study visits at 8,12,21,27 and 33 weeks.

Characteristics

Study-level characteristics

	Study (N = 123)
Women with type 1 diabetes on insulin pump therapy	
Sample Size	n = 27; % = 22

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Cochrane Risk of Bias Tool 2.0		
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (Prevalence of severe hypoglycaemia and the main outcome parameters in women using CGM was analysed per protocol.)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns (No sensitivity analysis conducted to account for missing data.)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High (Outcomes analysed per protocol. Additionally, sensitivity analysis not conducted to account for missing data.)
	Overall Directness	Indirectly applicable (Women used CGM intermittently (i.e., at 8, 12, 21, 27, and 33 weeks or more). Near-continuous realtime CGM use (at least 60% of the time) was only chosen by five (7%) women.)

E.2 Observational study

Kristensen 2019

Kristensen, 2019	
Bibliographic Reference	Kristensen, K.; Ogge, L.E.; Sengpiel, V.; Kjolhede, K.; Dotevall, A.; Elfvin, A.; Knop, F.K.; Wiberg, N.; Katsarou, A.; Shaat, N.; Kristensen, L.; Berntorp, K.; Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies; Diabetologia; 2019

Study details

Study type	**Retrospective cohort study**
Study location	Sweden
Study setting	Hospital setting
Study dates	2014 and 2017
Duration of follow-up	The dataset for each pregnancy was split into 14 day periods and trimesters (gestational weeks <13, 13-28 and >28).
Sources of funding	The study was funded by a research grant from Region Skane, Sweden, and the Oak Foundation.
Inclusion criteria	• Women with type 1 diabetes who received pregnancy care between 2014 and 2017. • All women above 18 years of age using a CGM device compatible with the internet-based Diasend system were eligible. • Required a minimum of 14 consecutive days of data with at least 80% coverage for inclusion
Exclusion criteria	Not specified
Sample size	186 singleton pregnancies with at least one 2 week episode with 80% coverage.
Loss to follow-up	3 women opted out. 3 women were excluded because of: termination of pregnancy due to chromosome aberration, intrauterine fetal demise and multiple gestation.
Interventions	**Continuous glucose monitoring** Dexcom 4G (Dexcom, San Diego, CA, USA), measures subcutaneous interstitial glucose concentration every 10s and generates a glucose value every 5 mins. The monitor requires calibration by the user against capillary plasma glucose twice a day. The women made their own choice of which CGM device to use. Monitoring system includes alarms that warns the user if the glucose is trending towards hypoglycaemia or hyperglycaemia. **Flash glucose monitoring** The Freestyle Libre system, shows continuous glucose measurements retrospectively at the time of checking. It uploads the glucose level every 60s and generates a glucose value every 15 mins. The device requires no calibration by the user.

Outcome measures	• Pre-eclampsia/ Pregnancy induced hypertension • Mode of birth- Caesarean section • Pre-term birth - < 37 weeks • Large for gestational age- Birthweight >2SD above expected birthweight for gestational age and sex • Macrosomia - birthweight >4500g • Neonatal hypoglycaemia - Plasma glucose <2.6mmol/L >3h after birth • NICU admission >24h • Hb1Ac (%)

Study arms

Continuous glucose monitoring (CGM) (N = 92) Dexcom 4G (Dexcom, San Diego, CA, USA). The monitor requires calibration by the user against capillary plasma glucose twice a day. Monitoring system includes alarms that warns the user if the glucose is trending towards hypoglycaemia or hyperglycaemia.
Flash glucose monitoring (N = 94) The Freestyle Libre system. The device requires no calibration by the user

Characteristics

Arm-level characteristics

	Continuous glucose monitoring (CGM) (N = 92)	Flash glucose monitoring (N = 94)
Age (years)		
MedianIQR	31 (19 to 41)	31 (21 to 44)
Diabetes duration (years)		
MedianIQR	17 (2 to 32)	14 (1 to 34)
Insulin pump		
Mean/SD	39 (42)	15 (16)

ROBINS-I Tool		
Section	Question	Answer

ROBINS-I Tool		
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate (No information on intervention discontinuations or switches. Authors did not use methods such as matching to control for confounding factors.)
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate (No correction for selection bias e.g. using inverse probability weights)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate (No information provided about analysis used to estimate effect of starting and adhering to the intervention.)
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate (32% of real-time CGM profiles were excluded compared to 12% of the iCGM profiles)
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious (No correction for selection bias e.g. using inverse probability weights. No information provided about analysis used to estimate effect of starting and adhering to the intervention. Methods such as matching not used to control for confounding factors. 32% of real-time CGM profiles were excluded compared to 12% of the iCGM profiles)
	Directness	Directly applicable

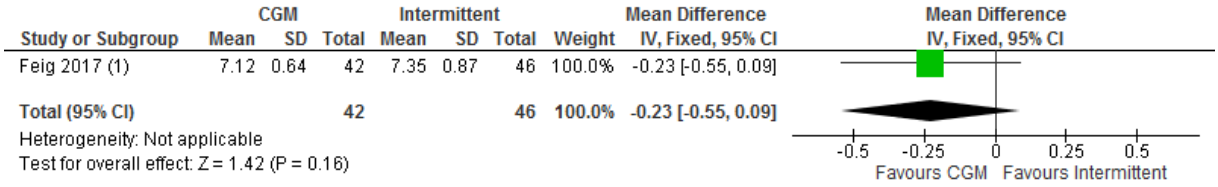
Appendix F – Forest plots

F.1 Preconception period (women who are planning to become pregnant)

Continuous glucose monitoring vs. Intermittent capillary blood glucose monitoring

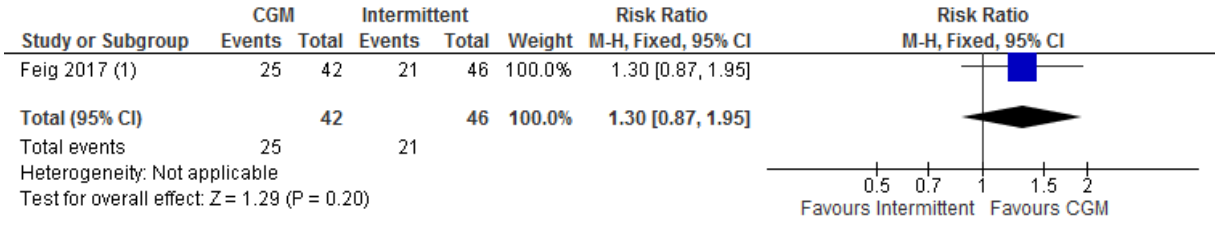
Maternal outcomes at ≤ 6 months

HbA1c (%)



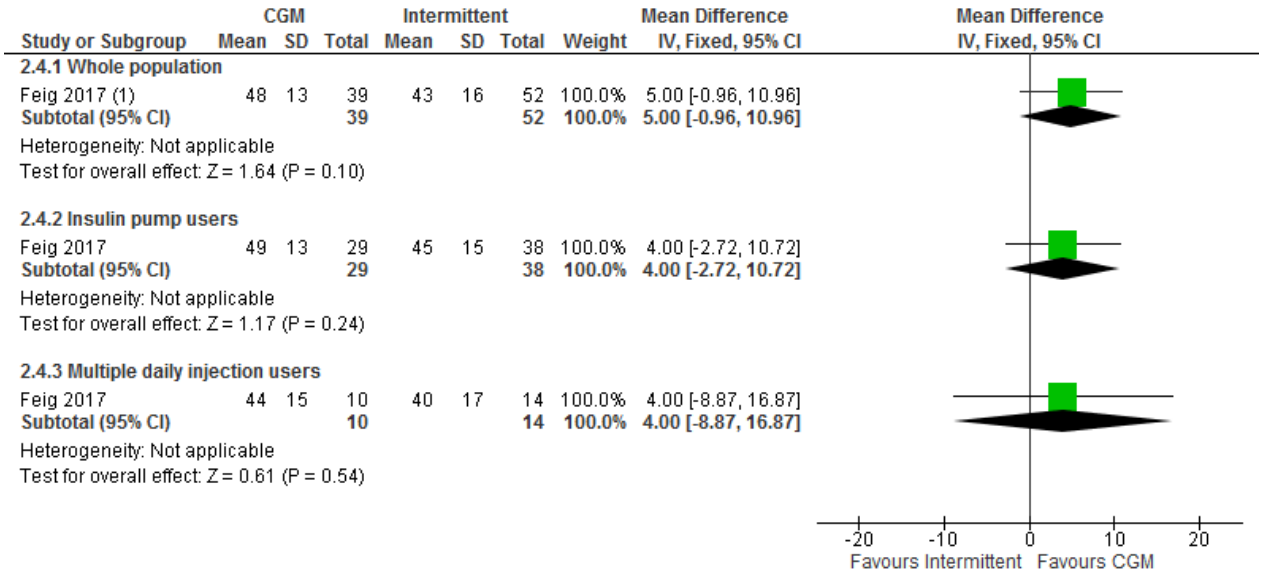
Footnotes
(1) 24 weeks

Achieved HbA1c target



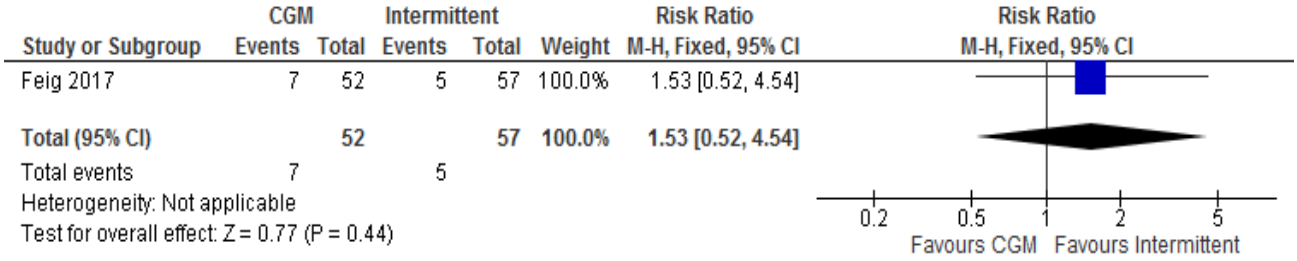
Footnotes
(1) 24 weeks. Target HbA1c levels no higher than 7.0% (53 mmol/ mol)

Time spent in glucose target range (%)

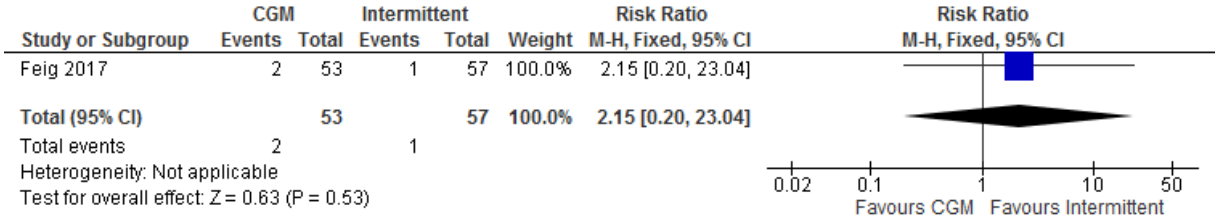


Footnotes
(1) 24 weeks. Glucose target range of 3.5-7.8 mmol/L.

Severe hypoglycaemia



Serious adverse events

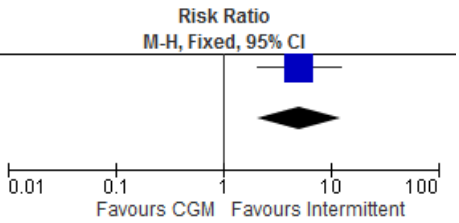


Adverse event- Diabetic ketoacidosis

Adverse event- local reaction (skin changes during trial)

Study or Subgroup	CGM Events	CGM Total	Intermittent Events	Intermittent Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Feig 2017 (1)	23	52	5	57	100.0%	5.04 [2.07, 12.29]
Total (95% CI)		**52**		**57**	**100.0%**	**5.04 [2.07, 12.29]**
Total events	23		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.56 (P = 0.0004)

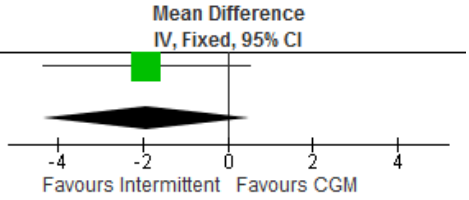


Skin changes included acute erythema, acute edema, chronic scabbing, chronic dry skin, chronic hypopigmentation and chronic hyperpigmentation.

Quality of life – BG Monitoring Systems Rating Questionnaire (BGMSRQ) Satisfaction subscale - higher score representing more of the characteristic

Study or Subgroup	CGM Mean	CGM SD	CGM Total	Intermittent Mean	Intermittent SD	Intermittent Total	Weight	Mean Difference IV, Fixed, 95% CI
Feig 2017	34.5	6.7	53	36.4	6.3	57	100.0%	-1.90 [-4.33, 0.53]
Total (95% CI)			**53**			**57**	**100.0%**	**-1.90 [-4.33, 0.53]**

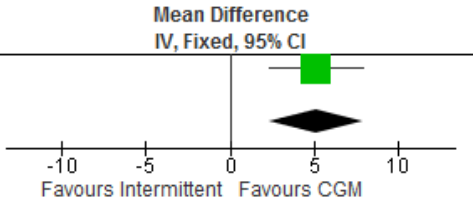
Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.13)



Quality of life – BG Monitoring Systems Rating Questionnaire (BGMSRQ) Impact subscale - higher score representing more of the characteristic

Study or Subgroup	CGM Mean	CGM SD	CGM Total	Intermittent Mean	Intermittent SD	Intermittent Total	Weight	Mean Difference IV, Fixed, 95% CI
Feig 2017	35.2	7.4	53	30.1	7.5	57	100.0%	5.10 [2.31, 7.89]
Total (95% CI)			**53**			**57**	**100.0%**	**5.10 [2.31, 7.89]**

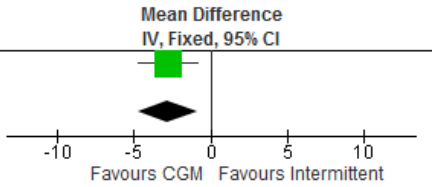
Heterogeneity: Not applicable
Test for overall effect: Z = 3.59 (P = 0.0003)



Quality of life – BG Monitoring Systems Rating Questionnaire (BGMSRQ) Obstruction subscale - higher score representing more of the characteristic

Study or Subgroup	CGM Mean	CGM SD	CGM Total	Intermittent Mean	Intermittent SD	Intermittent Total	Weight	Mean Difference IV, Fixed, 95% CI
Feig 2017	21.7	5.4	53	24.5	4.8	57	100.0%	-2.80 [-4.71, -0.89]
Total (95% CI)			**53**			**57**	**100.0%**	**-2.80 [-4.71, -0.89]**

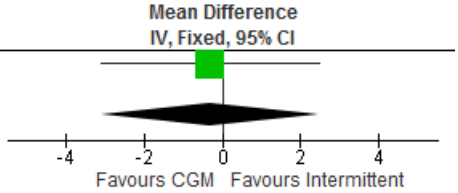
Heterogeneity: Not applicable
Test for overall effect: Z = 2.87 (P = 0.004)



Quality of life- Hypoglycaemia Fear Survey (HFS-II)– Behaviour subscale – Higher score indicates increased fear of hypoglycaemia

Study or Subgroup	CGM Mean	CGM SD	CGM Total	Intermittent Mean	Intermittent SD	Intermittent Total	Weight	Mean Difference IV, Fixed, 95% CI
Feig 2017 (1)	15.7	7.7	53	16	7.3	57	100.0%	-0.30 [-3.11, 2.51]
Total (95% CI)			**53**			**57**	**100.0%**	**-0.30 [-3.11, 2.51]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.83)

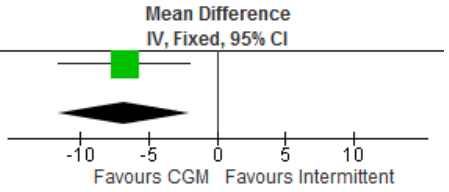


Footnotes
(1) Behaviour- avoid hypoglycaemia and its negative consequences

Quality of life- Hypoglycaemia Fear Survey (HFS-II)– Worry subscale - Higher score indicates increased fear of hypoglycaemia

	CGM			Intermittent				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Feig 2017 (1)	18.7	12.7	53	25.5	13.1	57	100.0%	-6.80 [-11.62, -1.98]
Total (95% CI)			**53**			**57**	**100.0%**	**-6.80 [-11.62, -1.98]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.76 (P = 0.006)

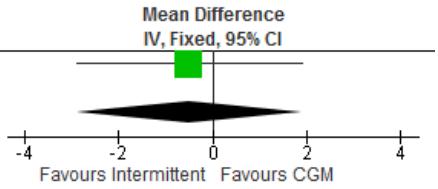


Footnotes
(1) Worry- worries about hypoglycaemia and its negative effect

Quality of life- Short form -12- Higher score indicates high level of health

	CGM			Intermittent				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Feig 2017	46	7.1	53	46.5	5.6	57	100.0%	-0.50 [-2.90, 1.90]
Total (95% CI)			**53**			**57**	**100.0%**	**-0.50 [-2.90, 1.90]**

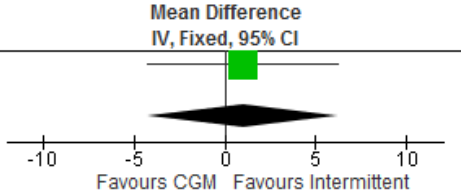
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)



Diabetes related distress – PAID score - Higher score reflecting greater emotional distress

	CGM			Intermitent				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Feig 2017	20	14.3	53	19	13.8	57	100.0%	1.00 [-4.26, 6.26]
Total (95% CI)			**53**			**57**	**100.0%**	**1.00 [-4.26, 6.26]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)

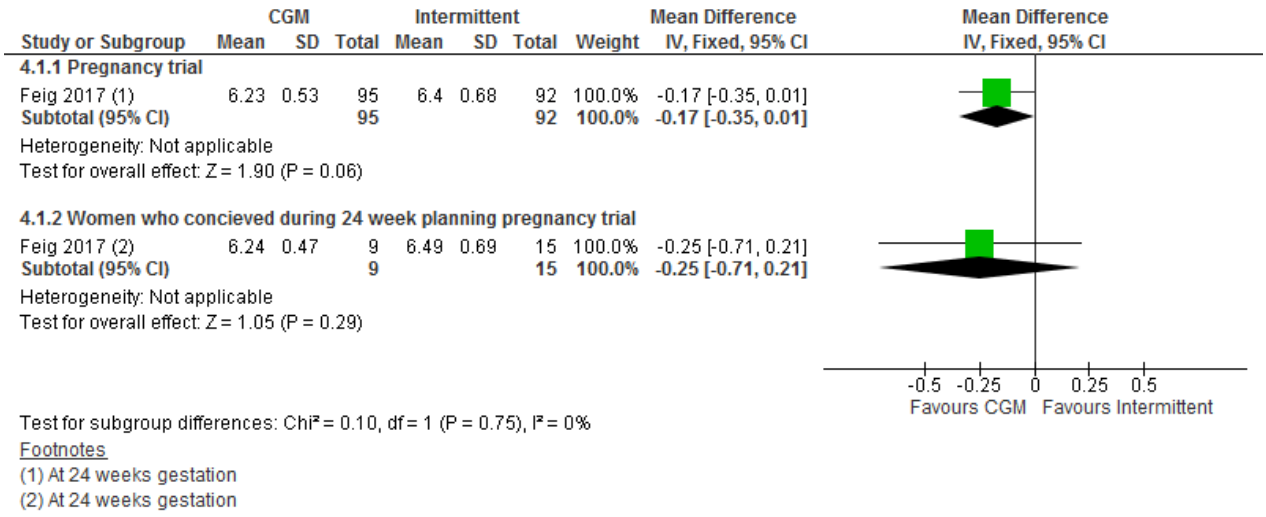


F.2 During pregnancy

Continuous glucose monitoring vs. intermittent capillary blood glucose monitoring

Maternal outcomes at ≤ 6 months

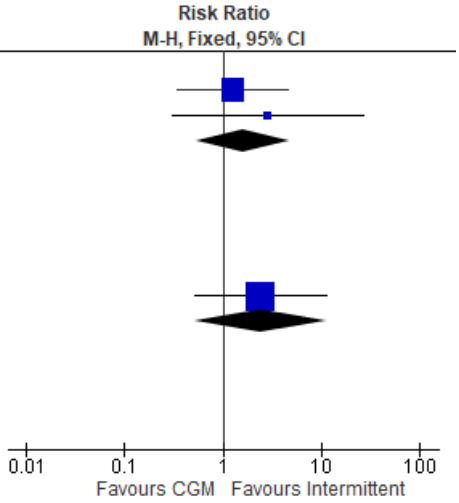
HbA1c (%)



Neonatal/ infant outcomes at ≤ 6 months

Pregnancy loss/ Miscarriage

Study or Subgroup	CGM Events	CGM Total	Intermittent Events	Intermittent Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.20.2 Pregnancy trial						
Feig 2017 (1)	5	105	4	106	79.5%	1.26 [0.35, 4.57]
Secher 2013 (2)	3	63	1	60	20.5%	2.86 [0.31, 26.71]
Subtotal (95% CI)		**168**		**166**	**100.0%**	**1.59 [0.53, 4.77]**
Total events	8		5			
Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						
3.20.3 Women who concieved during the 24 week planning pregnancy trial						
Feig 2017 (3)	4	14	2	17	100.0%	2.43 [0.52, 11.36]
Subtotal (95% CI)		**14**		**17**	**100.0%**	**2.43 [0.52, 11.36]**
Total events	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						



Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%

Footnotes

(1) Pregnancy loss <20 weeks

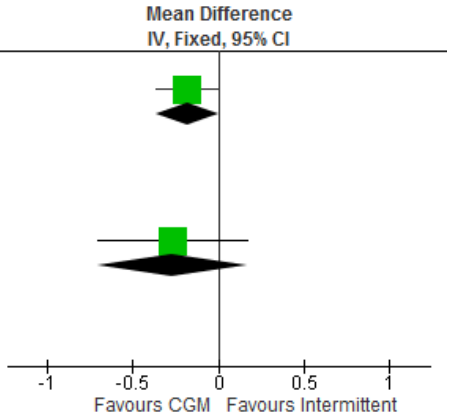
(2) Miscarriage defined as before 22 weeks

(3) Pregnancy loss <20 weeks

Maternal outcomes at > 6 months

HbA1c (%)

Study or Subgroup	CGM Mean	CGM SD	CGM Total	Intermittent Mean	Intermittent SD	Intermittent Total	Weight	Mean Difference IV, Fixed, 95% CI
4.2.1 Pregnancy trial								
Feig 2017 (1)	6.35	0.57	95	6.53	0.7	92	100.0%	-0.18 [-0.36, 0.00]
Subtotal (95% CI)			**95**			**92**	**100.0%**	**-0.18 [-0.36, 0.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.92 (P = 0.05)								
4.2.2 Women who concieved during 24 week planning pregnancy trial								
Feig 2017 (2)	6.36	0.42	9	6.63	0.68	15	100.0%	-0.27 [-0.71, 0.17]
Subtotal (95% CI)			**9**			**15**	**100.0%**	**-0.27 [-0.71, 0.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.20 (P = 0.23)								



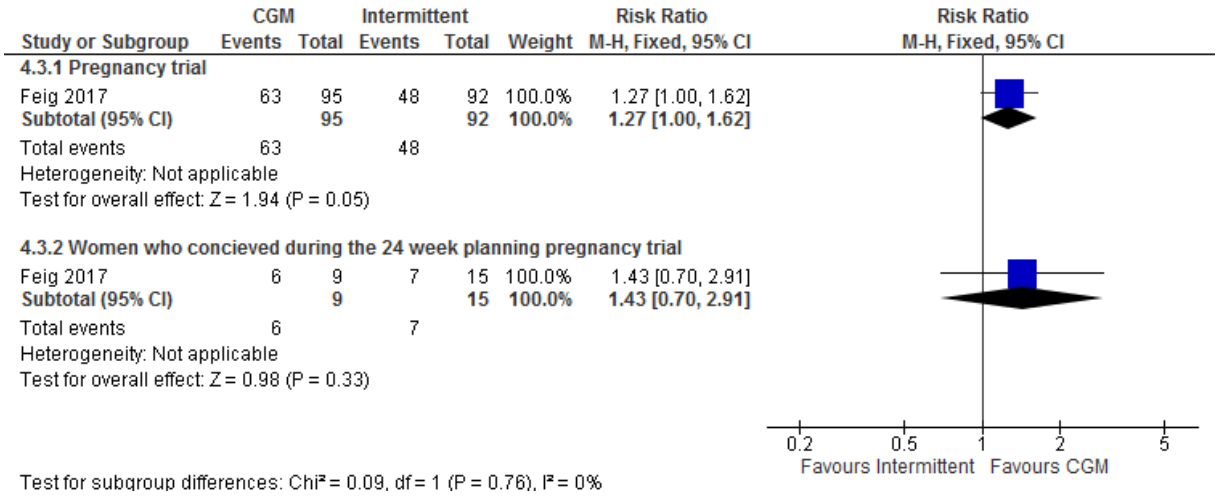
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%

Footnotes

(1) At 34 weeks' gestation

(2) At 34 weeks' gestation

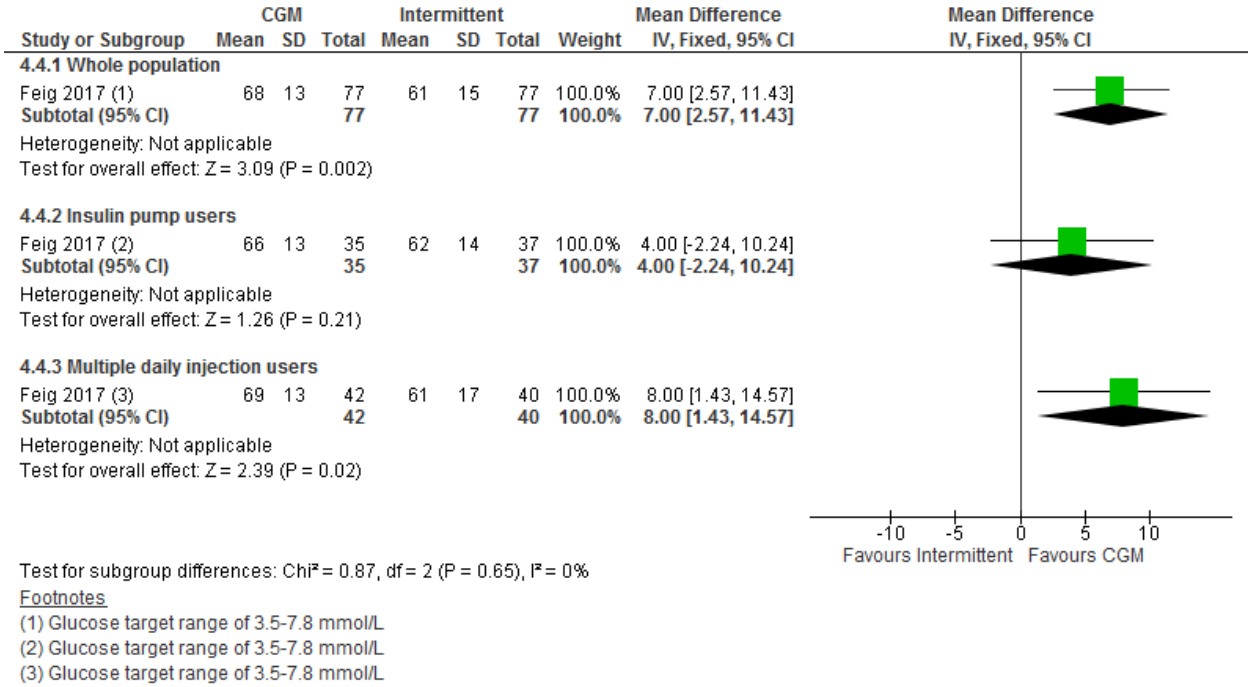
Achieved HbA1c target



Target in pregnancy trial: 6.5% (48 mmol/mol)

Target in women who conceived during 24-week planning pregnancy trial: 7.0% (53 mmol/mol) before pregnancy and 6.5% (48 mmol/mol after pregnancy)

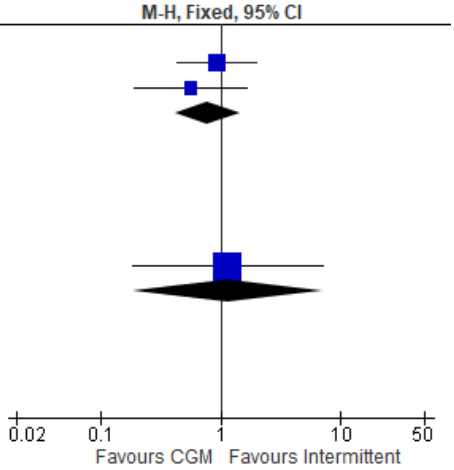
Time spent in target glucose range (%)



Footnotes
(1) Glucose target range of 3.5-7.8 mmol/L
(2) Glucose target range of 3.5-7.8 mmol/L
(3) Glucose target range of 3.5-7.8 mmol/L

Severe hypoglycaemia

Study or Subgroup	Favours CGM Events	Total	Intermittent Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Pregnancy trial						
Feig 2017 (1)	11	103	12	104	58.1%	0.93 [0.43, 2.00]
Secher 2013 (2)	4	38	11	59	41.9%	0.56 [0.19, 1.64]
Subtotal (95% CI)		**141**		**163**	**100.0%**	**0.77 [0.42, 1.44]**
Total events	15		23			
Heterogeneity: Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.81 (P = 0.42)						
3.5.2 Women who concieved during the 24 week planning pregnancy trial						
Feig 2017 (3)	2	14	2	16	100.0%	1.14 [0.18, 7.08]
Subtotal (95% CI)		**14**		**16**	**100.0%**	**1.14 [0.18, 7.08]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						



Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%

Footnotes

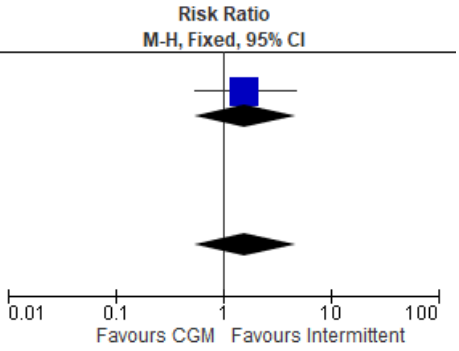
(1) Severe hypoglycaemia defined as an episode requiring third party assistance.

(2) Defined as self-reported eventswith symptoms of hypoglycemia requiringhelp from another person to actively administer oral...

(3) Severe hypoglycaemia defined as an episode requiring third party assistance.

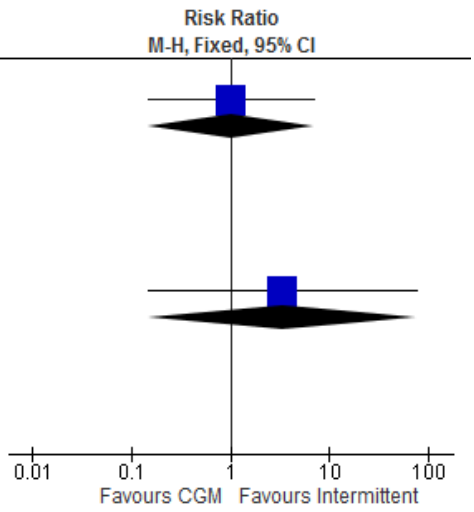
Serious adverse events

Study or Subgroup	CGM Events	Total	Intermittent Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.2 Pregnancy trial						
Feig 2017	8	107	5	107	100.0%	1.60 [0.54, 4.73]
Subtotal (95% CI)		**107**		**107**	**100.0%**	**1.60 [0.54, 4.73]**
Total events	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
Total (95% CI)		**107**		**107**	**100.0%**	**1.60 [0.54, 4.73]**
Total events	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
Test for subgroup differences: Not applicable						



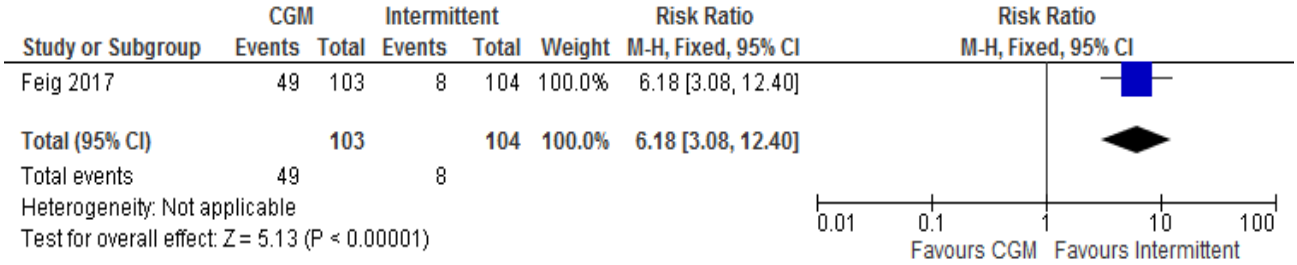
Adverse event – Diabetic ketoacidosis

Study or Subgroup	CGM Events	Total	Intermittent Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.8.1 Pregnancy trial						
Feig 2017	2	103	2	104	100.0%	1.01 [0.14, 7.03]
Subtotal (95% CI)		**103**		**104**	**100.0%**	**1.01 [0.14, 7.03]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
4.8.2 Women who concieved during the 24 week planning pregnancy trial						
Feig 2017	1	14	0	16	100.0%	3.40 [0.15, 77.34]
Subtotal (95% CI)		**14**		**16**	**100.0%**	**3.40 [0.15, 77.34]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						



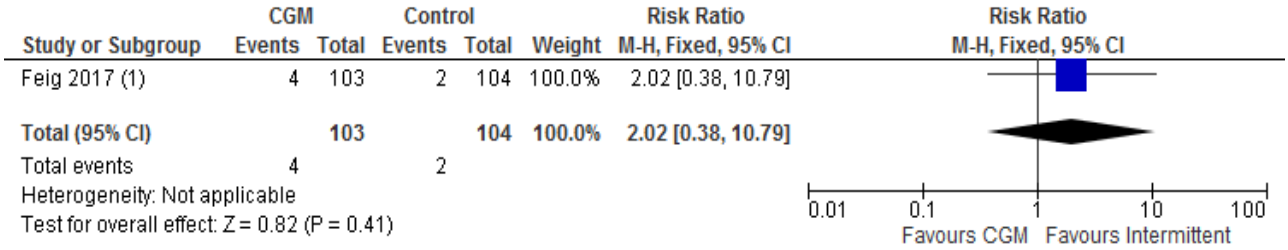
Test for subgroup differences: Chi² = 0.42, df = 1 (P = 0.52), I² = 0%

Adverse event- local reaction (skin changes during trial)



Skin changes included acute erythema, acute edema, chronic scabbing, chronic dry skin, chronic hypopigmentation and chronic hyperpigmentation.

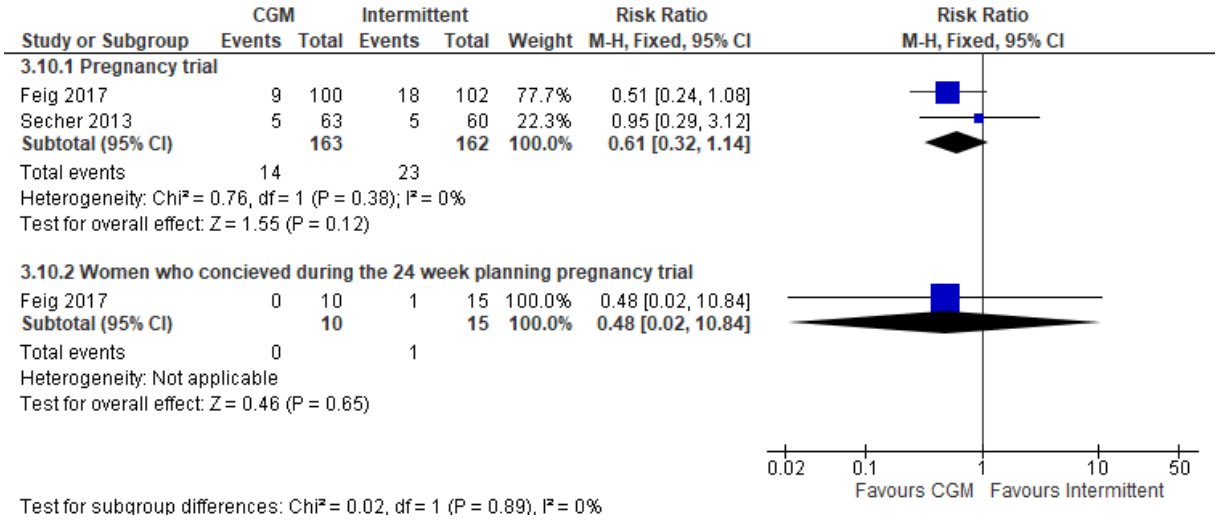
Adverse event- Diabetes related hospitalisation



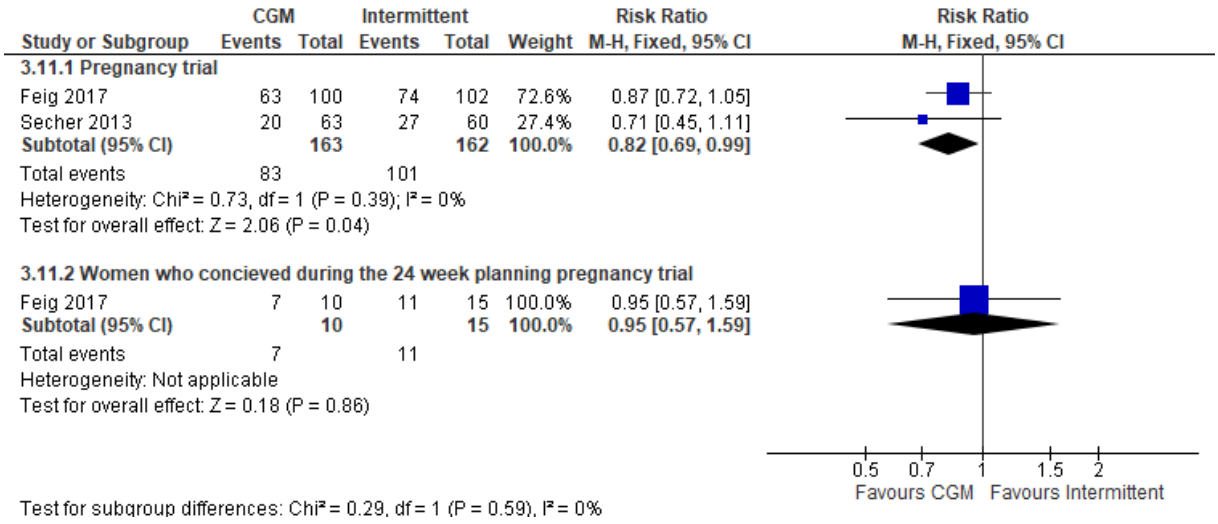
Footnotes

(1) Admission due to diabetic ketoacidosis and severe hypoglycaemia

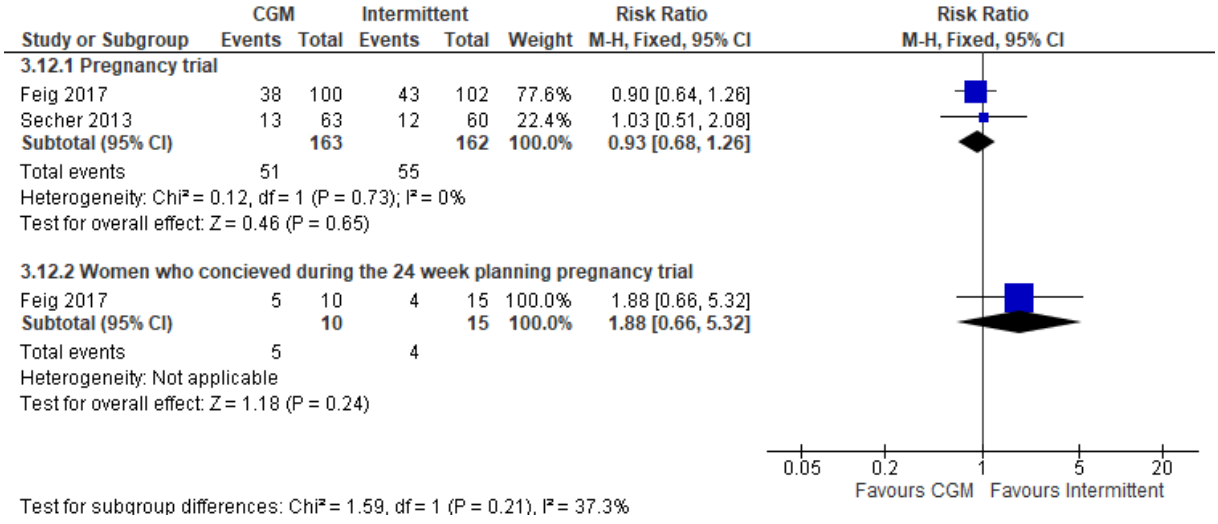
Pre-eclampsia



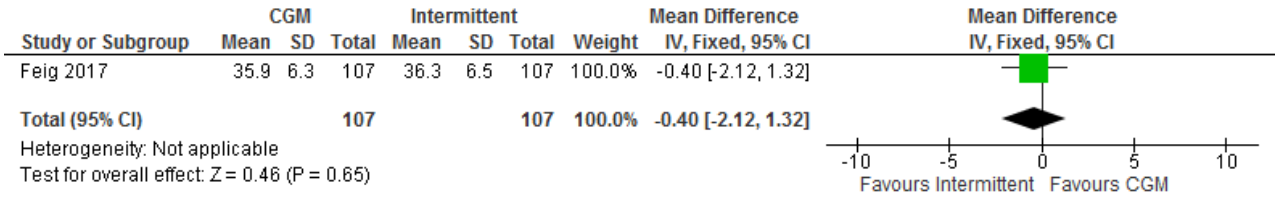
Mode of birth – Caesarean section



Preterm birth < 37 weeks



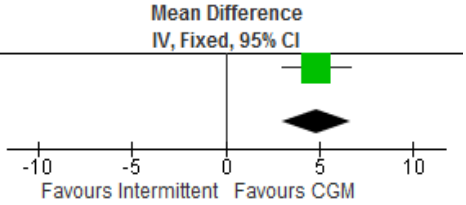
Quality of life- Blood Glucose Monitoring Systems Rating Questionnaire (BGMSRQ)- Satisfaction subscale- Higher score represents more of the characteristic represented in the scale name



Quality of life- Blood Glucose Monitoring Systems Rating Questionnaire (BGMSRQ)- Impact subscale- Higher score represents more of the characteristic represented in the scale name

	CGM			Intermittent				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Feig 2017	36.9	6.6	107	32.1	7	107	100.0%	4.80 [2.98, 6.62]
Total (95% CI)			**107**			**107**	**100.0%**	**4.80 [2.98, 6.62]**

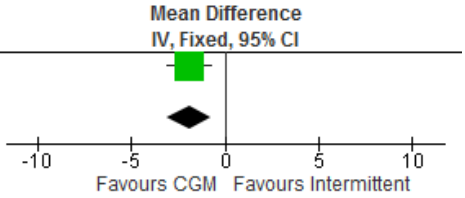
Heterogeneity: Not applicable
Test for overall effect: Z = 5.16 (P < 0.00001)



Quality of life- Blood Glucose Monitoring Systems Rating Questionnaire (BGMSRQ)- Obstruction subscale- Higher score represents more of the characteristic represented in the scale name

	CGM			Intermittent				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Feig 2017	23.5	4.4	107	25.4	4.5	107	100.0%	-1.90 [-3.09, -0.71]
Total (95% CI)			**107**			**107**	**100.0%**	**-1.90 [-3.09, -0.71]**

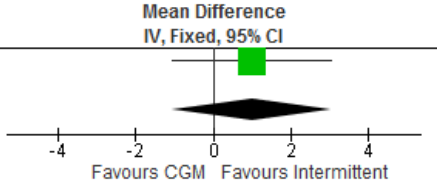
Heterogeneity: Not applicable
Test for overall effect: Z = 3.12 (P = 0.002)



Quality of life- Hypoglycaemia Fear Survey (HFS-II)- Behaviour subscale – Higher score indicates fear of hypoglycaemia

	CGM			Intermittent				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Feig 2017 (1)	16.4	8	107	15.4	7.4	107	100.0%	1.00 [-1.06, 3.06]
Total (95% CI)			**107**			**107**	**100.0%**	**1.00 [-1.06, 3.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)

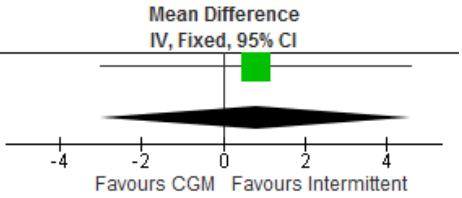


Footnotes
(1) Behaviour- avoid hypoglycaemia and its negative consequences

Quality of life- Hypoglycaemia Fear Survey (HFS-II)- Worry subscale – Higher score indicates fear of hypoglycaemia

	CGM			Intermittent				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Feig 2017 (1)	19.3	14.5	107	18.5	13.9	107	100.0%	0.80 [-3.01, 4.61]
Total (95% CI)			**107**			**107**	**100.0%**	**0.80 [-3.01, 4.61]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

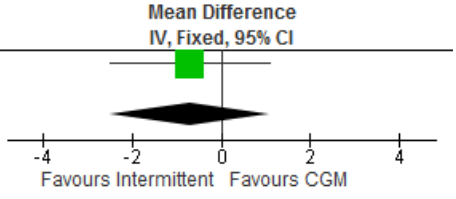


Footnotes
(1) Worry- worries about hypoglycaemia and its negative effects

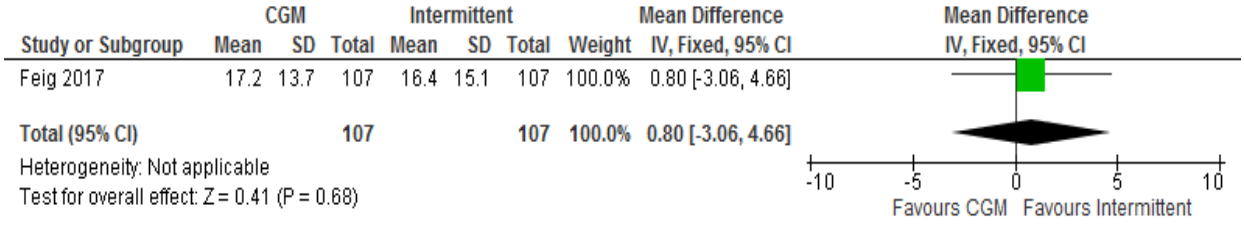
Quality of life- Short form -12- Higher score indicates high level of health

	CGM			Intermittent				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Feig 2017	41.7	6.9	107	42.4	6.5	107	100.0%	-0.70 [-2.50, 1.10]
Total (95% CI)			**107**			**107**	**100.0%**	**-0.70 [-2.50, 1.10]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.44)

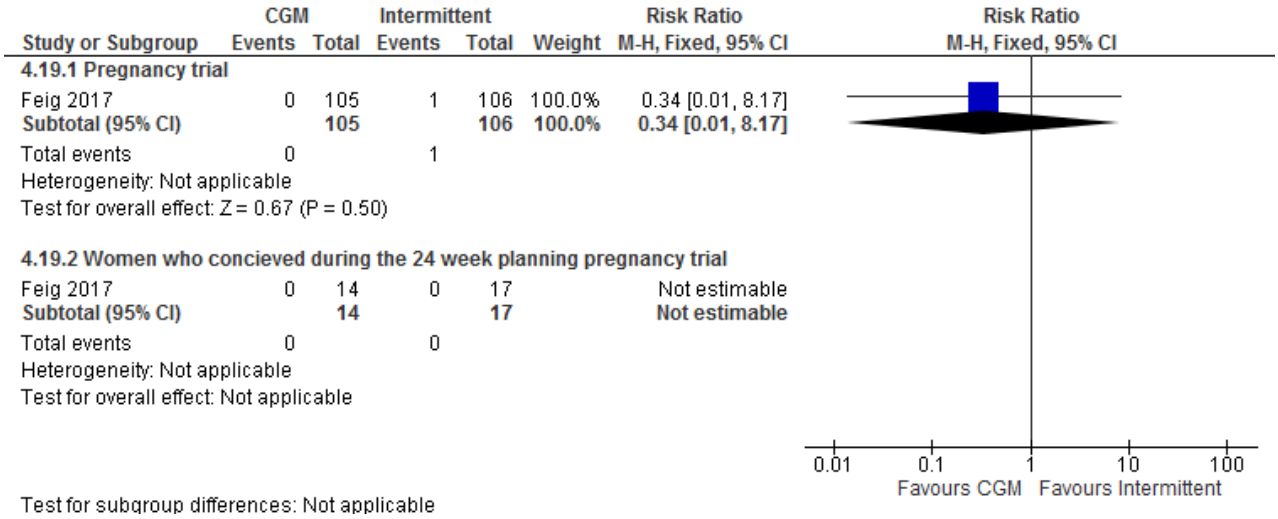


Diabetes related distress – PAID score - Higher score reflecting greater emotional distress

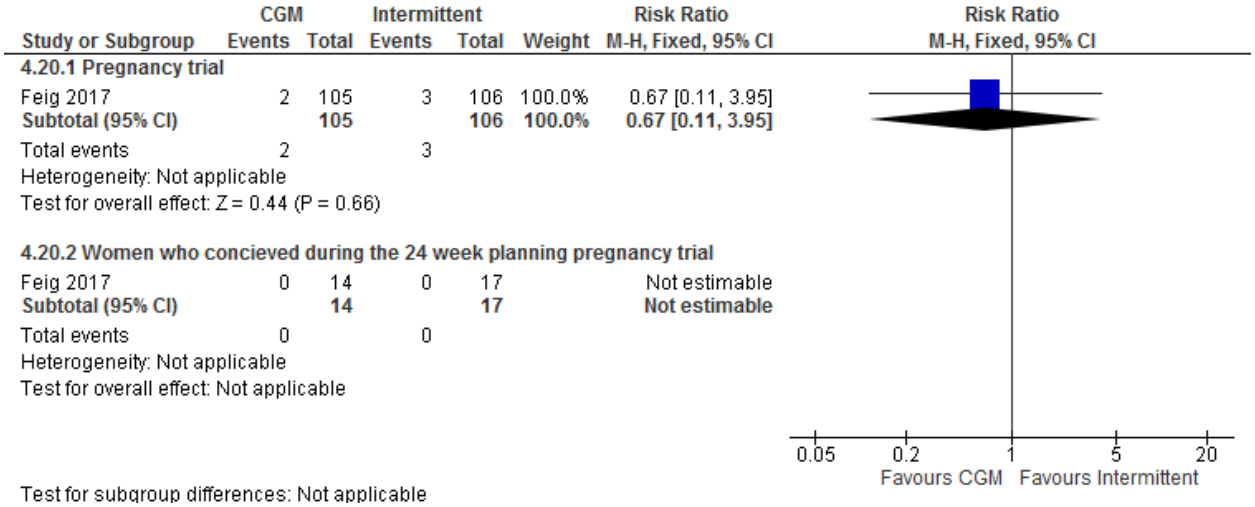


Neonatal/ infant outcomes at > 6 months

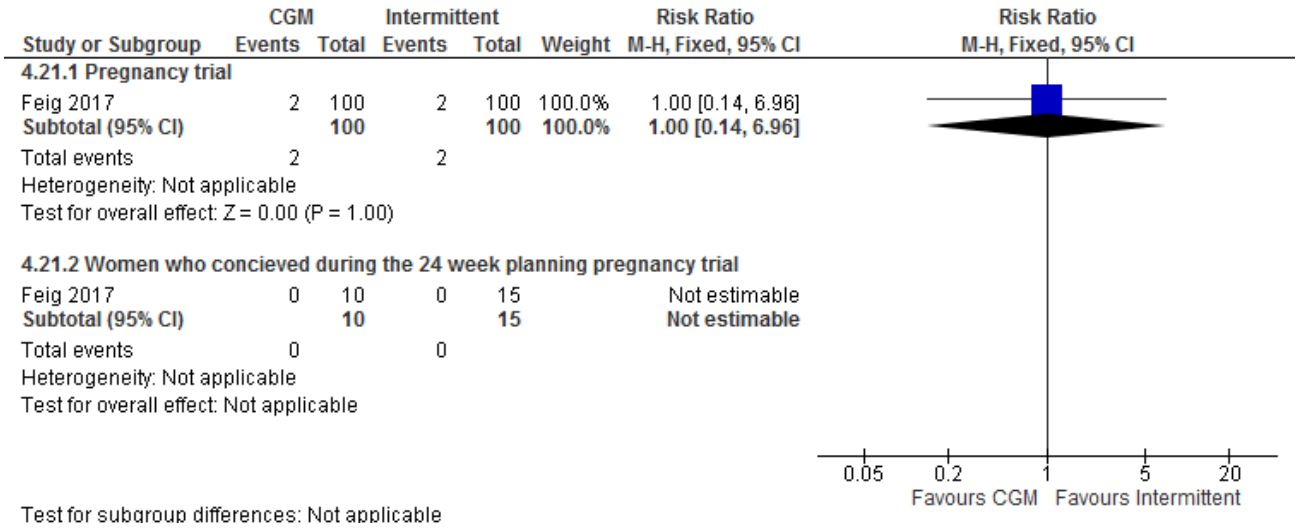
Still birth



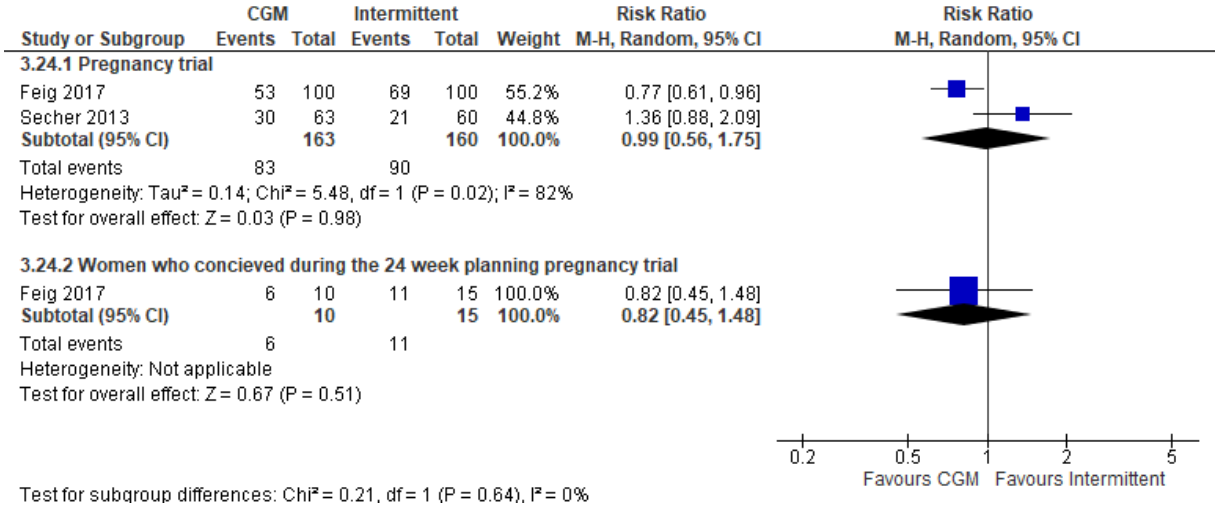
Congenital anomaly



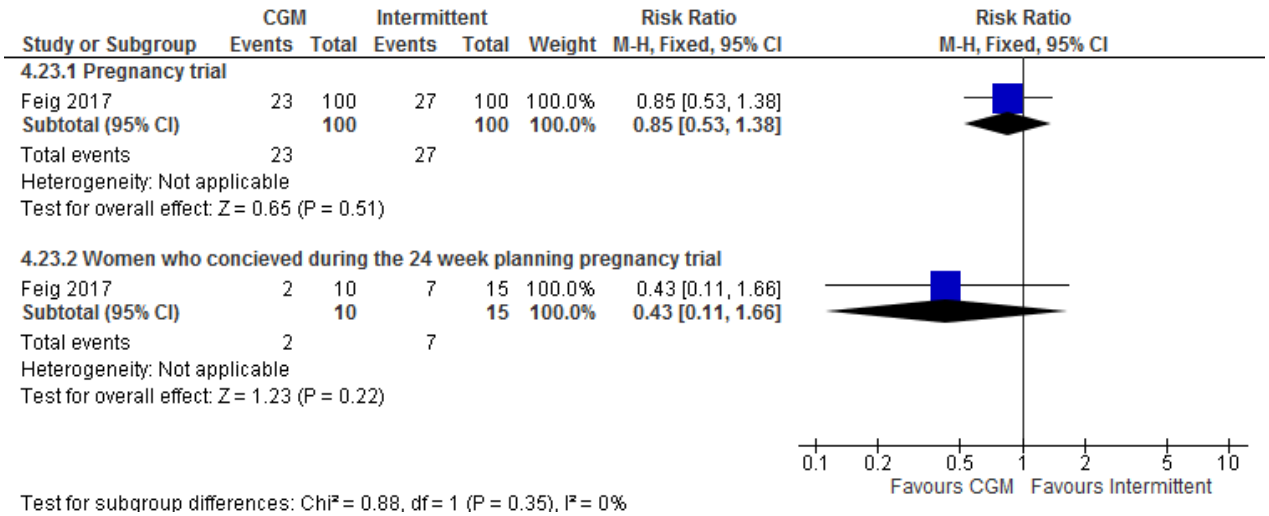
Small for gestational age



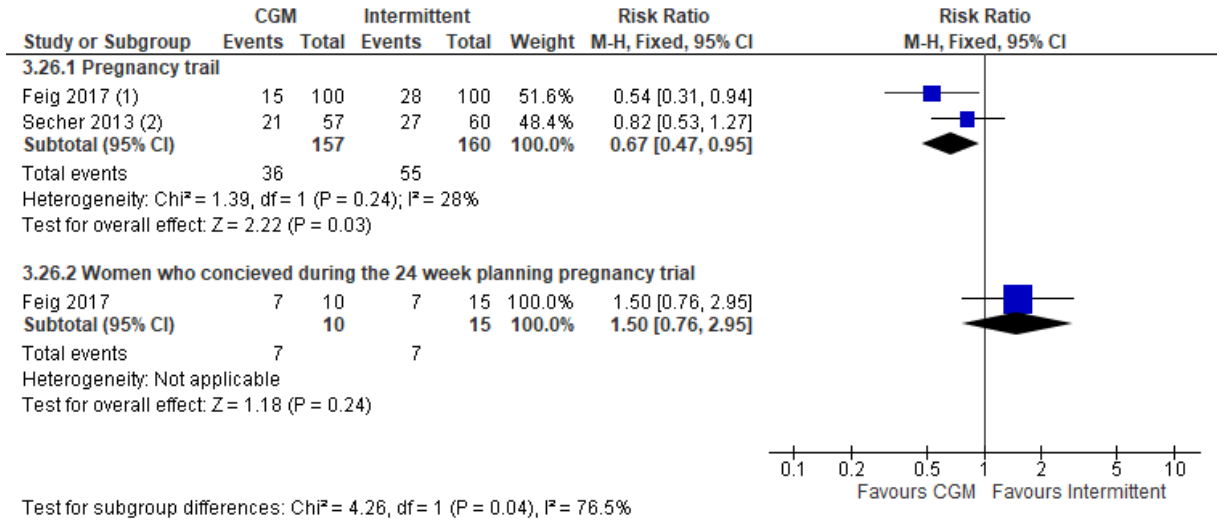
Large for gestational age



Macrosomia

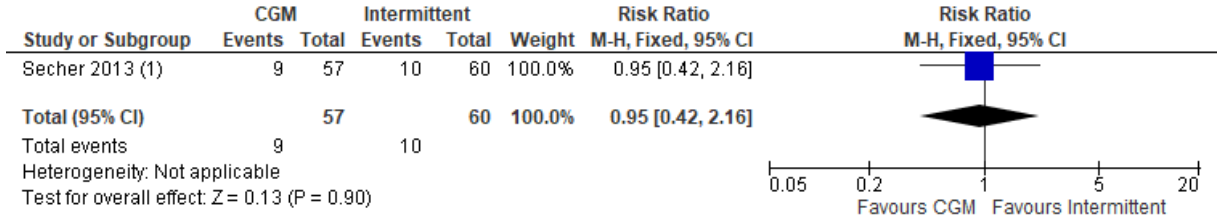


Neonatal hypoglycaemia



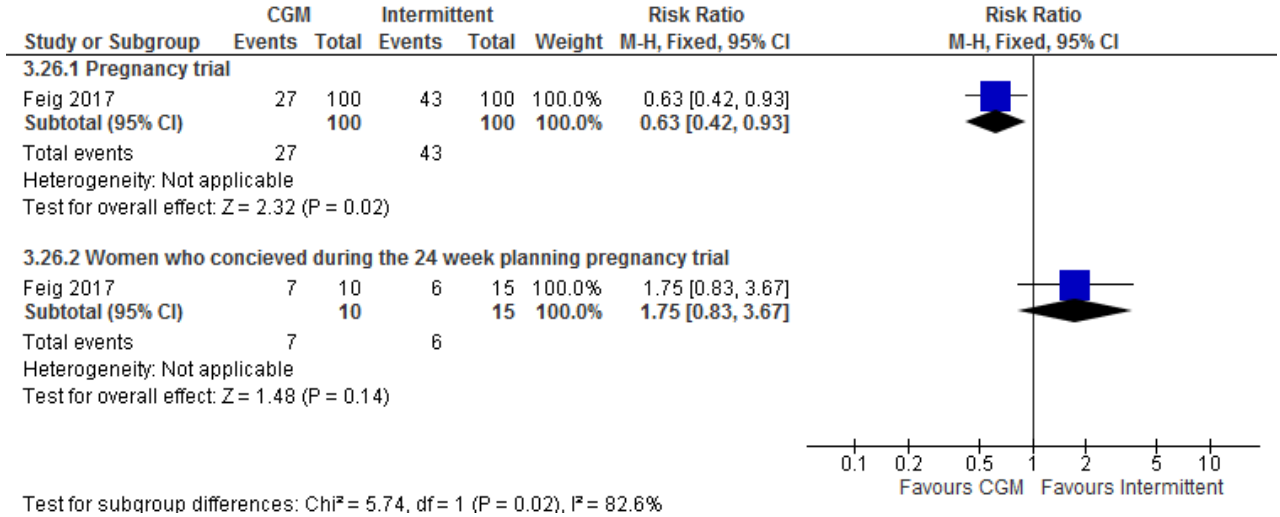
Footnotes
(1) Requiring intravenous dextrose
(2) 2-h plasma glucose <2.5mmol/L

Severe neonatal hypoglycaemia



Footnotes
(1) 2-h plasma glucose <2.5 mmol/Ltreated with intravenous glucose infusion

High level neonatal care (NICU) >24 hours



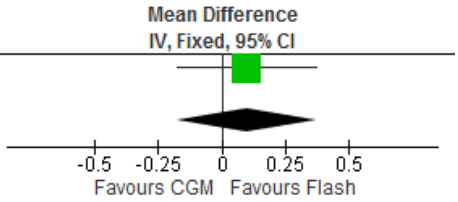
Continuous glucose monitoring vs. Flash glucose monitoring

Maternal outcomes at ≤ 6 months

HbA1c (%)

Study or Subgroup	CGM Mean	CGM SD	CGM Total	Flash Mean	Flash SD	Flash Total	Weight	Mean Difference IV, Fixed, 95% CI
Krisensen 2019	7	1	92	6.9	0.9	94	100.0%	0.10 [-0.17, 0.37]
Total (95% CI)			**92**			**94**	**100.0%**	**0.10 [-0.17, 0.37]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

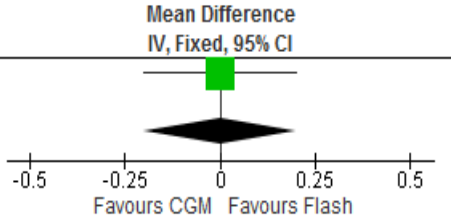


Maternal outcomes at > 6 months

HbA1c (%)

Study or Subgroup	CGM Mean	CGM SD	CGM Total	Flash Mean	Flash SD	Flash Total	Weight	Mean Difference IV, Fixed, 95% CI
Krisensen 2019	6.3	0.7	92	6.3	0.7	94	100.0%	0.00 [-0.20, 0.20]
Total (95% CI)			**92**			**94**	**100.0%**	**0.00 [-0.20, 0.20]**

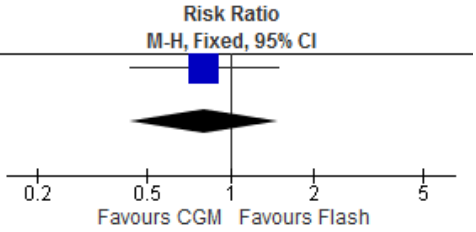
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Pre-eclampsia/ pregnancy induced hypertension

Study or Subgroup	CGM Events	CGM Total	Flash Events	Flash Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krisensen 2019	15	92	19	94	100.0%	0.81 [0.44, 1.49]
Total (95% CI)		**92**		**94**	**100.0%**	**0.81 [0.44, 1.49]**
Total events	15		19			

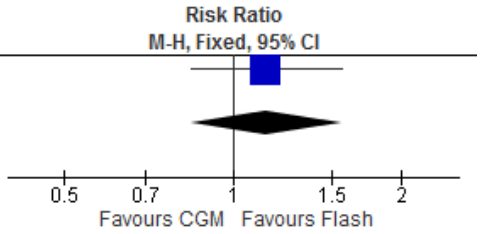
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



Mode of birth – Caesarean section

Study or Subgroup	CGM Events	CGM Total	Flash Events	Flash Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krisensen 2019	46	92	41	94	100.0%	1.15 [0.84, 1.56]
Total (95% CI)		**92**		**94**	**100.0%**	**1.15 [0.84, 1.56]**
Total events	46		41			

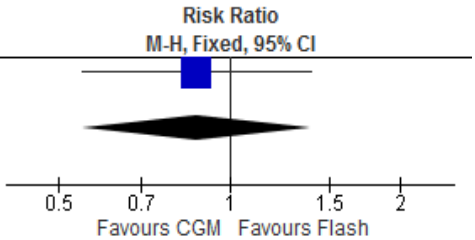
Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)



Pre-term birth >37 weeks

Study or Subgroup	CGM Events	CGM Total	Flash Events	Flash Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krisensen 2019	24	92	28	94	100.0%	0.88 [0.55, 1.39]
Total (95% CI)		**92**		**94**	**100.0%**	**0.88 [0.55, 1.39]**
Total events	24		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.57)

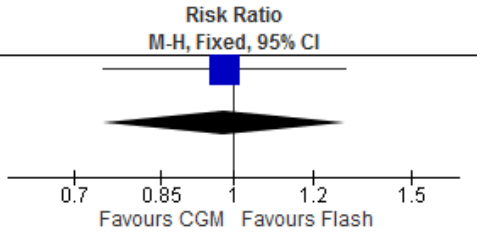


Neonatal/ infant outcomes at > 6 months

Large for gestational age

Study or Subgroup	CGM Events	CGM Total	Flash Events	Flash Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krisensen 2019	48	92	50	94	100.0%	0.98 [0.75, 1.29]
Total (95% CI)		**92**		**94**	**100.0%**	**0.98 [0.75, 1.29]**
Total events	48		50			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)

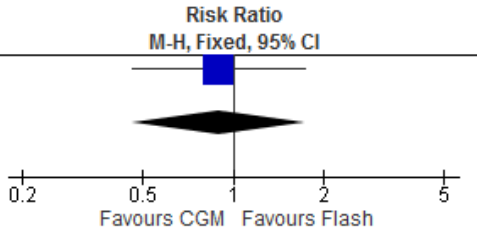


Macrosomia

Study or Subgroup	CGM Events	CGM Total	Flash Events	Flash Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krisensen 2019 (1)	14	92	16	94	100.0%	0.89 [0.46, 1.72]
Total (95% CI)		**92**		**94**	**100.0%**	**0.89 [0.46, 1.72]**
Total events	14		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

Footnotes
(1) Macrosomia defined as >4500g

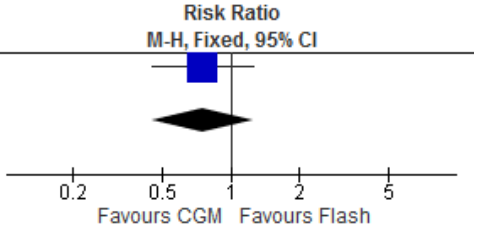


Neonatal hypoglycaemia

Study or Subgroup	CGM Events	CGM Total	Flash Events	Flash Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krisensen 2019 (1)	19	92	26	94	100.0%	0.75 [0.45, 1.25]
Total (95% CI)		**92**		**94**	**100.0%**	**0.75 [0.45, 1.25]**
Total events	19		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)

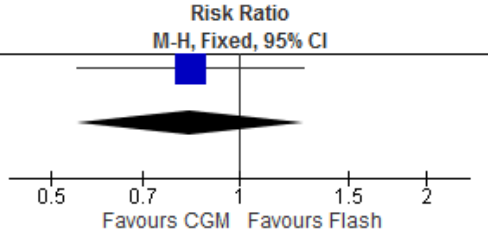
Footnotes
(1) Defined as plasma glucose < 2.6 mmol/l >3h after birth



NICU admission >24 hours

Study or Subgroup	CGM Events	CGM Total	Flash Events	Flash Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krisensen 2019	27	92	33	94	100.0%	0.84 [0.55, 1.27]
Total (95% CI)		**92**		**94**	**100.0%**	**0.84 [0.55, 1.27]**
Total events	27		33			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)



Appendix G – Additional data

Evidence was also identified for which GRADE could not be applied as the evidence was presented in the form of median and interquartile range. This evidence is presented here and summarised narratively in section1.1.10.

G.1 Continuous glucose monitoring (CGM) vs Intermittent capillary blood glucose monitoring

Preconception period (women who are planning to become pregnant)

	Whole population			Participants using insulin pump			Participants using multiple daily injection			Notes
	CGM	Control*	P value***	CGM	Control*	P value***	CGM	Control*	P value***	
Glycaemic variability measures: Coefficient of variation (CV%) at 24 weeks **										
Feig 2017	40% (35-44)	37% (33-42)	0.40	41% (36-44)	35% (33-40)	NA	36% (35-42)	41% (38-46)	NA	**Risk of bias:** No serious **Directness:** No serious
Glycaemic variability measures: SD (mmol/L) at 24 weeks **										
Feig 2017	3.3 (2.5-3.7)	3.2 (2.7-3.7)	0.54	3.3 (2.5-3.7)	3.0 (2.6-3.5)	NA	3.1 (2.6-3.4)	3.6 (3.2-4.5)	NA	
Glycaemic variability measures: Mean amplitude of glucose excursion (MAGE) (mmol/L) at 24 weeks **										
Feig 2017	6.4 (4.8-7.5)	6.7 (5.6-7.4)	0.53	6.4 (4.8-7.4)	6.5 (5.2-7.1)	NA	6.4 (5.7-7.5)	7.4 (5.9-8.2)	NA	
Glycaemic variability measures: Rate of change (mmol/l/h) at 24 weeks **										
Feig 2017	2.82 (2.24-3.25)	2.13 (1.77-2.45)	<0.001	-	-	-	-	-	-	
Percentage of time spent < 3.5 mmol//l										
Feig 2017	4 (1-8)	3 (1-6)	0.15	4 (2-8)	2 (0-5)	-	3 (1-7)	6 (3-9)	-	

* CGM measures were obtained using a masked sensor
** Data presented as median (IQR)
*** Two sided significance level of 0.05.

1 **During pregnancy**

Study name	Whole population			Participants using insulin pump			Participants using multiple daily injection			Notes
	CGM	Control	P value**	CGM	Control	P value**	CGM	Control	P value**	
Glycaemic variability measures: Coefficient of variation (CV%) at 24 weeks *										
Feig 2017	32% (28-37)	34% (29-39)	0.058	31% (28-37)	35% (33-40)	NA	33% (28-37)	34% (29-38)	NA	
Glycaemic variability measures: SD (mmol/L) at 24 weeks *										
Feig 2017	2.2 (1.8-2.5)	2.4 (2.0-2.8)	0.0359	2.2 (1.8-2.5)	2.4 (2.0-3.0)	NA	2.2 (1.8-2.5)	2.3 (2.0-2.8)	NA	
Glycaemic variability measures: Mean amplitude of glucose excursion (MAGE) (mmol/L) at 24 weeks *										
Feig 2017	4.2 (3.5-4.9)	4.6 (3.9-6.0)	0.0455	4.4 (3.5-4.8)	4.8 (3.9-6.1)	NA	4.2 (3.6-5.3)	4.6 (3.9-5.7)	NA	**Risk of bias:** No serious **Directness:** No serious
Glycaemic variability measures: Rate of change (mmol/l/h) at 24 weeks *										
Feig 2017	2.02 (1.70-2.26)	1.63 (1.31-1.96)	<0.001	-	-		-	-	-	
Percentage of time spent < 3.5 mmol//l*										
Feig 2017	3 (1-6)	4 (2-8)	0.10	3 (1-7)	4 (2-7)	-	3 (1-6)	5 (2-9)	-	
Maternal length of stay (days)										
Feig 2017	3.5 (2.6-5.3)	4.2 (2.9-6.8)	0.10	-	-	-	-	-	-	
Infant length of hospital stay(days)										
Feig 2017	3.1 (2.1-5.7)	4.0 (2.4-7.0)	0.0091	-	-	-	-	-	-	
HbA1c (%) at 21 weeks***										**Risk of bias:** High. Outcomes analysed per protocol.
Secher 2013	6.0 (5.2-7.4)	6.2 (4.9-7.7)	0.26	-	-	-	-	-	-	
HbA1c (%) at 36 weeks***										

Study name	Whole population			Participants using insulin pump			Participants using multiple daily injection			Notes
Secher 2013	6.0 (5.1-7.7)	6.2 (4.7-8.4)	0.37	-	-	-	-	-	-	Additionally, sensitivity analysis not conducted to account for missing data. **Directness:** Partially direct. Women used CGM intermittently (i.e., at 8, 12, 21, 27, and 33 weeks or more). Near-continuous realtime CGM use (at least 60% of the time) was only chosen by five (7%) women
* Data presented as median (IQR). CGM measures were obtained using a masked sensor **Two sided significance level of 0.05. *** Data presented as median (IQR).										

1

Appendix H - GRADE

H.1 Preconception period (women who are planning to become pregnant)

Continuous glucose monitoring vs. intermittent capillary blood glucose monitoring

Maternal outcomes at ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
HbA1c (%) – MD less than 0 favours CGM											
1 Feig 2017	RCT	88	-0.23 (-0.55, 0.09)	-	-	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Achieved HbA1c target (7.0% (53 mmol/mol)) - RR greater than 1 favours CGM											
1 Feig 2017	RCT	88	1.30 (0.87, 1.95)	46 per 100 people	59 more per 100 people (40 less, 46 more)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Time spent in glucose target range (%) (glucose target range of 3.5-7.8 mmol/L)- **whole population** – MD greater 0 favours CGM											
1 Feig 2017	RCT	91	5.00 (-0.96, 10.96)	-	-	-	No serious	NA[1]	No serious	Serious[4]	Moderate
Time spent in glucose target range (%) (glucose target range of 3.5-7.8 mmol/L)- **Insulin pump users** – MD greater 0 favours CGM											
1 Feig 2017	RCT	67	4.00 (-2.72, 10.72)	-	-	-	No serious	NA[1]	No serious	Serious[4]	Moderate
Time spent in glucose target range (%) (glucose target range of 3.5-7.8 mmol/L)- **Multiple daily injection users** – MD greater 0 favours CGM											
1	RCT	24	4.00 (-8.87, 16.87)	-	-	-	No serious	NA[1]	No serious	Very serious[5]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Feig 2017											
Severe hypoglycaemia (defined as an episode requiring third party assistance) – RR less than 1 favours CGM											
1 Feig 2017	RCT	109	1.53 (0.52, 4.54)	9 per 100 people	13 more per 100 people (5 les, 40 more)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Serious adverse events - RR less than 1 favours CGM											
1 Feig 2017	RCT	110	2.15 (0.20, 23.04)	2 per 100 people	4 more per 100 people (0 less, 40 more)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Adverse event – Diabetic ketoacidosis – RR less than 1 favours CGM											
1 Feig 2017	RCT	109	0.22 (0.01, 4.46)	4 per 100 people	1 less per 100 people (0 less,16 more)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Adverse event- local reaction (skin changes during trial) - RR less than 1 favours CGM											
1 Feig 2017	RCT	109	5.04 (2.07, 12.29)	9 per 100 people	44 more per 100 people (18 less,108 more)	-	No serious	NA[1]	No serious	No serious	High
Quality of life- Blood Glucose Monitoring Systems Rating Questionnaire (BGMSRQ) - Satisfaction subscale - higher score representing more of the characteristic - MD greater than 0 favours CGM											
1 Feig 2017	RCT	110	-1.90 (-4.33, 0.53)	-	-	3.15[7]	No serious	NA[1]	No serious	Serious[6]	Moderate
Quality of life- Blood Glucose Monitoring Systems Rating Questionnaire (BGMSRQ) – Impact subscale - higher score representing more of the characteristic - MD greater than 0 favours CGM											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Feig 2017	RCT	110	5.10 (2.31, 7.89)	-	-	3.75[8]	No serious	NA[1]	No serious	Serious[6]	Moderate
Quality of life- Blood Glucose Monitoring Systems Rating Questionnaire (BGMSRQ) – Obstruction subscale - higher score representing more of the characteristic - MD less than 0 favours CGM											
1 Feig 2017	RCT	110	-2.80 (-4.71, -0.89)	-	-	2.4[9]	No serious	NA[1]	No serious	Serious[6]	Moderate
Quality of life- Hypoglycaemia Fear Survey (HFS-II)– Behaviour subscale – Higher score indicates increased fear of hypoglycaemia – MD less than 0 favours CGM											
1 Feig 2017	RCT	110	-0.30 (-3.11, 2.51)	-	-	3.65[10]	No serious	NA[1]	No serious	No serious	High
Quality of life- Hypoglycaemia Fear Survey (HFS-II)– Worry subscale - Higher score indicates increased fear of hypoglycaemia – MD less than 0 favours CGM											
1 Feig 2017	RCT	110	-6.80 (-11.62, -1.98)	-	-	6.55[11]	No serious	NA[1]	No serious	Serious[6]	Moderate
Quality of life- Short form -12 – Higher score indicates high level of health- MD greater than 0 favours CGM											
1 Feig 2017	RCT	110	-0.50 (-2.90, 1.90)	-	-	2.8[12]	No serious	NA[1]	No serious	Serious[6]	Moderate
Diabetes related distress – PAID score – Higher score reflecting greater emotional distress- MD less than 0 favours CGM											
1 Feig 2017	RCT	110	1.00 (-4.26, 6.26)	-	-	6.9[13]	No serious	NA[1]	No serious	No serious	High

[1] Inconsistency not applicable for single study.

[2] Downgrade 1 level due to serious imprecision. 95% confidence interval crosses one end of the defined MID (-0.5%, 0.5%).

[3] Downgrade 1 level due to serious imprecision. 95% confidence interval crosses the line of no effect.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[4] Downgrade 1 level due to serious imprecision. 95% confidence interval crosses one end of the defined MID (-5%,5%).
[5] Downgrade 2 levels due to very serious imprecision. 95% confidence interval crosses both ends of the defined MID (-5%, 5%).
[6] Downgrade 1 level due to serious imprecision. 95% confidence interval crosses one end of estimated MID.
[7] MID = 0.5 of the median standard deviation of the comparison group (SD= 6.3).
[8] MID = 0.5 of the median standard deviation of the comparison group (SD= 7.5).
[9] MID = 0.5 of the median standard deviation of the comparison group (SD= 4.8).
[10] MID = 0.5 of the median standard deviation of the comparison group (SD= 7.3).
[11] MID = 0.5 of the median standard deviation of the comparison group (SD= 13.1).
[12] MID = 0.5 of the median standard deviation of the comparison group (SD= 5.6).
[13] MID = 0.5 of the median standard deviation of the comparison group (SD= 13.8).
* Derived by taking the overall number of event/ total number of participants and multiplying by 100.

H.2 During pregnancy

Continuous glucose monitoring vs. intermittent capillary blood glucose monitoring

Maternal outcomes at ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
HbA1c (%) – MD less than 0 favours CGM										
1 Feig 2017	RCT	187	-0.17 (-0.35, 0.01)	-	-	No serious	NA[1]	No serious	No serious	High
HbA1c (%) – In women who conceived during the 24-week planning for pregnancy trial - MD less than 0 favours CGM										
1 Feig 2017	RCT	24	-0.25 (-0.71, 0.21)	-	-	No serious	NA[1]	No serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
[1] Inconsistency not applicable for single study [2] Downgrade 1 level due to serious imprecision. 95% confidence interval crosses one end of the defined MID (-0.5%, 0.5%).										

1 **Neonatal/ infant outcomes at ≤ 6 months**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Pregnancy loss/ Miscarriage – RR less than 1 favours CGM										
2 Feig 2017 Secher 2013	RCT	334	1.59 (0.53, 4.77)	3 per 100 people	5 more per 100 people (2 less, 3 more)	No serious	No serious	No serious	Serious[1]	Moderate
Pregnancy loss/ Miscarriage – In women who conceived during the 24-week planning for pregnancy trial - RR less than 1 favours CGM										
1 Feig 2017	RCT	31	2.43 (0.52, 11.36)	12 per 100 people	29 more per 100 people (6 less, 134 more)	No serious	NA[2]	No serious	Serious[1]	Moderate
[1] Downgrade 1 level due to serious imprecision. Confidence interval crosses the line of no effect. [2] Inconsistency not applicable for single study * Derived by taking the overall number of event/ total number of participants and multiplying by 100										

2 **Maternal outcomes at > 6 months**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD**	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
HbA1c (%) – MD less than 0 favours CGM											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD**	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Feig 2017	RCT	187	-0.18 (-0.36, 0.00)	-	-	-	No serious	NA[1]	No serious	No serious	High
HbA1c (%) – In women who conceived during 24-week planning pregnancy trial - MD less than 0 favours CGM											
1 Feig 2017	RCT	24	-0.27 (-0.71, 0.17)	-	-	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Achieved HbA1c target (6.5% (48 mmol/mol))- RR greater than 1 favours CGM											
1 Feig 2017	RCT	187	1.27 (1.00, 1.62)	52 per 100 people	66 more per 100 people (52 less, 85 more)	-	No serious	NA[1]	No serious	No serious	High
Achieved HbA1c target (7.0% (53 mmol/mol) before pregnancy and 6.5% (48 mmol/mol after pregnancy)) - In women who conceived during 24-week planning pregnancy trial- RR greater than 1 favours CGM											
1 Feig 2017	RCT	24	1.43 (0.70, 2.91)	47 per 100 people	67 more per 100 people (33 les,136 more)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Time spent in target glucose range (%) (glucose target range of 3.5-7.8 mmol/L)- **whole population** – MD greater 0 favours CGM											
1 Feig 2017	RCT	154	7.00 (2.57, 11.43)	-	-	-	No serious	NA[1]	No serious	Serious[4]	Moderate
Time spent in glucose target range (%) (glucose target range of 3.5-7.8 mmol/L)- **Insulin pump users** – MD greater 0 favours CGM											
1 Feig 2017	RCT	72	4.00 (-2.24, 10.24)	-	-	-	No serious	NA[1]	No serious	Serious[4]	Moderate
Time spent in glucose target range (%) (glucose target range of 3.5-7.8 mmol/L)- **Multiple daily injection users** – MD greater 0 favours CGM											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD**	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Feig 2017	RCT	24	8.00 (1.43, 14.57)	-	-	-	No serious	NA	No serious	Serious[4]	Moderate
Severe hypoglycaemia – RR less than 1 favours CGM											
2 Feig 2017 Secher 2013	RCT	304	0.77 (0.42, 1.44)	14 per 100 people	11 less per 100 people (6 less,20 more)	-	No serious	No serious	No serious	Serious[3]	Moderate
Severe hypoglycaemia (defined as an episode requiring third party assistance) – In women who conceived during 24-week planning pregnancy trial - RR less than 1 favours CGM											
1 Feig 2017	RCT	30	1.14 (0.18, 7.08)	13 per 100 people	14 more per 100 people (2, 89)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Serious adverse events - RR less than 1 favours CGM											
1 Feig 2017	RCT	214	1.60 (0.54, 4.73)	5 per 100 people	7 more per 100 people (3 less,22 more)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Adverse event – Diabetic ketoacidosis – RR less than 1 favours CGM											
1 Feig 2017	RCT	207	1.01 (0.14, 7.03)	2 per 100 people	2 per 100 people (0 less,14 more)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Adverse event – Diabetic ketoacidosis – In women who conceived during 24-week planning pregnancy trial- RR less than 1 favours CGM											
1 Feig 2017	RCT	30	3.40 (0.15, 77.34)	0 per 100 people	Not estimable because of very low/ zero event	-	No serious	NA[1]	No serious	Serious[3]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD**	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Adverse event- local reaction (skin changes during trial) - RR less than 1 favours CGM											
1 Feig 2017	RCT	207	6.18 (3.08, 12.40)	8 per 100 people	48 more per 100 people (24 less, 95 more)	-	No serious	NA[1]	No serious	No serious	High
Adverse event- Diabetes related hospitalisation – RR less than 1 favours CGM											
Feig 2017	RCT	207	2.02 (0.38, 10.79)	2 per 100 people	4 more per 100 people (1 less,21 more)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Pre-eclampsia – RR less than 1 favours CGM											
2 Feig 2017 Secher 2013	RCT	325	0.61 (0.32, 1.14)	14 per 100 people	9 less per 100 people (5 less,16 more)	-	No serious	No serious	No serious	Serious[3]	Moderate
Pre-eclampsia – In women who conceived during 24-week planning pregnancy trial – RR less than 1 favours CGM											
1 Feig 2017	RCT	25	0.48 (0.02, 10.84)	7 per 100 people	3 less per 100 people (0 less, 72 more)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Mode of birth – Caesarean section – RR less than 1 favours CGM											
2 Feig 2017 Secher 2013	RCT	325	0.82 (0.69, 0.99)	62 per 100 people	51 less per 100 (43 less,62 more)	-	No serious	No serious	No serious	No serious	High
Mode of birth – Caesarean section – In women who conceived during 24-week planning pregnancy trial – RR less than 1 favours CGM											
1 Feig 2017	RCT	25	0.95 (0.57, 1.59)	73 per 100 people	70 less per 100 people (42 more, 117 less)	-	No serious	NA[1]	No serious	Serious[3]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD**	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Preterm birth <37 weeks – RR less than 1 favours CGM											
2 Feig 2017 Secher 2013	RCT	325	0.93 (0.68, 1.26)	34 per 100 people	32 less per 100 people (23 less, 43 more)	-	No serious	No serious	No serious	Serious[3]	Moderate
Preterm birth <37 weeks - In women who conceived during 24-week planning pregnancy trial – RR less than 1 favours CGM											
1 Feig 2017	RCT	25	1.88 (0.66, 5.32)	27 per 100 people	50 more per 100 people (18 less, 148 more)	-	No serious	NA[1]	No serious	Serious[3]	Moderate
Quality of life- Blood Glucose Monitoring Systems Rating Questionnaire (BGMSRQ) - Satisfaction subscale - higher score representing more of the characteristic - MD greater than 1 favours CGM											
1 Feig 2017	RCT	214	-0.40, (-2.12, 1.32)	-	-	3.25[6]	No serious	NA[1]	No serious	No serious	High
Quality of life- Blood Glucose Monitoring Systems Rating Questionnaire (BGMSRQ) – **Impact subscale - higher score representing more of the characteristic** - MD greater than 1 favours CGM											
1 Feig 2017	RCT	214	4.80 (2.98, 6.62)	-	-	3.5[7]	No serious	NA[1]	No serious	Serious[5]	Moderate
Quality of life- Blood Glucose Monitoring Systems Rating Questionnaire (BGMSRQ) – Obstruction subscale - higher score representing more of the characteristic - MD less than 1 favours CGM											
1 Feig 2017	RCT	214	-1.90 (-3.09, -0.71)	-	-	2.25[8]	No serious	NA[1]	No serious	Serious[5]	Moderate
Quality of life- Hypoglycaemia Fear Survey (HFS-II)– Behaviour subscale – Higher score indicates increased fear of hypoglycaemia – MD less than 1 favours CGM											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD**	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Feig 2017	RCT	214	1.00 (-1.06, 3.06)	-	-	3.7[9]	No serious	NA[1]	No serious	No serious	High
Quality of life- Hypoglycaemia Fear Survey (HFS-II)– Worry subscale - Higher score indicates increased fear of hypoglycaemia – MD less than 1 favours CGM											
1 Feig 2017	RCT	214	0.80 (-3.01, 4.61)	-	-	6.95[10]	No serious	NA[1]	No serious	No serious	High
Quality of life- Short form -12 – Higher score indicates high level of health- MD greater than 1 favours CGM											
1 Feig 2017	RCT	214	-0.70 (-2.50, 1.10)	-	-	3.25[11]	No serious	NA[1]	No serious	No serious	High
Diabetes related distress – PAID score – Higher score reflecting greater emotional distress- MD less than 1 favours CGM											
1 Feig 2017	RCT	214	0.80 (-3.06, 4.66)	-	-	7.55[12]	No serious	NA[1]	No serious	No serious	High

[1] Inconsistency not applicable for single study
[2] Downgrade 1 level due to serious imprecision. 95% confidence interval crosses one end of the defined MID (-0.5%, 0.5%).
[3] Downgrade 1 level due to serious imprecision. Confidence interval crosses the line of no effect.
[4] Downgrade 1 level due to serious imprecision. 95% confidence interval crosses one end of the defined MID (-5%,5%).
[5] Downgrade 1 level due to serious imprecision. 95% confidence interval crosses one end of the estimated MID.
[6] MID = 0.5 of the median standard deviation of the comparison group (SD= 6.5).
[7] MID = 0.5 of the median standard deviation of the comparison group (SD= 7).
[8] MID = 0.5 of the median standard deviation of the comparison group (SD= 4.5).
[9] MID = 0.5 of the median standard deviation of the comparison group (SD= 7.4).
[10] MID = 0.5 of the median standard deviation of the comparison group (SD= 13.9).

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD**	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[11] MID = 0.5 of the median standard deviation of the comparison group (SD= 6.5).

[12] MID = 0.5 of the median standard deviation of the comparison group (SD= 15.1).

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

1 **Neonatal/ infant outcomes at >6 months**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Still birth – RR less than 1 favours CGM										
1 Feig 2017	RCT	211	0.34 (0.01, 8.17)	1 per 100 people	0 less per 100 people (0 less ,8 more)	No serious	NA[1]	No serious	Serious[2]	Moderate
Still birth – In women who conceived during 24-week planning pregnancy trial – RR less than 1 favours CGM										
1 Feig 2017	RCT	31	RR not estimable due to zero event in both arms			No serious	NA[1]	No serious	Very serious[3]	Low
Congenital anomaly – RR less than 1 favours CGM										
1 Feig 2017	RCT	211	0.67 (0.11, 3.95)	3 per 100 people	2 less per 100 people (0 less, 11 more)	No serious	NA[1]	No serious	Serious[2]	Moderate
Congenital anomaly – In women who conceived during 24-week planning pregnancy trial – RR less than 1 favours CGM										
1 Feig 2017	RCT	31	RR not estimable due to zero event in both arms			No serious	NA[1]	No serious	Very serious[3]	Low
Small for gestational age – RR less than 1 favours CGM										
1 Feig 2017	RCT	200	1.00 (0.14, 6.96)	2 per 100 people	2 per 100 people (0	No serious	NA[1]	No serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					less ,14 more)					
Small for gestational age- In women who conceived during 24-week planning pregnancy trial – RR less than 1 favours CGM										
1 Feig 2017	RCT	31	RR not estimable due to zero event in both arms			No serious	NA[1]	No serious	Very serious[3]	Low
Large for gestational age – RR less than 1 favours CGM										
2 Feig 2017 Secher 2013	RCT	323	0.99 (0.56, 1.75)	56 per 100 people	56 per 100 people (56 less,98 more)	No serious	Very serious[4]	No serious	Serious[2]	Very low
Large for gestational age - In women who conceived during 24-week planning pregnancy trial – RR less than 1 favours CGM										
1 Feig 2017	RCT	25	0.82 (0.45, 1.48)	73 per 100 people	60 less per 100 people (33 less, 109 more)	No serious	NA[1]	No serious	Serious[2]	Moderate
Macrosomia – RR less than 1 favours CGM										
1 Feig 2017	RCT	200	0.85 (0.11, 1.65)	27 per 100 people	23 less per 100 people (14 less, 37 more)	No serious	NA[1]	No serious	Serious[2]	Moderate
Macrosomia- In women who conceived during 24-week planning pregnancy trial – RR less than 1 favours CGM										
1 Feig 2017	RCT	25	0.43 (0.11, 1.66)	47 per 100 people	20 less per 100 people (5 less,77 more)	No serious	NA[1]	No serious	Serious[2]	Moderate
Neonatal hypoglycaemia – RR less than 1 favours CGM										
2 Feig 2017 Secher 2013	RCT	317	0.67 (0.47, 0.95)	34 per 100 people	23 less per 100 people (16 less,33 more)	No serious	No serious	No serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Neonatal hypoglycaemia - In women who conceived during 24-week planning pregnancy trial – RR less than 1 favours CGM										
1 Feig 2017	RCT	25	1.50 (0.76, 2.95)	47 per 100 people	70 more per 100 people (35 less, 138 more)	No serious	NA[1]	No serious	Serious[2]	Moderate
Severe neonatal hypoglycaemia – RR less than 1 favours CGM										
1 Secher 2013	RCT	117	0.95 (0.42, 2.16)	17 per 100 people	16 less per 100 people (7 less,36 more)	Very serious[5]	NA[1]	Serious[6]	Serious[2]	Very low
High level neonatal care (NICU) >24 hours – RR less than 1 favours CGM										
1 Feig 2017	RCT	200	0.63 (0.42, 0.93)	43 per 100 people	27 less per 100 people (18 less, 40 more)	No serious	NA[1]	No serious	No serious	High
High level neonatal care (NICU) >24 hours - In women who conceived during 24-week planning pregnancy trial – RR less than 1 favours CGM										
1 Feig 2017	RCT	25	1.75 (0.83, 3.67)	40 per 100 people	70 more per 100 people (33 less, 147 more)	No serious	NA[1]	No serious	Serious[2]	Moderate

[1] Inconsistency not applicable for single study

[2] Downgrade 1 level due to serious imprecision. Confidence interval crosses the line of no effect.

[3] Downgrade 2 levels due to very serious imprecision. Effect size could not be calculated.

[4] Downgrade 2 levels due to serious very serious inconsistency. I^2 is greater than 66.7%

[5] Downgrade 2 levels due to very serious risk of bias. Outcomes analysed per protocol. Additionally, sensitivity analysis not conducted to account for missing data.

[6] Downgrade 1 level due to serious indirectness. Women used CGM intermittently (i.e., at 8, 12, 21, 27, and 33 weeks or more). Near-continuous realtime CGM use (at least 60% of the time) was only chosen by five (7%) women.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Continuous glucose monitoring vs. Flash glucose monitoring

Maternal outcomes at ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
HbA1c (%) – MD less than 0 favours CGM										
1 Kristensen 2019	Retrospective study	186	0.1 (-0.17, 0.37)	-	-	Very serious[1]	NA[2]	No serious	No serious	Low

[1] Downgrade 2 level due to very serious risk of bias. No correction for selection bias e.g. using inverse probability weights. No information provided about analysis used to estimate effect of starting and adhering to the intervention. Methods such as matching not used to control for confounding factors. Unclear if missing data is equal between both arms.

[2] Inconsistency not applicable for single study

Maternal outcomes at > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
HbA1c (%) – MD less than 0 favours CGM										
1 Kristensen 2019	Retrospective study	186	0.00 (-0.20, 0.20)	-	-	Very serious[1]	NA[2]	No serious	No serious	Low
Pre-eclampsia/ pregnancy induced hypertension- RR less than 0 favours CGM										
1 Kristensen 2019	Retrospective study	186	0.81 (0.44, 1.49)	20 per 100 people	16 less per 100 people (9 less, 30 more)	Very serious[1]	NA[2]	No serious	Serious[3]	Very low
Mode of birth – Caesarean section – RR less than 0 favours CGM										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Kristensen 2019	Retrospective study	186	1.15 (0.84, 1.56)	44 per 100 people	50 more per 100 people (37 less, 68 more)	Very serious[1]	NA[2]	No serious	Serious[3]	Very low
Pre-term birth >37 weeks – RR less than 0 favours CGM										
1 Kristensen 2019	Retrospective study	186	0.88 (0.55, 1.39)	30 per 100 people	26 less per 100 people (16 less, 41 more)	Very serious[1]	NA[2]	No serious	Serious[3]	Very low

[1] Downgrade 2 level due to very serious risk of bias. No correction for selection bias e.g. using inverse probability weights. No information provided about analysis used to estimate effect of starting and adhering to the intervention. Methods such as matching not used to control for confounding factors. Unclear if missing data is equal between both arms.

[2] Inconsistency not applicable for single study

[3] Downgrade 1 level due to serious imprecision. 95% CI cross line of no effect (0).

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

1 **Neonatal/ infant outcomes at >6 months**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Large for gestational age – RR less than 0 favours CGM										
1 Kristensen 2019	Retrospective study	186	0.98 (0.75, 1.29)	53 per 100 people	52 less per 100 people (40 less, 69 more)	Very serious[1]	NA[2]	No serious	Serious[3]	Very low
Macrosomia (>4500 g) **-** RR less than 0 favours CGM										
1 Kristensen 2019	Retrospective study	186	0.89 (0.46, 1.72)	17 per 100 people	15 less per 100 people	Very serious[1]	NA[2]	No serious	Serious[3]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					(8 less, 29 more)					
Neonatal hypoglycaemia (defined as plasma glucose < 2.6 mmol/l >3h after birth) **-** RR less than 0 favours CGM										
1 Kristensen 2019	Retrospective study	186	0.75 (0.45, 1.25)	28 per 100 people	21 less per 100 people (12 less, 35 more)	Very serious[1]	NA[2]	No serious	Serious[3]	Very low
NICU admission >24 hours - RR less than 0 favours CGM										
1 Kristensen 2019	Retrospective study	186	0.84 (0.55, 1.27)	35 per 100 people	29 less per 100 people (19 less, 45 more)	Very serious[1]	NA[2]	No serious	Serious[3]	Very low

[1] Downgrade 2 level due to very serious risk of bias. No correction for selection bias e.g. using inverse probability weights. No information provided about analysis used to estimate effect of starting and adhering to the intervention. Methods such as matching not used to control for confounding factors. Unclear if missing data is equal between both arms.

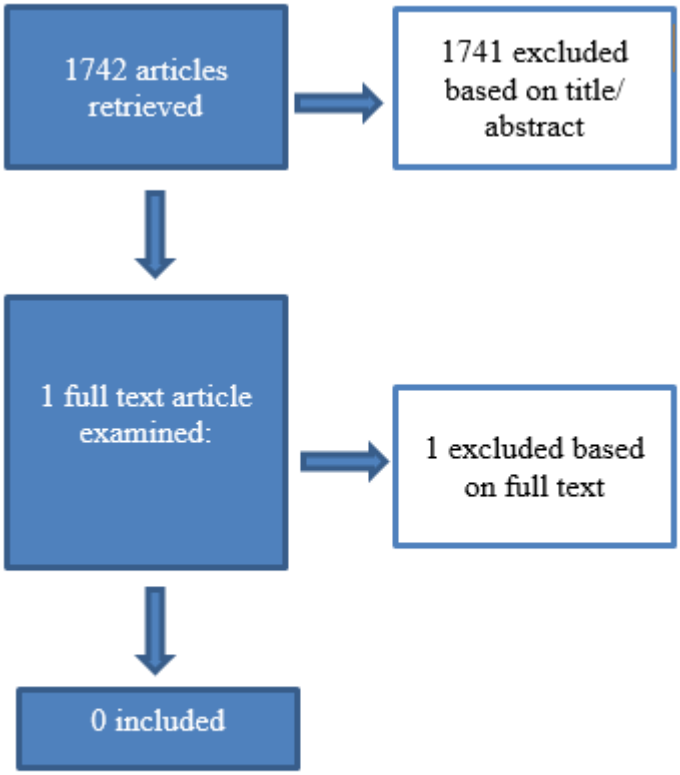
[2] Inconsistency not applicable for single study

[3] Downgrade 1 level due to serious imprecision. 95% CI cross line of no effect (0).

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

1

Appendix I – Economic evidence study selection



Appendix J – Economic evidence tables

No economic evidence was identified.

Appendix K – Excluded studies

K.1 RCTs

Studies highlighted in bold were included in the previous (2015) update.

Study	Reason
Alfadhli, E.; Osman, E.; Basri, T. (2016) Use of a real time continuous glucose monitoring system as an educational tool for patients with gestational diabetes. Diabetology and Metabolic Syndrome 8(1): 48	- Study included women with gestational diabetes
Asarani, N.A.M., Reynolds, A.N., Boucher, S.E. et al. (2019) Cutaneous Complications With Continuous or Flash Glucose Monitoring Use: Systematic Review of Trials and Observational Studies. Journal of Diabetes Science and Technology	- Systematic review used as source of primary studies. Systematic review did not meet the criteria listed in the review protocol.
Bidonde, Julia, Fagerlund, Beate Charlotte, Fronsdal, Katrine B. et al. (2017) FreeStyle Libre Flash Glucose Self-Monitoring System: A Single-Technology Assessment.	- Technology assessment did not include studies on the use of CGM in women who are pregnant/ planning on becoming pregnant
Cordua, S, Secher, A L, Ringholm, L et al. (2013) Real-time continuous glucose monitoring during labour and delivery in women with Type 1 diabetes - observations from a randomized controlled trial. Diabetic medicine : a journal of the British Diabetic Association 30(11): 1374-81	- Monitoring only conducted during labour and delivery. Monitoring began1 day prior to labour induction or elective caesarean section
Feig, D S and Murphy, H R (2018) Continuous glucose monitoring in pregnant women with Type 1 diabetes: benefits for mothers, using pumps or pens, and their babies. Diabetic medicine : a journal of the British Diabetic Association 35(4): 430-435	- Review article but not a systematic review
Golden, Sherita Hill, Brown, Todd, Yeh, Hsin-Chieh et al. (2012) Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. Comparative Effectiveness Review.	- Systematic review did not include studies on use of CGM in pregnant women with T1DM
Han, S; Crowther, CA; Middleton, P (2012) Interventions for pregnant women with hyperglycaemia not meeting gestational diabetes and type 2 diabetes diagnostic criteria. Cochrane Database of Systematic Reviews	- Review focuses on gestational diabetes and type 2 diabetes
Hoeks, L B E A; Greven, W L; de Valk, H W (2011) Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. Diabetic medicine : a journal of the British Diabetic Association 28(4): 386-94	- Review focused on type 1 and type 2 diabetes [In the general population]
John M. Eisenberg Center for Clinical Decisions and Communications, Science (2007) Insulin Delivery and Glucose Monitoring Methods for Diabetes Mellitus: Comparative Effectiveness.	- Review article but not a systematic review [Clinical research summary]

Study	Reason
Jones, Leanne V, Ray, Amita, Moy, Foong Ming et al. (2019) Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes. The Cochrane database of systematic reviews 5: cd009613	- Systematic review used as source of primary studies. Systematic review did not meet the criteria listed in the review protocol.
Kerssen A; de Valk HW; Visser GH (2006) Do HbA1c levels and the self-monitoring of blood glucose levels adequately reflect glycaemic control during pregnancy in women with type 1 diabetes mellitus?. Diabetologia 49(1): 25-28	**- Blinded CGM- Patients were unaware of the glucose measurement during CGM use.**
Kestila, Kirsimarja K; Ekblad, Ulla U; Ronnemaa, Tapani (2007) Continuous glucose monitoring versus self-monitoring of blood glucose in the treatment of gestational diabetes mellitus. Diabetes research and clinical practice 77(2): 174-9	**- Study included women with gestational diabetes**
Lane, A.S., Mlynarczyk, M.A., De Veciana, M. et al. (2019) Real-Time Continuous Glucose Monitoring in Gestational Diabetes: A Randomized Controlled Trial. American Journal of Perinatology 36(9): 891-897	- Study included women with gestational diabetes
Law, Graham R, Ellison, George T H, Secher, Anna L et al. (2015) Analysis of Continuous Glucose Monitoring in Pregnant Women With Diabetes: Distinct Temporal Patterns of Glucose Associated With Large-for-Gestational-Age Infants. Diabetes care 38(7): 1319-25	- Not a relevant study design [Not an RCT]
McCance, David R (2015) Diabetes in pregnancy. Best practice & research. Clinical obstetrics & gynaecology 29(5): 685-99	- Review article but not a systematic review
Medical Advisory, Secretariat (2011) Continuous glucose monitoring for patients with diabetes: an evidence-based analysis. Ontario health technology assessment series 11(4): 1-29	- Technology assessment did not include studies on the use of CGM in women who are pregnant/ planning on becoming pregnant
Murphy, H.R. (2019) Continuous glucose monitoring targets in type 1 diabetes pregnancy: every 5% time in range matters. Diabetologia 62(7): 1123-1128	- Review article but not a systematic review
Murphy, H.R., Raynian, G., Lewis, K. et al. (2009) Effectiveness of continuous glucose monitoring in pregnant women with diabetes: Randomized clinical trial. Obstetrical and Gynecological Survey 64(4): 216-218	- Commentary
Murphy, Helen R, Rayman, Gerry, Duffield, Katherine et al. (2007) Changes in the glycemic profiles of women with type 1 and type 2 diabetes during pregnancy. Diabetes care 30(11): 2785-91	- Blinded CGM- Patients were unaware of the glucose measurement during CGM use. [Adhoc analysis]
Murphy, Helen R, Rayman, Gerry, Lewis, Karen et al. (2008) Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ (Clinical research ed.) 337: a1680	**- Blinded CGM- Patients were unaware of the glucose measurement during CGM use.** **[Neither participants nor professionals had access to glucose measurements during sensor use.]**
Paramasivam, S S, Chinna, K, Singh, A K K et al. (2018) Continuous glucose monitoring results	- Study included women with gestational diabetes

Study	Reason
in lower HbA1c in Malaysian women with insulin-treated gestational diabetes: a randomized controlled trial. Diabetic medicine : a journal of the British Diabetic Association 35(8): 1118-1129	
Petrovski, Goran, Dimitrovski, Cedomir, Bogoev, Milco et al. (2011) Is there a difference in pregnancy and glycemic outcome in patients with type 1 diabetes on insulin pump with constant or intermittent glucose monitoring? A pilot study. Diabetes technology & therapeutics 13(11): 1109-13	- Study compared CGM used 24h/day with CGM used 14 days/ month [Study used Paradigm Veo system (closed loop system)]
Polsky, Sarit and Garcetti, Rachel (2017) CGM, Pregnancy, and Remote Monitoring. Diabetes technology & therapeutics 19(s3): 49-s59	- Systematic review used as source of primary studies. Systematic review did not meet the criteria listed in the review protocol.
Raman, P., Shepherd, E., Dowswell, T. et al. (2017) Different methods and settings for glucose monitoring for gestational diabetes during pregnancy. Cochrane Database of Systematic Reviews 2017(10): cd011069	- Review focuses on gestational diabetes
Temple, RC, Duffield, K, Lewis, K et al. (2006) Glycaemic control during pregnancy in women with long duration type 1 diabetes: lessons learn using continuous glucose monitoring systems. Diabetologia 49(suppl1): 78	- Conference abstract
Voormolen, Daphne N, DeVries, J Hans, Evers, Inge M et al. (2013) The efficacy and effectiveness of continuous glucose monitoring during pregnancy: a systematic review. Obstetrical & gynecological survey 68(11): 753-63	- Systematic review used as source of primary studies. Systematic review did not meet the criteria listed in the review protocol.
Voormolen, Daphne N, DeVries, J Hans, Sanson, Rieneke M E et al. (2018) Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): A multicentre randomized controlled trial. Diabetes, obesity & metabolism 20(8): 1894-1902	- Blinded CGM- Patients were unaware of the glucose measurement during CGM use.
Wei, Qiong, Sun, Zilin, Yang, Yue et al. (2016) Effect of a CGMS and SMBG on Maternal and Neonatal Outcomes in Gestational Diabetes Mellitus: a Randomized Controlled Trial. Scientific reports 6: 19920	- Study did not focus on pregnant women or women planning to become pregnant
Yogev, Y., Chen, R., Ben-Haroush, A. et al. (2003) Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. Obstetrics and Gynecology 101(4): 633-638	**- Blinded CGM- Patients were unaware of the glucose measurement during CGM use.** **[Observational study and CGM only used for 3 days.]**
Yu, Q., Aris, I.M., Tan, K.H. et al. (2019) Application and Utility of Continuous Glucose Monitoring in Pregnancy: A Systematic Review. Frontiers in Endocrinology 10: 697	- Systematic review used as source of primary studies. Systematic review did not meet the criteria listed in the review protocol.

K.2 Observational studies

Study	Code [Reason]
Buhling, Kai J, Winkel, Tessa, Wolf, Christiane et al. (2005) Optimal timing for postprandial glucose measurement in pregnant women with diabetes and a non-diabetic pregnant population evaluated by the Continuous Glucose Monitoring System (CGMS). Journal of perinatal medicine 33(2): 125-31	- Study does not match objectives of this review [Study aims included examining the physiological peak of postprandial glucose . Patients used CGM for 72 hours.]
Charleer, Sara, Mathieu, Chantal, Nobels, Frank et al. (2018) Effect of Continuous Glucose Monitoring on Glycemic Control, Acute Admissions, and Quality of Life: A Real-World Study. The Journal of clinical endocrinology and metabolism 103(3): 1224-1232	- Focus of paper was on T1DM in the whole population. Data not available for pregnant women/ women planning pregnancy.
Evers, I M, de Valk, H W, Mol, B W J et al. (2002) Macrosomia despite good glycaemic control in Type I diabetic pregnancy; results of a nationwide study in The Netherlands. Diabetologia 45(11): 1484-9	- Study does not match objectives of this review [Survey in women with Type 1 diabetes. Study did not specify if women were using CGM.]
Gupta, Resmi, Khoury, Jane, Altaye, Mekibib et al. (2017) Glycemic Excursions in Type 1 Diabetes in Pregnancy: A Semiparametric Statistical Approach to Identify Sensitive Time Points during Gestation. Journal of diabetes research 2017: 2852913	- Study does not match objectives of this review [Purpose of study was to develop a semi parametric mixed model to asses the precise timing and degree of rapid fluctuations in the glycaemic profiles of mothers with type 1 diabetes and to determine the extent to which these specific fluctuations are associated with delivery of large for gestational age baby.]
Kerssen, Anneloes; de Valk, Harold W; Visser, Gerard H A (2004) Day-to-day glucose variability during pregnancy in women with Type 1 diabetes mellitus: glucose profiles measured with the Continuous Glucose Monitoring System. BJOG : an international journal of obstetrics and gynaecology 111(9): 919-24	- CGM used for less than a week [2 days] - Study does not match objectives of this review
Kerssen, Anneloes; de Valk, Harold W; Visser, Gerard H A (2004) The Continuous Glucose Monitoring System during pregnancy of women with type 1 diabetes mellitus: accuracy assessment. Diabetes technology & therapeutics 6(5): 645-51	- Study does not match objectives of this review [Study examines accuracy of CGM.]
Leelarathna, L and Wilmot, E G (2018) Flash forward: a review of flash glucose monitoring. Diabetic medicine : a journal of the British Diabetic Association 35(4): 472-482	- Narrative review
Mazze, Roger; Yogev, Yariv; Langer, Oded (2012) Measuring glucose exposure and variability using continuous glucose monitoring in normal and abnormal glucose metabolism in pregnancy. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 25(7): 1171-5	- Study does not match objectives of this review [Study measured the average volatility or variability in glucose control in women with and without diabetes in pregnancy.]

Study	Code [Reason]
Mulla, Bethany M, Noor, Nudrat, James-Todd, Tamarra et al. (2018) Continuous Glucose Monitoring, Glycemic Variability, and Excessive Fetal Growth in Pregnancies Complicated by Type 1 Diabetes. Diabetes technology & therapeutics 20(6): 413-419	- Single arm study.
Murphy, H.R., Feig, D.S., Sanchez, J.J. et al. (2019) Modelling potential cost savings from use of real-time continuous glucose monitoring in pregnant women with Type 1 diabetes. Diabetic Medicine 36(12): 1652-1658	- Wrong study design [Economic analysis]
Nally, L.M., Bondy, N., Doiev, J. et al. (2019) A feasibility study to detect neonatal hypoglycemia in infants of diabetic mothers using real-time continuous glucose monitoring. Diabetes Technology and Therapeutics 21(4): 170-176	- Study does not match objectives of this review [Study examined the use of CGM in infants born after 34 weeks of gestation to mothers with diabetes.]
Ng, D.; Noor, N.M.; Yong, S.L. (2019) Prevalence of hypoglycaemia among insulin-treated pregnant women with diabetes who achieved tight glycaemic control. Journal of the ASEAN Federation of Endocrine Societies 34(1): 29-35	- Study utilised masked CGM - CGM used for less than a week
Restrepo-Moreno, Monica, Ramirez-Rincon, Alex, Hincapie-Garcia, Jaime et al. (2018) Maternal and perinatal outcomes in pregnant women with type 1 diabetes treated with continuous subcutaneous insulin infusion and real time continuous glucose monitoring in two specialized centers in Medellin, Colombia. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 31(6): 696-700	- Wrong study design [Non-comparative retrospective study]
Ringholm, L., Pedersen-Bjergaard, U., Thorsteinsson, B. et al. (2012) Hypoglycaemia during pregnancy in women with Type 1 diabetes. Diabetic Medicine 29(5): 558-566	- Review article. The bibliography was reviewed for possible includes
Scott, E.M.; Bilous, R.W.; Kautzky-Willer, A. (2018) Accuracy, User Acceptability, and Safety Evaluation for the FreeStyle Libre Flash Glucose Monitoring System When Used by Pregnant Women with Diabetes. Diabetes Technology and Therapeutics 20(3): 180-188	- Single arm study.
Secher, A L, Stage, E, Ringholm, L et al. (2014) Real-time continuous glucose monitoring as a tool to prevent severe hypoglycaemia in selected pregnant women with Type 1 diabetes - an observational study. Diabetic medicine : a journal of the British Diabetic Association 31(3): 352-6	- Single arm study.
Stenninger, E, Lindqvist, A, Aman, J et al. (2008) Continuous Subcutaneous Glucose Monitoring System in diabetic mothers during labour and postnatal glucose adaptation of their	- CGM used for less than a week [CGM used during the last 2 hours prior to delivery]

Study	Code [Reason]
infants. Diabetic medicine : a journal of the British Diabetic Association 25(4): 450-4	
Stewart, Zoe A, Thomson, Lynn, Murphy, Helen R et al. (2019) A Feasibility Study of Paired Continuous Glucose Monitoring Intrapartum and in the Newborn in Pregnancies Complicated by Type 1 Diabetes. Diabetes technology & therapeutics 21(1): 20-27	- CGM used for less than a week [Women had a CGM sensor inserted 2-3 days prior to delivery.]
Yamamoto, J.M., Corcoy, R., Donovan, L.E. et al. (2019) Maternal glycaemic control and risk of neonatal hypoglycaemia in Type 1 diabetes pregnancy: a secondary analysis of the CONCEPTT trial. Diabetic Medicine 36(8): 1046-1053	- CGM used for less than a week [Study focused on the intrapartum period which was defined as the 24 hours prior to birth]
Yoeli-Ullman, R., Maayan-Metzger, A., Zemet, R. et al. (2019) The association between novel glucose indices in parturients with type 1 diabetes mellitus and clinically significant neonatal hypoglycemia. Gynecological Endocrinology	- Wrong intervention [Study focused on sensor augmented pump technology.]
Yogev, Y, Ben-Haroush, A, Chen, R et al. (2003) Continuous glucose monitoring for treatment adjustment in diabetic pregnancies--a pilot study. Diabetic medicine : a journal of the British Diabetic Association 20(7): 558-62	- CGM used for less than a week [CGM used for 72 hours]

K.3 Health Economics

Study	[Reason
Murphy, H.R.; Feig, D.S.; Sanchez, J.J.; de Portu, S.; Sale, A. (2019) Modelling potential cost savings from use of real-time continuous glucose monitoring in pregnant women with Type 1 diabetes. Diabetic Medicine; 2019; vol. 36 (no. 12); 1652-1658)	- Cost Minimisation analysis [QoL not included in the analysis]

Appendix L – Research recommendations – full details

L.1 Research recommendation

In women with type 1 diabetes who are planning to become pregnant, what is the most effective method of glucose monitoring to improve maternal and infant outcomes:

- continuous glucose monitoring
- flash glucose monitoring
- intermittent capillary blood glucose monitoring?

Why this is important

There are several serious complications associated with pregnancy in women with type 1 diabetes. However, achieving optimal glycaemic control can reduce the risk of serious complications during pregnancy as well as childbirth. Glucose monitoring can enable women planning to become pregnant to achieve optimal glycaemic control, however there is a lack of evidence on the effectiveness of different glucose monitoring systems in this population.

Rationale for research recommendation

Only one study was identified which compared the use of CGM and intermittent capillary blood glucose monitoring in women planning to become pregnant. This study could not differentiate between the two monitoring methods in important outcomes such as time spent in glucose target range. Furthermore, evidence examining the use of flash glucose monitoring in this population was not identified. Due to the lack of evidence the committee were unable to make recommendations but noted that further robust research is required to ascertain the effectiveness of different glucose monitoring systems in this population.

Modified PICO table

Population	Women with type 1 diabetes who are planning to become pregnant
Interventions	• Continuous glucose monitoring • Flash glucose monitoring • Intermittent capillary blood glucose monitoring
Comparator	Compared to each other
Outcomes	• HbA1c • Time spent in target glucose range • Hypoglycaemia (including severe hypoglycaemia and nocturnal hypoglycaemia) • Time in hypoglycaemia • Awareness of hypoglycaemia • Adverse events (including diabetic ketoacidosis, diabetes related hospitalisation, local reaction due to CGM monitor, malfunction of monitor and serious adverse events) • Mode of birth • Perinatal and neonatal death (e.g. still birth) • Large for gestational age • Small for gestational age • Neonatal hypoglycaemia • Neonatal intensive care unit stay • Quality of life

Study design	Randomised controlled trial
Timeframe	Short term outcomes (≤6 months) Long term outcomes (> 6 months)
Additional information	Study should be adequately powered to explore maternal and neonatal outcomes

L.2 Research recommendation

In women with type 1 diabetes who are already pregnant, what is the most effective method of glucose monitoring to improve maternal and infant outcomes:

- continuous glucose monitoring
- flash glucose monitoring?

Why this is important

The NHS long-term plan currently states that flash glucose monitoring will be offered to pregnant women with type 1 diabetes. However, more evidence identifying the effectiveness of flash glucose monitoring compared to CGM in improving maternal and infant outcomes would be valuable.

Rationale for research recommendation

One retrospective cohort study was identified which compared the use of flash and CGM in pregnant women with type 1 diabetes. The study did could not differentiate between the two monitoring systems in outcomes such as HbA1c, pre-eclampsia, mode of birth, large for gestational age and NICU stay. The committee noted that robust evidence supporting the use of flash glucose monitoring in pregnant women with type 1 diabetes was required. The committee also highlighted that more information was required on the impact of flash on neonatal outcomes.

Modified PICO table

Population	Women with type 1 diabetes who are already pregnant
Interventions	• Continuous glucose monitoring • Flash glucose monitoring
Comparator	Compared to each other
Outcomes	**Maternal outcomes:** • Mode of birth: spontaneous vaginal delivery, instrumental vaginal delivery, caesarean section • Preterm birth (birth before 37 + 0 weeks' gestation) • HbA1c • Time spent in target glucose range • Hypoglycaemia including severe hypoglycaemia and nocturnal hypoglycaemia • Maternal satisfaction • Pregnancy induced hypertension • Pre-eclampsia • Time in hypoglycaemia • Awareness of hypoglycaemia • Glycaemic variability • Quality of life • Length of hospital stay

	• Adverse events:
	  ○ Diabetic ketoacidosis (DKA)
	  ○ Diabetes related hospitalisation
	  ○ local reaction due to CGM monitor
	  ○ malfunction of CGM monitor
	  ○ Postpartum haemorrhage
	  ○ Uterine rupture
	  ○ serious adverse events
	• Mental health outcomes measured using validated questionnaires
	Foetal/Neonatal outcomes:
	• Mortality - perinatal and neonatal death (e.g. still birth)
	• Large for gestational age
	• Small for gestational age
	• Neonatal intensive care unit length of stay 24 hours or greater (any term admission)
	• Length of hospital stay
	• Congenital abnormalities
	• Foetal growth restriction
	• Neonatal hypoglycaemia

Study design	Randomised controlled trial
Timeframe	Short term outcomes (≤6 months) Long term outcomes (> 6 months)
Additional information	Study should be adequately powered to explore maternal and neonatal outcomes

Appendix M– Original health economic analysis

M.1 Introduction

The committee identified glucose monitoring in pregnancy as a high-priority area for economic analysis. Commitments detailed in the NHS Long Term plan (NHS England, 2019) regarding both continuous glucose monitoring (CGM) and flash glucose monitoring (flash) confirm that the provision of technological glucose monitoring devices is a rapidly evolving area.

A literature review found no existing cost–utility studies applicable to glucose monitoring in pregnancy. Although there are cost–utility studies that analyse glucose monitoring in the broad population of people with type 1 diabetes, these are not appropriate to inform decision-making for women during pregnancy due to the limited time of a pregnancy as well as extra maternal and neonatal outcomes. Two recent papers (Feig et al., 2017 and Kristensen et al., 2019) have explored the effects of continuous and flash glucose monitoring for pregnant women with type 1 diabetes.

M.1.1 Decision problem

The review question this analysis addresses is:

In women with type 1 diabetes who are planning to become pregnant or who are already pregnant, what is the most effective method of glucose monitoring to improve maternal and infant outcomes:

- continuous glucose monitoring
- flash glucose monitoring
- intermittent capillary blood glucose monitoring?

Table HE001 summarises the review protocol, which is available in full in Appendix A.

Table HE001: PICO for review question

Population	Women with type 1 diabetes who are planning to become pregnant or are pregnant
Interventions	• Continuous glucose monitoring • Flash glucose monitoring • Intermittent capillary blood glucose monitoring
Comparators	Compared with each other
Outcomes	• Maternal outcomes including measures of diabetes control (HbA1c; time in range; hypoglycaemia), pregnancy complications (pre-eclampsia); mode of birth; quality of life; length of hospital stay • Foetal/neonatal outcomes including mortality; gestational age; birth weight (small/large for gestational age); critical care; length of hospital stay; neonatal hypoglycaemia

A systematic review of the clinical literature was carried out as part of this guideline (see above) and this informed the economic analysis.

The economic literature review did not find any cost–utility analyses that address the review question. This meant there were no formal includes for our systematic review (see 1.1.7 Economic evidence). However, we did find two cost-effectiveness studies which we compare with the outputs of our analysis in section M.4 to help contextualise our results.

The systematic review of clinical evidence did not find any evidence of differential outcomes for women planning pregnancy. As a result, our analysis only covers women with type 1 diabetes who are already pregnant.

M.2 Methods

M.2.1 Model overview

We developed a cohort model to calculate the cost-effectiveness of different types of glucose monitoring.

The evidence review found that different methods of glucose monitoring have differential effects on rates of caesarean section and length and type of neonatal hospital stay. We modelled these costs and consequences alongside the direct costs and quality of life (QoL) impact associated with the devices themselves.

Economic analysis of diabetes has traditionally used surrogate measures (e.g. HbA1c, blood pressure, lipid levels) to predict patient-relevant outcomes. In the clinical evidence for this question, a statistically significant benefit in HbA1c was found for CGM compared with self-monitoring of blood glucose SMBG; however, the absolute difference and its associated confidence interval (-0.18 percentage-points [-0.36, 0.00]) were below the minimally important difference (0.5 percentage-points; equivalent to 5.5 mmol/mol). Moreover, the period during which treatment will be offered is short (≤12 months), and the possible long-term consequences of better or worse control of HbA1c over such a period are uncertain. Therefore, we do not attempt to model these.

Previous economic analysis has also analysed the long-term impact of birth complications such as shoulder dystocia. However, our review found no evidence of differential rates of any such outcomes between the technologies of interest, so we do not model them.

M.2.1.1 Population(s)

Women with type 1 diabetes who are already pregnant.

The systematic review of clinical evidence did not find any evidence of differential outcomes for women planning pregnancy. As a result, we only model women who are already pregnant.

M.2.1.2 Interventions

The analysis simulates the following methods of glucose monitoring:

- continuous glucose monitoring
- flash glucose monitoring
- intermittent capillary blood glucose monitoring.

M.2.1.3 Type of evaluation, time horizon, perspective, discount rate

As per the NICE reference case, this evaluation is a cost–utility analysis (reporting health benefits in terms of QALYs), conducted from the perspective of the NHS/PSS. It assesses costs and health benefits using a lifetime horizon and uses a discount rate of 3.5% per annum for both costs and health benefits.

M.2.2 Model structure

The model calculates costs and QALYs for all 3 types of monitoring as a simple weighted sum of expected events and their consequences. In practice there is likely to be correlation between these outcomes but as there are no data available to account for this (and it will not affect mean outputs) we model the events independently. Figure HE001 provides a schematic depiction of the model structure.

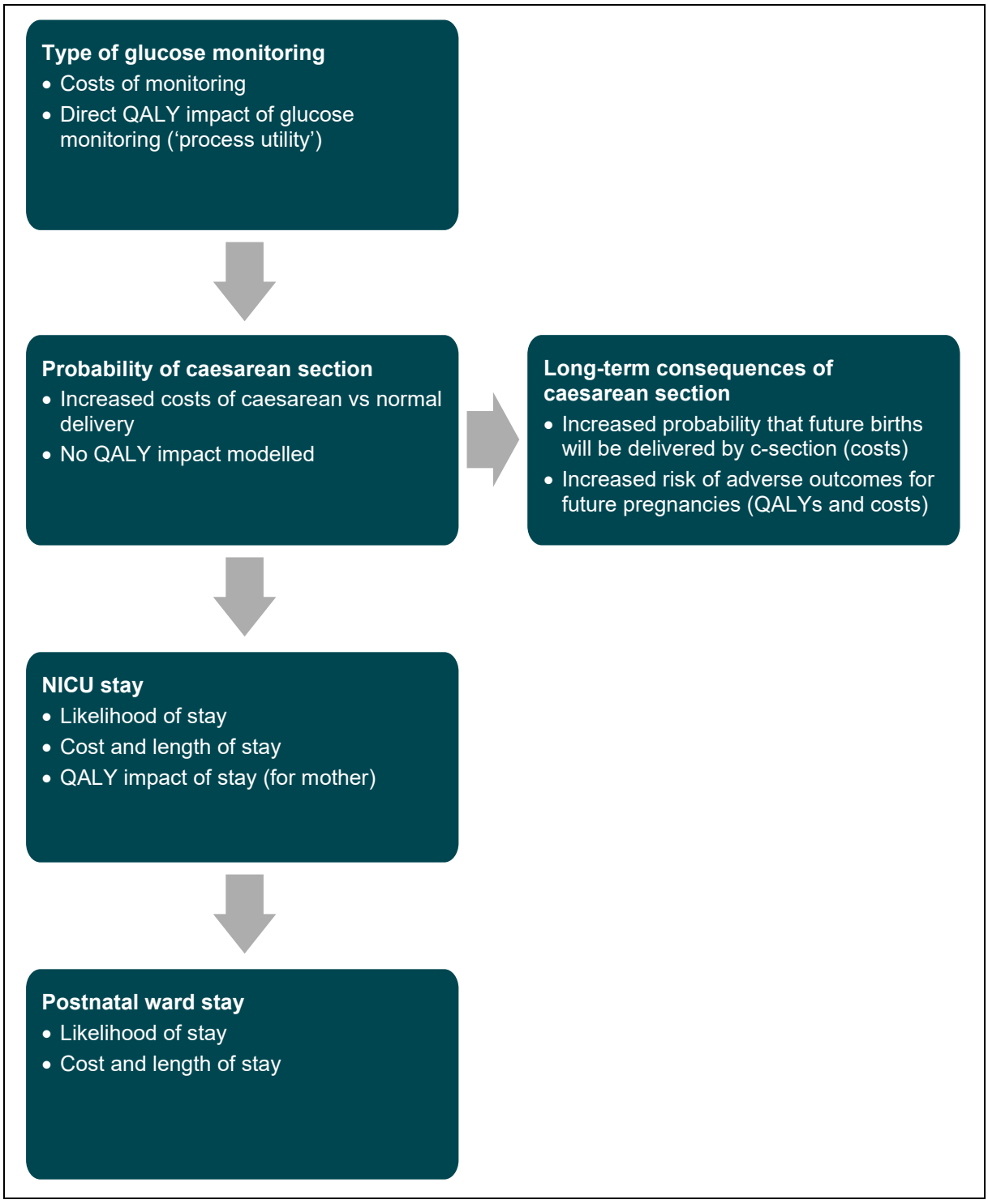


Figure HE001: Structure of original cost–utility model

This model does not rely on health states (with associated measure for quality of life). Instead of moving between predefined health states, each time an event occurs we assume the utility is additive. This method means that the results would be the same regardless of the baseline health state; therefore, none is required.

The model calculates the costs and consequences of each method of glucose monitoring. First, we calculate the expected cost of each method of blood glucose monitoring by adding the cost of the glucose monitoring device (if applicable) to the number of SMBG required for each monitoring type. Second, we calculate the likelihood of a caesarean section being required, with its corresponding costs and outcomes. Following this, the model calculates neonatal care costs and consequences, combining the likelihood, length of stay and QoL impact of neonatal intensive care unit (NICU) admission, and the cost and length of stay in a postnatal ward.

Finally, the model calculates the downstream consequences of a caesarean section (see Subappendix M.i) and adds these to the total costs and QALYs.

M.2.3 Model parameterisation

Identifying sources of parameters

With the exception of direct effectiveness evidence (glucose monitoring effects on relative caesarean risk, NICU admissions and postnatal ward stays), which came from the systematic review conducted for this research question (see below), we identified parameters through informal searches that aimed to satisfy the principle of ‘saturation’ (that is, to ‘identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis’ [Kaltenthaler et al., 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed), the Cochrane Database of Systematic Reviews and GoogleScholar.

When searching for quality of life, resource-use and cost parameters in particular, we conducted searches in specific databases designed for this purpose, the CEA (Cost-Effectiveness Analysis) Registry and the NHS Economic Evaluation Database (NHS EED) for example.

We asked the committee to identify papers of relevance. We reviewed the sources of parameters used in the published CUAs identified in our systematic review. During the review, we also retrieved articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

In cases where there was paucity of published literature for values essential to parameterise key aspects of the model, we obtained data from unpublished sources; further details are provided below.

Where data published in trials were insufficient, we requested extra data from the authors in order to reduce uncertainty in the model.

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should come from the UK population).

- All other things being equal, we preferred more powerful studies (based on sample size and/or number of events).
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.

M.2.4 Parameters

M.2.4.1 Cohort parameters

Starting demographics and characteristics

As this is a cohort model, it calculates treatment effects for pregnant women with type 1 diabetes based on a population average. While factors such as maternal age are likely to be correlated with adverse outcomes, we assume the treatment effect to be the average across the modelled population. This removes the need to model (and therefore include baseline risk factors for) high- and low-risk subgroups separately.

Baseline clinical data and natural history

We draw all baseline data from the source most accurately reflecting current practice; the committee agreed that this corresponds with SMBG. We acknowledge that, in practice, some pregnant women with type 1 diabetes will have used CGM or flash; however, we assume that – as this has historically been relatively unusual – retrospective data drawn from the whole population will be representative of women using SMBG.

We sourced the base rate for caesarean section and NICU admission from the National Pregnancy in Diabetes audit 2018 (NPID).

NICU admission is a key input in the model; the authors of included studies reported NICU admission >24 hours, with a median duration of stay (see clinical review). In order to account accurately for the total costs associated with NICU care, we needed the overall admission probability and the mean duration of stay. Therefore, we obtained additional data from the authors of Feig et al. (2017) to model postnatal ward admission rate and the expected length of stay for both NICU and the postnatal ward more accurately. We chose this paper as it is the most recent and largest RCT in the clinical review, and it also features a reasonable proportion of UK participants.

Table HE002 summarises all baseline parameters.

Table HE002: Model inputs – baseline clinical data (SMBG arm)

Parameter name	Value (95% CI)	Distribution and parameters	Source
Probability of caesarean	0.611 (0.586, 0.635)	Beta: α=910; β=580	NPID 2018
Probability of NICU admission	0.446 (0.424, 0.469)	Beta: α=850; β=1055	NPID 2018
NICU length of stay (for those admitted)	8.70 (6.11, 11.28)	Normal: μ=8.70; σ=1.32	Feig et al. (2017)[a]; SMBG arm
Probability of postnatal ward admission	0.85 (0.77, 0.91)	Beta: α=85.00; β=15.00	Feig et al. (2017)[a]; SMBG arm
Postnatal ward length of stay (for those admitted)	3.58 (2.63, 4.53)	Normal: μ=3.58; σ=0.48	Feig et al. (2017)[a]; SMBG arm

[a] *values derived from additional data provided by authors*

Mortality

The clinical review did not find any evidence of differential mortality for mothers or babies, nor any meaningful differences in surrogate predictors of death, so it is not modelled.

M.2.4.2 Treatment effects

Where possible, we took relative likelihoods from the clinical review. In all cases, we express differences relative to SMBG. For flash, this involved performing indirect comparison (Bucher et al., 1997) to join up data on the relative effectiveness of flash -v- CGM (Kristensen et al., 2019) and CGM -v- SMBG (Feig et al., 2017 and/or Secher et al., 2013). Where no data were available, we assumed that flash would have the same outcomes as CGM.

We found no evidence of differential rates of modelled outcomes between CGM devices, therefore the model assumes the effectiveness of all CGM devices is equivalent.

In some cases, we used extra data provided from Feig et al. (2017) to establish relative effects.

The clinical review presents relative effects for dichotomous outcomes as relative risks. However, it is mathematically convenient for the model to work on an odds scale; therefore, we calculated odds ratios from the same analyses, where necessary.

Table HE003 shows the relevant model inputs, with additional explanation below.

Caesarean Section

We take the relative likelihood of a caesarean section from the clinical review.

NICU stay

We take the relative likelihood of NICU admission for SMBG vs. CGM from the clinical review (using additional data requested from Feig et al. 2017). The relative likelihood for CGM vs Flash is taken from the clinical review. The former uses absolute rates obtained from the additional data whereas in the absence of additional data the latter uses the rates of NICU admission >24 hours. The additional Feig et al. (2017) data show that only 5 out of 75 NICU stays were less than 24 hours, and hence any uncertainty we introduce is likely to be small.

We calculated the mean difference in length of NICU stay using additional data provided by the authors of Feig et al. (2017). Although Kristensen et al. (2019) provide data on the likelihood of NICU admission for flash -v- CGM, they do not report on length of stay. In the absence of this information (and given the lack of any other significant differences between flash and CGM in Kristensen et al., 2019) we assume, for babies that require NICU, duration of critical care is the same for flash as that for CGM.

Postnatal ward stay

Data regarding postnatal (non-critical) ward stay was not available for Kristensen et al. (2019); therefore, the model assumes that the length and likelihood of a postnatal ward stay are the same for flash as they are for CGM.

Table HE003: Model inputs – relative effects

Parameter name	Value (95% CI)	Distribution and parameters	Source
Caesarean log-odds ratio			
CGM vs SMBG	-0.49 (-0.95, -0.04)	Normal: μ=-0.49; σ=0.23	Clinical review

Parameter name	Value (95% CI)	Distribution and parameters	Source
Flash vs SMBG	-0.75 (-1.49, -0.02)	Normal: μ=-0.75; σ=0.38	Clinical review
NICU admission log-odds ratio			
CGM vs SMBG	-0.713 (-1.313, -0.123)	Normal: μ=-0.71; σ=0.30	Feig 2017 raw data
Flash vs SMBG	-0.45 (-1.23, 0.41)	Normal: μ=-0.45; σ=0.439	Clinical review
NICU duration difference			
CGM vs SMBG	-2.70 (-5.09, -0.30)	Normal: μ=-2.70; σ=1.22	Feig 2017 raw data
Flash vs SMBG	-2.70 (-5.09, -0.30)	Normal: μ=-2.70; σ=1.22	Committee assumption
Postnatal ward log-odds ratio			
CGM vs SMBG	0.85 (-0.09, 1.80)	Normal: μ=0.85; σ=0.48	Feig 2017 raw data
Flash vs SMBG	0.85 (-0.09, 1.80)	Normal: μ=0.85; σ=0.48	Committee assumption
Postnatal ward duration difference			
CGM vs SMBG	-0.63 (-0.91, -0.36)	Normal: μ=-0.63; σ=0.14	Feig 2017 raw data
Flash vs SMBG	-0.63 (-0.91, -0.36)	Normal: μ=-0.63; σ=0.14	Committee assumption

M.2.4.3 Quality of life

This model assumes that all QALY impacts are additive; this is appropriate as events are not simultaneous and are handled independently. As a result, no baseline health state is necessary. There are 3 areas in the model where QoL is affected:

- Type of glucose monitoring
- Future consequences of mode of delivery (caesarean section -v- vaginal birth)
- NICU admission

Type of glucose monitoring

We do not model long-term morbidity (QALY effects) resulting from better or worse diabetic control during pregnancy (as there is no evidence of meaningful differences between monitoring approaches and no way of projecting the consequences of any small differences that may exist; see M.2.1). Therefore, the only utility difference modelled prenatally reflects quality of life impacts directly associated with the glucose monitoring methods themselves.

SMBG is the base treatment to which the 2 other options are compared, so it is associated with 0 incremental QALYs, in this domain. For flash, we rely on data reported by Matza et al. (2017). This study aimed to quantify the 'process utility' associated with flash monitoring compared with SMBG. In time trade-off interviews, the researchers asked general population participants in the United Kingdom (London and Edinburgh) to value health states that were drafted and refined on the basis of literature, clinician input and a pilot study. The health states had identical descriptions of diabetes and insulin treatment, differing only in glucose monitoring approach. This study showed a small but measurable utility benefit for flash.

There is no similar study available for CGM. However, there is reason to believe it is also associated with utility benefits over SMBG. Feig et al. (2017) reported higher treatment satisfaction and lower anxiety with CGM compared with intermittent monitoring. However,

these results rely on disease-specific measures that are not convertible to QALYs. In the absence of such data, the committee felt it was reasonable to assume a similar benefit to flash. Although CGM has a major potential benefit over flash of a hypoglycaemic alarm, committee members noted that, although some patients found this extremely useful, others found it intrusive. Therefore, they were content to assume equivalent gains with CGM and flash in the model's base case, and explore what difference greater or lesser impacts would have in sensitivity analysis.

Mode of delivery

NICE guidance (CG132) discusses the benefits and harms of planned caesarean section and planned vaginal birth, and specifies circumstances under which healthcare professionals should offer planned caesarean section at maternal request. Therefore, we assume that each woman's chosen mode of delivery reflects her personal preferences, and we should not use societal-level evidence to estimate any potential QALY impact of that choice.

However, if management during pregnancy leads to women experiencing the mode of delivery that does **not** reflect their preferences, we believe this is a harm that should be accounted for in our analysis. In practice, this consideration only applies to unplanned caesarean sections, as circumstances can lead women who wanted vaginal deliveries to need caesareans, whereas the reverse is improbable. Therefore, our analysis assumes that any excess of caesareans under 1 mode of diabetes monitoring versus another reflects unplanned events that do not match maternal preference, and we account for long-term QALY impact of those events only.

The particular long-term consequences we capture relate to future pregnancies: there is evidence that women who have had a caesarean section experience somewhat increased rates of miscarriage, ectopic pregnancy and stillbirth. Subappendix M.i details the derivation of the relevant QALY decrements. In addition, women who have had a caesarean section are much more likely to undergo caesareans for any future deliveries, and we account for the costs of these as well; see below.

As they all relate to future pregnancies, the long-term consequences we account for would not apply in the case of a woman who does not want any more children. To account for this scenario, we undertake a sensitivity analysis in which all long-term consequences of mode of delivery are removed.

NICU admission

We found no published information relating to the impact of neonatal intensive care. Due to the nature of the environment, the committee agreed that it did not seem appropriate to assume there is no impact on quality of life. Therefore, we have included an approximate estimate of the maternal impact of neonatal intensive care. We assume that the mother of a child in intensive care will be extremely anxious. We note that the EQ-5D utility value for an otherwise healthy person with extreme anxiety or depression is 0.414, which is 0.516 lower than the average for woman in the UK aged 25–34. This would give an annualised QALY decrement of 0.516, which equates to a loss of 0.0014 QALYs per day. The model therefore assumes that each day in NICU is associated with this level of QALY loss.

Clearly, there is a high degree of uncertainty regarding this figure. Potential underestimating factors are:

- This figure makes no attempt to quantify the QoL impact on the neonate or other family/carers,
- This figure also assumes that there is no longer-term impact (e.g. postnatal depression).

Conversely there are multiple levels of NICU severity, and many admitted neonates will not be in a critical condition, which could lead this figure to be an overestimation. Due to the uncertainty, we fitted a triangular distribution to vary this parameter in probabilistic analyses, and tested the impact in deterministic sensitivity analyses.

Table HE004: Model inputs – quality of life

Parameter name	Value (95% CI[a])	Distribution and parameters	Source
Flash glucose monitoring utility	+0.03 (+0.228, +0.372)	Normal: μ=0.03; σ=0.0037	Matza et al. (2017)
CGM utility	+0.03 (+0.228, +0.372)	Normal: μ=0.03; σ=0.0037	Committee assumption
NICU disutility (per day)	−0.001414 (−0.000308, −0.00250)	Triangular: Min=0; Mode=0.001414; Max=0.00283	Calculated
Caesarean downstream utility	−0.0233 (−0.0190, −0.0310)	Normal: μ=-0.0233; σ=0.0038	Various – see Subappendix M.i

(a) Confidence intervals represent the appropriate range from the sampling distribution specified; owing to rounding errors and distributional assumptions, these may not exactly match quoted intervals in source material

M.2.4.4 Cost and healthcare resource use

Direct costs of interventions

The existing NHS England guidance for flash glucose monitoring advises that it should be made available for 12 months. The committee agreed that it was realistic to assume that, in practice, women would continue to use the monitoring devices for a period after the delivery of their child. As a result, our base-case assumption is that the mode of monitoring simulated will last for 1 year.

We performed a scenario analysis to explore the implications of reducing the time to 7 months (to reflect the average duration in the largest RCT, Feig et al., 2017).

Monitoring device costs

We derived the cost for flash from NHS England's national arrangements (2019), which outline the cost to the NHS of flash glucose monitoring. The cost of each sensor is £35 and each lasts two weeks. The annual cost is therefore 26 x £35 = £910

For CGM, our base case assumes an annual cost of £2000. This is the ceiling price listed in the NHS England and NHS Improvement funding document (Sept 2020)

Table HE005: Model inputs – derivation of CGM device costs

	Cost	Lifespan	Annual Volume	Total Cost
NHS Annual Ceiling Price	£2000	1 year	N/A	£2000
Annual cost				£2000
7 month cost				**£1400**
The 7 month cost assumes 3 transmitters and 21 sensors are required				

Table HE006: Model inputs – annual costs of monitoring approaches

Parameter name	Value (95% CI)	Distribution and parameters	Source
Flash glucose monitoring	£910	Not varied for PSA	NHS CCG Guidelines
CGM	£2000	Not varied for PSA	NHS Improvement

SMBG costs

In the absence of a glucose monitoring device, SMBG is the sole method used to determine blood glucose levels. When a device is used, some self-monitoring will still be required.

The model estimates SMBG costs by multiplying the daily frequency of self-monitoring by the unit cost of strips and lancets (£0.26 combined). We obtained this cost from the average of all the strips and lancets reported as first-line diabetic equipment in the NHS Electronic Drug Tariff.

We did not identify any data regarding frequency of SMBG among pregnant women with type 1 diabetes. The committee provided estimates for SMBG frequency associated with all monitoring types, shown in Table HE007. We applied broad triangular distributions to reflect the level of uncertainty.

Table HE007: Model inputs – SMBG resource-use

Parameter name	Value (95% CI)	Distribution and parameters	Source
Daily self-monitoring			
SMBG	8 (6.63, 9.37)	Triangular: Min=6; Mode=8; Max=10	Committee estimate
Flash	2.5 (1.47, 3.53)	Triangular: Min=1; Mode=2.5; Max=4	Committee estimate
CGM	1 (0.32, 1.68)	Triangular: Min=0; Mode=1; Max=2	Committee estimate

Costs associated with events

The events that are associated with increased costs are:

- Type of delivery
- NICU stay
- Postnatal ward stay
- Costs of future pregnancies (as influenced by mode of delivery in the current pregnancy)

For all these costs, we used provider-level data from the 2016/2017 NHS Schedule of costs. This is the most recent year in which both excess bed days and interquartile ranges are available. We inflate the figures using the NHS cost inflation index (PSSRU 2020) to 2018/2019 values. To provide point-estimates for each category, we calculated average costs weighted by each provider's activity. In order to account for estimate dispersion for NHS reference cost parameters we use the interquartile ranges for provider-level returns.

Type of delivery

To calculate the increased cost of a caesarean section, we used costs from all codes beginning with NZ3/NZ4 (non-caesarean) and NZ5 (caesarean). SMBG is associated with higher caesarean rates and we assume the increase is associated with emergency

caesarean sections (NZ51). While some women will choose to have a caesarean section this proportion is expected to be the same between groups, meaning that any additional caesareans are likely to be unplanned. The model selects the treatment option with the lowest caesarean rate and assigns that proportion of caesareans a weighted average of codes drawn from NZ5. Any caesareans above this are assumed to be emergency and are assigned the higher cost – a weighted average of NZ51.

Critical care

To calculate the cost of a day in critical care, we used all codes beginning with XA0 except XA06Z (transport). Note that these codes estimate daily costs, instead of the episode-based costs that are more common in NHS reference costs publications.

There are multiple currency codes representing neonatal critical care, reflecting a spectrum of severity. It is not clear how these map to the level of care that the trials classify as 'intensive care'. However, the committee noted that data from Feig et al. (2017), show a range of reasons for NICU admission, ranging from relatively serious (respiratory distress) to fairly benign ('pre-term birth', without further qualification). The committee agreed that this spread was broadly reflective of the activity reported across all categories in the reference costs, so it is reasonable for this analysis to use the national average weightings for neonatal critical / special care.

Table HE008: Model inputs – costs associated with neonatal critical care

HRG Code	HRG Name	Proportion	Day cost (16/17 inflated to 18/19)
XA01Z	Neonatal Critical Care, Intensive Care	15%	£1,340
XA02Z	Neonatal Critical Care, High Dependency	17%	£929
XA03Z	Neonatal Critical Care, Special Care, without External Carer	49%	£597
XA04Z	Neonatal Critical Care, Special Care, with External Carer	14%	£432
XA05Z	Neonatal Critical Care, Normal Care	6%	£438
	Weighted average		**£729**

Postnatal ward stay

The 2018/2019 Schedule of costs does not include excess bed days, so we calculated the cost of an increased postnatal ward stay using the 2017/2018 reference costs. We used a weighted average of all XS days for codes beginning with PB (neonatal diagnoses).

Downstream caesarean costs

As a result of having a caesarean section it is likely that future costs will be incurred (primarily driven by an increased risk of future caesareans). Detail surrounding this cost is available in Subappendix M.i.

Table HE009: Model inputs – costs associated with perinatal management

Parameter name	Value (95% CI)	Distribution and parameters	Source
Caesarean Cost(£)	4400.31 (4338.27, 4462.34)	Normal: μ=4400.33; σ=32.33	16/17 Schedule of costs inflated to 18/19
Non- Caesarean(£)	2561.89 (2536.79, 2586.99)	Normal: μ=2562.33; σ=13.33	16/17 Schedule of costs inflated to 18/19

Parameter name	Value (95% CI)	Distribution and parameters	Source
Emergency Caesarean(£)	4947.42 (4851.79, 5043.06)	Normal: μ=4947.33; σ=49.33	16/17 Schedule of costs inflated to 18/19
NICU stay £ (daily)	729.56 (691.23, 767.88)	Normal: μ=730.33; σ=20.33	16/17 Schedule of costs inflated to 18/19
Postnatal ward stay £ (daily)	300.68 (283.04, 318.33)	Normal: μ=301.33; σ=9.33	16/17 Schedule of costs inflated to 18/19
Downstream caesarean costs (£)	761.9 (818.89, 707.93)	Normal: μ=762; σ=27.6	Various; see Subappendix M.i

M.2.4.5 Summary

All parameters used in the model are summarised in Table HE010, including details of the distributions and parameters used in probabilistic analysis.

Table HE010: All parameters in original cost–utility model

Parameter name	Value (95% CI[a])	Distribution and parameters	Source
Probability of caesarean	0.611 (0.586, 0.635)	Beta: α=910; β=580	NPID 2018
Probability of NICU admission	0.446 (0.424, 0.469)	Beta: α=850; β=1055	NPID 2018
NICU length of stay	8.70 (6.11, 11.28)	Normal: μ=8.70; σ=1.32	Feig et al. (2017)[a]; SMBG arm
Probability of postnatal ward admission	0.85 (0.77, 0.91)	Beta: α=85.00; β=15.00	Feig et al. (2017)[a]; SMBG arm
Postnatal ward length of stay	3.58 (2.63, 4.53)	Normal: μ=3.58; σ=0.48	Feig et al. (2017)[a]; SMBG arm
Caesarean log-odds ratio			
CGM vs SMBG	-0.49 (-0.95, -0.04)	Normal: μ=-0.49; σ=0.23	Clinical review
Flash vs SMBG	-0.75 (-1.49, -0.02)	Normal: μ=-0.75; σ=0.38	Clinical review
NICU admission log-odds ratio			
CGM vs SMBG	-0.713 (-1.313, -0.123)	Normal: μ=-0.71; σ=0.30	Feig 2017 raw data
Flash vs SMBG	-0.45 (-1.23, 0.41)	Normal: μ=-0.45; σ=0.439	Clinical review
NICU duration difference			
CGM vs SMBG	-2.70 (-5.09, -0.30)	Normal: μ=-2.70; σ=1.22	Feig 2017 raw data
Flash vs SMBG	-2.70 (-5.09, -0.30)	Normal: μ=-2.70; σ=1.22	Committee assumption
Postnatal ward log-odds ratio			
CGM vs SMBG	0.85 (-0.09, 1.80)	Normal: μ=0.85; σ=0.48	Feig 2017 raw data
Flash vs SMBG	0.85 (-0.09, 1.80)	Normal: μ=0.85; σ=0.48	Committee assumption
Postnatal ward duration difference			

Parameter name	Value (95% CI[a])	Distribution and parameters	Source
CGM vs SMBG	-0.63 (-0.91, -0.36)	Normal: μ=-0.63; σ=0.14	Feig 2017 raw data
Flash glucose monitoring utility	+0.03 (+0.228, +0.372)	Normal: μ=0.03; σ=0.0037	Matza et al. (2017)
Utility values			
CGM utility	+0.03 (+0.228, +0.372)	Normal: μ=0.03; σ=0.0037	Committee assumption
NICU disutility (per day)	−0.001414		
Caesarean downstream utility	−0.0233		
Device costs			
CGM (Dexcom g6) - Annual	£2000	Not varied for PSA	NHS ceiling price
Flash glucose monitoring - Annual	£910	Not varied for PSA	NHS CCG Guidelines
Daily self-monitoring			
SMBG	8 (6.63, 9.37)	Triangular: Min=6; Mode=8; Max=10	Committee estimate
CGM	1 (0.32, 1.68)	Triangular: Min=0; Mode=1; Max=2	Committee estimate
Flash	2.5 (1.47, 3.53)	Triangular: Min=1; Mode=2.5; Max=4	Committee estimate
Costs			
Caesarean cost	4400.31 (4338.27, 4462.34)	Normal: μ=4400.33; σ=32.33	16/17 Schedule of costs inflated to 18/19
Non-caesarean	2561.89 (2536.79, 2586.99)	Normal: μ=2562.33; σ=13.33	16/17 Schedule of costs inflated to 18/19
Emergency caesarean	4947.42 (4851.79, 5043.06)	Normal: μ=4947.33; σ=49.33	16/17 Schedule of costs inflated to 18/19
NICU stay £ (daily)	729.56 (691.23, 767.88)	Normal: μ=730.33; σ=20.33	16/17 Schedule of costs inflated to 18/19
Postnatal ward stay £ (daily)	300.68 (283.04, 318.33)	Normal: μ=301.33; σ=9.33	16/17 Schedule of costs inflated to 18/19

(a) Confidence intervals represent the appropriate range from the sampling distribution specified; owing to rounding errors and distributional assumptions, these may not exactly match quoted intervals in source material

M.2.5 Summary of key assumptions

Flash – neonatal hospital stay

Although Kristensen et al. (2019) reported NICU admissions > 24 hr, data were unavailable for length of NICU stay, likelihood of postnatal ward stay or length of postnatal ward stay.

However, because the author found no significant differences between CGM and flash, we assume neonatal hospital stay would also be equal.

Reduction in SMBG

Both flash and CGM are expected to reduce the frequency of SMBG; however, there are no empirical data in pregnant women. As a result, we asked the committee to estimate the frequency for all 3 monitoring types based on their clinical experience. We fitted triangular distributions to capture uncertainty.

CGM utility increase

No data are available for the direct impact on quality of life for CGM. As there are similarities between flash and CGM, and patients randomised to CGM in Feig et al. (2017) had increased treatment satisfaction and reduced anxiety, the committee felt it was reasonable to assume the same improvement as demonstrated for flash (Matza et al. 2017).

M.2.6 Subgroup analyses

We did not identify any subgroups of pregnant women for whom we could undertake evidence-based subgroup analysis.

M.2.7 Sensitivity analyses

M.2.7.1 Deterministic sensitivity analyses

We carried out deterministic sensitivity analysis on all parameters associated with a probability distribution.

More detailed 2-way sensitivity analyses show the level of cost or effectiveness at which treatments may become cost effective.

We performed more detailed 2-way sensitivity analysis on:

- CGM cost vs CGM utility improvement
- Flash effectiveness (caesarean section reduction vs NICU admission)

In addition, we also performed 2 scenario analyses to ascertain the impact on the model of:

- Removing the downstream impacts of caesarean section
- Reducing the monitoring time from 12 to 7 months.

M.2.7.2 Probabilistic sensitivity analyses

We configured the model to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. We specified probability distributions for all input variables except for the time for which glucose monitoring is expected and the future cost and QALY impact of caesarean section which are varied in scenario analysis. We decided the type of distribution with reference to the properties of data of that type (for example, we use beta distributions for probabilities that are bounded between 0 and 1 and we use gamma distributions for cost parameters that cannot be negative). Where possible, we parameterised each distribution using dispersion data from the source from which the value was obtained; where no such data were available, we gave consideration to applying plausible ranges based on committee advice and the usual properties of similar data.

M.3 Results

Clinical outcomes

Caesarean section and NICU ward stay are responsible for the majority of the cost and QALY differences - excluding those directly associated with the type of monitoring. Table HE011 shows the modelled base-case values for these key outcomes.

Compared with CGM and flash, SMBG is associated with higher probabilities of both caesarean and NICU admission, and a longer NICU duration. At their point-estimates, flash is associated with the lowest probability of caesarean section and CGM has the lowest NICU admission rate; however, at a 95% confidence level, the data are consistent with small advantages for either approach and no meaningful different between the 2 (see Table HE015).

Table HE011: Base-case key model outcomes

Intervention	Caesarean probability	NICU stay duration (days)	NICU admission probability)
CGM	49%	6.0	28%
Flash	43%	6.0	34%
SMBG	61%	8.7	45%

Table HE012 and Figure HE002 show disaggregated base-case costs. Delivery, monitoring and NICU are the main costs. The lowest overall cost is associated with flash glucose monitoring. In comparison, CGM has a higher monitoring cost. SMBG has the lowest monitoring costs but has the highest delivery, NICU and total cost.

Table HE012: Base-case model costs

Intervention	Monitoring		Delivery	NICU	Postnatal	Total
	Device[a]	Conventional				
CGM	£2,000	£95	£3,868	£1,239	£824	£8,026
Flash	£910	£237	£3,668	£1,484	£824	£7,123
SMBG	£0	£760	£4,251	£2,830	£914	£8,756

(a) Including all associated consumables (excluding conventional finger pricks)

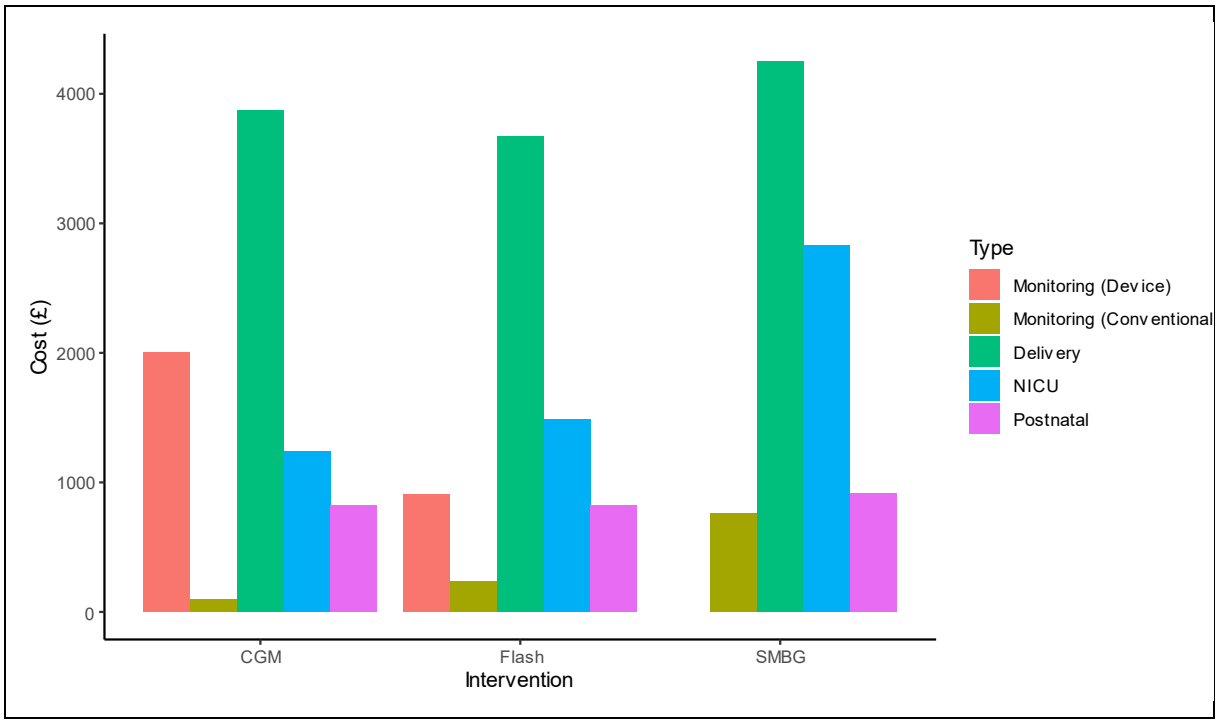


Figure HE002: Components of expected costs for each strategy

Table HE013 and Figure HE003 show the components of our base-case QALY estimates. SMBG is associated with the lowest QALYs in all 3 categories. Expected QALYs are very similar for CGM and flash; both are associated with a little under 0.04 additional QALYs, compared with SMBG – equivalent to about 2 weeks of perfect health.

Table HE013: Base-case QALYs

Intervention	Monitoring	NICU (impact on mother)	Caesarean (impact on future pregnancies)	Total
CGM	0.0300	-0.0024	-0.0114	0.0161
Flash	0.0300	-0.0029	-0.0099	0.01725
SMBG	0.0000	-0.0055	-0.0142	-0.0197

NB As caesarean section and NICU stay are associated with negative outcomes, they contribute a negative amount to the overall QALY value. Conversely, the direct utility associated with flash and CGM is modelled as a benefit above baseline (SMBG) and therefore contributes positively to the overall total.

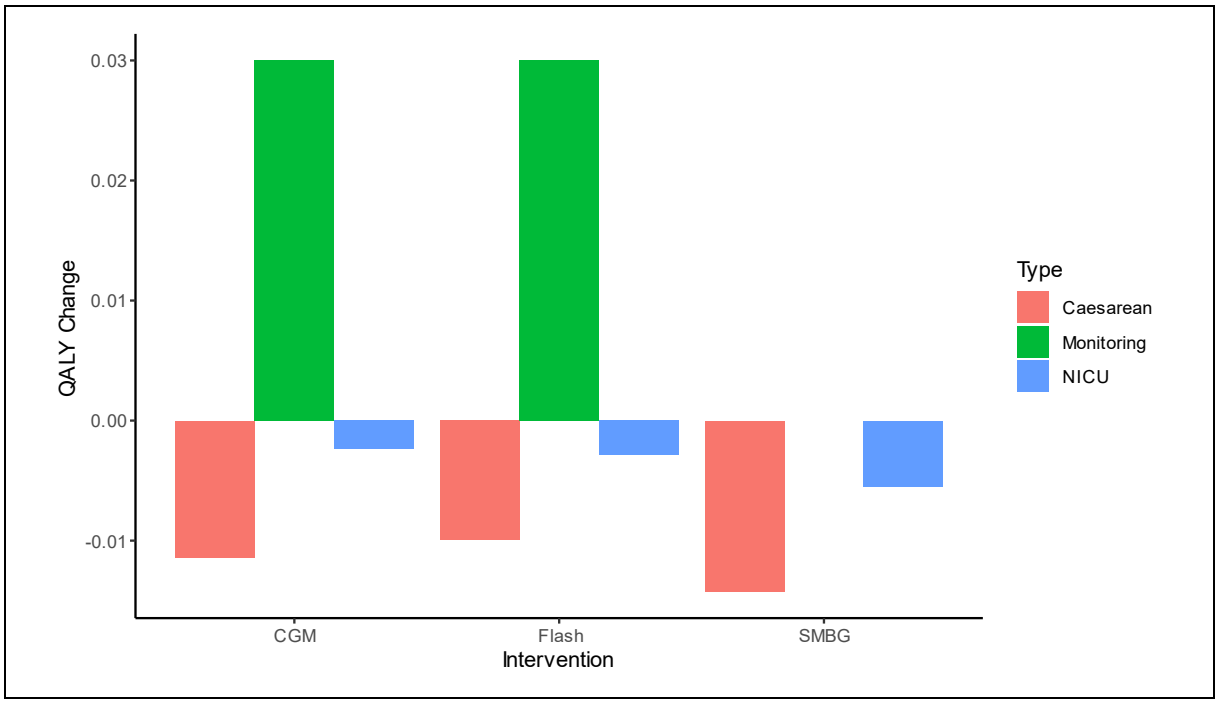


Figure HE003: Components of expected QALYs for each strategy

Base-case cost–utility results

Table HE014 shows base-case deterministic cost–utility results and Figure HE004 plots them on the cost–utility plane.

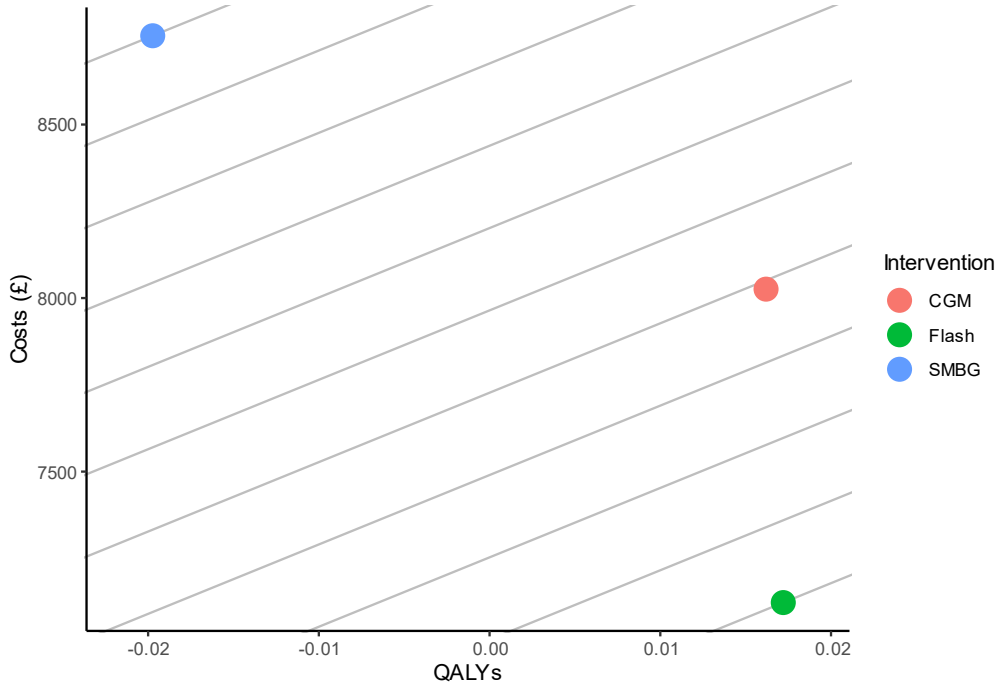
Table HE014: Base-case deterministic cost–utility results

	Absolute		Incremental			Absolute net health benefit[a]	
Strategy	Costs	QALYs[b]	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
Flash	£7,123	0.0172	-	-	-	-0.339	-0.220
CGM	£8,026	0.0162	£903	-0.0010	Dominated	-0.385	-0.251
SMBG	£8,756	-0.0197	£1,633	-0.0369	Dominated	-0.458	-0.312

(a) Higher values of absolute net health benefit (NHB) indicate better value for money (when QALYs are valued at the specified level). In this case, all values are negative, as the model only captures QALYs in domains where there are differences between treatments. Therefore, options with less negative NHB provide a better balance of costs and effects. Nothing should be inferred from the estimate for any individual option; only from the differences between options.

(b) Total QALYs may be negative as the model only captures QALYs in domains where there are differences between treatments, and some of these are expressed as QALY losses; see Table HE013.

Flash dominates both CGM and SMBG as it is both less expensive and results in the highest QALY gain (although, in the comparison with CGM, the difference is very small).



Diagonal lines represent iso–net-benefit when QALYs are valued at £20,000 each – that is, the gradient associated with an ICER of £20,000 per QALY.

Figure HE004: Base-case deterministic results – cost–utility plane

Sensitivity analysis

Probabilistic sensitivity analysis

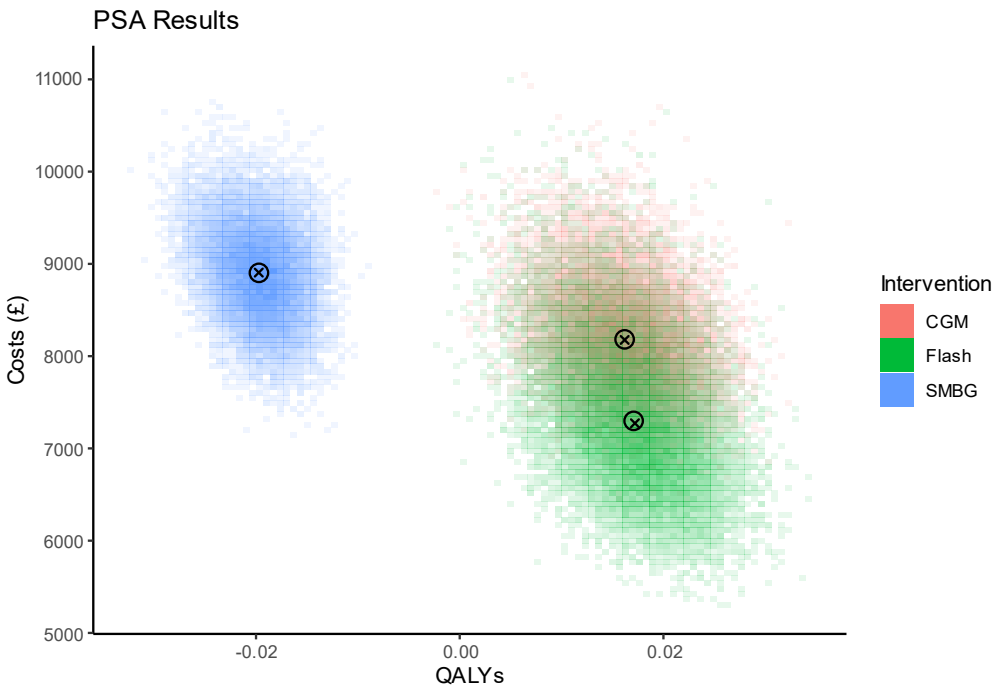
For the PSA, we ran the model 20,000 times; Table HE0015 shows the resulting event-rates and the corresponding 95% confidence intervals. Figure HE005 plots the cost–utility results.

Table HE015: Probabilistic key model outcomes

Intervention	Caesarean probability	NICU admission probability	NICU stay duration (days)[a]
CGM	49% (39%, 59%)	29% (19%, 39%)	6.00 (3.04, 8.97)[b]
Flash	43% (28%, 58%)	35% (20%, 51%)	5.99 (3.06, 8.94)[b]
SMBG	61% (59%, 63%)	45% (43%, 46%)	8.70 (6.55, 10.88)

(c) Mean value for babies requiring critical care
(d) Model inputs assumed to be the same, in the absence of specific information about flash; very small differences in output values reflect random ('Monte-Carlo') error in probabilistic model

The darker shading towards the centre of each result-cloud represents the increased density of model runs which are centred around the base-case results (indicated by the crosses at the centre of each cloud). It is obvious that there is no overlap between SMBG and the other options on the QALY axis – that is, we are certain that SMBG is the least effective approach. CGM and flash have an almost identical horizontal spread, suggesting that they about as effective as each other. However, there is a clear difference between the 2 clouds on the vertical axis, reflecting a fair degree of confidence that CGM is more expensive than flash.

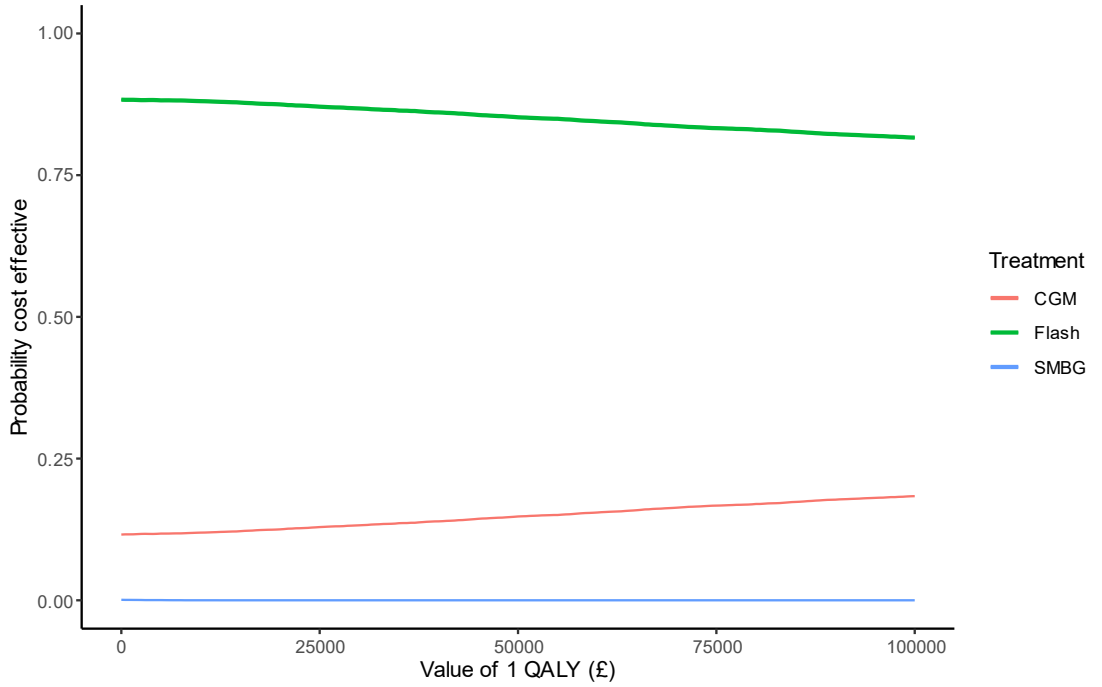


The mean PSA results are denoted by an 'X', and the deterministic base-case results are represented by an 'O'. For all treatments there is a negligible difference between them.

Figure HE005: Probabilistic cost–utility scatterplot

Figure HE006 shows the cost-effectiveness acceptability curve. Flash is associated with by far the highest likelihood of being cost effective regardless of the value that is ascribed to QALYs. When QALYs are valued at £20,000 each, CGM has a 12.5% chance of being optimal; this rises to 13.2% at £30,000. Even if QALYs are valued at £100,000 each, CGM would only have an 18% chance of offering best value for money.

For all QALY values, SMBG is associated with a 0% chance of offering best value for money.



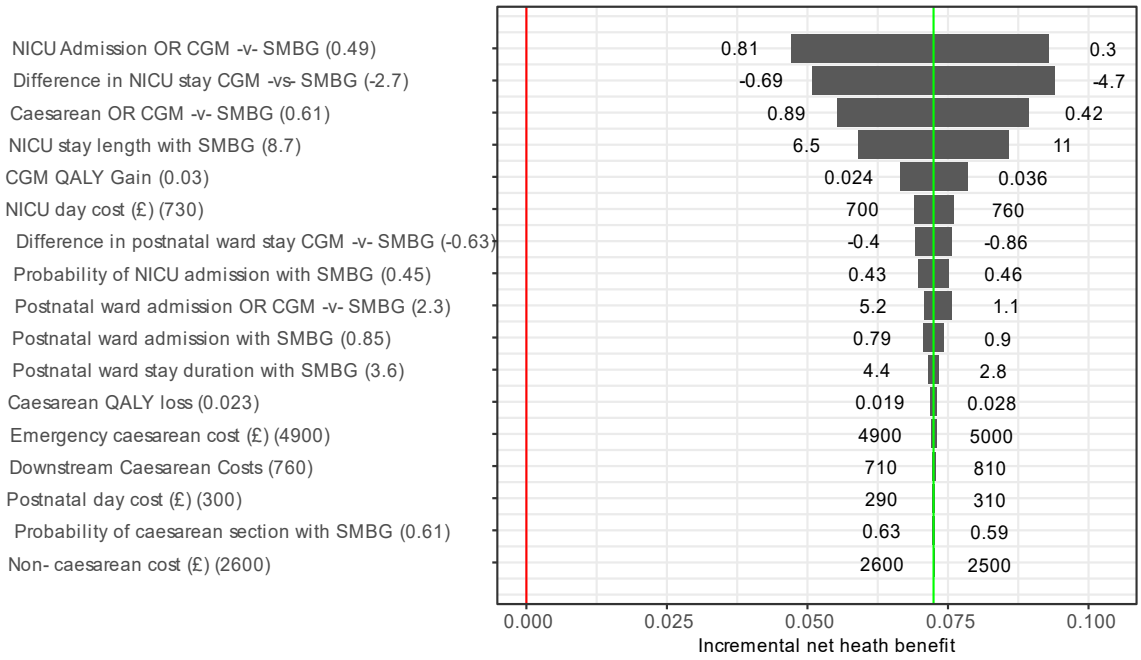
The bold line shows the cost-effectiveness acceptability frontier (CEAF).

Figure HE006: Cost-effectiveness acceptability curve

Deterministic sensitivity analysis

CGM compared with SMBG

Figure HE007 shows one-way sensitivity analyses for CGM compared with SMBG. No bars cross the INHB=0 line, suggesting that, if flash is removed from the decision space, CGM would be very likely to be associated with an ICER of £20,000 QALY or better compared with SMBG.

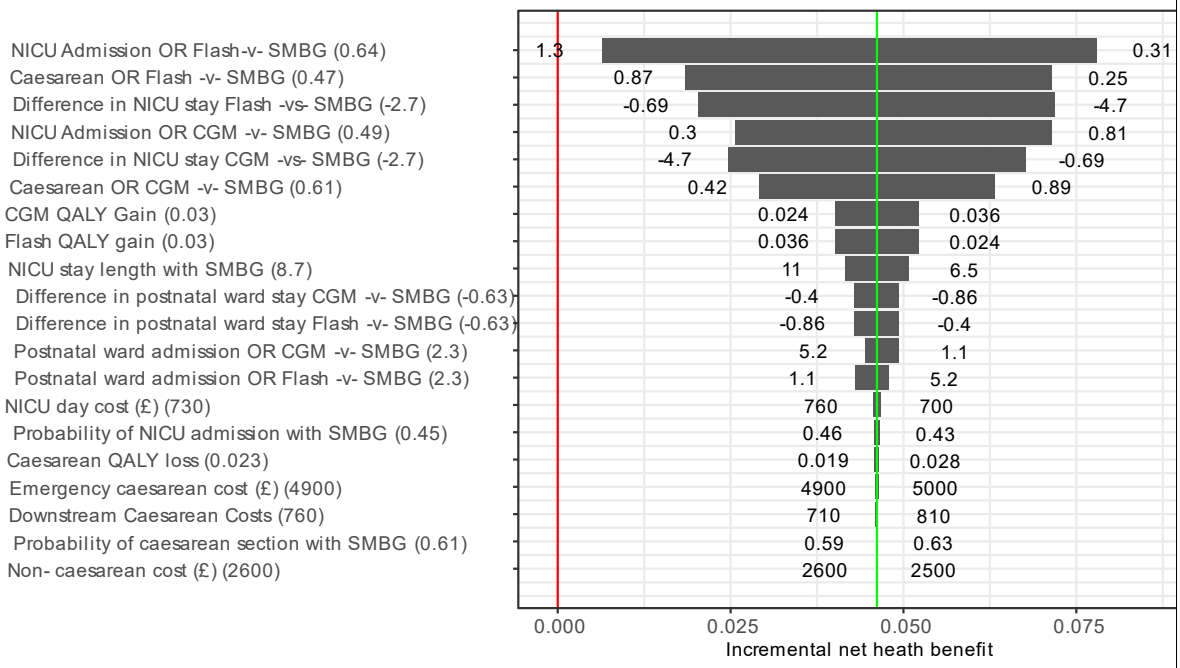


Bars show incremental net health benefit (assuming QALYs are valued at £20,000 each) when the parameter is varied to the values shown adjacent to the ends of the bar. The range tested usually reflects the parameter's 95% confidence limits. Positive values indicate CGM has greater net benefit than SMBG – that is, it would be associated with an ICER of £20,000/QALY or better compared with SMBG. For SMBG to be considered better value for money than CGM, the bar would have to cross the red line at INHB=0. Base-case parameter values are shown in parentheses at end of parameter names.

Figure HE007: One-way sensitivity analysis – CGM -v- SMBG

Flash compared with CGM

Figure HE008 shows one-way sensitivity analyses for flash compared with CGM. None of the extreme values tested resulted in model outputs that crossed the INHB=0 line (shown in red). This suggests that CGM is unlikely to be associated with an ICER of better than £20,000 per QALY compared with flash.



Bars show incremental net health benefit (assuming QALYs are valued at £20,000 each) when the parameter is varied to the values shown adjacent to the ends of the bar. The range tested usually reflects the parameter's 95% confidence limits. Positive values indicate flash has greater net benefit than CGM – that is, it would be associated with an ICER of £20,000/QALY or better compared with CGM. For CGM to be considered better value for money than flash, the bar would have to cross the red line at INHB=0. Base-case parameter values are shown in parentheses at end of parameter names.

Figure HE008: One-way sensitivity analysis – flash -v- CGM

CGM cost and QALY impact

As noted in M.2.4.3, we assume in our base case that the direct quality of life improvement for pregnant women using CGM, compared with SMBG, is identical to the benefit that was established in a study comparing flash with SMBG (Matza et al., 2017). Furthermore, the cost of CGM is an NHS Improvement ceiling price. The committee's view was that there was a high degree of uncertainty regarding the cost of CGM as the market is constantly evolving. As a result, we carry out two CGM cost-specific analyses over a wide range of possible values

Figure 009 shows the incremental net health benefit of CGM compared with Flash with annual CGM cost values ranging between £600 and £3000. There is a critical point at which the net health benefit of both lines is equal to 0. This occurs at approximately £1000. Below this value CGM could be associated with a positive net health benefit. As the difference in QALYs is both small and uncertain, cost is the main driver of the net health benefit.

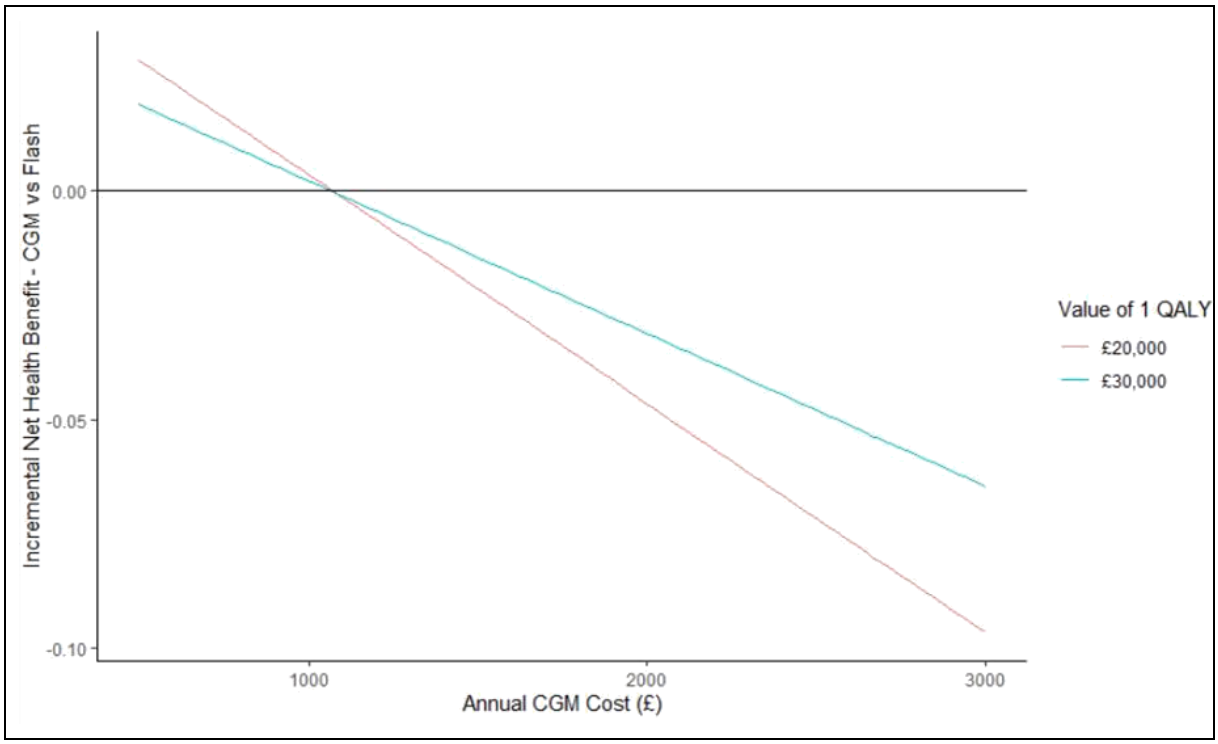
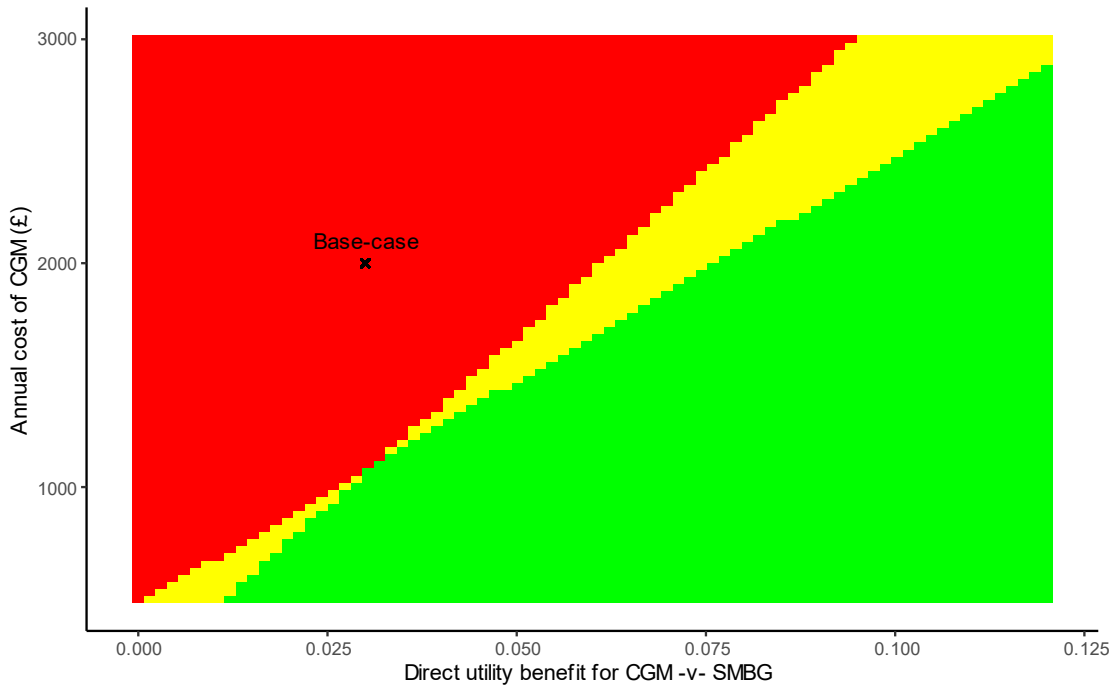


Figure HE009: CGM cost sensitivity analysis

In the literature no CGM specific process-utility value was found and hence the same value as flash was used (0.03). We therefore carried out a 2-way sensitivity analysis, varying both parameters over a broad range for CGM (compared with flash, which is held at its base cost and quality-of-life change). Figure HE010 provides results.

The green and red areas meet at a point around (0.03, £1000). This represents the critical point where flash and CGM are equal in cost and effectiveness. The model assumes 1.5 more finger pricks per day with flash compared with CGM. This means that the critical point is at a slightly higher cost than flash (£910)



Key:
** Red area: ICER for CGM compared with flash is £30,000 per QALY or worse.*
** Yellow area: ICER for CGM compared with flash is worse than £20,000 but better than £30,000 per QALY.*
** Green area: ICER for CGM compared with flash is £20,000 per QALY or better.*

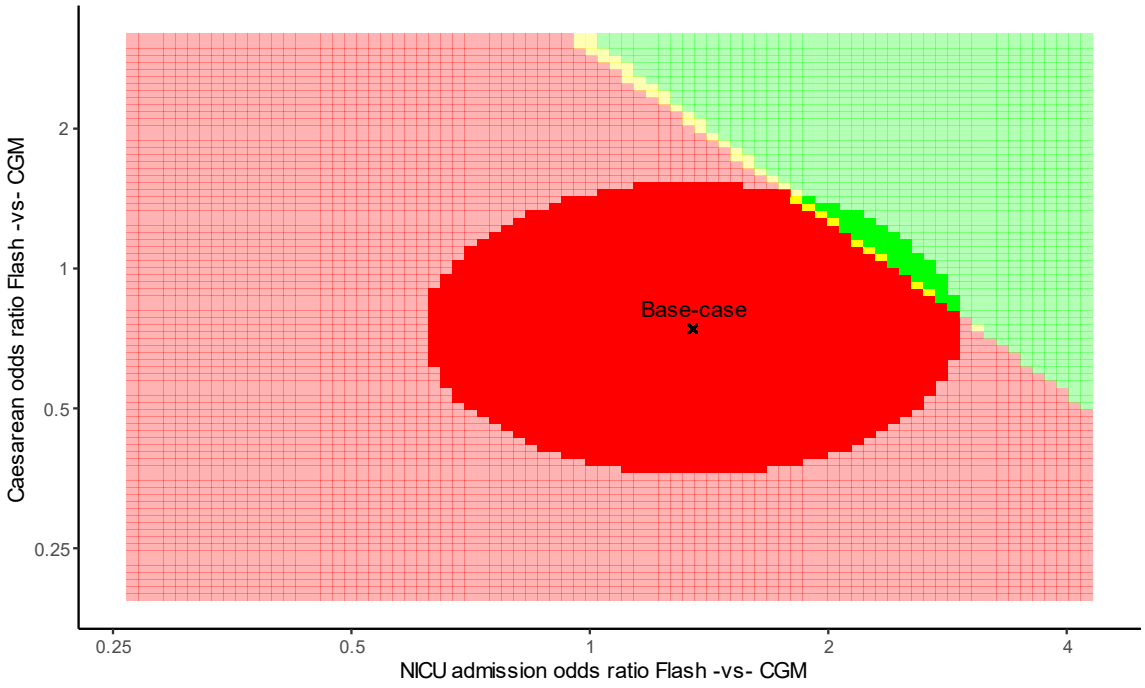
Figure HE010: Two-way sensitivity analysis – cost and direct QoL benefit of CGM, impact on comparison between flash and CGM

In order to be associated with an ICER of £20,000 / QALY or better, the cost of a CGM device would have to reduce significantly and the quality of life associated with using it would need to rise substantially. Figure HE010 shows that, if its cost were to reduce by £500, the quality of life benefit for CGM compared with SMBG would need to be almost twice the level seen for flash glucose monitoring. If the cost differential were to remain the same, the direct utility benefit of CGM would need to be around 2 times greater than that observed with flash.

Flash effectiveness

Effectiveness data for flash are drawn from a single observational study that did not attempt to control for any factors that might confound or obscure differences between treatments (Kristensen et al. 2019). Therefore, we have less confidence in the outcomes than we would in those from a similar RCT. To address this uncertainty, we explore the effect of changing NICU admission rates and caesarean rates as a result of flash glucose monitoring in a 2-way sensitivity analysis. A 95% confidence ellipse is plotted to give an indication of which results could be considered likely given the underlying data. While this does not address any potential concerns of bias in the observational study, it gives a useful indication of a reasonable range through which to vary the parameters.

It is important to note that the NICU stay length is assumed to be the same for flash and CGM in this two-way analysis.

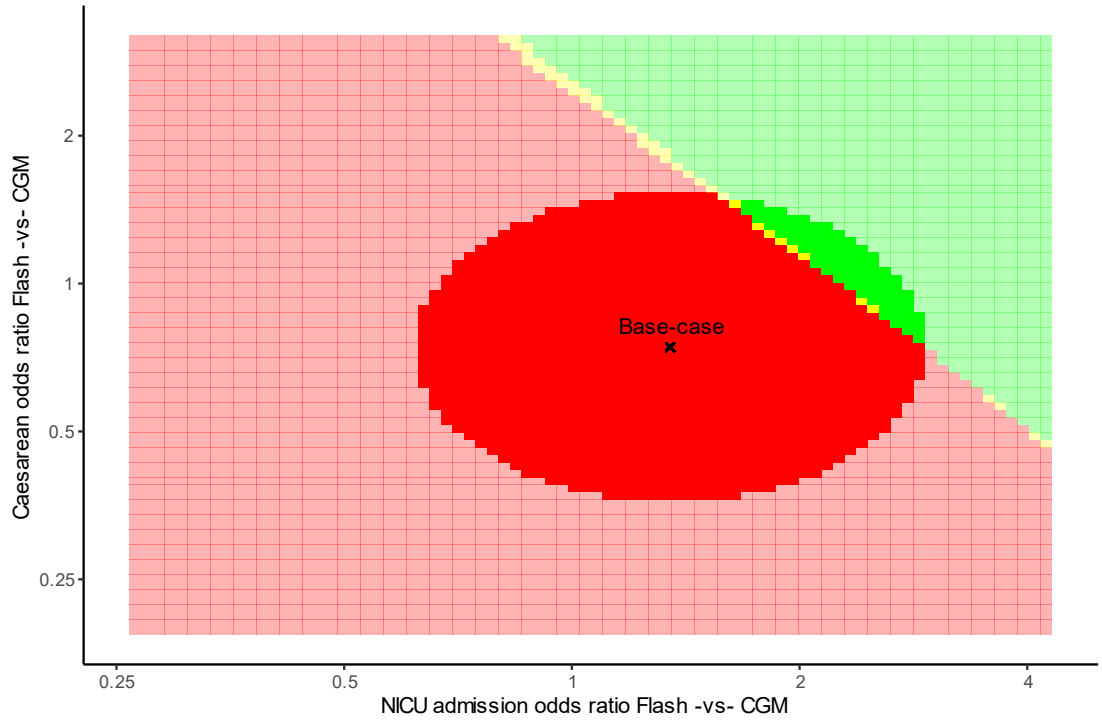


Key:
** Red area: ICER for CGM compared with flash is £30,000 per QALY or worse.*
** Yellow area: ICER for CGM compared with flash is worse than £20,000 but better than £30,000 per QALY.*
** Green area: ICER for CGM compared with flash is £20,000 per QALY or better.*
The shaded area represents the 95% confidence ellipse associated with the 2 flash effectiveness parameters, assuming independence between the 2.

Figure HE11 HE011: Two-way sensitivity analysis – effectiveness of flash compared with CGM in 2 key areas: probability of caesarean and probability of admission to NICU

Figure HE11 shows that CGM is highly likely to be associated with an ICER of £30,000 or worse (shown in red). No values with the 95% confidence ellipse are associated with an ICER of £30,000 or better.

Figure HE012 demonstrates the effect of using a lower cost for CGM of £1908 as detailed in scenario 3 in section 3.3.3 .



Key:
** Red area: ICER for CGM compared with flash is £30,000 per QALY or worse.*
** Yellow area: ICER for CGM compared with flash is worse than £20,000 but better than £30,000 per QALY.*
** Green area: ICER for CGM compared with flash is £20,000 per QALY or better.*
The shaded area represents the 95% confidence ellipse associated with the 2 flash effectiveness parameters, assuming independence between the 2.

Figure HE12 HE012: Two-way sensitivity analysis – effectiveness of flash compared with CGM in 2 key areas: probability of caesarean and probability of admission to NICU using a lower cost for CGM

Figure HE12 shows that CGM is highly likely to be associated with an ICER of £30,000 or worse (shown in red). Some values within the 95% confidence ellipse are associated with an ICER of £20,000 or better (shown in green) however it is important to note that the majority of green shaded area would assume that the NICU admission odds ratios associated with flash is higher than that associated with SMBG (2.01).

Scenario analysis

Length of glucose monitoring

The existing NHS England guidance for flash glucose monitoring advises that it should be made available for 12 months. The committee agreed that this was a reasonable time for glucose monitoring to be offered as there would be practical difficulties associated with discontinuing a glucose monitoring device soon after a woman has given birth.

In order to test the impact of a shorter modelling period, the model was re-run with a monitoring period of 7 months; this was the mean monitoring duration in Feig et al. (2017; see Table HE016). This scenario reduces the monitoring costs for all options, but CGM remains more expensive than flash with marginally fewer QALYs.

Table HE016: Scenario analysis – glucose monitoring for 7 months

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
Flash	£6,733	0.005	-	-	-	-0.332	-0.219
CGM	£7,153	0.004	£508	-0.0010	Dominated	-0.354	-0.235
SMBG	£8,565	-0.019	£1,832	-0.0241	Dominated	-0.447	-0.305

Future impact of caesarean section

The base-case model incorporates consequences of caesarean sections in terms of increased future costs (mostly driven by the increased likelihood of future caesareans) and QALY impact (driven by the increased risk of stillbirth). This scenario is appropriate for women who have an average expectation of future pregnancies.

All other costs and QALYs in the model occur within a single year, and so a scenario was re-run excluding all downstream costs and consequences. This removes uncertainty regarding future discounted values, and would be appropriate for any decision where there is reasonable certainty that the woman is not going to have any more babies.

As shown in Table HE017, SMBG remains dominated in this scenario. However, because flash no longer gains QALY benefits from its numerically lower rate of caesareans, CGM becomes the most effective option by a very small margin (0.0004 QALYs – equivalent to 3 hours of perfect health). However, this tiny benefit remains associated with a substantial incremental cost, compared with flash, leading to an extremely high ICER of £3.6 million per QALY.

Table HE017: Scenario analysis – No downstream caesarean impact

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
Flash	£6,797	0.027	-	-	-	-0.312	-0.199
CGM	£7,653	0.028	£855	0.0005	£1,802,677	-0.355	-0.228
SMBG	£8,288	-0.005	£1,491	-0.0323	Dominated	-0.419	-0.281

Lower CGM Cost

The base-case analysis uses the NHS Improvement ceiling price which is detailed in Table HE005. It is currently possible for individuals to obtain CGM for a reduced price of £159 per month for a year (Dexcom g6)

Despite this reduction in cost CGM remains more expensive than flash with no change in QALYs from the base case.

Table HE018: Scenario analysis – reduced cost of CGM

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
Flash	£7,211	0.018	-	-	-	-0.343	-0.223
CGM	£8,036	0.017	£825	-0.0011	Dominated	-0.385	-0.251
SMBG	£8,882	-0.019	£1,671	-0.0366	Dominated	-0.463	-0.315

Conclusions

In the base-case analysis, flash glucose monitoring is associated with the lowest costs and the highest QALYs. Flash dominates both SMBG and CGM. If QALYs are valued at £30,000 each or lower, CGM has no more than a 13% chance of offering the highest net health benefit.

Evidence for flash effectiveness was taken from an observational study (Kristensen et al. 2019) which is a source of uncertainty. The odds of caesarean section and NICU admission with flash would have to be more than double that found in the study for CGM to be a better use of NHS resources. The committee believed that this it was plausible based on their expertise and clinical evidence that flash offers no benefit over SMBG, and that neonatal outcomes are linked to time in range which is higher with CGM compared with flash. While there was no evidence of differences in hypoglycaemic events between any treatment options the committee strongly felt that CGM would lead to improved outcomes due to being the only glucose monitoring method to offer the combination of real time monitoring and alarms.

M.4 Discussion

Principal findings

The model found flash glucose monitoring to be the cost-effective option in all scenarios and throughout all reasonable ranges in deterministic sensitivity analyses.

Despite having the lowest monitoring cost, SMBG is associated with the highest overall cost. NICU admission costs are the main driver of the increased non-monitoring cost. SMBG is also associated with the lowest QALY value, primarily because, unlike flash and CGM, there is no direct quality of life gain associated with the approach itself.

Flash glucose monitoring dominates CGM in the base-case analysis, and the PSA shows that it has a 87% chance of being the optimal option when QALYs are valued at £20–30,000 each. This result is almost entirely driven by the conspicuously higher costs associated with CGM compared with flash, given the absence of significant differences in outcomes between the 2 (Kristensen et al. 2019). Although the latter is based on low-quality evidence, and the true magnitude of differences is unknown, our analysis shows that they would have to be very substantial before CGM would justify its extra outlay, assuming QALYs are valued at usual levels.

If we remove flash from the decision space, then CGM is highly likely to be cost effective compared with SMBG.

Strengths of the analysis

This is the first cost–utility analysis of continuous glucose monitoring in pregnancy. We use high-quality evidence from a formal literature review and QALY measures specific to the decision-problem and explore all outcomes the committee considered relevant.

This model uses accurate UK-specific costing data which ensure that the results are highly relevant to for glucose monitoring in the UK.

By modelling the long-term impact of caesarean section on both costs and QALYs along with incorporating the QALY impact of NICU admissions, the model captures a broad range of costs and QALYs associated with glucose monitoring in pregnancy.

Sensitivity analysis is carried out for:

- Cost of CGM
- Effectiveness of CGM
- Effectiveness of Flash

, in addition to specified scenario analyses. The broad scope of the sensitivity analyses gives confidence in the results across all key parameters

Limitations of the analysis

A key weakness is the use of data to compare flash and CGM from the Swedish observational study (Kristensen et al. 2019). In order to account for this, we carry out 2-way sensitivity analysis to examine the level of true (in)effectiveness associated with flash which would lead to CGM presenting the better balance of costs and benefits.

While there were data available to show the increased QALYs associated with using flash there was no such study available for CGM. We carried out sensitivity analysis to establish how many times larger the QALY improvement would need to be for CGM to be preferred to flash and found it to be 4 times higher.

The analysis made no attempt to account for the benefits for the mother of improved glycaemic control. This choice was driven by the absence of meaningful HbA_{1c} differences in any study. There was some evidence that CGM results in less time spent below target than flash (Kristensen et al. 2019). In theory, this may have benefits including reduced hypoglycaemic events; however, no such benefit was observed in the study.

The model does not account for potential differences in effectiveness between CGM devices. The evidence comparing CGM with flash uses a different device to that comparing CGM with SMBG and it is possible that the devices are not clinically equivalent. As there is no evidence comparing CGM devices on the modelled outcomes, we have no alternative but to assume equivalence.

Comparison with other CUAs

We did not find any existing CUAs. However, we identified 2 studies comparing costs of CGM and SMBG. These did not include QALY measures, so we did not include them in the formal economic evidence review; however, they provide a potential point of validation for some of our findings.

Welsh HTA

The analysis found that CGM was cost-saving vs. SMBG (£5,129 vs £6,158). Despite being based on the same key study (Feig et al. 2017), there are some key differences between this analysis and our own.

The Welsh HTA estimates the (base-case) cost of NICU as £1,105 per day, compared with £808 in our economic analysis. The difference is due to the fact that the Welsh HTA uses the weighted average of the highest 2 categories of NICU. Our committee agreed it is more appropriate to take a weighted average of all types of critical/special care, noting the high prevalence of NICU admissions in Feig et al. (2017) for less severe reasons (e.g. neonatal hypoglycaemia, pre-term birth). The Welsh HTA conducted robust sensitivity analysis on this key variable and found that a NICU cost of £622 would mean that the 2 treatment costs were equal.

The second major difference is the length of time for which the analyses assume the glucose monitoring device is used. The Welsh HTA uses 28 weeks to reflect the length of the trials.

Our committee felt that it would not be practical to discontinue a monitoring device soon after birth and that 1 year would be more appropriate. By using 28 weeks the total cost difference between SMBG and CGM is reduced. The authors did not explore this in sensitivity analysis.

There was limited analysis of the cost of flash glucose monitoring. A scenario assuming flash has clinical and cost equivalence of SMBG 8 times a day showed that CGM would be cost saving. This scenario did not use the results of the available observational study which found no significant differences in outcomes between CGM and flash.

Feig et al. (2019)

This cost-minimisation analysis examines NICU, delivery complications and postnatal ward stay alongside the monitoring costs. It found that CGM is associated with significant cost savings.

The daily NICU stay cost in this study was £3,743. The derivation of this number is unclear: it is over double the highest level of neonatal critical care (£1,516) in the NHS reference costs and over 4 times the cost used in our analysis (£808). Although the authors tested this parameter in sensitivity analysis, the minimum value used was £2,400, which is still far higher than any known NHS cost. This makes it difficult to draw meaningful comparisons between this study and our own.

M.5 References

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NHS schedule of costs 16/17 - https://improvement.nhs.uk/resources/reference-costs/
ONS Childbearing data - https://www.ons.gov.uk/generator?uri=/peoplepopulationandcommunity/birthsdeathsandmarriages/conceptionandfertilityrates/bulletins/childbearingforwomenbornindifferentyearsenglandandwales/2018/3858a112&format=csv

Subappendix M.i: Consequences of caesarean section

Introduction

A caesarean section is associated with increased risks during future pregnancy: ectopic pregnancy, miscarriage and stillbirth. It is also associated with an increased likelihood of having another caesarean section.

Events

Using ONS childbearing data, we calculate that 55% of live deliveries will have at least 1 subsequent live delivery. The mean number of expected future live deliveries, among women who have at least 1 more child, is 1.46. 14.3% of pregnancies will not result in a live birth post-caesarean (HE025); therefore 1.704 pregnancies would occur to produce 1.46 live births.

In order to discount the costs of future pregnancies appropriately we also need to understand the expected length of time between pregnancies. ONS birth interval figures shown that the median birth interval is 35 months.

Table HE019: Expected future births

Expected future deliveries	Proportion of women	Median birth interval	Proportion of future births
1	100%	35	68%
2	36%	70	25%
3	10%	105	7%

By combining this with the number of future expected births (if>0), we can estimate the mean birth interval until a future delivery as:

35 × 0.68 + 70 × 0.25 + 105 × 0.07 = 48.5 months

This is equal to 4.04 years.

Consequences of caesarean section for future pregnancies – additional caesareans

The clearest consequence of a caesarean section is that it substantially raises the chances that any future babies the mother has will also be delivered by caesarean. Data from the NHS Maternity Audit (2019) show that the rate of vaginal birth after caesarean (VBAC) is 24.9%; we use the complement of this value directly to estimate the probability of caesarean in all future births for women whose current baby is delivered by caesarean section. However, to quantify how much a caesarean in the current birth raises this probability, we also need to know what the probability of caesarean would have been if the current baby had not been delivered by caesarean section. We approximate this figure using data from NHS maternity statistics. We multiply the proportion of women who did not have a VBAC by the proportion of women who had a caesarean for their first delivery: 0.749 × 0.306 = 22.9%. We then assume that the remaining caesareans came from mothers who did not have a caesarean for their first child; see Table HE020.

Table HE020: Mode of delivery for subsequent pregnancies

Type	Value	Source / derivation
VBAC (a)	25.1% (12,449/49,542)	Maternity Audit 2019 (England)
Primiparous caesareans (b)	30.6% (46,839/153,279)	NHS maternity statistics (2018–19)
Multiparous caesareans (c)	30.3% (39,240/129,364)	NHS maternity statistics (2018–19)
As proportion of multiparous births		
Caesarean after caesarean (d)	22.9%	b × (1−a)
Caesarean after non-caesarean (e)	7.5%	c−d
Non-caesarean after caesarean	7.7%	b × a
Non-caesarean after non-caesarean	62.0%	(1−b)−e
Probabilities		
Caesarean given prior caesarean	0.749	1−a
Caesarean given no prior caesarean	0.107	(c−d) / (1−b)

Consequences of caesarean section for future pregnancies – adverse outcomes

The model also uses evidence that women who have had a caesarean section are at higher risk of ectopic pregnancy, miscarriage or stillbirth in future pregnancies, based on a published meta-analysis (Keag et al. 2018).

The model applies these relative effects to estimates of absolute risk of each event drawn from the literature:

- 1.1% for ectopic pregnancy; following NICE NG126, we draw this estimate from a 3-year review of adverse pregnancy events in Britain and Ireland (Lewis et al. 2007).
- 12.8% for miscarriage, based on a large, recent cohort study from Norway (Magnus et al., 2019).
- 4.1 stillbirths per 1,000 total births in England, based on ONS 2017 data.

However, each of these absolute risks represents a mixture of women who have not undergone a previous caesarean section and those who have. We need to adjust for this to arrive at a best estimate of event-rates with and without the exposure. We do this using 3 pieces of information: the observed probability in all women (which we convert to odds), the odds ratio for exposed -v- unexposed, and an estimate of the proportion of women who have the exposure. From the NHS maternity statistics 2018–19, we estimate that approximately one-fifth of pregnant women have a history of caesarean section (82,949 ÷ 426,698 = 19.4%; 82,949 = [421,552 births − 153,279 to exclude primiparous] × 0.306 [b in Table HE020]).

Using these 3 values, we note that the observed odds of experiencing the event (o_{all}) are a combination of the odds with the exposure (o_{CS}) and odds without the exposure (o_{noCS}) weighted according to the probability of exposure (p_{CS}):

$$o_{all} = o_{CS}p_{CS} + o_{noCS}(1 - p_{CS}) \quad \textbf{(1)}$$

And the relation between the exposed and unexposed odds is defined by our odds ratio ($OR_{CS\text{-}v\text{-}noCS}$):

$$o_{CS} = o_{noCS}OR_{CS\text{-}v\text{-}noCS} \quad \textbf{(2)}$$

These 2 expressions may be treated as simultaneous equations and rearranged as:

$$o_{noCS} = \frac{o_{all}}{(1 - p_{CS}) + p_{CS} OR_{CS\text{-}v\text{-}noCS}} \quad (3)$$

Once we have a result for the unexposed, we plug it into equation (2) to estimate odds in the exposed. Finally, we convert the resulting odds to probabilities. The results of these calculations are shown in Table HE021.

Table HE021: Future pregnancy events

Event	Baseline probability	Source	Odds ratio prev. caesarean -v- none (95%CI)	Source	Probability according to prev. caesarean	
					No	Yes
Miscarriage	12.8% (53,906 / 421,201)	Magnus et al. (2019)	1.21 (1.04 to 1.40)	Keag et al. (2018)	12.4%	14.6%
Ectopic	1.1% (32,100 / 2,891,892)	Lewis et al. (2007)	1.17 (1.03 to 1.32)	Keag et al. (2018)	1.07%	1.26%
Stillbirth	0.41% (2,689 / 659,765)	ONS 2018	1.27 (1.15 to 1.40)	Keag et al. (2018)	0.39%	0.49%

Quality of life

The model assumes caesarean delivery is associated with a negative impact on QALYs from an increased risk of ectopic pregnancy, miscarriage and stillbirth in future pregnancies.

The model assumes miscarriage is associated with an absolute decrement of 0.1 QALYs. This replicates the assumption used in NICE's guideline on ectopic pregnancy and miscarriage (NG126). However, it should be noted that there is no empirical basis to the value; rather, it was used as a starting-point for a range of sensitivity analyses in the absence of an evidence-based parameter. Similarly, we did not identify a suitable source for utility decrement of ectopic pregnancy, so we assume it has the same QALY impact as miscarriage, and test a broad range of values in sensitivity analysis.

For each stillbirth, the model subtracts an expected lifetime's discounted QALYs to reflect the loss of a life (25.08 QALYs when discounted at 3.5% per year). While we acknowledge that this event will also have a profound impact on the child's parents, we did not identify any suitable sources to help us quantify this effect. In discussion with the committee, we agreed that any attempt to approximate the true impact would be inadequate, and it is better simply to note this as a limitation of our analysis.

Cost and healthcare resource use

Miscarriage

Our approach to estimating the costs of miscarriage is substantially based on the methods used by the National Guideline Alliance (NGA) in work commissioned by the Human Fertilisation and Embryology Authority and others (2018). We calculate the average cost of a miscarriage requiring hospital care (Table HE022) and apply that to the proportion of events that receive that level of care. Here, we diverge from the NGA's estimate. They assume only 20% of miscarriages fall into this category, based on a suggestion that there are up to 250,000 miscarriages per year in the UK, compared with around 50,000 episodes in the NHS Reference Costs. We agree that a little under 50,000 episodes is a reasonable numerator (see Table HE022); however, we believe that, for our purposes, 250,000 is an overestimate of the total number of events we should account for. This is partially because it relates to the whole of the UK (whereas NHS reference costs cover England alone). Moreover, while we

do not doubt that it may be an accurate estimate of the total number of miscarriages per year including those that do not come to the attention of medical services or even the woman herself, we need to estimate those incurring medical costs. Evidence used elsewhere in our analysis suggests that 12.8% of pregnancies result in miscarriage that is recorded in medical records (Magnus et al., 2019; see 0). Applying this proportion to the number of live births in England (603,766 in 2018/19) suggests that we would expect around 90,000 medically recorded miscarriages. Therefore, to avoid the appearance of spurious precision, we make the simple assumption that half of miscarriages coming to medical attention require hospital care. We then adopt the NGA's assumption that all miscarriages require an average of 1 GP appointment (costed at £39.23 each, per the Unit Costs of Health and Social Care, 2019). This gives us a final estimate of £666.47 × 0.5 + £39.23 = £372.47 per simulated event.

Table HE022: Unit costs for miscarriages requiring hospital treatment

Categories and codes	Submissions	Episodes	Mean (SE[a])
Nonelective			
MB08A	203	1,025	£2,034.51 (£55.34)
MB08B	363	3,495	£1,641.42 (£25.77)
Nonelective excess bed-days			
MB08A	27	274	£427.27 (£11.37)
MB08B	208	1,480	£607.04 (£13.87)
Nonelective total			
MB08A			£2,148.72
MB08B			£1,898.48
Elective			
MB08A	29	38	£2,082.31 (£262.98)
MB08B	114	882	£1,011.10 (£70.68)
Elective excess bed-days			
MB08A	3	8	£279.47 (£0.00[b])
MB08B	9	41	£157.45 (£19.21)
Elective total			
MB08A			£2,141.15
MB08B			£1,018.42
Nonelective short-stay			
MB08A	156	317	£859.99 (£28.43)
MB08B	648	39,204	£497.77 (£8.64)
Day case			
MB08A	5	7	£584.16 (£248.72)
MB08B	146	2,363	£383.85 (£21.43)
Regular admission			
MB08B	8	66	£91.01 (£0.00)
Overall total			
MB08A		1,387	£1,846.08
MB08B		46,010	£607.72
Weighted average		47,397	£643.95
Inflated from 2016/17 to 2018/19			£666.47

MB08A Threatened or Spontaneous Miscarriage, with Interventions
MB08B Threatened or Spontaneous Miscarriage, without Interventions

Categories and codes	Submissions	Episodes	Mean (SE[a])

(a) Estimated from published interquartile range and number of submissions: SE = ([UQ−LQ] ÷ 1.349) ÷ √n, where 1.349 is 2 × the 0.75th quantile of the standard normal distribution.
(b) SE unavailable because IQR=0 owing to low volume of activity

Ectopic pregnancy

The developers of NICE's guidance on ectopic pregnancy and miscarriage (NG126) undertook detailed costing for 3 ways of managing ectopic pregnancies: salpingectomy, salpingotomy and medical management. They estimated average costs of £1,608, £2,205 and £1,432, respectively. We then required an estimate of the relative frequency of each, in order to arrive at a weighted average for the typical ectopic pregnancy. However, we were unable to find any suitable data in the literature or in publicly available routine data. Therefore, we obtained a dedicated extract of Hospital Episode Statistics (HES), detailing all episodes under ICD-10 code O00. This showed that a substantial majority of activity was recorded under 11 codes: 5 indicate that salpingectomy was the major procedure in the episode (Q231, Q233, Q234, Q242, Q259; 6,880 episodes); 1 relates to salpingotomy (Q304; 71 episodes); and 3 show that no invasive procedure was carried out, suggesting medical management only (No procedure, Q555, X373; 2,449 episodes). The remaining 2 codes (Q111, Q311) relate to aspiration of products of conception, for which we have no cost estimate; however, this represents a small volume of cases (<300 total episodes), so we exclude them from calculations. We are left with a 0.732 : 0.008 : 0.261 weighting for salpingectomy, salpingotomy and medical management; applying this gives us a mean cost of £1,566.66 which, when inflated to 2018/19 value, amounts to £1,776.68. This is the cost we apply for all additional ectopic pregnancies arising in future pregnancies.

Stillbirth

Following NICE's guideline on Intrapartum care for women with existing medical conditions or obstetric complications and their babies (NG121), we obtain our estimate of the costs of stillbirth from a dedicated costing study (Campbell et al. 2017). This suggests that an average stillbirth is associated with healthcare costs of £4,191.00; when inflated to 2018/19 value, this becomes £4,527.47.

Caesarean delivery

Using 2016/2017 Reference Costs inflated to 2019 shown in Table HE009 the increased cost associated with a caesarean compared with a non-caesarean delivery is £1,839

Totals

We calculate that the total increased expected cost is £761 and the QALY loss is 0.0233. The probability distributions used in the PSA are shown in tables Table HE004 (QALYs) and Table HE009 (costs).

Subappendix M.ii: Original economic model checklist

Original economic model		
Category	**Rating**	**Comments**
Applicability		

Original economic model		
Category	**Rating**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	Flash Monitoring process utility taken from a time trade-off study
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Partly	Some differences between CGM and Flash identified by the committee have not been studied and cannot be included in the model
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	The evidence for flash glucose monitoring was of low quality and as such led to significant model uncertainty which limited the model's capacity to inform decision making.
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Partly	These are estimated where there is no available data

Original economic model		
Category	**Rating**	**Comments**
2.8 Are the unit costs of resources from the best available source?	Yes	Costs for CGM are very uncertain but were explored extensively
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	NA	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	