National Institute for Health and Care Excellence

Draft for consultation

Type 1 diabetes in adults: diagnosis and management

[A] Evidence reviews for continuous glucose monitoring in adults with type 1 diabetes

NICE guideline NG17

Evidence reviews underpinning recommendations 1.7.3 to 1.7.7 and research recommendations in the NICE guideline

[November 2021]

Draft for consultation

These evidence reviews were developed by Guideline Updates Team

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN:

Contents

.

1 Continuous glucose monitoring in adults with type 1 diabetes

1.1 Review question

In adults with type 1 diabetes, what is the most effective method of glucose monitoring to improve glycaemic control:

- continuous glucose monitoring (real-time continuous glucose monitoring - rtCGM)
- flash glucose monitoring (intermittently scanned continuous glucose monitoring - isCGM)
- intermittent capillary blood glucose monitoring (self-monitoring of blood glucose - SMBG)?

1.1.1 Introduction

NICE guidelines state that people with diabetes should be empowered to self-monitor their blood glucose, and be educated about how to measure it and interpret the results. Routine blood glucose testing is typically done using a finger-prick capillary blood sample. Currently, continuous monitoring of interstitial fluid glucose levels using a continuous glucose monitor is not recommended for routine use but can be considered for some people.

New studies identified by surveillance of the NICE guideline on type 1 diabetes and the possibility of decreasing cost and increasing access to continuous glucose management technologies suggests the evidence should be reviewed to ascertain the effectiveness of rtCGM and isCGM versus standard blood glucose monitoring techniques. It should also be considered whether rtCGM/ isCGM use is now more appropriate for different types and subpopulations of diabetes, as defined in the protocol. Table 1:Summary of the protocol

PICO Table	
Population	Adults (aged 18 years and older) with type 1 diabetes
Intervention	• Continuous glucose monitoring (rtCGM) • Flash glucose monitoring (isCGM) • Intermittent capillary blood glucose monitoring (SMBG)
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.

Outcomes	**Primary outcomes**
	All outcomes will be sorted into up to 3 months, up to 6 months, up to 12 months, >12 months
	• HbA1c (dichotomous or continuous outcome, depending how it is reported)
	• Time spent in target glucose range
	  ○ Time spent above target glucose range
	  ○ Time spent below target glucose range
	• Hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) including:
	  ○ severe hypoglycaemia
	  ○ nocturnal hypoglycaemia
	• Glycaemic variability
	• Mortality
	• Diabetic ketoacidosis (DKA)
	• % of data captured
	Secondary outcomes

PICO Table	

	• Other adverse events (dichotomous) limited to:
	  ○ Diabetes related hospitalisation
	  ○ malfunction of CGM monitor
	  ○ serious adverse events
	• Mental health outcomes:
	  ○ Diabetes distress (including fear of hypoglycaemia and diabetes burnout)
	  ○ Diabetes related depression
	  ○ Body image issues due to CGM monitor
	  ○ Eating disorders due to diabetes
	• Awareness of hypoglycaemia
	• Adherence (dichotomous)
	
	• 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))

1.1.2 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.

Summary of evidence is presented in section 1.1.5. This summarises the effect size, quality of evidence and interpretation of the evidence in relation to the significance of the data.

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is **an effect**.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an **effect, but it is less than the defined MID**.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is **no meaningful difference**.
- Where the 95% CI crosses the line of no effect, and it is not completely between the MID, (i.e., it crosses one or both MIDs) the evidence **could not differentiate** between the comparators.

The committee highlighted that in diabetes practice, people up to the age of 19 would be under paediatric care due to commissioning arrangements. The committee noted that this is a definition worth highlighting in the review protocol alongside the usual definition of an adult.

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

1.1.3 Effectiveness evidence

1.1.3.1 Included studies

A total of 3,433 RCTs and systematic reviews were screened at title and abstract stage after deduplication.

Following title and abstract screening, 285 studies were included for full text screening.

Of the 285 included studies, 150 were relevant for the T1 diabetes question, whilst 135 were set aside to be screened for the other diabetes questions in this update.

These studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A). Overall, 17 studies were included. 18 papers covered 12 parallel RCTs, 3 papers covered 1 factorial RCT, and 7 papers covered 4 Crossover RCTs.

The studies included examined the following interventions:

- rtCGM vs isCGM (3 studies with data for meta-analysis)
- rtCGM vs standard self-monitoring of blood glucose (SMBG) (13 studies with data for meta-analysis)
- isCGM vs SMBG (1 study with data for meta-analysis)

Table 2: List of comparisons and associated studies/trials

Comparison	TRIAL (*Study)*
rtCGM vs isCGM (3 studies)	• **ALERTT1** (*Visser 2021*) • **CORRIDA** (*Haskova 2020*) • **I-HART CGM** (A*vari 2019, Reddy 2018a, Reddy 2018b*)
rtCGM vs SMBG (13 studies)	• *Battelino 2011* • **DIAMOND** *(Beck 2017)* • **GLADIS** (*New 2015*) • **GOLD** (*Lind 2017, Olafsdottir 2018, Olafsdottir 2020, Seyed Ahmadi 2020*) • **HypoDE** (*Heinemann 2018*) • **HypoCOMPaSS** (*Little 2018, Little 2014, Speight 2019*) • **IN CONTROL** *(van Beers 2016, van Beers 2017)* • **JDRF** *(JDRF 2018, JDRF 2010a, JDRF 2010b, Tansey 2011)* • **SWITCH** (*Battelino 2014*) • *Riveline 2012* • *Tanenberg 2004*

Comparison	TRIAL (*Study)*
	• *Tumminia 2015* • **WISDM** (*Pratley 2020*)
isCGM vs SMBG (1 study)	• **IMPACT** (*Bolinder 2016, Oskarsson 2018*)

Based on our definition in the protocol the committee felt the one study comparing isCGM and SMBG (IMPACT) provided sufficient evidence for this comparison. Therefore, a further search for additional observational data was not carried out as it this would not have yielded sufficiently high-quality information.

See Appendix E for evidence tables and the reference list in section 1.1.10 References – included studies.

1.1.3.2 Excluded studies

Overall, 53 studies were excluded at title and abstract and full text level. See Appendix K for the list of excluded studies with reasons for their exclusion.

1.1.4 Summary of studies included in the effectiveness evidence

Table 3: Real-time continuous glucose monitoring (rtCGM) vs Intermittently scanned continuous glucose monitoring (isCGM)

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
Avari 2019 Reddy 2018a Reddy 2018b	RCT	40	• Aged 18 years and above • Duration of diabetes >3 years • Using an intensified multiple daily injection (MDI) regimen for over six months • Participants had a severe hypoglycemic event in last 12 months requiring third party assistance or Gold score of >= 4	**rtCGM** Real-time continuous glucose monitoring (rtCGM) using Dexcom G5	**isCGM** Intermittently scanned continuous glucose monitoring (iscCGM) using Abbott Freestyle Libre	16 weeks	• HbA1c • Time in range ○ Percentage time spent in target (3.9–10 mmol/l) • Time spent above/below target glucose range ○ Percentage time spent in hypoglycaemia <2.8, 3.5 and 3.9 mmol/l ○ Percentage time in euglycaemia (3.9–7.8 mmol/l) ○ Percentage time spent in hyperglycaemia >7.8, >10 and >15 mmol/l ○ Change in time spent in hypoglycaemia (<3.3 mmol/l) • Hypoglycaemia • Severe hypoglycaemia • Glycaemic variability • Mental health outcomes ○ Hypoglycaemia fear (HFS-II) ○ Diabetes-related emotional distress (PAID questionnaire) • Awareness of hypoglycaemia ○ Gold score
Haskova 2020	RCT	60	• Age ≥18 years • Duration of diabetes >2 years	**rtCGM**	**isCGM**	4 weeks	• Time in range

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
			• Gold score <4 • No history of severe hypoglycaemia within last 6 months prior to the study initiation • No previous experience with rtCGM and/or isCGM	Real-time continuous glucose monitoring (rtCGM) using Guardian Connect Mobile	Intermittently scanned continuous glucose monitoring (isCGM) using FreeStyle Libre Flash Glucose Monitoring System		○ Changes in time in range (3.9–10.0mmol/L [70–180 mg/dL). • Time spent above/below target glucose range ○ Percentage of time spent in hypoglycaemia (<3.9 mmol/L [<70 mg/dL] and <3.0 mmol/L [<54 mg/dL]) • Hypoglycaemia • Severe hypoglycaemia • Glycaemic variability • Diabetic ketoacidosis • Quality of life ○ WHOQOL-BREF
Visser 2021	RCT	254	• Age: ≥18 years • Duration of diabetes: >= 6 months • Treatment with MDI or insulin pump • HbA1c <=10% • Exclusive isCGM use for 6 months	**rtCGM** Dexcom G6 (10-day wear)	**isCGM** FreeStyle Libre; (14-day wear)	6 months	• HBA1C: 6 months • Time in range: 3.9 – 7.8/10 mmol/L • Time spent above/below target glucose range: < 3.9, >10, >13.9 mmol/l • Glycaemic variability: CV, SD, number of low glucose events • Quality of life measured by validated tools: HFS-Worry

Table 4: Real-time continuous glucose monitoring (rtCGM) vs Intermittent capillary blood glucose monitoring (SMBG)

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
Battelino 2011	RCT	120	• Aged between 10 and 65 years	**rtCGM**	**isCGM**	6 months	• HbA1c

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
			• Duration of diabetes >1 year • Reasonable metabolic control assessing carbohydrate intake and self-adjusting insulin • HbA1c <7.5% • Using intensive insulin treatment with either an insulin pump or multiple daily injections • Not using a real-time continuous glucose monitoring device for at least 4 weeks	Real-time continuous glucose monitoring with the FreeStyle Navigator	Standard self-monitoring of blood glucose (SMBG)		• Time in range • 70 to 180 mg/dL or 90 to 180 mg/dL • Time spent above/below target glucose range ○ Amount of time per day the glucose level was - hypoglycaemic (<63 mg/dL, <70 mg/dL, or <55 mg/dL) - hyperglycaemic (>180 mg/dL or >250 mg/dL). ○ Time spent in hypoglycaemia (<63 mg/dL) during the 26-week study period • Hypoglycaemia • Severe hypoglycaemia • Diabetic ketoacidosis • Adverse events ○ device-related ○ study-related untoward events ○ serious adverse events regardless of cause
Battelino 2014	Crossover RCT with 4-months washout	81	• Aged 19 to 70 years • Duration of diabetes >1 year • Treatment with continuous subcutaneous insulin infusion (CSII) therapy with rapid-acting insulin analogues for more than 6 months • HbA1c between 7.5% and 9.5%	**SMBG (Sensor Off)/ rtCGM (Sensor On)** Guardian REAL-Time Clinical; Medtronic	**rtCGM (Sensor On)/ SMBG (Sensor Off)** Guardian REAL-Time Clinical; Medtronic	6 months	• HbA1c • Time in range ○ Changes in the time spent in euglycaemia (3.9–10 mmol/l). • Time spent above/below target glucose range

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
			• Naive to CGM • Had successfully completed a five-question multiple choice test concerning pump therapy and general understanding of diabetes				○ Changes in the time spent in hypoglycaemia (<3.9 mmol/l) ○ and hyperglycaemia (>10 mmol/l) • Hypoglycaemia • Severe hypoglycaemia • Diabetic ketoacidosis • Adverse events
Beck 2017	RCT	158	• Aged 25 years or older • HbA1c 7.5% to 10.0% • Treated for at least 1 year with multiple daily insulin injections • No home use of a personal CGM device in the 3 months before the trial • Performed blood glucose tests approximately four times per day • A negative pregnancy test for women of childbearing potential	**rtCGM** Dexcom G4 Platinum GM System with software 505	**SMBG** Continue with usual care basing diabetes management decisions on SMBG alone	24 weeks	• HbA1c ○ Change in HbA1c ○ Participants with HbA1c <7.0%. • Time in range ○ CGM-measured time in range (70 to 180 mg/dL) • Time spent above/below target glucose range ○ duration of hypoglycaemia (<70 mg/dL, <60 mg/dL, and <50 mg/dL) ○ duration of hyperglycaemia (>180 mg/dL, >250 mg/dL, and >300 mg/dL) • Hypoglycaemia • Severe hypoglycaemia • Glycaemic variability • Coefficient of variation. • Diabetic ketoacidosis • Adverse events • Awareness of hypoglycaemia

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
							• Quality of life ○ CGM Satisfaction Survey
Heinemann 2018	RCT	149	• Age ≥18 years • Duration of diabetes ≥1 year • Treated with multiple daily insulin injections • Prandial insulin at each major meal and at least one dose of basal insulin. • HbA1c ≤9.0% • Problematic hypoglycaemia • Treatment with continuous subcutaneous insulin infusion (CSII) therapy	**rtCGM** Real-time continuous glucose monitoring (rtCGM) using Dexcom G5 Mobile system	**SMBG** Usual therapy with SMBG	6 months	• Time in range ○ Duration of glucose readings derived from continuous glucose monitoring per day (>3.9 mmol/L to ≤10.0 mmol/L [>70 mg/dL to 180 mg/dL]). • Time spent above/below target glucose range ○ Duration of glucose readings derived from continuous glucose monitoring per day - ≤3.0 mmol/L [≤54 mg/dL] - ≤3.9 mmol/L [≤70 mg/dL] - >10.0 mmol/L [>180 mg/dL]). • Hypoglycaemia • Changes in nocturnal hypoglycaemic events • Severe hypoglycaemia • Glycaemic variability • Adverse events • Mental health outcomes ○ Diabetes Distress Scale for type 1 diabetes (T1-DDS) ○ Hypoglycaemia Fear Survey • Awareness of hypoglycaemia • Quality of life

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
							○ Self-reported health status assessed with the European Quality of Life 5 Dimensions questionnaire (EQ-5D)
JDRF 2008 JDRF 2010a JDRF 2010b Tansey 2011	RCT	98	• Aged 8 years and older • Duration of diabetes ≥1 year • Using an insulin pump or receiving at least three daily insulin injections • HbA1c 7.0 to 10.0% • Not used continuous glucose monitoring at home in the 6 months leading up to the trial	**rtCGM** DexCom Seven or the FreeStyle Navigator	**SMBG** Blood glucose meters and test strips	26 weeks	• HbA1c • Time in range ○ Amount of time per day the glucose level was 71 to 180 mg per decilitre (3.9 to 10.0 mmol per litre) • Time spent above/below target glucose range ○ Amount of time per day the glucose level was - hypoglycaemic (≤70 mg per decilitre or ≤50 mg per decilitre [≤3.9 or ≤2.8 mmol per litre]) - hyperglycaemic (>180 mg per decilitre or >250 mg per decilitre [10.0 or 13.9 mmol per litre]) • Hypoglycaemia • Severe hypoglycaemia • Glycaemic variability • Diabetic ketoacidosis • Adverse events • Quality of life ○ Participants ≥18 years old completed the Hypoglycaemia Fear Survey (HFS) and Social

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
							Functioning Health Survey (SF-12) version 2 ○ Continuous Glucose Monitoring Satisfaction Scale (CGM-SAT)
Lind 2017 Olafsdottir 2018 Olafsdottir 2020 Seyed Ahmadi 2020	Crossover RCT with 4 months washout	142	• Age ≥18 years • Duration of diabetes >1 year • HbA1c ≥7.5 • Treated with multiple daily insulin injections • Fasting C-peptide levels <0.91 ng/mL	**rtCGM** Dexcom G4 PLATINUM stand-alone system	**SMBG** Conventional therapy using only SMBG	16 months	• HbA1c • Time in range ○ Amount of time in glucose levels 70 to 180 mg/dL • Time spent above/below target glucose range ○ Amount of time in hypoglycaemia (glucose levels <70 mg/dL) ○ Amount of time in hyperglycaemia (glucose levels >180 mg/dL) • Hypoglycaemia • severe hypoglycaemia • Nocturnal hypoglycaemia • Glycaemic variability • Adverse events • Adherence (dichotomous) • Quality of life ○ Hypoglycaemic Fear Behaviour Scale ○ Hypoglycaemic Fear Worry Scale
Little, 2018 Little, 2014	2X2 factorial RCT	48	• Aged 18 to 74 years • C-peptide–negative type 1 diabetes • Impaired awareness of hypoglycaemia	**rtCGM and Intermittent SMBG in Multiple daily**	**SMBG in MDI** SMBG with MDI	24 months	• HbA1c • Time spent above/below target glucose range

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
Speight 2019			• Confirmed by Gold score ≥4	**injections (MDI)** iPro1 and SMBG with MDI **rtCGM and Intermittent SMBG in continuous subcutaneous insulin infusion (CSII)** iPro1 and SMBG with CSII	**SMBG in CSII** SMBG with CSII		○ Percentage time with glucose ≤3 mmol/L. • Hypoglycaemia • Severe hypoglycaemia • Diabetic ketoacidosis • Adverse events • Awareness of hypoglycaemia ○ Gold score ○ Clarke questionnaire ○ Hypoglycaemia Awareness Questionnaire (HypoAQ) 'impaired awareness' subscale score • Quality of life ○ Satisfaction with glucose monitoring device using the Glucose Monitoring Experience Questionnaire (GME-Q) • Hypoglycaemia Fear Survey-II (HFS-II)
New 2015	RCT	96	• Aged 18 to 65 years • Treated with either CSII or MDI >6 months • Aged 18 to 65 years • HbA1c 7 to 11% • SMBG an average of 2 to 7 times per day	**rtCGM with alarms** CGM with alarms unmasked FreeStyle Navigator	**rtCGM without alarms** CGM without alarms unmasked FreeStyle Navigator *[data not used]* **SMBG**	100 days	• HbA1c • Time spent above/below target glucose range ○ Time spent outside a glucose target of 3.9–10.0 mmol/l (70–180 mg/dl) • Glycaemic variability • Adverse events • Quality of life

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
					Standard SMBG using a masked FreeStyle Navigator		○ The Short-Form-8 Health Survey • The Diabetes Distress Scale questionnaire
Pratley 2020	RCT	203	• At least 60 years old • No use of real-time CGM in the 3 months prior to enrolment • HbA1c <10.0% • To be using either an insulin pump or multiple daily insulin injections	**rtCGM** Dexcom G5 with a study blood glucose meter as needed	**SMBG** Standard capillary blood glucose monitoring with the study blood glucose meter without CGM	6 months	• HbA1c • Time in range ○ 70 to 180 mg/dL • Time spent above/below target glucose range ○ Percentage of time spent with a glucose value - <70 mg/dL - <54 mg/dL - <60 mg/dL - >180 mg/dL - >250 mg/dL - >300 mg/dL • Hypoglycaemia • Glycaemic variability • Diabetic ketoacidosis • Adverse events • Mental health outcomes ○ Diabetes distress (Type 1 Diabetes Distress Scale) • Awareness of hypoglycaemia ○ Clarke Survey • Quality of life ○ General quality of life (PROMIS Global Health Short Form; National

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
							Institutes of Health [NIH] Toolbox Emotion Battery) ○ Hypoglycaemia fear (Hypoglycaemia Fear Survey II–Worry subscale)
Riveline 2012	RCT	123	• Age between 8 and 60 years • Duration of diabetes >12 months • Treated with either CSII or MDI • HbA1c ≥8.0% • SMBG performed at least twice daily	**rtCGM patient-led** Patient-led use of CGM with FreeStyle Navigator glucose needle-type sensor system	**rtCGM physician-prescribed** Physician-led use of continuous glucose monitoring with FreeStyle Navigator glucose needle-type sensor system *[data not used]* **SMBG** Standard home SMBG	12 months	• HbA1c • Hypoglycaemia • Severe hypoglycaemia • Glycaemic variability • Diabetic ketoacidosis • % of CGM data captured • Adverse events • Quality of life • Diabetes Quality of Life (DQoL) • SF-36 questionnaire
Tanenberg 2004	RCT	109	• Aged 19 to 76 years • Insulin-treated diabetes • Inadequate metabolic control • HbA1c >7.9%	**rtCGM** CGM system Medtronic MiniMed	**SMBG** SMBG using a home blood glucose metre (OneTouch FastTake, Lifescan)	12 weeks	• HbA1c • Time spent above/below target glucose range ○ Hypoglycaemia 60 mg/dL or less ○ hyperglycaemia 200 mg/dL or higher • Hypoglycaemia • Severe hypoglycaemia

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
							• Adverse events
Tumminia 2015	Crossover RCT with 2 months washout	20	• Aged 18 to 60 years old • Duration of diabetes >1 year • HbA1c >8.0%	**rtCGM** Guardian real-time Clinical; Medtronic	**SMBG** SMBG	6 months	• HbA1c • Time spent above/below target glucose range ○ Hyperglycaemia glucose>200 mg/dL/day ○ Hypoglycaemia glucose <70 mg/dL/day • Glycaemic variability • Diabetic ketoacidosis
van Beers 2016 van Beers 2017	Crossover RCT with 12 weeks washout	52	• Aged 18 to 75 years • Impaired awareness of hypoglycaemia with Gold score ≥4 • Treated with either CSII or MDI • Undertaking at least three SMBG measurements per day	**rtCGM** Paradigm Veo system with a MiniLink transmitter and an Enlite glucose sensor	**SMBG** SMBG	16 weeks	• HbA1c • Time in range ○ 4.0–10.0 mmol/L • Time spent above/below target glucose range ○ Percentage of time participants spent in - Hypoglycaemia (blood glucose ≤3.9 mmol/L) - Hyperglycaemia (>10.0 mmol/L). • Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • Glycaemic variability • Adverse events • Mental health outcomes ○ Psychological distress scores

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
							- World Health Organisation Well-being Index 5 [WHO-5] - Problem Areas in Diabetes 5 [PAID-5] - Hypoglycaemia Fear Survey [HFS] Worry • Awareness of hypoglycaemia ○ Gold ○ Clarke • Quality of life ○ Diabetes-specific measures of quality of life - PAID-5 - HFS - CIDS - EQ5D - WHO-5 - Satisfaction with use of CGM assessed by the CGM-SAT questionnaire

1 **Table 5: Intermittently scanned continuous glucose monitoring (isCGM) vs Intermittent capillary blood glucose monitoring (SMBG)**

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
Bolinder 2016 Oskarsson 2018	RCT	• Aged 18 years and above • Duration of diabetes ≥5 years	**isCGM** Sensor-based flash glucose monitoring system (Freestyle Libre)	**SMBG** Self-monitoring glucose concentrations using the FreeStyle Lite	6 months	• HbA1c • Time in range ○ Time with glucose in range 3.9–10.0 mmol/L (70–180 mg/dL). • Time spent above/below target glucose range

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
		• Current insulin regimen for at least 3 months before study entry • HbA1c ≤7.5% • Reported self-monitoring of blood glucose levels on a regular basis (equivalent to ≥3 times a day) for 2 months or more before study entry • Considered by the investigator to be technically capable of using the flash sensor-based glucose monitoring system		meter and test strips		○ Time spent in hypoglycaemia (<3.9 mmol/L [<70 mg/dL]) for the 14 days preceding the end of the 6-month study period (days 194–208) • Hypoglycaemia • Severe hypoglycaemia • Glycaemic variability • Diabetic ketoacidosis • % of CGM data captured • Adverse events • Mental health outcomes ○ Hypoglycaemia Fear Survey (HFS) ○ Diabetes Distress Scale (DDS) • Quality of life ○ Diabetes Quality of Life Questionnaire (DQoL)

1

1.1.5 Summary of the effectiveness evidence

Table 5: Summary of GRADE: rtCGM vs isCGM

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
HbA1c (%) <= 6 months	254	MD -0.36 (-0.48, -0.24)	+/- 0.50	High	No meaningful difference
HbA1c <7% <= 6 months	254	RR 1.50 (1.09, 2.06)	0.80 , 1.25	Moderate	Effect (Favours rtCGM)
Time in range (%) [3.9/4 - 10 mmol/l] <= 3 months	100	MD 5.56 (0.31, 10.81)	+/- 5.00	Low	Effect (Favours rtCGM)
Time in range (%) [3.9/4 - 10 mmol/l] <= 6 months	254	MD 6.85 (4.36, 9.34)	+/- 5.00	Moderate	Effect (Favours rtCGM)
Time below range (%) <3.9 mmol/l <= 3 months	100	MD -2.56 (-4.25, -0.88)	+/- 3.55	Low	Effect less than MID (Favours rtCGM)
Time below range (%) <3.0 mmol/l <= 3 months	60	MD -0.82 (-1.70, 0.06)	+/- 0.87	Moderate	Could not differentiate
Time below range <3.0 mmol/l <= 6 months	254	MD -0.35 (-0.61, -0.09)	+/- 0.53	Moderate	Effect less than MID (Favours rtCGM)
Time above range >10 mmol/l <= 3 months	100	MD -2.72 (-11.40, 5.95)	+/- 7.15	Very low	Could not differentiate
Time above range >13.9 mmol/l <= 3 months	60	MD -4.19 (-8.00, -0.38)	+/- 3.76	Moderate	Effect (Favours rtCGM)
Glycemic variability: SD <= 3 months	60	MD -0.29 (-0.70, 0.12)	+/- 0.41	Moderate	Could not differentiate
Glycemic variability: SD <= 6 months	254	MD -0.33 (-0.45, -0.21)	+/- 0.24	Moderate	Effect (Favours rtCGM)
Glycemic variability: coefficient of variation <= 3 months	60	MD -0.01 (-0.10, 0.08)	+/- 0.09	Moderate	Could not differentiate
Glycemic variability: coefficient of variation <= 6 months	254	MD -1.38 (-2.30, -0.46)	+/- 1.87	Moderate	Effect less than MID (Favors rtCGM)
Glycemic variability: mean amplitude of glucose excursions (MAGE) <= 3 months	60	MD -0.61 (-1.50, 0.28)	+/- 0.88	Moderate	Could not differentiate
Nocturnal hypoglycemia [0000 - 0600] <3.9 mmol/l <= 3 months	60	MD -3.96 (-7.30, -0.62)	+/- 3.30	Moderate	Effect (Favours rtCGM)

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Nocturnal hypoglycemia [0000-0600] <3.0 mmol/l <= 3 months	60	MD -2.79 (-4.90, -0.68)	+/- 2.08	Moderate	Effect (Favours rtCGM)
Quality of life - physical health <= 3 months	60	MD 0.10 (-0.71, 0.91)	+/- 0.85	Moderate	Could not differentiate
Quality of life - psychological health <= 3 months	60	MD -0.20 (-1.04, 0.64)	+/- 0.80	Moderate	Could not differentiate
Quality of life - social relationships <= 3 months	60	MD 0.50 (-0.92, 1.92)	+/- 1.40	Moderate	Could not differentiate
Quality of life - environment <= 3 months	60	MD -0.60 (-1.59, 0.39)	+/- 0.90	Moderate	Could not differentiate
Hypoglycemia fear scale (worry) <= 6 months	254	MD -2.62 (-4.52, -0.72)	+/- 3.86	Moderate	Effect less than MID (Favours rtCGM)
DTSQ - status <= 6 months	254	MD 2.34 (1.15, 3.53)	+/- 2.42	Moderate	Effect less than MID (Favours rtCGM)
Severe hypoglycemia (events) <= 6 months	254	RR 0.08 (0.03, 0.25)	0.80 , 1.25	High	Effect (Favours rtCGM)

Table 6: Summary of GRADE: rtCGM vs SMBG

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Change from baseline HbA1c (%) - <= 6 months	1259	MD -0.37 (-0.49, -0.24)	+/- 0.50	Very low	No meaningful difference
Change from baseline HbA1c (%) - <= 3 months	346	MD -0.19 (-0.67, 0.28)	+/- 0.50	Very low	Could not differentiate
Change from baseline HbA1c (%) - > 6 months	123	MD -0.52 (-0.80, -0.24)	+/- 0.50	Very low	Effect (Favours rtCGM)
HbA1c (mmol/mol) <= 3 months	82	MD 2.00 (-3.23, 7.23)	+/- 5.50	Very low	Could not differentiate
Change in HbA1c (mmol/mol) <= 6 months	477	MD -2.05 (-4.99, 0.88)	+/- 5.50	Low	No meaningful difference
HbA1c achieved target <7.5% <= 3 months	155	RR 1.77 (0.61, 5.10)	0.80 , 1.25	Very low	Could not differentiate

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
HbA1c achieved target <7.5% <= 6 months	155	RR 2.02 (1.18, 3.46)	0.80 , 1.25	Low	Effect (Favours rtCGM)
HbA1c achieved target <7.0% <= 3 months	155	RR 2.34 (0.83, 6.56)	0.80 , 1.25	Low	Could not differentiate
HbA1c achieved target <7.0% <= 6 months	155	RR 1.80 (1.00, 3.22)	0.80 , 1.25	Low	Effect (Favours rtCGM)
Time in range (%) [3.9/4 - 10 mmol/l] <= 6 months	1023	MD 7.03 (4.88, 9.19)	+/- 5.00	Very low	Effect (Favours rtCGM)
Time below range (%) <3.9 mmol/l <= 6 months	371	MD -1.46 (-5.06, 2.14)	+/- 1.45	Very low	Could not differentiate
Time below range (%) <55mg/dL <= 6 months	116	MD -3.15 (-5.19, -1.11)	+/- 4.21	Very low	Effect less than MID (Favours rtCGM)
Time below range (%) <63mg/dL <= 6 months	116	MD -2.04 (-3.86, -0.22)	+/- 3.23	Very low	Effect less than MID (Favours rtCGM)
Time above range >10mmol/l <= 6 months	511	MD -3.48 (-6.47, -0.48)	+/- 7.08	Very low	No meaningful difference
Time above range >13.9 mmol/l <= 6 months	319	MD -3.08 (-4.45, -1.72)	+/- 3.19	Very low	Effect less than MID (Favours rtCGM)
Glycemic variability: SD <= 6 months	298	MD -8.75 (-11.55, -5.95)	+/- 6.90	Moderate	Effect (Favours rtCGM)
Glycemic variability: SD > 6 months	123	MD -8.70 (-21.21, 3.81)	+/- 16.20	Very low	Could not differentiate
Glycemic variability: coefficient of variation <= 6 months	584	MD -4.35 (-6.72, -1.99)	+/- 3.35	Very low	Effect (Favours rtCGM)
Glycemic variability: MAGE <= 6 months	282	MD -19.64 (-26.41, -12.88)	+/- 22.40	Moderate	Effect less than MID (Favours rtCGM)
Hypoglycaemia (events/day) <3.9 mmol/l <= 3 months	109	MD -0.30 (-0.73, 0.13)	+/- 0.60	Very low	Could not differentiate
Hypoglycaemia (events/week) <3.9 mmol/l <= 6 months	310	MD -0.50 (-0.80, -0.20)	+/- 3.29	High	No meaningful difference
Hypoglycaemia (events/week) <3 mmol/l <= 6 months	399	MD -0.37 (-0.88, 0.13)	+/- 1.40	Low	No meaningful difference
Hypoglycaemia event duration (minutes) <= 3 months	109	MD -31.60 (-50.90, -12.30)	+/- 30.55	Very low	Effect (Favours rtCGM)

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Hypoglycaemia event duration (minutes) <= 6 months	52	MD -37.80 (-44.60, -31.00)	+/- 6.25	High	Effect (Favours rtCGM)
Severe hypoglycaemia <= 6 months	1000	RR 0.65 (0.44, 0.97)	0.80 , 1.25	Low	Effect (Favours rtCGM)
Severe hypoglycaemia >= 6 months	123	RR 2.46 (1.02, 5.92)	0.80 , 1.25	Very low	Effect (Favours SMBG)
Nocturnal Hypoglycaemia (% of time) <3.9 mmol/l <= 6 months	194	MD -3.97 (-6.95, -0.98)	+/- 2.30	Very low	Effect (Favours rtCGM)
Nocturnal hypoglycaemia number of events / night <3.9 mmol/l <= 6 months	335	MD -0.08 (-0.11, -0.05)	+/- 0.88	High	No meaningful difference
DKA <= 6 months	849	RR 0.50 (0.15, 1.64)	0.80 , 1.25	Very low	Could not differentiate
DKA > 6 months	123	RR 0.98 (0.14, 6.76)	0.80 , 1.25	Very low	Could not differentiate
Hospitalisation <= 6 months	203	RR 1.46 (0.25, 8.53)	0.80 , 1.25	Very low	Could not differentiate
SAE <= 6 months	158	RR 2.55 (0.12, 52.12)	0.80 , 1.25	Very low	Could not differentiate
Diabetes distress - PAID - <= 6 months	226	MD -0.10 (-3.85, 3.65)	+/- 7.30	Moderate	No meaningful difference
Fear of hypoglycaemia (HFS) <= 6 months	226	MD -2.70 (-6.01, 0.61)	+/- 6.80	Moderate	No meaningful difference
Fear of hypoglycaemia (HFS-II) <= 6 months	96	MD 0.00 (-9.80, 9.80)	+/- 12.00	Low	No meaningful difference
Fear of hypoglycaemia (HFS-SWE) <= 6 months	280	MD 0.02 (-0.12, 0.16)	+/- 0.30	High	No meaningful difference
Hypoglycaemia awareness - Clarke score <= 6 months	303	MD -0.20 (-0.56, 0.16)	+/- 0.90	Moderate	No meaningful difference
Hypoglycaemia awareness - GOLD score	148	MD -0.37 (-0.72, -0.03)	+/- 0.80	High	No meaningful difference
Quality of life - DTSQ	369	MD 1.72 (-1.51, 4.94)	+/- 3.88	Very low	Could not differentiate
Quality of life - Sf-8 physical - 3 months	82	MD 0.30 (-3.45, 4.05)	+/- 4.33	Very low	No meaningful difference

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Quality of life - Sf-8 mental - 3 months	82	MD 3.60 (-0.47, 7.67)	+/- 4.70	Very low	Could not differentiate
Quality of life - Who-5 general wellbeing index - 6 months	279	MD 3.39 (-0.66, 7.44)	+/- 7.66	High	No meaningful difference
Quality of life -Sf 12 physical - 6 months	226	MD 1.40 (-0.70, 3.50)	+/- 5.00	Moderate	No meaningful difference
Quality of life - Sf-12 mental - 6 months	226	MD -0.30 (-2.87, 2.27)	+/- 4.80	Moderate	No meaningful difference

Table 7: Summary of GRADE: isCGM vs SMBG

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Change from baseline HbA1c (%)	238	MD 0.00 (-0.01, 0.01)	+/- 0.50	Moderate	No meaningful difference
Change from baseline HbA1c (mmol/mol)	238	MD 0.00 (-0.17, 0.17)	+/- 5.50	Moderate	No meaningful difference
Time in range (%) [3.9/4 - 10 mmol/l]	238	MD 4.16 (3.84, 4.48)	+/- 5.00	Moderate	Effect (Favours isCGM)
Time below range (%) <3.9 mmol/l	238	MD -5.17 (-5.42, -4.91)	+/- 0.50	Moderate	Effect (Favours isCGM)
Time below range (%) <3.1 mmol/l	238	MD -3.42 (-4.85, -1.99)	+/- 2.81	Low	Effect (Favours isCGM)
Time below range (%) <2.5 mmol/l	238	MD -2.29 (-2.44, -2.14)	+/- 0.29	Moderate	Effect (Favours isCGM)
Time below range (%) <2.2 mmol/l	238	MD -1.92 (-2.05, -1.79)	+/- 0.25	Moderate	Effect (Favours isCGM)
Time above range >13.9 mmol/l	238	MD -1.54 (-1.71, -1.37)	+/- 0.34	Moderate	Effect (Favours isCGM)
Glycemic variability: SD	238	MD -5.00 (-5.29, -4.71)	+/- 0.58	Moderate	Effect (Favours isCGM)

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Glycemic variability: coefficient of variation	238	MD -4.40 (-4.56, -4.24)	+/- 0.31	Moderate	Effect (Favours isCGM)
Glycemic variability: MAGE	238	MD -8.00 (-8.76, -7.24)	+/- 1.50	Moderate	Effect (Favours isCGM)
Hypoglycaemia <3.1 mmol/l	241	RR 0.20 (0.01, 4.16)	0.80 , 1.25	Very low	Could not differentiate
Severe hypoglycaemia	241	RR 0.67 (0.11, 3.95)	0.80 , 1.25	Very low	Could not differentiate
Nocturnal hypoglycaemia [2300-0600] (time in h) <3.1mmol/l	238	MD -0.30 (-0.32, -0.28)	+/- 0.04	Moderate	Effect (Favours isCGM)
Discontinuation	241	RR 6.05 (0.74, 49.50)	0.80 , 1.25	Very low	Could not differentiate
Serious adverse events	241	RR 1.01 (0.30, 3.39)	0.80 , 1.25	Very low	Could not differentiate
CGM monitor malfunction	241	RR 21.17 (1.25, 357.32)	0.80 , 1.25	Moderate	Effect (Favours SMBG)

1

1.1.6 Economic evidence

1.1.6.1 Included studies

A systematic literature search was undertaken to identify published health economic evidence relevant to the review questions. Studies were identified by searching EconLit, Embase, CRD NHS EED, International HTA database, MEDLINE, PsycINFO and NHS EED. All searches were updated on 5th May 2021, and no papers published after this date were considered. This returned 3,040 references (see appendix C for the literature search strategy). After deduplication and title and abstract screening against the review protocol, 3,021 references were excluded, and 19 references were ordered for screening based on their full texts.

Of the 19 references screened as full texts, 2 were systematic reviews. Both were investigated as a source of references, from which one more study was added (Healthcare Improvement Scotland 2018). In total, there were 14 primary studies that contained cost-utility analyses evaluating some of the following methods of glucose monitoring to improve glycaemic control: 1) continuous glucose monitoring (rtCGM); 2) flash glucose monitoring (isCGM); 3) intermittent capillary blood glucose monitoring (SMBG). Two UK studies were included in this evidence review in full as the most relevant evidence, with the others being excluded as not sufficiently applicable to the UK context. The health economic evidence study selection is presented as a flowchart in appendix H. Full economic evidence tables along with the checklists for study applicability and study limitations are shown in appendix I.

1.1.6.2 Excluded studies

Studies excluded in the full text review, together with reasons for exclusion, are listed in appendix K.

1.1.7 Summary of included economic evidence

Of the 2 UK studies, 1 study assessed the cost-effectiveness of real-time continuous glucose monitoring (rtCGM) among type 1 diabetes patients, and the other assessed the Freestyle Libre flash glucose monitoring device for type 1 diabetes patients (isCGM). Both studies found that the devices assessed were likely to be cost effective compared with self-monitoring of blood glucose (SMBG).

Study	Population and setting	Model	Comparators	Perspective and time horizon	Results	Quality assessment
Healthcare Improvement Scotland 2018	T1DM & T2DM who require intensive insulin treatment (only the results for T1DM are included here) Scotland	A simple two state structure (alive or dead) Two different model structures were used: 1) Restricted model, only taking into account the cost of monitoring and the direct impact of the device on health utility scores. 2) Full model, as above but also incorporating hypoglycaemic events and the associated impact on utility scores and NHS resource use.	Intervention: Freestyle Libre flash glucose monitoring (isCGM) Comparator: self-monitoring of blood glucose (SMBG)	Scottish NHS Lifetime	Base case: 1) Restricted analysis: ICER=£12,340/QALY for T1DM; 2) Full analysis: ICER=£2,459/QALY for T1DM; Deterministic sensitivity analysis: ICER is most sensitive to: annual number of hypoglycaemic events; reduction in blood tests used; hypoglycaemia disutilities; Freestyle Libre utility; and consumables costs. Freestyle Libre remained cost-effective across these scenarios. Probabilistic sensitivity analysis: Freestyle Libre is likely to be cost-effective compared with SMBG.	Applicability: Partially applicable Limitations: Potentially serious limitations

Study	Population and setting	Model	Comparators	Perspective and time horizon	Results	Quality assessment
Roze 2020	T1DM UK	IQVIA CORE Diabetes Model	Intervention: real-time continuous glucose monitoring (RT-CGM) Comparator: self-monitoring of blood glucose (SMBG)	U.K. health care payer (NHS and personal social services) Lifetime	Base case: ICER=£9,558/QALY Deterministic sensitivity analyses: If QoL benefit with RT-CGM was zero, ICER= £28,225/QALY No other sensitivity analyses took the ICER above £20,000/QALY Similar results obtained for the cohort with baseline HbA1c ≥8.5% However, ICER was more sensitive to changes in HbA1c treatment effect. Probabilistic sensitivity analysis: Not conducted	Applicability: Partially applicable Limitations: Potentially serious limitations

1

1.1.8 Economic model

An original cost-effectiveness analysis was undertaken for this review question. A summary is included here, with the full analysis available in the economic model report.

Model structure

The economic analysis was done using the IQVIA CORE Diabetes model (CDM) version 9.5. IQVIA CDM is a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. The model has been previously validated against epidemiological and clinical studies of type 1 diabetes. A more detailed description of IQVIA CDM has been published by Palmer et al (2004). The model allows for transition probabilities and management strategies to be differentiated by type of diabetes. In our analysis, type 1 diabetes data was used where available.

Diabetes progression with the IQVIA CDM is simulated using a series of interlinked, inter-dependent sub-models which simulate the following complications:

- angina
- myocardial infarction
- congestive heart failure
- stroke
- peripheral vascular disease
- diabetic retinopathy
- macular oedema
- cataract
- hypoglycaemia
- ketoacidosis
- lactic acidosis
- nephropathy and end-stage renal disease
- neuropathy
- foot ulcer
- amputation
- non-specific mortality

The Markov sub models listed above use time, state, and diabetes type-dependent probabilities from published sources. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables.

The analysis simulates the following methods of glucose monitoring:

- real-time continuous glucose monitoring (rtCGM)
- flash glucose monitoring (isCGM)
- self-monitoring of blood glucose (SMBG)

Analyses of rtCGM versus SMBG, and isCGM versus SMBG were conducted. The committee agreed an analysis of rtCGM versus isCGM would not be useful. This was because of the limited clinical data available for this comparison, and because the choice of

device often depended on individual characteristics of the person, and therefore the average cost-effectiveness across the population may not be particularly useful.

Analysis

A cohort of type 1 diabetes patients were defined using patient demographics, racial characteristics, baseline risk factors, and baseline complications to reflect an adult type 1 diabetes population in the UK. The analysis was performed across a lifetime horizon with costs and outcomes discounted at an annual rate of 3.5%. Discounted outcomes and costs were used to calculate the net monetary benefit (NMB) of automated glucose monitoring methods at a willingness to pay (WTP) per QALY of £20,000 and £30,000. The analysis was undertaken from the perspective of the UK NHS and Personal Social Services.

Treatment effectiveness was characterised using a range of outcomes including reduction in HbA1c levels, severe hypoglycaemic events, non-severe hypoglycaemic events, fear of hypoglycaemia and patient preferences for different methods of monitoring.

UK specific sources were identified model inputs relating to costs, utilities, and other management parameters. In cases where UK specific sources were not available, default IQVIA CDM parameters were used. Treatment specific costs were calculated using published national sources.

Results

There are two versions for the base case analyses: scenario 1 does not include the additional utility benefit associated with reduced fear of hypoglycaemia (FoH) with rt-CGM, while scenario 2 does include this benefit. The committee noted that because isCGM was already found to be clearly cost-effective without the inclusion of this additional benefit, it was unnecessary to run a version of the model including this benefit for isCGM (given the lack of data on fear of hypoglycaemia with isCGM).

The base case results in scenario 1 (Table 8) showed that isCGM was a cost-effective treatment compared with SMBG under a threshold of £20,000 per QALY, while rtCGM only appeared cost effective at the £30,000 threshold. In scenario 2 rtCGM was cost-effective compared with SMBG at a threshold of £20,000 per QALY (Table 9).

Table 8 Base-case deterministic cost–utility results (without utility benefits associated with reduced fear of hypoglycaemia)

Treatments	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (vs SMBG)
SMBG	52,979	11.641			
isCGM	61,156	12.446	8,177	0.805	10,157
rtCGM	75,668	12.569	22,688	0.928	24,436

Table 9: Base-case deterministic cost–utility results (with utility benefits associated with reduced fear of hypoglycaemia)

Treatments	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (vs SMBG)
SMBG	52,979	11.641			
rtCGM	75,668	13.028	22,688	1.388	16,351

1.1.9 The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee agreed that outcomes such as HbA1c and time in range (TIR) were important for measuring a person's blood sugar levels over time. HbA1c was limited by it reflecting the previous 3 months of therapy, whereas time in range was a measurement over a shorter time period. The committee also highlighted TIR to be a better measure than HbA1c as it captures variation and can be more directly linked to risk of complications. They also predicted that TIR would be the more appropriate measure going forward and will be used to assess the clinical effectiveness of CGM interventions. As more people with diabetes use these interventions in everyday practice, routine collection of this data will become much easier on a larger scale.

For time in, above, or below range, the committee focused on the range pre-specified in the protocol, and reported in most papers, which was 3.9-10mmol/l for time in range. The committee noted there was a clinically meaningful positive effect on time in range for rtCGM vs both isCGM and SMBG, as well as isCGM vs SMBG, at these thresholds. This was based on the pre-set MID of a 5% change.

Hypoglycaemia events, severe hypoglycaemia events, and nocturnal hypoglycaemia were also considered to be important outcomes. These are often highlighted by people living with Type 1 diabetes as key due to the fear these events generate and the impact they can have on quality of life (for example suspension of driving licence in the event of severe hypoglycaemia episodes). Therefore, a reduction in hypoglycaemia events results in significant improvements to quality of life, particularly for nocturnal hypoglycaemia, where people worry more because they feel they won't be able to react to hypoglycaemia symptoms whilst asleep.

The committee stated that the coefficient of variation was the most important outcome for glycemia variability, as a score of less than 33% represented a significant reduction in risk of hypoglycaemia, and unlike standard deviation this outcome took into account mean glucose levels.

Other key outcomes can be seen in the review protocol in Appendix A.

The quality of the evidence

rtCGM vs isCGM

This comparison had evidence for all primary outcomes other than mortality, DKA events and percentage of data captured.

The committee was concerned about the reporting decision in the I-HART CGM study (Avari 2019, Reddy 2018a, Reddy 2018b), as reporting medians over means often suggests a skew in the data, and thus this study was reported as having "some concerns" in the risk of bias assessment. Haskova (2020) had some risk of bias around the difference in measurement between isCGM and rtCGM monitors, where there may have been a bias due to participants only deciding or remembering to measure using their isCGM at specific times. This means that users would have tested their glucose levels at times when glucose control was good, and glucose data outside the target range was omitted. This is in contrast to rtCGM where monitoring was continuous and unconnected to the activity of participants. These differences in data collection would affect time in range monitors. However, the committee agreed that isCGM measure in the Haskova (2020) study (encouragement to scan the sensor 10 times a day) were sufficient to be comparable to rtCGM. The committee agreed Visser (2021) was a low risk of bias study.

The committee noted that both HbA1c and time in range outcomes had high/ moderate quality results for effectiveness. The committee did note that for HbA1c it was the dichotomous outcome of <7% that showed an effect, while the higher quality outcome of continuous HbA1c at the same timepoint showed no meaningful difference. As a result of this they could not conclude whether HbA1c was more effective in rtCGM or were influenced by these HbA1c findings, Whilst time in range data was both effective as an outcome and had moderate quality evidence at 6 months, the committee noted Visser 2021 was not a UK based study.

rtCGM vs SMBG

This comparison had evidence for all primary outcomes other than mortality and percentage of data captured.

The committee highlighted that Riveline (2012) and the GOLD trial had a study entry of >=8% HbA1c threshold for inclusion for adults with T1 diabetes, and yet both produced effective results for rtCGM vs SMBG. They noted this as positive as it suggests that rtCGM can be effective even when diabetes is less well managed at baseline.

Battelino (2011) was downgraded for indirectness due to just under 50% of participants being in the paediatric age range. Despite meeting the definition of an adult population defined in the protocol, the committee considered this study population was only partially directly applicable due to the large proportion of paediatric patients in the study sample.

The GOLD study and Tumminia (2015) reported a positive effect for rtCGM vs SMBG for standard deviation of blood glucose levels and mean amplitude of glucose excursions (MAGE), however the GOLD study did not report the coefficient of variation. The committee noted that this was why the standard deviation and MAGE was reported as having an effect whilst the coefficient of variation was not. The results from the GOLD study were by far the most heavily weighted in glycaemic variability scores and the committee agreed with this weighting.

rtCGM vs SMBG was also the only comparison where a subgroup analysis could be conducted between those on multiple daily injections (MDI) and those on continuous subcutaneous insulin infusion (CSII), however there was not enough data for subgroup analysis for every outcome. The committee were satisfied that the result of no differences between multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) (the only subgroup comparison that was possible) reflected their own clinical practice, and that a recommendation for rtCGM to apply to all insulin dosing methods was appropriate.

The Heinemann (2018) study did cause some issues with its unclear reporting of which direction of effect its outcomes were in. The committee noted it odd that time above range would increase whilst time in range also increased, but this result was assumed to be correct based on reported values so no action was taken to downgrade.

Only 2 studies included data from a UK population (HypoCOMPaSS trial and New 2015), the committee acknowledged that more UK data in key outcomes would have been preferable, but they agreed that the review data overall was applicable and more importantly recent enough to make recommendations. Access to CGM devices and diabetes demographics can vary significantly depending on the type of healthcare system a country possesses (i.e., privately vs publicly funded) so the committee found it difficult to apply this to the publicly funded UK healthcare system.

The committee was aware that the quality of evidence in this comparison is the lowest of the three comparisons, particularly for key outcomes of HbA1c and time in range.

isCGM vs SMBG

This comparison had evidence for all primary outcomes other than mortality and DKA events and percentage of data captured.

There was only 1 trial (IMPACT) available comparing isCGM to SMBG (IMPACT). Whilst Bolinder 2016, the study from which the IMPACT trial data is extracted from, rated as “some concerns” in risk of bias assessment (due to lack of information on allocation concealment), the committee accepted this study was of sufficient quality and large enough to be used to judge the effectiveness of isCGM vs SMBG alongside the rtCGM evidence. The study reported no meaningful difference in HbA1c outcomes. However, the committee judged the reported increase in time in range and decrease of time below range, as well as decrease in glycaemic variability (moderate quality evidence) to be evidence of an effect.

Given the rapid advances in the technology, the committee made a research recommendation to investigate what are the best metrics to collect routine real-world data in healthcare systems to learn about the effects of CGM devices. If routine healthcare data is collected it can show the direct effect of implemented technology on the population, rather than it being interpreted through the results of trials. Furthermore, increased monitoring of routine healthcare data will ensure a broader population is captured, rather than just those eligible for clinical trials.

Overall summary

The committee noted that the wearing of blinded CGM monitors in these trials could potentially have affected the behaviour of participants in control arms, as measures were being recorded.

The committee agreed to not downgrade studies for lack of blinding, as it was not thought to be feasible to blind study participants to interventions when knowledge of the intervention was inherent to its use (participants had to look at CGM as part of trial).

The committee acknowledged that most of the evidence was for CGM vs SMBG, but there was some evidence available for CGM vs isCGM,

Benefits and harms

The committee agreed that there was sufficient evidence in key outcomes such as HbA1c, time in range and severe/ nocturnal hypoglycaemia, as covered in the quality of evidence section, to justify recommending both rtCGM and isCGM over standard self-monitoring of blood glucose. However, they considered that the evidence in pooled and single studies for rtCGM vs isCGM was not of high quality nor adequate enough in sample size to justify recommending one technology over another when combined with cost-effectiveness evidence. This was compounded by the most recent isCGM technologies evolving to become more similar to rtCGM.

The committee, when considering clinical and cost-effectiveness evidence, found themselves in a position of equipoise between rtCGM (more effective less cost-effective) and isCGM (less effective more cost effective), the range of personal factors to consider when choosing a CGM device (highlighted in box 1) and the continuing progression towards similarity of the two device types, they decided to recommend both evenly.

For rtCGM vs isCGM, the effectiveness was derived from the time in range results at 6 months, as they gave more weight compared to the continuous HbA1c outcome at 6 months that was high quality and showed no meaningful difference between rtCGM and isCGM.

rtCGM vs SMBG showed an effect in dichotomous HbA1c outcomes and time in range, however there were a large number of outcomes of low quality in GRADE often due to inconsistency.

isCGM vs SMBG had higher quality key outcomes but was in a single study (Bolinder 2016) and was supported more strongly by cost-effectiveness evidence.

These three results left the committee in a position of equipoise where based on the balance of evidence they could not judge whether rtCGM or isCGM was superior to the other, considering the potential budget impact of such a decision.

However, the committee stated that glucose-monitoring devices are being released on the market and evolving so quickly that making recommendations for a specific device is not desirable. CGM devices can vary in their need for calibration, and the presence of alarms that alert people to nocturnal hypoglycaemia. The committee highlighted that rapidly advancing technology and increasing overlap between isCGM and rtCGM meant there was no advantage to recommending a specific device over another, and that the specific choice of isCGM vs rtCGM devices should be decided by the healthcare professional and healthcare service user based on user preferences and needs.

The committee highlighted that the individual choice element of different CGM devices would be a benefit to healthcare service users, as the 'best' device for each individual would depend on their preferences, needs and characteristics. They therefore included a summary table in the recommendations outlining the factors to consider when choosing a CGM device. The committee stated that this freedom of choice is more beneficial to the user than being limited to a specific device.

The committee noted that in their clinical experience if a person living with type 1 diabetes managed their diabetes quite well but wanted to improve this, they did not meet the criteria in the previous recommendations for access to a CGM monitor and felt "punished" for good diabetes management. The committee highlighted that it was important that access to CGM was increased, so the new recommendations take what was a stringent and absolute set of characteristics and transform them into a set of discussion points between the individual and their clinician. For example, some people are trying to find out what works best with their insulin delivery system e.g., some are using it as part of a self-funded hybrid closed loop system, some have a separate reader and some need a link to their smartphone. People with type 1 diabetes who use an insulin pump would be encouraged to opt for CGM as they would want to be enabled to use a hybrid closed loop system.

The committee noted that alarms and alerts are an important factor in people's choice of CGM device, as these can help alleviate the fear of nocturnal hypoglycemia. This benefit can also be for both the user and their carer. The committee also noted that variation in hypoglycemia profile should be taken into account when deciding on device, as levels of fear, frequency, awareness and severity would affect how often they would want to monitor their glucose levels. Variation caused by exercise and how this would affect readings was also a committee consideration regarding type of device.

The committee highlighted that some devices rely on people being familiar with certain technologies (e.g., a smartphone) and that this technology is not accessible/preferable for everyone. The committee acknowledged that technological limitations could apply on both the service user and healthcare practitioner side, with some practitioners needing to become more familiar with technological advances, and that being "skilled up" in these monitoring devices is an ongoing process. Therefore this is why it was important for the patient to interact with an expert team as outlined in the recommendations.

The use of this technology also caused concerns regarding those with limited dexterity, as they may struggle to use a device that requires use of small mechanical features to take readings. Whereas in some cases smartphones can have modes designed to support greater accessibility. Calibration was also raised as a concern, as some may need assistance with this process, or for people who need to wear device for long periods of time frequent calibration or sensor replacement may be an issue. For some people who need assistance in decision making around devices they may also benefit from a device where

data can be extracted and shared with their healthcare provider. The committee wished to highlight that the cosmetic appearance of a device is an important consideration to some people, whether the sensor is on the abdomen or on the upper arm. This concern should be discussed as part of the device decision making process.

The committee noted that once a person with type 1 diabetes has chosen a closed loop hybrid system they're "locked in" to this device for a contracted number of years, so keeping the person using the device up to date on emerging devices on the market before decision points is key. The committee reported that feelings of "missing out" on a new emerging device could lead to a negative impact on quality of life. The committee agreed this would be addressed through education by a team with expertise in CGM use. It should also be discussed as an option to consider.

Overall, the committee considered that the clinical evidence base could have been greater and of a higher quality for rtCGM and isCGM. However, the evidence presented had an adequate amount of effective results in key outcomes to justify the recommendations, combined with positive health economic results.

The committee clarified that the service user should consult with a member of the diabetes care team with expertise in the use of CGM. Furthermore, people using CGM with language difficulties or learning disabilities would also benefit from this team's support. The committee also highlighted that community-based specialist teams are now available and are no longer always based in secondary care. The term "centre" was changed to team from the previous recommendation to make this point clearer.

Despite multiple quality of life scores in the studies, none showed any meaningful difference between CGM and SMBG. Many studies used different scales for distress, fear, and quality of life effects of diabetes.

Cost effectiveness and resource use

The committee noted that both published UK cost-effectiveness studies (one in rtCGM and one in isCGM) found these technologies to be cost-effective compared to intermittent capillary blood glucose monitoring. They agreed they were both generally well conducted analyses, with the key limitations being they were both based on a single RCT (rather than all available evidence on clinical effectiveness), and the study on rtCGM was based on data that may not be fully representative of the relevant UK population. Original modelling was therefore undertaken to overcome these limitations, where possible.

The committee discussed the results of the original economic modelling (undertaken using the IQVIA Core Diabetes Model) regarding glucose monitoring among people with type 1 diabetes. This model uses HbA1c rather than the committee's preferred measure of time in range to predict future outcomes, but since similar results were found for continuous glucose monitoring for both these outcomes, the committee were confident this was not a substantial limitation. They noted that rtCGM and isCGM could both help people with T1DM to achieve better glycaemic control and reduce the risk of severe and non-severe hypoglycaemic episodes, and there was evidence that people preferred the use of these monitoring techniques, over and above their benefits on clinical outcomes. They concluded that, based on the results of economic modelling (using clinical data from the RCTs included in the clinical review), isCGM glucose monitoring was clearly cost-effective for the overall population of people with type 1 diabetes, and this finding was robust to all the sensitivity analyses undertaken.

The ICERs for rtCGM were higher than those for isCGM, principally driven by the higher costs used for the devices in the base-case analysis. The committee were presented with two separate analyses; one which included a utility benefit associated with reduced fear of hypoglycaemia (calculated by using a published mapping to convert values from the Hypoglycaemia Fear Survey to the EQ-5D) from the use of rtCGM, and one that did not

include this benefit (and therefore only included benefits for HbA1c, hypoglycaemia, and patient monitoring preferences). The committee were strongly of the opinion that fear of hypoglycaemia was an important consideration for many people with type 1 diabetes (over and above the harms caused by the hypoglycaemic episodes themselves) and therefore focused their decision-making on this scenario. They noted hypoglycaemia is a life-threatening condition, and the fear of future episodes can lead to serious physical and psychological sequelae. They discussed whether there was any concern about double counting of benefits with this approach, but agreed that since the Hypoglycaemia Fear Survey specifically asks about worry caused by the potential for hypoglycaemia, not symptoms during a hypoglycaemic event, and that people would spend the large majority of their time not in a hypoglycaemic state, that these should represent separate quality of life gains. In this scenario, the ICER for rtCGM versus intermittent capillary blood glucose monitoring was below £20,000/QALY (and robust to various sensitivity analyses), and therefore the committee were confident rtCGM was also a cost-effective technology.

The committee recognised the fact that the base case analysis uses £2,000 as the annual cost for rtCGM. This is the NHS ceiling price for this technology when used for people with diabetes who are pregnant, and was taken as a proxy for the potential likely cost of rtCGM were it to be rolled out more widely (the technology was first adopted most widely in pregnancy). In a sensitivity analysis, the cost was increased to £3,000, representing an upper bound for the possible cost of the technology (assuming the full prices from the NHS supply chain catalogue, with no discounts). In this scenario, the ICER was between £20,000/QALY and £30,000/QALY, meaning there is less certainty in cost-effectiveness. However, the committee noted that in practice, due to technological developments and the number of different rtCGM devices available leading to price competition, it was likely that the NHS would be able to procure devices for considerably less than this maximum threshold price. They also noted that the prices for rtCGM had reduced over previous years, and therefore the base-case analysis was a more accurate reflection of the likely cost-effectiveness of the technology going forwards.

The committee considered whether a preference should be specified between isCGM and rtCGM in the recommendations. They noted that there was limited evidence directly comparing rtCGM and isCGM, that the technologies were rapidly evolving, with newer versions being released over time, and that although isCGM monitoring was currently cheaper than rtCGM, there was no guarantee this would remain the case in the future. They considered whether a comparison between these two options in the economic modelling, would help to address these concerns, and agreed that such a comparison would provide limited value. In particular, they noted that for various parameters data was only available for one type of device or the other (for example, fear of hypoglycaemia data only being available for rtCGM, and 'process' utility data only being available for isCGM). Whilst this was not a major limitation when comparing to SMBG, as the committee were happy in places to extrapolate data from one type of device to the other, it would make modelling comparisons between the two devices less useful, as in places they would be based on the same set of effectiveness data.

Additionally, the committee noted that different devices may be more appropriate for different individuals, based on their characteristics and the features of those devices, and that matching the correct device to the correct person would be likely to improve adherence, and therefore cost-effectiveness. They therefore agreed that both rtCGM and isCGM should be made available within the NHS and people and clinicians should be able to choose between them according to their preference and needs. They did also note, however, that the overall cost impact of introducing these technologies could be high (due to the large number of people with type 1 diabetes) and that therefore if there were multiple different devices available that would meet the person's needs, the cheapest of those available devices should be used.

The recommendations on structured education and monitoring for people using rtCGM or isCGM were not expected to require substantial additional resources. This is because both education and monitoring are already recommended for all people with type 1 diabetes and would be necessary whether a person was using rtCGM, isCGM or intermittent capillary blood glucose monitoring. Therefore, whilst the content of the education/monitoring may be different based on the type of monitoring the person is using, the amount of time needed for this is unlikely to substantially change.

Other factors the committee took into account

The committee noted that broader access to isCGM and rtCGM devices should reduce inequalities, as often those with more time and knowledge to self-advocate are more likely to gain access to these devices.

The committee also considered the needs of certain groups such as older adults, people with frailty and people with physical disability, mental health related or learning disability. The committee highlighted that these groups require assistance from district nurses or a carer and therefore may need support in using their CGM device. These groups may also have limitations with their dexterity which can cause difficulties in using the device and obtaining readings. The committee also noted that people from lower socio-economic groups may experience difficulties in using CGM if their device requires access to particular higher cost technologies (such as a smartphone, computer for sharing readings with their health care professional and up to date phone software).

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.10 to 1.6.14.

1.1.10 References – included studies

1.1.10.1 Effectiveness

Avari, P., Moscardo, V., Jugnee, N. et al. (2019) Glycemic Variability and Hypoglycemic Excursions With Continuous Glucose Monitoring Compared to Intermittently Scanned Continuous Glucose Monitoring in Adults With Highest Risk Type 1 Diabetes. Journal of Diabetes Science and Technology

Battelino, T., Conget, I., Olsen, B. et al. (2014) The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: A randomized controlled trial. Diabetes Technology and Therapeutics 16(suppl1): 101-s102

Battelino, Tadej, Phillip, Moshe, Bratina, Natasa et al. (2011) Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes care 34(4): 795-800

Beck, Roy W, Riddlesworth, Tonya, Ruedy, Katrina et al. (2017) Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA 317(4): 371-378

Bolinder, Jan, Antuna, Ramiro, Geelhoed-Duijvestijn, Petronella et al. (2016) Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet (London, England) 388(10057): 2254-2263

Haskova, Aneta, Horova, Eva, Navratilova, Vendula et al. (2020) Real-time cgm is superior to flash glucose monitoring for glucose control in type 1 diabetes: The corrida randomized controlled trial. Diabetes Care 43(11): 2744-2750

Heinemann, Lutz, Freckmann, Guido, Ehrmann, Dominic et al. (2018) Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or

severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet (London, England) 391(10128): 1367-1377

JDRF (2010) Effectiveness of Continuous Glucose Monitoring in a Clinical Care Environment. Diabetes care 33(1): 17-22

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Beck, Roy W, Lawrence, Jean M et al. (2010) Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial. Diabetes care 33(10): 2175-7

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Tamborlane, William V, Beck, Roy W et al. (2008) Continuous glucose monitoring and intensive treatment of type 1 diabetes. The New England journal of medicine 359(14): 1464-76

Lind, Marcus, Polonsky, William, Hirsch, Irl B et al. (2017) Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. JAMA 317(4): 379-387

Little, Stuart A, Leelarathna, Lalantha, Walkinshaw, Emma et al. (2014) Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 x 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). Diabetes care 37(8): 2114-22

Little, Stuart A, Speight, Jane, Leelarathna, Lalantha et al. (2018) Sustained Reduction in Severe Hypoglycemia in Adults With Type 1 Diabetes Complicated by Impaired Awareness of Hypoglycemia: Two-Year Follow-up in the HypoCOMPaSS Randomized Clinical Trial. Diabetes care 41(8): 1600-1607

New, J P, Ajjan, R, Pfeiffer, A F H et al. (2015) Continuous glucose monitoring in people with diabetes: the randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). Diabetic medicine: a journal of the British Diabetic Association 32(5): 609-17

Olafsdottir, AF, Bolinder, J, Heise, T et al. (2020) Majority of people with type 1 diabetes and multiple daily insulin injection benefit by using Continuous Glucose Monitoring: an analysis based on the GOLD randomised trial (GOLD-5). Diabetes, obesity & metabolism

Olafsdottir, Arndis F, Polonsky, William, Bolinder, Jan et al. (2018) A Randomized Clinical Trial of the Effect of Continuous Glucose Monitoring on Nocturnal Hypoglycemia, Daytime Hypoglycemia, Glycemic Variability, and Hypoglycemia Confidence in Persons with Type 1 Diabetes Treated with Multiple Daily Insulin Injections (GOLD-3). Diabetes technology & therapeutics 20(4): 274-284

Oskarsson, Per, Antuna, Ramiro, Geelhoed-Duijvestijn, Petronella et al. (2018) Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy: a pre-specified subgroup analysis of the IMPACT randomised controlled trial. Diabetologia 61(3): 539-550

Pratley, Richard E, Kanapka, Lauren G, Rickels, Michael R et al. (2020) Effect of Continuous Glucose Monitoring on Hypoglycemia in Older Adults With Type 1 Diabetes: A Randomized Clinical Trial. JAMA 323(23): 2397-2406

Reddy, M, Jugnee, N, El Laboudi, A et al. (2018) A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with Type 1 diabetes and impaired awareness of hypoglycaemia. Diabetic medicine: a journal of the British Diabetic Association 35(4): 483-490

Reddy, Monika, Jugnee, Narvada, Anantharaja, Sinthuka et al. (2018) Switching from Flash Glucose Monitoring to Continuous Glucose Monitoring on Hypoglycemia in Adults with Type 1 Diabetes at High Hypoglycemia Risk: The Extension Phase of the I HART CGM Study. Diabetes technology & therapeutics 20(11): 751-757

Riveline, Jean-Pierre, Schaepelynck, Pauline, Chaillous, Lucy et al. (2012) Assessment of patient-led or physician-driven continuous glucose monitoring in patients with poorly controlled type 1 diabetes using basal-bolus insulin regimens: a 1-year multicenter study. Diabetes care 35(5): 965-71

Seyed Ahmadi, Shilan, Westman, Klara, Pivodic, Aldina et al. (2020) The Association Between HbA1c and Time in Hypoglycemia During CGM and Self-Monitoring of Blood Glucose in People With Type 1 Diabetes and Multiple Daily Insulin Injections: A Randomized Clinical Trial (GOLD-4). Diabetes care 43(9): 2017-2024

Speight, J., Holmes-Truscott, E., Little, S.A. et al. (2019) Satisfaction with the use of different technologies for insulin delivery and glucose monitoring among adults with long-standing type 1 diabetes and problematic hypoglycemia: 2-Year follow-up in the HypoCOMPaSS randomized clinical trial. Diabetes Technology and Therapeutics 21(11): 619-626

Tanenberg, Robert, Bode, Bruce, Lane, Wendy et al. (2004) Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. Mayo Clinic proceedings 79(12): 1521-6

Tansey, M, Laffel, L, Cheng, J et al. (2011) Satisfaction with continuous glucose monitoring in adults and youths with Type 1 diabetes. Diabetic medicine: a journal of the British Diabetic Association 28(9): 1118-22

Tumminia, Andrea, Crimi, Salvatore, Sciacca, Laura et al. (2015) Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled crossover trial. Diabetes/metabolism research and reviews 31(1): 61-8

van Beers, Cornelis A J, de Wit, Maartje, Kleijer, Susanne J et al. (2017) Continuous Glucose Monitoring in Patients with Type 1 Diabetes and Impaired Awareness of Hypoglycemia: Also Effective in Patients with Psychological Distress? Diabetes technology & therapeutics 19(10): 595-599

van Beers, Cornelis A J, DeVries, J Hans, Kleijer, Susanne J et al. (2016) Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. The lancet. Diabetes & endocrinology 4(11): 893-902

Visser MM, Charleer S, Fieuws S et al. (2021) Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial. Lancet (London, England) 397(10291): 2275-2283

1.1.10.2 Economic

Healthcare Improvement Scotland (2018). "What is the clinical and cost effectiveness of Freestyle Libre flash glucose monitoring for patients with diabetes mellitus treated with intensive insulin therapy?" Advice on health technologies Retrieved 11 July, 2021.

Roze, S., et al. (2020). "Long-term Cost-Effectiveness of Dexcom G6 Real-time Continuous Glucose Monitoring Versus Self-Monitoring of Blood Glucose in Patients With Type 1 Diabetes in the U.K." Diabetes care 43(10): 2411.

1

2

Appendices

Appendix A – Review protocols

Review protocol for continuous glucose monitoring in adults with type 1 diabetes

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Glucose monitoring in adults with type 1 diabetes
2.	Review question	***Guideline:*** Type 1 diabetes in adults: diagnosis and management (NG17) ***Question***: In adults with type 1 diabetes, what is the most effective method of glucose monitoring to improve glycaemic control: - 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 glycaemic control in adults with type 1 diabetes
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 There was no data limit set for these searches. Other searches: • N/A The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Type 1 diabetes in adults.

6.	Population	Adults with type 1 diabetes Adult is defined as aged 18 years and above.
7.	Intervention	• Continuous glucose monitoring • Flash glucose monitoring • Intermittent capillary blood glucose monitoring Definitions: **Continuous glucose monitoring:** Consists of a subcutaneous sensor which continuously measures the glucose levels in the interstitial fluid. Data on glucose level and direction/rate of change is automatically sent to a display device (a handheld monitor, smart phones or pump) and the user can obtain real-time data as well as trends. 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 realtime CGM (rtCGM).

		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 as intervention group. (e.g., rapid acting, short acting, intermediate, long acting or mixed insulin) as the treatment group.
9.	Types of study to be included	• RCTs • Systematic review of RCTs • If insufficient[1] RCT evidence is identified for individual comparisons, comparative prospective observational studies ○ If no prospective cohort studies are identified, comparative retrospective observational studies will be included.

		Note: Only cohort and other 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 included. [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 a large enough quantity of data to form the basis for a recommendation.

E 10.	Other exclusion criteria	• Exclude studies <1-week duration
		• Studies with mixed adult and children populations will be excluded if:
		  o data has not been reported for the subgroup of adults AND
		  o ≤50% of people are aged >18 years
		• Rare forms of diabetes (eg. MODY, LADA, Type 3c diabetes)
		• Studies with indirect, or mixed diabetes (type 1 diabetes and type 2 diabetes) populations will be excluded if:
		  o data has not been reported for the subgroup of type 1 diabetes patients OR,
		  o the population contains ≤70% of type 1 diabetes patients
		• Non-English language studies

		• Conference abstracts • Studies which examine retrospective (blinded) glucose monitoring • Studies with closed-loop systems as covered in update of NICE DG21 guideline
11.	Context	This review is part of an update of the NICE guideline on Type 1 diabetes in adults: diagnosis and management (NG17). https://www.nice.org.uk/guidance/ng17 This update covers continuous glucose monitoring in adults with type 1 diabetes. This guideline will also cover all settings where NHS healthcare is provided or commissioned.

12.	Primary outcomes (critical outcomes)	All outcomes will be sorted into up to 3 months, up to 6 months, up to 12 months, >12 months
		• HbA1c (dichotomous or continuous outcome, depending how it is reported)
		• Time spent in target glucose range
		  ○ Time spent above target glucose range
		  ○ Time spent below target glucose range
		• Hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) including:
		  ○ severe hypoglycaemia
		  ○ nocturnal hypoglycaemia

		• Glycaemic variability • Mortality • Diabetic ketoacidosis (DKA) • % of data captured
13.	Secondary outcomes (important outcomes)	• Other adverse events (dichotomous) limited to: o Diabetes related hospitalisation o malfunction of CGM monitor o serious adverse events • Mental health outcomes: o Diabetes distress (including fear of hypoglycaemia and diabetes burnout) o Diabetes related depression o Body image issues due to CGM monitor o Eating disorders due to diabetes • Awareness of hypoglycaemia • Adherence (dichotomous) • 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))
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 be dependent on study design. Cohort studies will be assessed using the Cochrane ROBINS-I 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: • ≤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 • Different testing sites in SMBG The following groups will be considered for subgroup analysis if heterogeneity is present: • People who are frail • People with learning difficulties or autism • People with renal impairment • People who have hypoglycaemic unawareness • Long duration of diabetes (>10 years) • People who are unable to self-test • People with distress/ depression/ co-morbid mental ill-health • Frequency of CGM (real time) • Frequency of intermittent capillary blood glucose monitoring • Generic vs individualised range (for time in range) • Target HbA1c % • Target Time in range • Ethnicity (Whether people are from an ethnic minority)
	Type and method of review	☒ Intervention

18.		☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	01/05/2021		
22.	Anticipated completion date	*18/08/2021*		
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 **5c Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		

25.	Review team members	From the Guideline Updates Team: • Caroline Mulvihill • Joseph Crutwell • Kusal Lokuge • Joshua Pink • David Nicholls
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, 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	

36.	Details of final publication	www.nice.org.uk

1

2

Appendix B – Methods

Development of the guideline

What this guideline covers

This guideline covers the updated of Type 1 diabetes recommendations regarding continuous blood glucose monitoring.

What this guideline does not cover

This does not cover type 2 diabetes, or type 1 diabetes in children and young people <18

Methods

This guideline was developed using the methods described in the 2018 NICE guidelines manual.

Declarations of interest were recorded according to the NICE conflicts of interest policy.

Developing the review questions and outcomes

The review question developed for this guideline was based on the key areas identified in the guideline scope. They were drafted by the NICE guideline updates team and refined and validated by the guideline committee.

The review questions were based on the following frameworks:

- Population, Intervention, Comparator and Outcome [and Study type] (PICO[S]) for reviews of interventions

Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

Reviewing research evidence

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review. Where possible, review protocols were prospectively registered in the PROSPERO register of systematic reviews.

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2018 NICE guidelines manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The following evidence reviews made use of the priority screening functionality within the EPPI-reviewer software: [insert links to evidence reviews that used the priority screening functionality in EPPI]. This functionality 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. Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstracts can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination) and was always a minimum of 250.

As an additional check to ensure this approach did not miss relevant studies, systematic reviews (or qualitative evidence syntheses in the case of reviews of qualitative studies) were included in the review protocol and search strategy for all review questions. Relevant systematic reviews or qualitative evidence syntheses were used to identify any papers not found through the primary search. Committee members were also consulted to identify studies that were missed. If additional studies were found that were erroneously excluded during the priority screening process, the full database was subsequently screened.

The decision whether or not to use priority screening was taken by the reviewing team depending on the perceived likelihood that stopping criteria would be met, based on the size of the database, heterogeneity of studies included in the review and predicted number of includes. If it was thought that stopping criteria were unlikely to be met, priority screening was not used, and the full database was screened.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies. Study investigators were contacted for missing data when time and resources allowed (when this occurred, this was noted in the evidence review and relevant data was included).

Methods of combining evidence

Data synthesis for intervention studies

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. Network meta-analyses was considered in situations where there were at least 3 treatment alternatives. When there were 2 treatment alternatives, pairwise meta-analysis was used to compare interventions.

Pairwise meta-analysis

Pairwise 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. using the package 'metafor'. 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).

A pooled mean difference was calculated for continuous outcomes (using the inverse variance method) when the same scale was used to measure an outcome across different studies. 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 (SMDs, Hedges' g).

For continuous outcomes analysed as mean differences, change from baseline values were used in the meta-analysis if they were accompanied by a measure of spread (for example standard deviation). Where change from baseline (accompanied by a measure of spread) were not reported, the corresponding values at the timepoint of interest were used. If only a subset of trials reported change from baseline data, final timepoint values were combined with change from baseline values to produce summary estimates of effect. For continuous outcomes analysed as standardised mean differences this was not possible. In this case, if all studies reported final timepoint data, this was used in the analysis. If some studies only reported data as a change from baseline, analysis was done on these data, and for studies where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient derived from studies reporting both baseline and endpoint data, or if no such studies were available, assuming a correlation of 0.5 as a conservative estimate (Follman et al., 1992; Fu et al., 2013).. In cases where SMDs were used they were back converted to a single scale to aid interpretation by the committee where possible.

Random effects models were fitted when there was 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.

For all other syntheses, fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. 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 there was 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 were less heterogeneous (with $I^2 < 50\%$) the results from these subgroups were reported using fixed effects models. This may have led to situations where pooled results were reported from random-effects models and subgroup results were reported from fixed-effects models.

Where sufficient studies were available, meta-regression was considered to explore the effect of study level covariates.

Appraising the quality of evidence

Intervention studies (relative effect estimates)

RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Non-randomised controlled trials and cohort studies were quality assessed using the ROBINS-I tool. Other study types (for example controlled before and after studies) were assessed using the preferred option specified in the NICE guidelines manual 2018 (appendix H). Evidence on each outcome for 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.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. 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 agreed a consensus clinical decision threshold 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 a clinical decision threshold to be defined to act as a non-inferiority margin.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes. Clinical decision threshold that were used in the guideline are given in **Error! Reference source not found.** and also reported in the relevant evidence reviews.

Table 10: Identified Clinical decision thresholds

Outcome	Clinical decision threshold	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	Battelino 2019
*Full reference provided in reference section.		

For continuous outcomes expressed as a mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For continuous outcomes expressed as a standardised mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 standard deviations was used. For SMDs that were back converted to one of the original scales to aid interpretation, rating of imprecision was carried out before back calculation. For relative risks and hazard ratios, where no other clinical decision threshold was available, a default clinical decision threshold for dichotomous outcomes of 0.8 to 1.25 was used. Odds ratios were converted to risk ratios before presentation to the committee to aid interpretation.

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials, non-randomised controlled trials and cohort studies (which were quality assessed using the Cochrane risk of bias tool or ROBINS-I) were initially rated as high quality while data from other study types were initially 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 **Error! Reference source not found.**.

Table 11: 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.

GRADE criteria	Reasons for downgrading quality
	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
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.
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.
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), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. 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.
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

For outcomes that were originally assigned a quality rating of 'low' (when the data was from observational studies that were not appraised using the ROBINS-I checklist), the quality of evidence for each outcome was upgraded if any of the following three conditions were met and the risk of bias for the outcome was rated as 'no serious':

- Data from studies showed an effect size sufficiently large that it could not be explained by confounding alone.
- Data showed a dose-response gradient.
- Data where all plausible residual confounding was likely to increase our confidence in the effect estimate.

Appendix C – Literature search strategies

Clinical evidence

Previous searching undertaken on 18th December 2019. During Medline reload

Databases	Date searched	Version/files	No. retrieved	After de-dupe	EPPI-R5 data
Cochrane Central Register of Controlled Trials (CENTRAL)	11/05/2021	Issue 4 of 12, April 2021	556	252	7218172-7218724
Cochrane Database of Systematic Reviews (CDSR)	11/05/2021	Issue 5 of 12, May 2021	4	1	7218729
Database of Abstracts of Reviews of Effect (DARE)	11/05/2021	n/a	0	0	-
Embase (Ovid)	11/05/2021	1974 to 2021 May 10	420	284	7217750-7218168
MEDLINE (Ovid)	11/05/2021	1946 to May 10, 2021	232	138	7217384-7217615
MEDLINE In-Process (Ovid)	11/05/2021	1946 to May 10, 2021	100	7	7217641-7217703
MEDLINE Epub Ahead of Print	11/05/2021	May 10, 2021	34	7	7217720-7217744
PsycINFO (Ovid)	11/05/2021	1806 to May Week 1 2021	2	0	-

Search strategies

Database: Medline

1 exp Diabetes Mellitus/ or Pregnancy in diabetics/ (447120)

2 diabet*.tw. (571506)

3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (1733)

4 lada.tw. (559)

5 (dm1 or iddm or t1d* or dka).tw. (20360)

6 (dm2 or t2d* or mody or niddm).tw. (35344)

7 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (4485)

8 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (327)

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

10 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (93)

11 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (882)

12 (DM adj4 (keto* or acidi* or gastropare*)).tw. (78)

13 or/1-12 (639053)

14 Blood Glucose Self-Monitoring/ or Monitoring, Ambulatory/ or Blood Glucose/ (179100)

15 (continu* or flash or real-time or "real time" or realtime).tw. (1134222)

16 14 and 15 (14656)

17 (continu* adj4 glucose adj4 monitor*).tw. (3962)

18 (ambulatory adj4 glucose adj4 monitor*).tw. (48)

19 (CGM or CGMS or CBGM).tw. (2373)

20 Extracellular Fluid/ or Extracellular Space/ (29241)

21 ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw. (27970)

22 IPRO2*.tw. (25)

23 (("real time" or real-time or realtime or retrospective*) adj4 (glucose adj4 monitor*)).tw. (394)

24 (RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM").tw. (151)

25 flash.tw. (16110)

26 FGM.tw. (938)

27 glucorx.tw. (2)

28 (medtronic* adj4 (enlight* or veo* or guardian* or envision*)).tw. (55)

29 (Senseonic* adj4 eversense*).tw. (3)

30 (Dexcom* adj4 (G4* or G5* or G6* or 7* or seven*)).tw. (134)

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. (121)

34 "free style libre*".tw. (6)

35 or/16-34 (82580)

36 13 and 35 (10249)

37 animals/ not humans/ (4789549)

38 36 not 37 (8912)

39 limit 38 to english language (8359)

40 randomized controlled trial.pt. (529163)

41 randomi?ed.mp. (838229)

42 placebo.mp. (202187)

43 or/40-42 (891167)

44 (MEDLINE or pubmed).tw. (184319)

45 systematic review.tw. (140329)

46 systematic review.pt. (150382)

47 meta-analysis.pt. (131111)

48 intervention$.ti. (133667)

49 or/44-48 (420086)

50 43 or 49 (1191929)

51 39 and 50 (1970)

52 limit 51 to ed=20191201-20210511 (232)

1

Database: EMBASE

1 exp diabetes mellitus/ (1026910)

2 diabet*.tw. (1002188)

3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (4229)

4 lada.tw. (1067)

5 (dm1 or iddm or t1d* or dka).tw. (42866)

6 (dm2 or t2d* or mody or niddm).tw. (78155)

7 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (11255)

8 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (774)

9 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (117)

10 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (170)

11 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (1965)

12 (DM adj4 (keto* or acidi* or gastropare*)).tw. (204)

13 or/1-12 (1220893)

14 blood glucose monitoring/ (28563)

15 glucose blood level/ (267376)

16 glucose level/ (3054)

17 or/14-16 (287556)

18 (continuous or flash or real-time or "real time" or realtime).tw. (943263)

19 17 and 18 (18714)

20 continuous glucose monitoring system/ (2116)

21 (continu* adj4 glucose adj4 monitor*).tw. (9327)

22 (ambulatory adj4 glucose adj4 monitor*).tw. (84)

23 (CGM or CGMS or CBGM).tw. (7090)

24 extracellular fluid/ (7666)

25 ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw. (36962)

26 IPRO2*.tw. (190)

27 IPRO2*.dv. (98)

28 (("real time" or real-time or retrospective*) adj4 (glucose adj4 monitor*)).tw. (900)

29 (RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM").tw. (414)

30 flash.tw. (26074)

31 FGM.tw. (1697)

32 glucorx.tw. (4)

33 (medtronic* adj4 (enlight* or veo* or guardian* or Envision*)).tw. (196)

34 (enlight* or veo* or guardian*).dv. (670)

35 (Senseonic* adj4 eversense*).tw. (23)

36 eversense*.dv. (48)

37 (Dexcom* adj4 (G4* or G5* or G6* or 7* or seven*)).tw. (642)

38 (G4* or G5* or G6* or G7*).dv. (827)

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

40 (A6* or TouchCare*).dv. (49)

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

42 navigator*.dv. (452)

43 ((freestyle* adj4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*)).tw. (642)

44 (libre* or FSL-Pro* or "FSL Pro*" or FSLPro*).dv. (343)

45 or/19-44 (91653)

46 13 and 45 (19043)

47 nonhuman/ not human/ (4870423)

48 46 not 47 (17503)

49 limit 48 to english language (16679)

50 random:.tw. (1680671)

51 placebo:.mp. (480236)

52 double-blind:.tw. (222680)

53 or/50-52 (1945300)

54 (MEDLINE or pubmed).tw. (299467)

55 exp systematic review/ or systematic review.tw. (355218)

56 meta-analysis/ (217009)

57 intervention$.ti. (219364)

58 or/54-57 (743001)

59 53 or 58 (2455815)

60 49 and 59 (3456)

61 limit 60 to (conference abstract or conference paper or "conference review") (1446)

62 60 not 61 (2010)

63 limit 62 to dc=20191201-20210511 (420)

1

2

Database: PsychINFO
1 exp Diabetes Mellitus/ (8904)
2 diabet*.tw. (33238)
3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (92)
4 lada.tw. (12)
5 (dm1 or iddm or t1d* or dka).tw. (1147)
6 (dm2 or t2d* or mody or niddm).tw. (1891)
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. (55)
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. (239)
13 or/1-12 (34051)
14 Blood Sugar/ (1252)
15 (continuous or flash or real-time or "real time" or realtime).tw. (71491)
16 14 and 15 (57)
17 (continu* adj4 glucose adj4 monitor*).tw. (78)
18 (ambulatory adj4 glucose adj4 monitor*).tw. (1)
19 (CGM or CGMS or CBGM).tw. (106)
20 ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw. (1235)
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. (19)
24 flash.tw. (3733)
25 FGM.tw. (226)
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 (5402)
35	13 and 34 (121)
36	animals/ not humans/ (7304)
37	35 not 36 (121)
38	limit 37 to english language (118)
39	randomized controlled trial.pt. (0)
40	randomi?ed.mp. (90533)
41	placebo.mp. (41565)
42	(MEDLINE or pubmed).tw. (25778)
43	systematic review.tw. (32190)
44	systematic review.pt. (0)
45	meta-analysis.pt. (0)
46	intervention*.ti. (75755)
47	or/39-46 (213483)
48	38 and 47 (18)
49	limit 48 to yr=2019-2021 (2)

1

2

Database: Cochrane (CDSR/CENTRAL)	
#1	MeSH descriptor: [Diabetes Mellitus] explode all trees 32244

#2 MeSH descriptor: [Pregnancy in Diabetics] this term only 226

#3 (diabet*):ti,ab,kw 97681

#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 266

#5 (lada):ti,ab,kw 71

#6 ((dm1 or iddm or t1d* or dka)):ti,ab,kw 3621

#7 ((dm2 or t2d* or mody or niddm)):ti,ab,kw 11261

#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 1286

#9 ((DM near/4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw):ti,ab,kw 409

#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 202

#12 ((DM near/4 (earl* or sudden onset or juvenile or child*))):ti,ab,kw 236

#13 ((DM near/4 (keto* or acidi* or gastropare*))):ti,ab,kw 12

#14 {or #1-#13} 99309

#15 MeSH descriptor: [Blood Glucose Self-Monitoring] this term only 812

#16 MeSH descriptor: [Monitoring, Ambulatory] this term only 554

#17 MeSH descriptor: [Blood Glucose] this term only16312

#18 {or #15-#17} 16993

#19 ((continu* or flash or real-time or "real time" or realtime)):ti,ab,kw 144707

#20 #18 and #19 2203

#21 ((continu* near/4 glucose near/4 monitor*)):ti,ab,kw 2435

#22 ((ambulatory near/4 glucose near/4 monitor*)):ti,ab,kw 26

#23 ((CGM or CGMS or CBGM)):ti,ab,kw 1897

#24 MeSH descriptor: [Extracellular Fluid] this term only 65

#25 MeSH descriptor: [Extracellular Space] this term only 119

#26 (((extracellular* or interstitial* or intercellular*) near/4 (fluid* or space))):ti,ab,kw 940

#27 (IPRO2*):ti,ab,kw 63

#28 ((("real time" or real-time or retrospective*) near/4 (glucose near/4 monitor*))):ti,ab,kw 281

#29 ((RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM")):ti,ab,kw 118

#30 (flash):ti,ab,kw 1144

#31 (FGM):ti,ab,kw 166

#32 (glucorx):ti,ab,kw 1

#33 ((medtronic* near/4 (enlight* or veo* or guardian*))):ti,ab,kw 38

#34 ((Senseonic* near/4 eversense*)):ti,ab,kw 6

#35 ((Dexcom* near/4 (G4* or G5* or G6* or 7* or seven*))):ti,ab,kw 201

#36 ((medtrum* near/4 (A6* or TouchCare*))):ti,ab,kw 4

#37 ((freestyle* near/4 navigator*)):ti,ab,kw19

#38 (((freestyle* near/4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*))):ti,ab,kw 164

#39 "free style libre*" 99

#40 {or #20-#39} 6558

#41 #14 and #40 3848

#42 (clinicaltrials or trialsearch):so 364015

#43 #41 not #42 with Publication Year from 2019 to 2021, in Trials 556

#44 #41 not #42 with Cochrane Library publication date Between Dec 2019 and May 2021, in Cochrane Reviews, Cochrane Protocols 4

1

2

Database: CRD

☐	1	MeSH DESCRIPTOR Diabetes Mellitus EXPLODE ALL TREES IN DARE	1327
☐	2	MeSH DESCRIPTOR Pregnancy in Diabetics EXPLODE ALL TREES IN DARE	23
☐	3	((diabet*))	4478
☐	4	(((DM near4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I))))	2
☐	5	((lada))	1

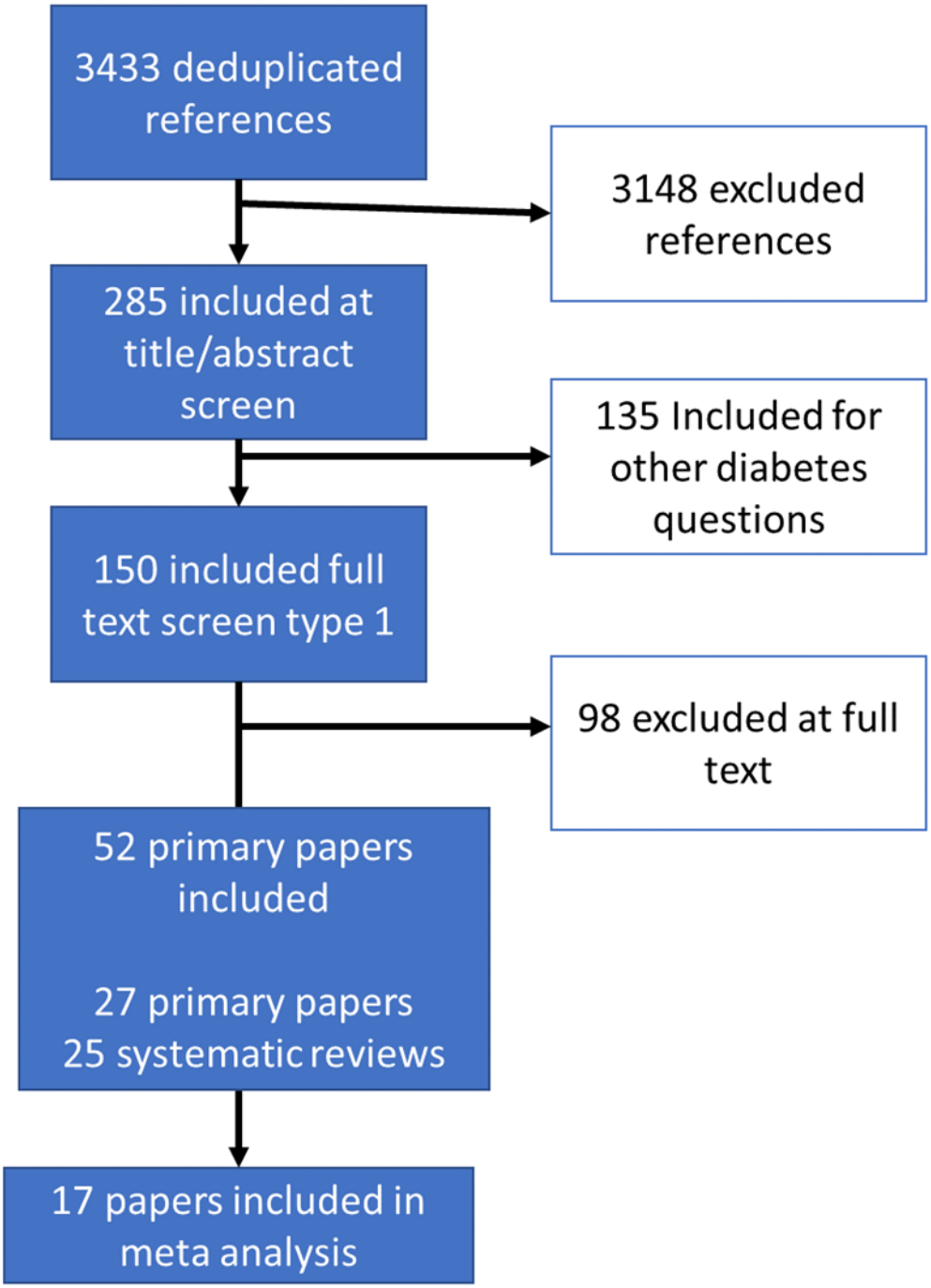
☐	6	(((dm1 or iddm or t1d* or dka)))	53
☐	7	(((dm2 or t2d* or mody or niddm)))	83
☐	8	(((DM near4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II))))	4
☐	9	((DM near4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)))	0
☐	10	(((DM near4 onset* near4 (maturit* or adult* or slow*))))	0
☐	11	(((DM near4 depend* near4 (non-insulin* or non insulin* or noninsulin*))))	0
☐	12	(((DM near4 (earl* or sudden onset or juvenile or child*))))	1
☐	13	(((DM near4 (keto* or acidi* or gastropare*))))	0
☐	14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	4521
☐	15	MeSH DESCRIPTOR Blood Glucose Self-Monitoring IN DARE	44
☐	16	MeSH DESCRIPTOR Monitoring, Ambulatory IN DARE	22
☐	17	MeSH DESCRIPTOR Blood Glucose IN DARE	340
☐	18	#15 OR #16 OR #17	373
☐	19	(((continu* or flash or real-time or "real time" or realtime)))	6720
☐	20	#18 AND #19	53
☐	21	(((continu* near4 glucose near4 monitor*)))	51
☐	22	(((ambulatory near4 glucose near4 monitor*)))	1

☐	23	(((CGM or CGMS or CBGM)))	20
☐	24	MeSH DESCRIPTOR Extracellular Fluid IN DARE	1
☐	25	MeSH DESCRIPTOR Extracellular Space IN DARE	0
☐	26	((((extracellular* or interstitial* or intercellular*) near4 (fluid* or space))))	13
☐	27	((IPRO2*))	0
☐	28	((((“real time” or real-time or retrospective*) near4 (glucose near4 monitor*))))	11
☐	29	(((RTCGM or RT-CGM or “RT CGM” or R-CGM or RCGM or “R CGM”)))	3
☐	30	((flash))	19
☐	31	((FGM))	6
☐	32	((glucorx))	0
☐	33	(((medtronic* near4 (enlight* or veo* or guardian*))))	0
☐	34	(((Senseonic* near4 eversense*)))	0
☐	35	(((Dexcom* near4 (G4* or G5* or G6* or 7* or seven*))))	0
☐	36	(((medtrum* near4 (A6* or TouchCare*))))	0
☐	37	(((freestyle* near4 navigator*)))	1
☐	38	((((freestyle* near4 libre*) or (FSL-Pro* or “FSL Pro*” or FSLPro*))))	0
☐	39	(“free style libre*”)	0

☐	40	#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 OR #39	126
☐	41	#14 AND #40	84
☐	42	(#14 and #40) IN DARE WHERE LPD FROM 01/12/2019 TO 11/05/2021	0

1
2

Appendix D – Effectiveness evidence study selection



1 Appendix E – Effectiveness evidence

2 Avari, 2019

Bibliographic Reference	Avari, P.; Moscardo, V.; Jugnee, N.; Oliver, N.; Reddy, M.; Glycemic Variability and Hypoglycemic Excursions With Continuous Glucose Monitoring Compared to Intermittently Scanned Continuous Glucose Monitoring in Adults With Highest Risk Type 1 Diabetes; Journal of Diabetes Science and Technology; 2019

3

4 Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Reddy, M, Jugnee, N, El Laboudi, A et al. (2018) A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with type 1 diabetes and impaired awareness of hypoglycaemia. Diabetic medicine : a journal of the British Diabetic Association 35(4): 483-490 Reddy, Monika, Jugnee, Narvada, Anantharaja, Sinthuka et al. (2018) Switching from Flash Glucose Monitoring to Continuous Glucose Monitoring on Hypoglycemia in Adults with type 1 Diabetes at High Hypoglycemia Risk: The Extension Phase of the I HART CGM Study. Diabetes technology & therapeutics 20(11): 751-757
Trial registration number and/or trial name	I-HART CGM; NCT03028220
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	A single specialist site in the UK
Study dates	Not reported
Sources of funding	This work was supported by DEXCOM.
Inclusion criteria	People with T1D Age ≥18 years

	Duration of diabetes >3 years Using an intensified MDI regimen for over six months Adults
Intervention(s)	Both continuous glucose monitoring and flash glucose monitoring (rtCGM and iscCGM systems) were used non-adjunctively in accordance with product licenses. After eight weeks, participants using iscCGM were switched to the Dexcom G5, and those using Dexcom G5 were offered the opportunity to continue with the Dexcom G5 for a further eight-week period. Low glucose alert settings for rtCGM were standardised at 4.4 mmol/L (79 mg/dL) for all participants at the start of the study and were then reduced to 4.0 mmol/L (72 mg/dL) at week 2 depending on participant preference. High glucose alerts were initially set at >11.1 mmol/L (200 mg/dL), but could later be personalised.
Outcome measures	HBA1C Time in range Percentage time spent in target (3.9–10 mmol/l). Time spent above/below target glucose range Percentage time spent in hypoglycaemia <2.8, 3.5 and 3.9 mmol/l, percentage time in euglycaemia (3.9–7.8 mmol/l), percentage time spent in hyperglycaemia >7.8, >10 and >15 mmol/l. These definitions were taken from Reddy 2018. Change in time spent in hypoglycaemia (<3.3 mmol/l). Hypoglycaemia Number of hypoglycaemic episodes; each episode of hypoglycaemia was defined based on a minimum duration of 20 minutes and a separation time of 15 minutes. Glucose thresholds of <3.0 mmol/L (54 mg/dL) and <3.9 mmol/L (70 mg/dL) were measured. Severe hypoglycaemia (requiring third-party assistance to treat). Glycaemic variability Measures of glycaemic variability (GV) were computed using EasyGV (v10.0) software. Evaluated GV measures are SD, CV, MAGE, CONGA, MODD, LI, MAG, GVP, PGS, M-value, IGC, RI, GRADE, ADRR, J-index, HBGI, and LBGI. Glycaemic risk assessment diabetes equation score is also reported as GRADE% hypoglycaemia, GRADE% euglycaemia, and GRADE% hyperglycaemia representing percentages of GRADE scores attributable to glucose values <3.9 mmol/L (<70 mg/dL), and between 3.9 to 7.8 mmol/L (70-140 mg/dL) and >7.8 mmol/L (>140 mg/dL), respectively.

	Mental health outcomes Hypoglycaemia fear (HFS-II) and diabetes-related emotional distress (PAID questionnaire). Awareness of hypoglycaemia Gold score
Number of participants	Continuous glucose monitoring N=20 Flash glucose monitoring N=20
IGNORE	
Type of insulin delivery system	Multiple daily injections
Duration of follow-up	8 and 16 weeks
Loss to follow-up	
Additional comments	All participants had experienced a severe hypoglycaemic event within the last 12 months requiring third-party assistance or had a Gold score of greater than or equal to 4. All individuals had received structured education either as group or in a one to one environment from a specialist educator. All participants were commenced on blinded rtCGM (Dexcom G4, San Diego, CA, United States) for a two-week run-in phase. Calibration to capillary blood glucose was carried out a minimum of twice daily. From this, the baseline data were calculated. Type of insulin regimen was not reported.

1

2 Study arms

3 Continuous glucose monitoring (N = 20)

Loss to follow-up	There were 4 dropouts

4 Real-time continuous glucose monitoring (rtCGM) using Dexcom G5

Flash glucose monitoring (N = 20)

Loss to follow-up	None reported

Intermittently scanned continuous glucose monitoring (iscCGM) using Abbott Freestyle Libre

Characteristics

Study-level characteristics

Characteristic	**Study (N = 40)**
% Female Nominal	40
Mean age (SD) (years) Median (IQR)	49.5 (37.5 to 63.5)
Time since diabetes diagnosis (years) Median (IQR)	30 (21 to 36.5)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomly assigned to CGM (Dexcom G5) or flash glucose monitoring (Abbott Freestyle Libre) in a 1 :1 ratio using an online randomization tool (sealedenvelope.com) [Reddy 2018])*
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 *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Moderate (results selected from median and mean and no explanation given for why certain analysis were preferred. Median not mentioned in protocol)
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unblinded nature of studies not marked down, nature of each outcomes usefulness RE: measurement and objectivity will be discussed with committee. Unclear reporting decisions.)*
Overall bias and Directness	Overall Directness	Directly applicable

1

2 Battelino, 2014

Bibliographic Reference	Battelino, T.; Conget, I.; Olsen, B.; Schutz-Fuhrmann, I.; Hommel, E.; Hoogma, R.; Schierloh, U.; Sulli, N.; Bolinder, J.; The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: A randomized controlled trial; Diabetes Technology and Therapeutics; 2014; vol. 16 (no. suppl1); 101-s102

3

4 Study details

Trial registration number and/or trial name	SWITCH; NCT00598663
Study type	Cross-over randomised controlled trial
Study location	Europe
Study setting	Four adult sites in Europe with experience in the use of insulin pumps and CGM.
Study dates	January 2008 to July 2010
Sources of funding	The study was funded by Medtronic International Trading Sarl, Tolochenaz, Switzerland.
Inclusion criteria	People with T1D

	Duration of diabetes >1 year Adults Participants were aged 19−70 years Treatment with continuous subcutaneous insulin infusion (CSII) therapy with rapid-acting insulin analogues for more than 6 months HbA1c between 7.5% and 9.5% (58.5 and 80.3 mmol/mol) Naive to CGM Had successfully completed a five-question multiple choice test concerning pump therapy and general understanding of diabetes
Exclusion criteria	Hypoglycaemia unawareness (i.e. hypoglycaemia without symptoms) Concomitant chronic illness known to affect diabetes control and any pharmacological treatment that might modify glycaemic values ≥3 incidents of severe hypoglycaemia in the last 12 months
Intervention(s)	"During a 1-month run-in phase, participants used a glucometer (Bayer Ascensia Contour; Bayer Diabetes Care, Basel, Switzerland) and an insulin pump system (Mini-Med Paradigm REAL-Time System; Medtronic, Tolochenaz, Switzerland) able to integrate CGM in the study phase. All participants received structured training on diabetes management and device use and had their knowledge assessed. Each treatment period was 6 months long, with a 4-month washout phase between the two periods. All participants wore a continuous glucose monitor (Guardian REAL-Time Clinical; Medtronic, Tolochenaz, Switzerland), which they were blinded to (the device screen was turned off), for 2 weeks prior to randomisation and prior to crossover. Participants in the Sensor Off arm wore the device for 2 weeks prior to each study visit. No common treatment protocols or fixed algorithms were provided to the centres, and therapy adjustments were made in consultation with participants at clinic visits. Participants were individually encouraged to make self-adjustments to their treatment using real-time CGM values, hyper- and hypoglycaemic alerts and trends, or to incorporate self-monitoring of blood glucose (SMBG) results into treatment adjustments, with written examples of therapy changes provided in the optional patient diary. Participants completed a ten-question test to demonstrate technical knowledge on the pump (4 weeks before randomisation) and a 12-question test on CGM (at visit 1 of the On/Off sequence or visit 6 of the Off/On sequence)."
Outcome measures	HBA1C

	Difference in HbA1c levels between the Sensor On and Sensor Off arms after 6 months of follow-up, adjusting for baseline levels. Time in range Changes in the time spent in euglycaemia (3.9–10 mmol/l). Time spent above/below target glucose range Changes in the time spent in hypoglycaemia (<3.9 mmol/l) and hyperglycaemia (>10 mmol/l). Hypoglycaemia The number of SMBG values <3.9 mmol/l were calculated from the glucose meter downloads for 15 days prior to the end of each period. Severe hypoglycaemia was defined as an episode requiring assistance from another person or neurological recovery in response to restoration of plasma glucose to normal. Diabetic ketoacidosis Ketoacidosis events were defined as episodes of hyperglycaemia (blood glucose >13.9 mmol/l) with low serum bicarbonate (<15 mmol/l), low pH (<7.3) or both, together with either ketonaemia or ketonuria, that required treatment in a healthcare facility. Adverse events
Number of participants	Continuous glucose monitoring Sensor On/Sensor Off N=76 Continuous glucose monitoring Sensor Off/Sensor On N=77
IGNORE	
Type of insulin delivery system	Continuous subcutaneous insulin infusion Insulin pump
Type of insulin regimen	Rapid acting
Duration of follow-up	6 months
Loss to follow-up	Reported for all participants without separate information for adults.
Additional comments	Sensor data for the secondary endpoints were extracted from CareLink Clinical (CareLink Therapy Management System for Diabetes-Clinical, Medtronic, Tolochenaz, Switzerland) during the 15-day period prior to the end-of period (6-month) visit. For the Sensor On arm, 100% sensor use

	was calculated as the number of days in the Sensor On period multiplied by 288, the maximum number of sensor readings per day. The study also included children but only data from adults was extracted for this evidence review.

Study arms

Continuous glucose monitoring Sensor Off/Sensor On (N = 41)

Guardian REAL-Time Clinical; Medtronic, Tolochenaz, Switzerland

Continuous glucose monitoring Sensor On/Sensor Off (N = 40)

Guardian REAL-Time Clinical; Medtronic, Tolochenaz, Switzerland

Characteristics

Arm-level characteristics

Characteristic	Continuous glucose monitoring Sensor Off/Sensor On (N = 41)	Continuous glucose monitoring Sensor On/Sensor Off (N = 40)
% Female Nominal	51	55
Mean age (SD) (years) Mean (SD)	42 (11)	42 (10)
BMI (years) Mean (SD)	26 (3.2)	25 (3.3)
Time since diabetes diagnosis (kg/m²) Mean (SD)	21 (8.9)	24 (11)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) T1 Cross-over trial

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low *(4 months long enough to lose CGM learning effect? Committee opinion.Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
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	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*
Overall bias and Directness	Overall Directness	Directly applicable *(Only data on adults was taken from this study.)*

1

2 Battelino, 2011

Bibliographic Reference	Battelino, Tadej; Phillip, Moshe; Bratina, Natasa; Nimri, Revital; Oskarsson, Per; Bolinder, Jan; Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes.; Diabetes care; 2011; vol. 34 (no. 4); 795-800

3

4 Study details

Secondary publication of another included	

study- see primary study for details	
Other publications associated with this study included in review	
Trial registration number and/or trial name	International navigator hypoglycaemia study; NCT00843609
Study type	Randomised controlled trial (RCT)
Study location	Sweden
Study setting	All eligible patients identified from the local diabetes registries
Study dates	October 2008 to May 2009
Sources of funding	This study was supported by Abbott Diabetes Care.
Inclusion criteria	People with T1D Duration of diabetes >1 year Aged between 10 and 65 years Reasonable metabolic control assessing carbohydrate intake and self-adjusting insulin HbA1c level <7.5% Using intensive insulin treatment with either an insulin pump or multiple daily injections Not using a real-time continuous glucose monitoring device for at least 4 weeks
Intervention(s)	**Continuous glucose monitoring** Patients were assigned to real-time continuous glucose monitoring, wearing individual sensors for 5 days continuously for 26 weeks (continuous monitoring group).

	Intermittent capillary blood glucose monitoring Patients were assigned to home monitoring with a FreeStyle blood glucose meter and a masked continuous glucose monitor to be worn for 5 days every second week (control group).
Outcome measures	HBA1C Time in range Continuous glucose monitoring data in both groups were used to estimate the amount of time per day the glucose level was in the target range (70 to 180 mg/dL or 90 to 180 mg/dL). Time spent above/below target glucose range Continuous glucose monitoring data in both groups were used to estimate the amount of time per day the glucose level was hypoglycaemic (<63 mg/dL, <70 mg/dL, or <55 mg/dL), hyperglycaemic (>180 mg/dL or >250 mg/dL). Time spent in hypoglycaemia (<63 mg/dL) during the 26-week study period. Hypoglycaemia The number of hypoglycaemic excursions (<55 and <63 mg/dL) per day and separately during the night period of 0000–0600 h was calculated. An excursion was defined as all consecutive recordings outside the boundary covering at least 10 min. The duration of an excursion was defined as the elapsed time from first excursion to the first reading indicating return inside the excursion boundary. Diabetic ketoacidosis Adverse events Including severe hypoglycaemia, hyperglycaemia resulting in ketoacidosis requiring intravenous fluids, device-related or study-related untoward events, and serious adverse events regardless of cause.
Number of participants	Continuous glucose monitoring N=62 Intermittent capillary blood glucose monitoring N=58
Type of insulin delivery system	Multiple daily injections Insulin pump
Duration of follow-up	6 months
Additional comments	Patients entered a 4-week run-in period during which self-monitoring of blood glucose (SMBG) was conducted according to patients' standard glycaemic management regimen. A FreeStyle blood glucose meter (Abbott

	Diabetes Care, Alameda, CA) was provided to familiarise patients with FreeStyle test strips and collect baseline SMBG frequency and glucose levels. Diaries were distributed for recording events of hypoglycaemia and associated food intake, insulin doses, and exercise. Type of insulin regimen was not reported.

Study arms

Continuous glucose monitoring (N = 62)

Loss to follow-up	Did not receive allocated control treatment (n=1; withdrew immediately, too busy to use device) Discontinued (n=9): • Too busy to use device (n=4) • Too difficult to operate device (n=2) • Too difficult to operate device/technical problems with sensor (n=1) • Skin inflammation at insertion site (n=1) • Transmitter falls off during sport (n=1)

Real-time continuous glucose monitoring with the FreeStyle Navigator (Abbott Diabetes Care)

Intermittent capillary blood glucose monitoring (N = 58)

Loss to follow-up	Discontinued (n=9): • Alarms too frequent (n=3) • Alarms too frequent/too difficult to operate (n=1) • Device too big (n=2) • Too busy to use device (n=1) • Too difficult to operate device (n=1) • Too frequent adhesive failure (n=1)
Methods of analysis	

Standard self-monitoring of blood glucose (SMBG)

Characteristics

Arm-level characteristics

Characteristic	Continuous glucose monitoring (N = 62)	Intermittent capillary blood glucose monitoring (N = 58)
% Female Nominal	42	33
Mean age (SD) (years) Mean (SD)	25.7 (14.1)	26 (14.6)
BMI (kg/m²) Mean (SD)	22.4 (3.8)	22 (3.8)
Time since diabetes diagnosis (years) Mean (SD)	11.6 (11.3)	11.4 (11.4)
Previous CGM Sample size	n = 21 ; % = 34	n = 18 ; % = 31

1

2

3 Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

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 *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
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	Some concerns *(Wearing of blinded CGM monitors in control group may affect behaviour and outcome relying on CGM data check with committee.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Wearing of blinded CGM monitors in control group may affect behaviour and outcome relying on CGM data check with committee.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Under 50% were paediatric patients.)*

1

2 Beck, 2017

Bibliographic Reference	Beck, Roy W; Riddlesworth, Tonya; Ruedy, Katrina; Ahmann, Andrew; Bergenstal, Richard; Haller, Stacie; Kollman, Craig; Kruger, Davida; McGill, Janet B; Polonsky, William; Toschi, Elena; Wolpert, Howard; Price, David; DIAMOND Study, Group; Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial.; JAMA; 2017; vol. 317 (no. 4); 371-378

3

4 Study details

Trial registration number and/or trial name	DIAMOND; NCT02282397
Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	25 endocrinology practices
Study dates	October 2014 to December 2015
Sources of funding	Dexcom, Inc. (San Diego, CA).
Inclusion criteria	People with T1D Treated for at least 1 year with multiple daily insulin injections HbA1c 7.5% to 10.0% No home use of a personal CGM device in the 3 months before the trial Performed blood glucose tests approximately four times per day

	25 years or older A negative pregnancy test for women of childbearing potential
Intervention(s)	Participants in both groups were provided with a Bayer Contour Next USB meter and test strips; they were provided general diabetes management education, and clinicians were encouraged to review downloaded glucose data at each visit to inform treatment recommendations, which were at clinicians discretion and not prescriptive in the protocol. **Continuous glucose monitoring (CGM)** Participants in the CGM group were provided with a CGM system (Dexcom G4 Platinum CGM System with an enhanced algorithm, software 505, Dexcom Inc). The CGM group was instructed to use the CGM daily, calibrate the CGM twice daily, and verify the CGM glucose concentration with the blood glucose meter before injecting insulin (as per the regulatory labelling on the device at the time the trial was conducted). General guidance were provided to participants about using CGM, and individualised recommendations were made by their clinician about incorporating CGM trend information into their diabetes management. **Intermittent capillary blood glucose monitoring** Participants in the control group were asked to perform home blood glucose monitoring at least 4 times daily.
Comparator	
Outcome measures	HBA1C Change in the central laboratory-measured HbA1c level. Percentage of participants with HbA1c levels less than 7.0%. Time in range CGM-measured time in range (70 to 180 mg/dL). Time spent above/below target glucose range Duration of hypoglycaemia (<70 mg/dL, <60 mg/dL, and <50 mg/dL), duration of hyperglycaemia (>180 mg/dL, >250 mg/dL, and >300 mg/dL). Hypoglycaemia Change in frequency of hypoglycaemic events based on the International Hypoglycaemia Study Group (IHSG) which considered serious, clinically important hypoglycaemia as glucose concentrations below 3.0 mmol/L. A hypoglycaemic event was defined as a series of at least two sensor glucose values less than 3.0 mmol/L (54 mg/dL), lasting at least 20 min, with no intervening values of 3.0 mmol/L or more. The end of a hypoglycaemic event was defined as a minimum of 15 consecutive minutes

	with at least two sensor glucose values of at least 3.0 mmol/L and at least 0.6 mmol/L (10 mg/dL) above the nadir of the event. A new event was temporally separated from any previous event by 15 min or more, with no intervening values less than 3.0 mmol/L. Glycaemic variability Coefficient of variation. Diabetic ketoacidosis Adverse events Severe hypoglycaemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions), diabetic ketoacidosis, and serious adverse events regardless of casualty. Awareness of hypoglycaemia Change in hypoglycaemia unawareness. Quality of life measured by validated tools Satisfaction with CGM was assessed by completion at 24 weeks of the CGM Satisfaction Survey (44 items on a 1 to 5 Likert scale, with the computed score representing the mean of the 44 items and subscales of benefits and lack of hassles).
Number of participants	Continuous glucose monitoring N=105 Intermittent capillary blood glucose monitoring N=53
IGNORE	
Type of insulin delivery system	Multiple daily injections
Type of insulin regimen	Short acting Long acting
Duration of follow-up	24 weeks
Loss to follow-up	
Additional comments	All participants were required to complete a 2-week pre-randomisation phase using a CGM system that was configured to record glucose concentrations not visible to the participant (blinded CGM). Eligibility required that the blinded CGM be worn at least 85% of possible days, the CGM be calibrated at least 2 times per day, and blood glucose meter

	testing (with a study-provided meter and test strips) be performed at least 3 times daily.

Study arms

Continuous glucose monitoring (N = 105)

Loss to follow-up	Discontinued study (n=3) • Lost to follow-up (n=1) • Site withdrew participant (n=1) • Participant requested to withdraw (n=1) Completed study but discontinued continuous glucose monitoring (n=2)
Methods of analysis	

Dexcom G4 Platinum GM System with software 505 (Dexcom Inc., San Diego, CA).

Intermittent capillary blood glucose monitoring (N = 53)

Loss to follow-up	0

Continue with usual care basing diabetes management decisions on self-monitoring blood glucose alone.

Characteristics

Arm-level characteristics

Characteristic	Continuous glucose monitoring (N = 105)	Intermittent capillary blood glucose monitoring (N = 53)
% Female Nominal	45	43
Mean age (SD) (years) Mean (SD)	46 (14)	51 (11)
BMI (kg/m²) Mean (SD)	28 (6)	27 (5)

Characteristic	Continuous glucose monitoring (N = 105)	Intermittent capillary blood glucose monitoring (N = 53)
Time since diabetes diagnosis (years) Median (IQR)	19 (9 to 29)	19 (11 to 35)
Previous CGM Sample size	n = 17 ; % = 16	n = 9 ; % = 17

1

2

3 Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*
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 *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
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 *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study.)*
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	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*
Overall bias and Directness	Overall Directness	Directly applicable

1

2 Bolinder, 2016

Bibliographic Reference	Bolinder, Jan; Antuna, Ramiro; Geelhoed-Duijvestijn, Petronella; Kroger, Jens; Weitgasser, Raimund; Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial.; Lancet (London, England); 2016; vol. 388 (no. 10057); 2254-2263

3

4 Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Oskarsson, Per, Antuna, Ramiro, Geelhoed-Duijvestijn, Petronella et al. (2018) Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy: a pre-specified subgroup analysis of the IMPACT randomised controlled trial. Diabetologia 61(3): 539-550
Trial registration number and/or trial name	IMPACT; NCT02232698
Study type	Randomised controlled trial (RCT)
Study location	Sweden, Austria, Germany, Spain, and the Netherlands
Study setting	23 European diabetes centres
Study dates	Sept 4, 2014, to Feb 12, 2015
Sources of funding	Abbott Diabetes Care
Inclusion criteria	Age ≥18 years Duration of diabetes ≥5 years Current insulin regimen for at least 3 months before study entry

	Screening HbA1c concentration of 58 mmol/mol (7.5%) or lower Reported self-monitoring of blood glucose levels on a regular basis (equivalent to ≥3 times a day) for 2 months or more before study entry Considered by the investigator to be technically capable of using the flash sensor-based glucose monitoring system
Exclusion criteria	Hypoglycaemia unawareness Diabetic ketoacidosis or myocardial infarction in the preceding 6 months Known allergy to medical-grade adhesives Used continuous glucose monitoring within the preceding 4 months Currently using sensor-augmented pump therapy Pregnant or planning pregnancy Receiving oral steroid therapy for any disorders
Intervention(s)	**Flash glucose monitoring** After randomisation, the device was unblinded for participants in the intervention group who then continuously used sensor glucose data as per the device labelling for self-management of glucose throughout the duration of the study (6 months). Participants in the intervention group were given access to the device software, which they could use at home to review their sensor data if they wished. No training was provided to these participants for interpretation of glucose-sensor data. **Intermittent capillary blood glucose monitoring** Participants in the control group self-monitored glucose concentrations using the FreeStyle Lite meter and test strips (Abbott Diabetes Care, Witney, Oxon, UK). In the 14 days preceding the 3 month and 6 month timepoints (days 91 and 194, respectively), participants in the control group wore the flash sensor while continuing to manage their diabetes with self-monitoring of blood glucose.
Outcome measures	HBA1C Sensor-derived day 208 HbA1c concentrations Time in range Time with glucose in range 3.9–10.0 mmol/L (70–180 mg/dL). Time spent above/below target glucose range Time spent in hypoglycaemia (<3.9 mmol/L [<70 mg/dL]) for the 14 days preceding the end of the 6 month study period (days 194–208).

	Sensor-derived glycaemic measures comprised: number and duration of hypoglycaemic episodes (sensor glucose <3.9 mmol/L in 24 h, by day [0600–2300 h], and night [2300–0600 h]; <3.1 mmol/L in 24 h, and <2.2 mmol/L in 24 h [<70 mg/dL, <55 mg/dL, and <40 mg/dL, respectively]; an episode was defined as at least two consecutive readings, at 15 min intervals, outside the predefined glucose range, the end of an episode was one reading at or higher than the threshold); number and duration of hyperglycaemic episodes (>10.0 mmol/L and >13.3 mmol/L [>180 mg/dL and >240 mg/dL, respectively]). Hypoglycaemia Number of events of symptomatic hypoglycaemia. Number of severe hypoglycaemia events (requiring third-party assistance) were assessed and compared across the two study groups. Glycaemic variability Diabetic ketoacidosis % of CGM data captured System utilisation for days 15–208 (defined as the percentage of data collected, assuming continuous device wear) Adverse events Mental health outcomes Hypoglycaemia Fear Survey (HFS), Diabetes Distress Scale (DDS) Quality of life measured by validated tools Diabetes Quality of Life Questionnaire (DQoL)
Number of participants	Flash glucose monitoring N=120 Intermittent capillary blood glucose monitoring N=121
Type of insulin delivery system	Multiple daily injections Continuous subcutaneous insulin infusion
Duration of follow-up	6 months
Additional comments	All participants wore a FreeStyle Libre device locked into masked mode for the 14 day baseline period; sensor glucose measurements were not visible to the participant or the investigator during this time (blinded). After randomisation, sensor data for participants in the intervention group were made available to them and the investigators. Glucose management was supported by self-monitoring of blood glucose, using the strip port built into the reader and compatible test strips (Abbott Diabetes Care, Witney, Oxon,

	UK). Participants were asked to record capillary glucose concentrations in a glucose diary and to log other events (eg, severe hypoglycaemia, hospitalisation, and additional health visits or treatment) in an event diary. Participants with sensor data for at least 50% of the blinded wear period (or ≥650 individual sensor readings) were then centrally randomised to the two groups. All sensor glucose data were blinded for both participants and investigators. Type of insulin regimen was not reported.

Study arms

Flash glucose monitoring (N = 119)

Loss to follow-up	10 withdrew or were excluded after randomisation • 1 excluded due to pregnancy • 1 met exclusion criteria • 7 had device-associated symptoms • 1 due to non-compliance with study device
Methods of analysis	

Sensor-based flash glucose monitoring system (Freestyle Libre; Abbott Diabetes Care, Witney, Oxon, UK).

Intermittent capillary blood glucose monitoring (N = 120)

Loss to follow-up	20 withdrew or were excluded • 1 excluded due to pregnancy • 4 due to non-compliance with study device • 1 met exclusion criteria • 3 because allocated to control group • 11 for other reasons

Self-monitoring glucose concentrations using the FreeStyle Lite meter and test strips (Abbott Diabetes Care, Witney, Oxon, UK)

Characteristics

Arm-level characteristics

Characteristic	Flash glucose monitoring (N = 119)	Intermittent capillary blood glucose monitoring (N = 120)
% Female Nominal	35	51
Mean age (SD) (years) Median (IQR)	42 (33 to 51)	45 (33 to 57)
BMI (kg/m²) Mean (SD)	25.2 (3.6)	24.8 (3.5)
Time since diabetes diagnosis (years) Median (IQR)	20 (13 to 27)	20 (12 to 32)

1

2

3 Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*
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 *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
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	Some concerns *(No information on whether allocation sequence was concealed until participants*

Section	Question	Answer
		were enrolled and assigned to interventions.)
Overall bias and Directness	Overall Directness	Directly applicable

1

2 Haskova, 2020

Bibliographic Reference	Haskova, A; Radovnicka, L; Petruzelkova, L; Parkin, CG; Grunberger, G; Horova, E; Navratilova, V; Kade, O; Matoulek, M; Prazny, M; et, al.; Real-time CGM Is Superior to Flash Glucose Monitoring for Glucose Control in Type 1 Diabetes: the CORRIDA Randomized Control Trial; Diabetes care; 2020

3

4 Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	
Trial registration number and/or trial name	CORRIDA; NCT04358263
Study type	Randomised controlled trial (RCT)
Study location	Czech Republic
Study setting	Department of Internal Medicine, Faculty of Medicine, Charles University
Study dates	Not reported
Sources of funding	This study was initiated, designed, and performed by the investigators and supported by Agency for Healthcare Research (AZV) of the Czech Republic grant 15-26705A (program RVO-VFN00064165) and by the Research Project of Charles University (Progres Q25).

Inclusion criteria	People with T1D Age ≥18 years Duration of diabetes >2 years Gold score <4 The Gold method poses the question “do you know when your hypos are commencing?” The respondent then completes a 7-point Likert scale (1, “always aware” to 7, “never aware”). A score of ≥4 implies impaired awareness of hypoglycaemia. No history of severe hypoglycaemia within last 6 months prior to the study initiation No previous experience with rtCGM and/or isCGM
Exclusion criteria	Previous rtCGM or isCGM use Hypoglycaemia unawareness Known severe diabetic retinopathy and/or macular oedema Lactation, pregnancy, or intending to become pregnant during the study Having a condition likely to require MRI Use of acetaminophen-containing medication Unwillingness to use the study device
Intervention(s)	**Continuous glucose monitoring** Training included the use of the absolute value, rate of change arrow, and glucose trend line. Only basic threshold alarms (4.4–10.0 mmol/L [80–180 mg/dL]) were set for the rtCGM system. Advanced alerts such as rise rate, alert before high or fall rate, and alert before low were not activated. An urgent low alert at glucose level 3.1 mmol/L was not available in the version of Guardian Connect Mobile CGM system used in the study. Participants with rtCGM were shown how to calibrate the system using self-monitored blood glucose values. All participants were instructed to change their sensors according to the manufacturer’s recommendations: every 6 days for rtCGM users. **Flash glucose monitoring** Training included the use of the absolute value, rate of change arrow, and glucose trend line. Advanced alerts such as rise rate, alert before high or fall rate, and alert before low were not activated. All participants were

	instructed to change their sensors according to the manufacturer's recommendations: every 14 days for isCGM users. Participants randomised to the isCGM arm ("Libre arm") simultaneously initiated the masked CGM (iPro2) and were then monitored for 6 days. Patients randomised to isCGM were encouraged to scan the sensor at least 10 times/day.
Comparator	
Outcome measures	Time in range Changes in time in range (3.9–10.0mmol/L [70–180 mg/dL). Time spent above/below target glucose range Percentage of time spent in hypoglycaemia (<3.9 mmol/L [<70 mg/dL] and <3.0 mmol/L [<54 mg/dL]) during the 4-day exercise phase, 4-week home phase, and combined exercise and home phases. Hypoglycaemia Incidence of severe hypoglycaemia (requiring third-party assistance to treat). Glycaemic variability Expressed as the coefficient of variation (%CV). Diabetic ketoacidosis Quality of life measured by validated tools Changes in quality of life were assessed using the WHOQOL-BREF, a validated, non–diabetes-specific questionnaire.
Number of participants	Continuous glucose monitoring N=30 Flash glucose monitoring N=30
Duration of follow-up	4-day training program focused on physical activity and over 4 weeks of follow-up home use
Loss to follow-up	None reported
Additional comments	All participants initiated professional (masked) CGM (iPro2; Medtronic, Inc.) and were then monitored for 6 days. For subsequent calibration of professional CGM, all participants were also instructed to measure capillary blood glucose values at least four times per day. Type of insulin regimen was not reported.

1

Study arms

Continuous glucose monitoring (N = 30)

Type of insulin delivery system	Multiple daily injections Multiple dose injections in 69% participants

Real-time continuous glucose monitoring (rtCGM) using Guardian Connect Mobile; Medtronic, Inc.

Flash glucose monitoring (N = 30)

Type of insulin delivery system	Multiple daily injections Multiple dose injections in 55% participants

Intermittently scanned continuous glucose monitoring (isCGM) using FreeStyle Libre Flash Glucose Monitoring System

Characteristics

Arm-level characteristics

Characteristic	Continuous glucose monitoring (N = 30)	Flash glucose monitoring (N = 30)
% Female Nominal	48	71
Mean age (SD) (years) Mean (SD)	39.6 (12.2)	37.8 (12.7)
BMI (kg/m²) Mean (SD)	26 (4.2)	24.9 (3.7)
Time since diabetes diagnosis (years) Mean (SD)	15.9 (11.4)	14.4 (10.2)
Yes Sample size	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	Continuous glucose monitoring (N = 30)	Flash glucose monitoring (N = 30)
No Sample size	n = 30 ; % = 100	n = 30 ; % = 100

1

2

3 Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

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 *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
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 bias and Directness	Overall Directness	Directly applicable

5

6 Heinemann, 2018

Bibliographic Reference	Heinemann, Lutz; Freckmann, Guido; Ehrmann, Dominic; Faber-Heinemann, Gabriele; Guerra, Stefania; Waldenmaier, Delia; Hermanns, Norbert; Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial.; Lancet (London, England); 2018; vol. 391 (no. 10128); 1367-1377

7

1 Study details

Trial registration number and/or trial name	HypoDE; NCT02671968
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	12 specialised diabetes practices
Study dates	March 4, 2016, to Jan 12, 2017
Sources of funding	Dexcom Inc.
Inclusion criteria	People with T1D Age ≥18 years Duration of diabetes ≥1 year Treated with multiple daily insulin injections Prandial insulin at each major meal and at least one dose of basal insulin. HbA1c ≤9.0% (≤75 mmol/mol) Problematic hypoglycaemia Defined as having had at least one severe hypoglycaemia event requiring third-party assistance for recovery in the previous year, or having impaired hypoglycaemia awareness as defined by a total score of 4 or more in the hypoglycaemia unawareness questionnaire developed by Clarke and colleagues. Treatment with continuous subcutaneous insulin infusion (CSII) therapy
Exclusion criteria	Pregnancy Use of the rtCGM system or another rtCGM device in the previous 3 months
Intervention(s)	**Continuous glucose monitoring** Participants in the rtCGM group received instructions on optimal use of rtCGM in three sessions. Topics included how to wear an rtCGM system, importance of calibration, when confirmation of results by SMBG is necessary, use of trend arrows and glucose profiles for treatment adjustments, and use and setting of hypoglycaemic or hyperglycaemic alerts. The first training session was done at the randomisation visit, the

	second at the additional 1-week visit, and the third at the regular 4-week visit, which was also attended by control group participants. **Intermittent capillary blood glucose monitoring** Participants in the SMBG group continued SMBG measurements and received their usual care. Both groups used their respective glucose monitoring device (rtCGM or SMBG system) for the subsequent 22 weeks to make therapeutic decisions. Both groups attended a visit at 12 weeks and were contacted by phone calls at weeks 8, 16, 20, and 24 following randomisation; SMBG group participants had an additional visit at week 22, when masked rtCGM systems were handed out again.
Outcome measures	Time in range Duration of glucose readings derived from continuous glucose monitoring per day (>3.9 mmol/L to ≤10.0 mmol/L [>70 mg/dL to 180 mg/dL]). Time spent above/below target glucose range Duration of glucose readings derived from continuous glucose monitoring per day (≤3.0 mmol/L [≤54 mg/dL], ≤3.9 mmol/L [≤70 mg/dL], >10.0 mmol/L [>180 mg/dL]). Hypoglycaemia Number of hypoglycaemic events measured by rtCGM during the follow-up phase compared with baseline. The follow-up phase lasted from weeks 22 to 26. A hypoglycaemic event derived from rtCGM was defined as glucose values of 3.0 mmol/L (≤54 mg/dL) or lower for at least 20 min, preceded by a minimum of 30 min with glucose values greater than 3.0 mmol/L (>54 mg/dL). The number of hypoglycaemic events was examined for each patient during each recording phase and standardised to an incidence of low glucose values per 28 days. The frequency of severe hypoglycaemia events was defined as the number of hypoglycaemic events requiring third-party assistance to administer carbohydrate, glucagon, or intravenous glucose injections during the therapy and follow-up phases. Severe hypoglycaemia was further divided into two additional categories: events requiring medical assistance to inject glucagon or glucose or associated with hospital admission; and events requiring third-party assistance without medical assistance. The number of severe hypoglycaemia events during therapy and the follow-up phase was standardised as the incidence of severe hypoglycaemia per patient-year. Changes in nocturnal hypoglycaemic events (0000 h to 0600 h).

	Glycaemic variability Assessed by coefficient of variation and the low blood glucose index (LBGI), as a risk indicator for severe hypoglycaemia, was calculated for the baseline and follow-up phases with rtCGM and SMBG data. Adverse events Mental health outcomes Diabetes distress assessed with the Diabetes Distress Scale for type 1 diabetes (T1-DDS); fear of hypoglycaemia assessed with the Hypoglycaemia Fear Survey. Awareness of hypoglycaemia Impaired hypoglycaemia awareness assessed with the hypoglycaemia unawareness questionnaire. Quality of life measured by validated tools Self-reported health status assessed with the European Quality of Life 5 Dimensions questionnaire (EQ-5D).
Number of participants	Continuous glucose monitoring N=75 Intermittent capillary blood glucose monitoring N=74
Type of insulin delivery system	Multiple daily injections
Duration of follow-up	6 months
Loss to follow-up	
Additional comments	The study was done in three phases: the baseline phase, therapy phase, and follow-up phase. The number of study visits was equal between the two groups, but differently distributed. However, the distribution of visits did not have an effect on baseline or follow-up data collection. During the baseline phase, all participants wore a masked rtCGM system (Dexcom G4 with software 505) for 4 weeks. All participants were instructed on how to insert and secure the glucose sensor and how to calibrate the system. The SMBG systems used by study participants were assessed for accuracy. If accuracy was considered insufficient, an SMBG system with sufficient measurement accuracy was made available. In the therapy phase, before randomisation, all rtCGM and SMBG data were uploaded at the study sites and downloaded at the study coordination centre via an electronic data management tool (DIASEND/Glooko, Goteborg, Sweden), and participant adherence to use of rtCGM was checked. Participants assigned to the rtCGM group received an unmasked rtCGM system (Dexcom G5 Mobile system, Dexcom Inc, San Diego, CA,

	USA). Analytical performance of the Dexcom G5 Mobile system and G4 505 system is identical. The differences between the two systems are in the handheld device for data display and connectivity options, which the Dexcom G5 Mobile system offers. Glucose alerts were individualised to each participant at their respective study centre. The follow-up phase began at week 22. SMBG group participants again wore the masked Dexcom G4 505 system, and participants in the rtCGM group continued with the Dexcom G5 Mobile system during the next 4 weeks. At the final visit (week 26), rtCGM data were again uploaded at the study sites and downloaded at the study coordination centre. Patient questionnaires were administered and blood samples for HbA1c measurement were collected.

Study arms

Continuous glucose monitoring (N = 75)

Loss to follow-up	0

Real-time continuous glucose monitoring (rtCGM) using Dexcom G5 Mobile system (Dexcom Inc, San Diego, CA, USA).

Intermittent capillary blood glucose monitoring (N = 74)

Loss to follow-up	8 discontinued • 1 adverse event • 2 withdrew consent • 4 used flash sensor based glucose monitoring system • 1 death

Usual therapy with self-monitoring of blood glucose (SMBG).

Characteristics

Arm-level characteristics

Characteristic	Continuous glucose monitoring (N = 75)	Intermittent capillary blood glucose monitoring (N = 74)
% Female Nominal	47	34

Characteristic	Continuous glucose monitoring (N = 75)	Intermittent capillary blood glucose monitoring (N = 74)
Mean age (SD) (years) Mean (SD)	45.8 (12)	47.3 (11.7)
BMI (kg/m²) Mean (SD)	26.1 (6.7)	26 (4.6)
Time since diabetes diagnosis (years) Mean (SD)	20.9 (14)	21.6 (13.9)

1

2

3 Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

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 *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
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 *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study.)*
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 bias and Directness	Overall Directness	Directly applicable

5

6 JDRF, 2010

Bibliographic Reference	JDRF; Effectiveness of Continuous Glucose Monitoring in a Clinical Care Environment; Diabetes care; 2010; vol. 33 (no. 1); 17-22

Study details

Secondary publication of another included study- see primary study for details	Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Tamborlane, William V, Beck, Roy W et al. (2008) Continuous glucose monitoring and intensive treatment of type 1 diabetes. The New England journal of medicine 359(14): 1464-76

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, 2010

Bibliographic Reference	Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group; Beck, Roy W; Lawrence, Jean M; Laffel, Lori; Wysocki, Tim; Xing, Dongyuan; Huang, Elbert S; Ives, Brett; Kollman, Craig; Lee, Joyce; Ruedy, Katrina J; Tamborlane, William V; Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial.; Diabetes care; 2010; vol. 33 (no. 10); 2175-7

Study details

Secondary publication of another included study- see primary study for details	Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Tamborlane, William V, Beck, Roy W et al. (2008) Continuous glucose monitoring and intensive treatment of type 1 diabetes. The New England journal of medicine 359(14): 1464-76

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, 2008

Bibliographic Reference	Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group; Tamborlane, William V; Beck, Roy W; Bode, Bruce W;

Buckingham, Bruce; Chase, H Peter; Clemons, Robert; Fiallo-Scharer, Rosanna; Fox, Larry A; Gilliam, Lisa K; Hirsch, Irl B; Huang, Elbert S; Kollman, Craig; Kowalski, Aaron J; Laffel, Lori; Lawrence, Jean M; Lee, Joyce; Mauras, Nelly; O'Grady, Michael; Ruedy, Katrina J; Tansey, Michael; Tsalikian, Eva; Weinzimer, Stuart; Wilson, Darrell M; Wolpert, Howard; Wysocki, Tim; Xing, Dongyuan; Continuous glucose monitoring and intensive treatment of type 1 diabetes.; The New England journal of medicine; 2008; vol. 359 (no. 14); 1464-76

1

2 Study details

Other publications associated with this study included in review	Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group (2010) Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. Diabetes care 33(1): 17-22 Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Beck, Roy W, Lawrence, Jean M et al. (2010) Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial. Diabetes care 33(10): 2175-7 Tansey, M, Laffel, L, Cheng, J et al. (2011) Satisfaction with continuous glucose monitoring in adults and youths with Type 1 diabetes. Diabetic medicine : a journal of the British Diabetic Association 28(9): 1118-22
Trial registration number and/or trial name	JDRF; NCT00406133
Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	10 participating centres, which included academic, community, and managed care-based practices.
Study dates	February - December 2007
Sources of funding	Supported by grants from the Juvenile Diabetes Research Foundation.
Inclusion criteria	People with T1D Duration of diabetes ≥1 year 8 years of age or older Using an insulin pump or receiving at least three daily insulin injections

	HbA1c level 7.0 to 10.0% Not used continuous glucose monitoring at home in the 6 months leading up to the trial
Intervention(s)	**Continuous glucose monitoring** Each of the devices for CGM consisted of a glucose oxidase–based electrochemical sensor, which was placed subcutaneously and replaced every 3 to 7 days (depending on the type of device), along with a receiver to which interstitial glucose measurements were sent wirelessly and stored. Since the purpose of the study was to evaluate a treatment strategy using the technology of continuous glucose monitoring and not a specific device, a device was assigned to each patient by the clinical centre on the basis of device features and the participants' preferences. Participants were instructed to use the device on a daily basis and to verify the accuracy of the glucose measurement with a home blood glucose meter (provided by the study) before making management decisions, according to the regulatory labelling of the devices. **Intermittent capillary blood glucose monitoring** Participants were given blood glucose meters and test strips and asked to perform home blood glucose monitoring at least four times daily.
Outcome measures	HBA1C Time in range Amount of time per day the glucose level was in the target range (71 to 180 mg per decilitre [3.9 to 10.0 mmol per litre]). Time spent above/below target glucose range Amount of time per day the glucose level was hypoglycaemic (≤70 mg per decilitre or ≤50 mg per decilitre [≤3.9 or ≤2.8 mmol per litre]) or hyperglycaemic (>180 mg per decilitre or >250 mg per decilitre [10.0 or 13.9 mmol per litre]). Hypoglycaemia Severe hypoglycaemia defined as an event that required assistance from another person to administer oral carbohydrate, glucagon, or other resuscitative actions. Glycaemic variability Diabetic ketoacidosis Hyperglycaemia resulting in ketoacidosis. Adverse events

	Severe hypoglycaemia, ketoacidosis, unexpected study-related or device-related events, and serious adverse events regardless of cause. Quality of life measured by validated tools Participants ≥18 years old completed the Hypoglycaemia Fear Survey (HFS) and Social Functioning Health Survey (SF-12) version 2; reported by JDRF (2010). Continuous Glucose Monitoring Satisfaction Scale (CGM-SAT); reported by Tansey (2011).
Number of participants	Continuous glucose monitoring N=52 Intermittent capillary blood glucose monitoring N=46
IGNORE	
Type of insulin delivery system	Multiple daily injections Insulin pump
Duration of follow-up	26 weeks
Additional comments	Participants completed a run-in phase using a continuous glucose monitor that was modified so that the glucose values were recorded in the receiver but were not visible to the participant; this was referred as a “blinded” continuous glucose monitor. Eligibility required that participants wore a sensor for at least 6 of 7 days before randomisation, with a minimum of 96 hours of glucose values including at least 24 hours overnight, and that home blood glucose monitoring be performed at least three times daily. Data regarding continuous glucose monitoring in both arms after the 26-week visit (blinded monitors in the intermittent capillary blood glucose monitoring arm and unblinded monitors in the continuous glucose monitoring arm) were used to estimate time spent in range, time spent above target glucose range and time spent below target blood glucose range. Type of insulin regimen was not reported.

Study arms

Continuous glucose monitoring (N = 52)

Loss to follow-up	2 participants dropped

Participants were provided with one of the following devices: the DexCom Seven (DexCom), the MiniMed Paradigm Real-Time Insulin Pump and Continuous Glucose Monitoring System (Medtronic), or the FreeStyle Navigator (Abbott Diabetes Care).

Intermittent capillary blood glucose monitoring (N = 46)

Loss to follow-up	0

Participants were given blood glucose meters and test strips.

Characteristics

Arm-level characteristics

Characteristic	Continuous glucose monitoring (N = 52)	Intermittent capillary blood glucose monitoring (N = 46)
% Female Nominal	60	57
Mean age (SD) (years) Mean (SD)	41.2 (11.2)	44.6 (12.3)
Less than -0.5 Sample size	n = 8 ; % = 15	n = 9 ; % = 20
-0.5 to 0.5 Sample size	n = 34 ; % = 65	n = 28 ; % = 61
>0.5 Sample size	n = 10 ; % = 19	n = 9 ; % = 20
Time since diabetes diagnosis (years) Mean (SD)	23.6 (10.6)	21.8 (10.4)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on whether allocation sequence was concealed until participants were*

Section	Question	Answer
		enrolled and assigned to interventions.)
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 *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
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 *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study.)*
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	Some concerns *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
Overall bias and Directness	Overall Directness	Directly applicable *(The JDRF trial included children, young people and adults but data was reported separately for adults ≥25 years old.)*

1

2 Lind, 2017

Bibliographic Reference	Lind, Marcus; Polonsky, William; Hirsch, Irl B; Heise, Tim; Bolinder, Jan; Dahlqvist, Sofia; Schwarz, Erik; Olafsdottir, Arndis Finna; Frid, Anders; Wedel, Hans; Ahlen, Elsa; Nystrom, Thomas; Hellman, Jarl; Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial.; JAMA; 2017; vol. 317 (no. 4); 379-387

3

4 Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Olafsdottir, Arndis F, Polonsky, William, Bolinder, Jan et al. (2018) A Randomized Clinical Trial of the Effect of Continuous Glucose Monitoring on Nocturnal Hypoglycemia, Daytime Hypoglycemia, Glycemic Variability, and Hypoglycemia Confidence in Persons with Type 1 Diabetes Treated with Multiple Daily Insulin Injections (GOLD-3). Diabetes technology & therapeutics 20(4): 274-284
Trial registration number and/or trial name	GOLD; NCT02092051
Study type	Cross-over randomised controlled trial
Study location	Sweden
Study setting	15 sites
Study dates	From February 24, 2014, to June 1, 2016
Sources of funding	The trial was sponsored by the NU Hospital Group, Trollhättan and Uddevalla, Sweden.
Inclusion criteria	People with T1D Age ≥18 years Duration of diabetes >1 year HbA1c ≥7.5% (≥58 mmol/mol) Treated with multiple daily insulin injections Fasting C-peptide levels <0.91 ng/mL
Exclusion criteria	Treated with insulin pumps
Intervention(s)	All participants received basic instruction on insulin dosing, such as bolus correction, food choices, and the effect of physical activity on glucose control. A graph was displayed for participants showing the proportion of insulin at time of injection (100%) and the proportion of insulin remaining to give effect at various time points after injection. Assessment of HbA1c was blinded to treatment status. During the 17-week washout period, patients used conventional therapy and masked CGM was performed for 2weeks.

	Continuous glucose monitoring Participants received general guidelines for interpreting glucose levels and trends obtained by CGM. During the first week, no alarms were set on the CGM device for low glucose levels except for acute hypoglycaemia (<55mg/dL [to convert to mmol/L, multiply by 0.0555]). Alarm settings were introduced no later than 2 weeks after randomisation. At each visit, patients were encouraged to use CGM information at least every 1 to 2 hours during daytime. **Intermittent capillary blood glucose monitoring** Participants were encouraged to measure blood glucose levels according to guidelines (ie, ≥4 times daily). Insulin dosing was based on self-measurement of blood glucose and not CGM values.
Outcome measures	HBA1C Difference in HbA1c between arms at weeks 26 and 69. Time in range Amount of time in euglycaemia hypoglycaemia (glucose levels 70 to 180 mg/dL) during CGM use. Time spent above/below target glucose range Amount of time in hypoglycaemia (glucose levels <70 mg/dL) and in hyperglycaemia (glucose levels >180 mg/dL) during CGM use. Hypoglycaemia Self-measurements of blood glucose and rate of severe hypoglycaemia, defined as unconsciousness from hypoglycaemia or requiring assistance from another person. Nocturnal hypoglycaemia was evaluated for two different hypoglycaemia cut-offs (definition and data reported by Olafsdottir 2018 [GOLD-3]): • 70 mg/dL (<3.9 mmol/L) and • 54 mg/dL (<3.0 mmol/L) Two different time frames were used or nocturnal hypoglycaemia: • 22:00–05:59 and • 00:00–05:59 Glycaemic variability Adverse events Adherence (dichotomous)

	Overall mean time of CGM use, estimated by the proportion of CGM data downloaded in relation to follow-up time. Quality of life measured by validated tools Hypoglycaemic Fear Behaviour Scale (minimum, 0; maximum,4; higher value indicates greater fear) and Hypoglycemic Fear Worry Scale (minimum, 0; maximum, 4; higher value indicates greater fear).
Number of participants	Continuous glucose monitoring N=82 Intermittent capillary blood glucose monitoring N=79
Type of insulin delivery system	Multiple daily injections
Duration of follow-up	26 weeks
Loss to follow-up	
Additional comments	During a 6-week run in, patients completed masked CGM for 2 weeks, glucose levels were recorded but were not seen by the patient. After masked CGM, patients were excluded if they either did not believe they would wear the CGM sensor more than 80% of the time or did not perform adequate calibrations during the run in (on average ≥12 of 14 during a 7-day period). During conventional therapy, masked CGM was also performed during 2 of the 4 last weeks to evaluate total time in hypoglycaemia, euglycaemia, hyperglycaemia, and glycaemic variability. Type of insulin regimen was not reported.

1

2 Study arms

3 Continuous glucose monitoring (N = 69)

Loss to follow-up	**At period 1**
	
	Discontinued (n=12)
	
	• Withdrew consent (n=5)
	• Safety reason (n=1)
	• Other reasons (n=6)
	  ○ dermatological reaction (n=1)
	  ○ preference to continuing use of CGM (n=2)
	  ○ preference to switch to insulin pump (n=1)
	  ○ paracetamol (acetaminophen) use for shoulder pain (n=1)

	○ unwillingness to proceed (n=1) **At period 2** Discontinued (n=1; study non-compliance: patient had no follow-up data reported during period 2 of the study)
Methods of analysis	

Dexcom G4 PLATINUM stand-alone system.

Intermittent capillary blood glucose monitoring (N = 73)

Loss to follow-up	**At period 1** Discontinued (n=6) • Withdrew consent (n=3) • Died of prostate cancer (n=1) • Other reasons (n=2) ○ lack of time (n=1) ○ patient request (n=1) **At period 2** Discontinued (n=1; lost to follow-up: follow-up data maintained during period 2 of the study)

Conventional therapy using only self-monitoring of blood glucose (SMBG)

Characteristics

Arm-level characteristics

Characteristic	Continuous glucose monitoring (N = 69)	Intermittent capillary blood glucose monitoring (N = 73)
% Female Nominal	46.4	41.1
Mean age (SD) (years) Mean (SD)	46.7 (13)	42.6 (12.2)
BMI (kg/m²) Mean (SD)	27 (4.1)	27.2 (4.8)

Characteristic	Continuous glucose monitoring (N = 69)	Intermittent capillary blood glucose monitoring (N = 73)
Time since diabetes diagnosis (years) Mean (SD)	23.4 (11.9)	21 (11.7)

1 Full analysis set population at baseline and randomisation

2

3

4 Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) T1 Cross-over trial

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low *(4 months long enough to lose CGM learning effect? Committee opinion. Some patients dropped out of intervention arm due to not wanting to crossover to placebo, however total dropout number balanced across arms.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(Small amount of missing data for intervention group, discontinuation reasoning suggests greater disc in int group due to wanting to stay on CGM, this mean actual results would skew against intervention as presumably these patients were experiencing positive outcomes for CGM)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study)*
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 *(Based on Lind 2017)*
Overall bias and Directness	Overall Directness	Directly applicable

6

1 Little, 2014

Bibliographic Reference	Little, Stuart A; Leelarathna, Lalantha; Walkinshaw, Emma; Tan, Horng Kai; Chapple, Olivia; Lubina-Solomon, Alexandra; Chadwick, Thomas J; Barendse, Shalleen; Stocken, Deborah D; Brennand, Catherine; Marshall, Sally M; Wood, Ruth; Speight, Jane; Kerr, David; Flanagan, Daniel; Heller, Simon R; Evans, Mark L; Shaw, James A M; Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 x 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS).; Diabetes care; 2014; vol. 37 (no. 8); 2114-22

2

3 Study details

Secondary publication of another included study- see primary study for details	Little, Stuart A, Speight, Jane, Leelarathna, Lalantha et al. (2018) Sustained Reduction in Severe Hypoglycemia in Adults With Type 1 Diabetes Complicated by Impaired Awareness of Hypoglycemia: Two-Year Follow-up in the HypoCOMPaSS Randomized Clinical Trial. Diabetes care 41(8): 1600-1607
Other publications associated with this study included in review	

4

5

6 Little, 2018

Bibliographic Reference	Little, Stuart A; Speight, Jane; Leelarathna, Lalantha; Walkinshaw, Emma; Tan, Horng Kai; Bowes, Anita; Lubina-Solomon, Alexandra; Chadwick, Thomas J; Stocken, Deborah D; Brennand, Catherine; Marshall, Sally M; Wood, Ruth; Kerr, David; Flanagan, Daniel; Heller, Simon R; Evans, Mark L; Shaw, James A M; Sustained Reduction in Severe Hypoglycemia in Adults With Type 1 Diabetes Complicated by Impaired Awareness of Hypoglycemia: Two-Year Follow-up in the HypoCOMPaSS Randomized Clinical Trial.; Diabetes care; 2018; vol. 41 (no. 8); 1600-1607

7

8 Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Little, Stuart A, Leelarathna, Lalantha, Walkinshaw, Emma et al. (2014) Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 x 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). Diabetes care 37(8): 2114-22 Speight, J., Holmes-Truscott, E., Little, S.A. et al. (2019) Satisfaction with the use of different technologies for insulin delivery and glucose monitoring among adults with long-standing type 1 diabetes and problematic hypoglycemia: 2-Year follow-up in the HypoCOMPaSS randomized clinical trial. Diabetes Technology and Therapeutics 21(11): 619-626
Trial registration number and/or trial name	HypoCOMPaSS; ISRCTN52164803
Study type	2 X 2 factorial randomised controlled trial
Study location	UK
Study setting	Five tertiary-referral diabetes centres
Study dates	Not reported
Sources of funding	The study was funded by a peer reviewed grant from Diabetes UK (07/0003556). The National Institute for Health Research and the Cambridge National Institute for Health Research Biomedical Research Centre funded data entry and trial support.
Inclusion criteria	People with T1D C-peptide–negative type 1 diabetes 18 to 74 years Impaired awareness of hypoglycaemia Confirmed by Gold score ≥4
Intervention(s)	Following randomisation, the number of study visits was the same for all participants, tailored for each group to technical aspects of their insulin administration and glucose monitoring intervention. All participants, whether allocated aspart insulin delivery by CSII (Paradigm Veo insulin pump; Medtronic) or MDIs (aspart/glargine) were given an insulin pump enabling benefit from direct transmission of SMBG levels to bolus calculator. Those randomized to RT-CGM (Medtronic) were trained on sensor insertion, calibration, and use of monitor including trend analysis and hypo-/hyperglycaemia alerts. Participants were able to individualise

	alarm settings but did not use the low-glucose suspend (LGS) feature. Continuous RT use was encouraged but not mandatory. Participants recorded severe hypoglycaemia episodes prospectively and were recalled every 4 weeks up to 24 weeks. All participants were given identical written guidance on insulin titration primarily targeted toward absolute avoidance of biochemical hypoglycaemia.
Outcome measures	HBA1C Overall glycaemic control. Time spent above/below target glucose range Percentage time with glucose ≤3 mmol/L. Hypoglycaemia Severe hypoglycaemia rate and proportion affected, biochemical hypoglycaemia (identified by blinded CGM profile: percentage time with glucose ≤3 mmol/L). Diabetic ketoacidosis Adverse events Safety end points were hospital admissions, diabetic ketoacidosis, and insulin delivery/glucose monitoring–related infections. Awareness of hypoglycaemia Difference (between baseline and 24 months and between randomised groups) in hypoglycaemia awareness determined by Gold score. Differences between interventions in hypoglycaemia awareness assessed by Clarke questionnaire and Hypoglycaemia Awareness Questionnaire (HypoAQ) 'impaired awareness' subscale score. Quality of life measured by validated tools Satisfaction with glucose monitoring device was assessed using the 22-item Glucose Monitoring Experience Questionnaire (GME-Q). Participants indicate their level of agreement (1='strongly disagree' to 5= 'strongly agree') with 22 statements about their current monitoring device. Monitoring experience is assessed across three domains: 'effectiveness' (9 items), 'intrusiveness (6 items)', 'convenience' (7 items). Within each domain, item scores are summed and divided by the number of items resulting in a composite score (range=1-5), with higher scores indicating greater experience of that domain. A GME-Q composite score ('total satisfaction') can also be calculated, where higher scores indicate more positive overall experience of (greater satisfaction with) their monitoring device. For the 'effectiveness' and 'convenience' domain scores, and the 'total satisfaction' score, negatively worded items are reversed before

	scoring. The GME-Q was designed to be applicable for both SMBG and CGM users. Fear of hypoglycaemia assessed using the Hypoglycaemia Fear Survey-II [HFS-II]).
Number of participants	Continuous glucose monitoring and Intermittent capillary blood glucose monitoring in MDI N=26 Continuous glucose monitoring and Intermittent capillary blood glucose monitoring in CSII N=22 Intermittent capillary blood glucose monitoring in MDI N=24 Intermittent capillary blood glucose monitoring in CSII N=24
Type of insulin delivery system	Multiple daily injections Continuous subcutaneous insulin infusion Insulin pump
Type of insulin regimen	Short acting Aspart Mixed insulin Aspart/glargine
Duration of follow-up	24 months
Loss to follow-up	
Additional comments	For 4 weeks after recruitment, participants recorded daily four-point and weekly eight-point glucose profiles (CONTOUR LINK glucometer; Bayer Healthcare) and undertook 7-day blinded CGM (iPro1; Medtronic). Prior to randomisation, all participants attended a single 1- to 2-h standardised education session derived from the pilot study, individually or in small groups of up to four. This comprised facilitated discussions targeted specifically toward rigorous avoidance of biochemical hypoglycaemia while maintaining overall glycaemic control. The four points of the hypo-compass established the imperatives: never delay hypoglycaemia treatment; recognize personalized times of increased risk; detect subtle symptoms; and confirm low glucose levels through regular self-monitoring, particularly for nocturnal hypoglycaemia. Also included was advice on self-adjustment of insulin doses according to carbohydrate intake, SMBG, and planned activity and recommendation for oral carbohydrate administration for all glucose levels <4.0mmol/L.

1

2 Study arms

Continuous glucose monitoring and Intermittent capillary blood glucose monitoring in MDI (N = 26)

Loss to follow-up	Discontinued intervention due to glargine intolerance (n=1) Lost to follow-up (n=1)	Discontinued intervention due to glargine intolerance (n=1) Lost to follow-up (n=1)	Discontinued intervention due to glargine intolerance (n=1) Lost to follow-up (n=1)

Multiple daily insulin injections (MDI) (aspart/glargine insulin) with conventional self-monitoring blood glucose (SMBG) and real-time continuous glucose monitoring system (RT-CGM) (iPro1; Medtronic)

Continuous glucose monitoring and Intermittent capillary blood glucose monitoring in CSII (N = 22)

Loss to follow-up	Did not received intervention - too busy (n=1)	Did not received intervention - too busy (n=1)	Did not received intervention - too busy (n=1)

Continuous subcutaneous insulin infusion (CSII) (aspart insulin) with SMBG and RT-CGM

Intermittent capillary blood glucose monitoring in MDI (N = 24)

Loss to follow-up	Did not received intervention - disappointed with randomisation/too busy (n=2) Lost to follow-up (n=2)	Did not received intervention - disappointed with randomisation/too busy (n=2) Lost to follow-up (n=2)	Did not received intervention - disappointed with randomisation/too busy (n=2) Lost to follow-up (n=2)

MDI with SMBG

Intermittent capillary blood glucose monitoring in CSII (N = 24)

Loss to follow-up	Did not receive intervention - too busy (n=2) Discontinued intervention - anxiety regarding CSII (n=1) Lost to follow-up (n=2)	Did not receive intervention - too busy (n=2) Discontinued intervention - anxiety regarding CSII (n=1) Lost to follow-up (n=2)	Did not receive intervention - too busy (n=2) Discontinued intervention - anxiety regarding CSII (n=1) Lost to follow-up (n=2)

CSII with SMBG

1 Characteristics

2 Study-level characteristics

Characteristic	Study (N = 96)
% Female Nominal	64
Mean age (SD) (years) Mean (SD)	48.6 (12.2)
BMI (kg/m²) Mean (SD)	26.5 (4.4)
Time since diabetes diagnosis (years) Mean (SD)	28.9 (12.3)

3

4

5 Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

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)	High *(There was a mixed of intention to-treat analysis and per protocol analysis (see Little 2014).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(Most of the participants crossed over from continuous glucose monitoring to intermittent capillary blood glucose monitoring in the follow-up after the first 24 weeks (see supplementary CONSORT diagram in Little 2018). Per protocol analysis for the follow-up when participants were allowed to cross-over.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study.)*
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 *(There was a mixed of intention to-treat analysis and per protocol analysis (see Little 2014).Most of the participants crossed over from continuous glucose monitoring to intermittent capillary blood glucose monitoring in the follow-up after the first 24 weeks (see supplementary CONSORT diagram in Little 2018). Per protocol analysis for the follow-up when participants were allowed to cross-over.)*
Overall bias and Directness	Overall Directness	Directly applicable

1

2 New, 2015

Bibliographic Reference	New, J P; Ajjan, R; Pfeiffer, A F H; Freckmann, G; Continuous glucose monitoring in people with diabetes: the randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS).; Diabetic medicine : a journal of the British Diabetic Association; 2015; vol. 32 (no. 5); 609-17

3

4 Study details

Secondary publication of another included study- see primary study for details	
Trial registration number and/or trial name	GLADIS

Study type	Randomised controlled trial (RCT)
Study location	UK and Germany
Study setting	Study centres
Study dates	February 2011 and January 2012
Sources of funding	This work was funded by Abbott Diabetes Care.
Inclusion criteria	Treated with either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDI) >6 months Type 1 or type 2 diabetes Aged 18 to 65 years HbA1c 7 to 11% (53–97 mmol/mol) SMBG an average of 2 to 7 times per day
Exclusion criteria	Pregnant or planning pregnancy Concomitant disease or a condition influencing metabolic control Participating in another glucose monitoring device study Using drugs that could affect glucose management CGM use in the last 6 months
Intervention(s)	**Continuous glucose monitoring with alarms** Participants wore an unmasked FreeStyle Navigator with enabled alarms for the remainder of the study (days 21 to 100). **Continuous glucose monitoring without alarms** Participants wore an unmasked FreeStyle Navigator with the low, high and projected alarms switched off (data loss and calibration alarms were still active) and were instructed to leave the alarms disabled for the duration of the study. **Intermittent capillary blood glucose monitoring** Participant managed their blood glucose with standard SMBG using a masked FreeStyle Navigator for a further two 20-day periods (study days 40–60 and 80–100). These data were not used by the participant or study staff as part of the participant's monitoring or management regimens.
Outcome measures	HBA1C

	HbA1c difference between arms; proportion of participants with a reduction in HbA1c concentration of ≥6 mmol/mol (≥0.5%) in the three arms Time spent above/below target glucose range Time spent outside a glucose target of 3.9–10.0 mmol/l (70–180 mg/dl). Glycaemic variability Adverse events Quality of life measured by validated tools The Short-Form-8 Health Survey and the Diabetes Distress Scale questionnaire.
Number of participants	Continuous glucose monitoring with alarms N=49 Continuous glucose monitoring without alarms N=48 Intermittent capillary blood glucose monitoring N=48
Type of insulin delivery system	Multiple daily injections Continuous subcutaneous insulin infusion
Duration of follow-up	100 days
Additional comments	After consent, screening and enrolment, participants completed a 20-day baseline phase during which they self-managed blood glucose using the FreeStyle meter built into the masked FreeStyle Navigator, which collected continuous glucose data. Participants were randomised if they had CGM data for 50% of the baseline period (or at least 1400 individual CGM readings). Type of insulin regimen was not reported.

1

2 Study arms

3 Continuous glucose monitoring with alarms (N = 49)

Duration of follow-up	3 participants withdrew before day 60, reasons: • 1 adverse event • 1 protocol deviation • 1 withdrew consent; too frequent alarms 1 participant withdrew before day 100, reasons:	3 participants withdrew before day 60, reasons: • 1 adverse event • 1 protocol deviation • 1 withdrew consent; too frequent alarms 1 participant withdrew before day 100, reasons:

	• 1 adverse event	• 1 adverse event
Loss to follow-up		

1 CGM with alarms unmasked FreeStyle Navigator.

2

3 Continuous glucose monitoring without alarms (N = 48)

Loss to follow-up	1 participant withdrew before day 60, reasons: • 1 adverse event 2 participants withdrew before day 100, reasons: • 1 withdrew consent; too busy to use device • 1 protocol deviation	1 participant withdrew before day 60, reasons: • 1 adverse event 2 participants withdrew before day 100, reasons: • 1 withdrew consent; too busy to use device • 1 protocol deviation

4 CGM without alarms unmasked FreeStyle Navigator.

5

6 Intermittent capillary blood glucose monitoring (N = 48)

Loss to follow-up	6 participants withdrew before day 60, reasons:
	• 1 adverse event
	• 5 withdrew consent
	  ○ 2 too busy to use device
	  ○ 1 too frequent alarms
	  ○ 1 device did not provide expected information
	  ○ reason not given
	
	3 participant withdrew before day 100, reasons:
	• 2 withdrew consent
	  ○ 1 too frequent alarms
	  ○ 1 other; motivation no benefit
	• 1 other; sudden reaction to plaster adhesive
		6 participants withdrew before day 60, reasons:
		• 1 adverse event
		• 5 withdrew consent
		  ○ 2 too busy to use device
		  ○ 1 too frequent alarms
		  ○ 1 device did not provide expected information
		  ○ reason not given
		
		3 participant withdrew before day 100, reasons:
		• 2 withdrew consent
		  ○ 1 too frequent alarms
		  ○ 1 other; motivation no benefit
		• 1 other; sudden reaction to plaster adhesive

Standard SMBG using a masked FreeStyle Navigator.

Characteristics

Arm-level characteristics

Characteristic	Continuous glucose monitoring with alarms (N = 49)	Continuous glucose monitoring without alarms (N = 48)	Intermittent capillary blood glucose monitoring (N = 48)
% Female Nominal	57.1	39.6	41.7
Mean age (SD) (Median (range) in years) Custom value	47 (20 to 65)	47 (19 to 65)	42 (18 to 65)
BMI (kg/m²) Mean (SD)	27.1 (5.8)	28.5 (5.5)	25.9 (4.9)
No Sample size	n = 40 ; % = 81.6	n = 39 ; % = 81.3	n = 36 ; % = 75
Yes Sample size	n = 9 ; % = 18.4	n = 9 ; % = 18.7	n = 12 ; % = 25

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*
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 *(Per protocol analysis. Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(No information on whether an appropriate analysis was used to estimate the effect of adhering to the intervention.)*
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 *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study.)*
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 *(Per-protocol analysis and no information on whether an appropriate analysis was used to estimate the effect of adhering to the intervention.)*
Overall bias and Directness	Overall Directness	Partially applicable *(<15% had type 2 diabetes)*

1

2 Olafsdottir, 2020

Bibliographic Reference	Olafsdottir, AF; Bolinder, J; Heise, T; Polonsky, W; Ekelund, M; Wijkman, M; Pivodic, A; Ahlen, E; Schwarcz, E; Nystrom, T; et, al.; Majority of people with type 1 diabetes and multiple daily insulin injection benefit by using Continuous Glucose Monitoring: an analysis based on the GOLD randomised trial (GOLD-5); Diabetes, obesity & metabolism; 2020

3

4 Study details

Trial registration number and/or trial name	GOLD-5; NCT02092051
Study type	Cross-over randomised controlled trial
Study location	Sweden

Study setting	Not reported
Study dates	February 2014 to June 2016
Sources of funding	The trial was sponsored by the NU Hospital Group, Trollhättan and Uddevalla, Sweden.
Inclusion criteria	Age ≥18 years Duration of diabetes >1 year HbA1c ≥7.5% (≥58 mmol/mol) Treated with multiple daily insulin injections Fasting C-peptide levels <0.91 ng/mL
Exclusion criteria	Treated with insulin pumps
Intervention(s)	All participants received basic instruction on insulin dosing, such as bolus correction, food choices and the effect of physical activity on glucose control. A graph was used to explain the effect of active insulin in the body. The participants received guidelines for interpreting glucose levels and trends obtained by the CGM system. During the first week, no alarms were set on the CGM device for low glucose levels except for acute hypoglycaemia (<55 mg/dL; <3.1 mmol/L). Alarm settings were introduced no later than 2 weeks after randomisation; all the alarm settings were individualised. At each visit, participants were encouraged to use CGM information at least every 1-2 hours during daytime. During the SMBG period, participants were encouraged to measure blood glucose levels according to the guidelines (i.e. at least four times daily). During both periods, participants were instructed to adjust insulin doses based on SMBG and not CGM values. For the SMBG measurement, participants used their own glucose meters, which came from various manufacturers. During the 17-week wash-out period, participants used SMBG and masked CGM was performed during the last 2 weeks.
Comparator	
Outcome measures	HBA1C Patients with a reduction in HbA1c of more than 0.4% (4.7 mmol/mol) between treatments were considered to be HbA1c responders. Time in range For time in range, an improvement of greater than 5% was used for responders. Time spent above/below target glucose range For time in hypoglycaemia two glucose cut-offs were used: 70 mg/dL (3.9 mmol/L) and 54 mg/dL (3.0 mmol/L).

	Percentage of time with glucose levels lower than 70 mg/dL (>3.9 mmol/L), and lower than 53 mg/dL (>3.0 mmol/L) and greater than 250 mg/dL (>13.9 mmol/L). Hypoglycaemia The average number of hypoglycaemias experienced per week during the last 2 months at inclusion; the number of severe hypoglycaemias in the last year and the last 5 years; the hypoglycaemic confidence questionnaire total score. Glycaemic variability Measured by standard deviation (SD) of glucose levels and coefficient of variation (CV).
Number of participants	Continuous glucose monitoring / Intermittent capillary blood glucose monitoring N=69 Intermittent capillary blood glucose monitoring / Continuous glucose monitoring N=73
Duration of follow-up	26 weeks
Loss to follow-up	19 participants did not have follow-up data for both the CGM and SMBG phases.
Additional comments	During a 6-week run-in phase, participants completed masked CGM for 2 weeks. During masked CGM, glucose levels were recorded but not seen by participants. After masked CGM, participants were excluded if they either did not believe they would wear the CGM more than 80% of the time or did not perform adequate calibrations during run-in (on average, at least 12 of 14 during a 7-day period). Masked CGM was performed 2 weeks before both treatment phases. During SMBG, masked CGM was also performed during 2 of the last 4 weeks to evaluate total time in hypoglycaemia, euglycaemia, hyperglycaemia and glycaemic variability. At all visits, CGM and SMBG data were downloaded and used for optimizing glycaemic control. Participants were not allowed to have any extra visits for improving glycaemic control to ensure the number of visits were equal in both treatment groups. Type of insulin regimen was not reported.

Study arms

Continuous glucose monitoring / Intermittent capillary blood glucose monitoring (N = 69)

Continuous glucose monitoring: real-time continuous glucose monitoring (rtCGM) using Dexcom G4 PLATINUM (San Diego, CA, USA), followed by intermittent capillary blood glucose monitoring: self-measurement of blood glucose (SMBG) using participants own glucose meters, which came from various manufacturers.

Intermittent capillary blood glucose monitoring / Continuous glucose monitoring (N = 73)

Intermittent capillary blood glucose monitoring: Self-measurement of blood glucose (SMBG) using participants own glucose meters, which came from various manufacturers; followed by continuous glucose monitoring: real-time continuous glucose monitoring (rtCGM) using Dexcom G4 PLATINUM (San Diego, CA, USA).

Characteristics

Arm-level characteristics

Characteristic	Continuous glucose monitoring / Intermittent capillary blood glucose monitoring (N = 69)	Intermittent capillary blood glucose monitoring / Continuous glucose monitoring (N = 73)
% Female Nominal	46.4	41.1
Mean age (SD) Mean (95% CI)	46.7 (43.6 to 49.8)	42.6 (39.8 to 45.5)
BMI (kg/m²) Mean (95% CI)	27 (26.1 to 28)	27.2 (26 to 28.3)
Time since diabetes diagnosis (years) Mean (95% CI)	23.4 (20.5 to 26.2)	21 (18.3 to 23.7)

Olafsdottir, 2018

Bibliographic Reference	Olafsdottir, Arndis F; Polonsky, William; Bolinder, Jan; Hirsch, Irl B; Dahlqvist, Sofia; Wedel, Hans; Nystrom, Thomas; Wijkman, Magnus; Schwarcz, Erik; Hellman, Jarl; Heise, Tim; Lind, Marcus; A Randomized Clinical Trial of the Effect of Continuous Glucose Monitoring on Nocturnal Hypoglycemia, Daytime Hypoglycemia, Glycemic Variability, and

Hypoglycemia Confidence in Persons with Type 1 Diabetes Treated with Multiple Daily Insulin Injections (GOLD-3).; Diabetes technology & therapeutics; 2018; vol. 20 (no. 4); 274-284

Study details

Secondary publication of another included study- see primary study for details	Lind, Marcus, Polonsky, William, Hirsch, Irl B et al. (2017) Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. JAMA 317(4): 379-387

Oskarsson, 2018

Bibliographic Reference	Oskarsson, Per; Antuna, Ramiro; Geelhoed-Duijvestijn, Petronella; Kroger, Jens; Weitgasser, Raimund; Bolinder, Jan; Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy: a pre-specified subgroup analysis of the IMPACT randomised controlled trial.; Diabetologia; 2018; vol. 61 (no. 3); 539-550

Study details

Secondary publication of another included study- see primary study for details	Bolinder, Jan, Antuna, Ramiro, Geelhoed-Duijvestijn, Petronella et al. (2016) Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet (London, England) 388(10057): 2254-2263

Pratley, 2020

Bibliographic Reference	Pratley, Richard E; Kanapka, Lauren G; Rickels, Michael R; Ahmann, Andrew; Aleppo, Grazia; Beck, Roy; Bhargava, Anuj; Bode, Bruce W; Carlson, Anders; Chaytor, Naomi S; Fox, D Steven; Goland, Robin;

Hirsch, Irl B; Kruger, Davida; Kudva, Yogish C; Levy, Carol; McGill, Janet B; Peters, Anne; Philipson, Louis; Philis-Tsimikas, Athena; Pop-Busui, Rodica; Shah, Viral N; Thompson, Michael; Vendrame, Francesco; Verdejo, Alandra; Weinstock, Ruth S; Young, Laura; Miller, Kellee M; Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) Study, Group; Effect of Continuous Glucose Monitoring on Hypoglycemia in Older Adults With Type 1 Diabetes: A Randomized Clinical Trial.; JAMA; 2020; vol. 323 (no. 23); 2397-2406

Study details

Trial registration number and/or trial name	WISDM; NCT03240432
Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	22 endocrinology practices
Study dates	October 2017 to June 2018
Sources of funding	This study was funded by JDRF and the Leona M. and Harry B. Helmsley Charitable Trust by a grant provided to the Jaeb Center for Health Research. The National Center for Research Resources and the National Center for Advancing Translational Sciences of the NIH (grant UL1TR001878) support the Center for Human Phenomic Science at the University of Pennsylvania. Dexcom provided study CGM devices and sensors.
Inclusion criteria	At least 60 years old No use of real-time CGM in the 3 months prior to enrolment HbA1c less than 10.0% To be using either an insulin pump or multiple daily insulin injections
Intervention(s)	Participants in both groups were provided general diabetes management education, and clinicians were encouraged to review downloaded glucose data at each visit to inform treatment recommendations at their discretion. **Continuous glucose monitoring** The CGM group was instructed to use the continuous glucose monitor daily, to calibrate the monitor twice daily, and to set the low alert (recommended to be set at 70mg/dL). The continuous glucose monitor includes an urgent low alert at 55 mg/dL that cannot be turned off. General guidelines were provided to participants about using CGM. Additional instructions were provided on using CGM trend arrows to adjust insulin dosing based on guidelines specific to an at-risk older adult population.

	Intermittent capillary blood glucose monitoring The standard BGM group was asked to perform home BGM at least 4 times daily.
Outcome measures	HBA1C Mean change from baseline, percentage with HbA1c <7.0%, percentage with HbA1c <7.5%, percentage with relative reduction in HbA1c of at least 10%, percentage with absolute reduction in HbA1c of at least 0.5%, percentage with absolute reduction in HbA1c of at least 1%, and percentage with absolute reduction in HbA1c of at least 0.5% or HbA1c <7.0%. Time in range Percentage of time with glucose values in the range of 70 to 180 mg/dL. Time spent above/below target glucose range CGM-measured percentage of time spent with a glucose value less than 70 mg/dL during follow-up using data pooled from approximately 7 days prior to the 8, 16, and 26-week visits. (To convert glucose values to millimoles per liter, multiply by 0.0555). Percentage of time with a glucose value less than 54 mg/dL, percentage of time with a glucose value less than 60 mg/dL. Hyperglycaemia outcomes included percentages of time with glucose values greater than 180 mg/dL, greater than 250 mg/dL, and greater than 300 mg/dL. Hypoglycaemia Rate of hypoglycaemia events per week (with an event defined as 15 consecutive minutes with a sensor glucose value <54 mg/dL). Glycaemic variability Coefficient of variation defined as ratio of the standard deviation to the mean. Diabetic ketoacidosis Adverse events Reportable adverse events included severe hypoglycaemia (defined as an event that required assistance from another person because of altered consciousness), hyperglycaemia resulting in treatment at a health care facility or that involved diabetic ketoacidosis (as defined by the Diabetes Control and Complications Trial), device-related events with potential effect on participant safety, falls, fractures, emergency department visits, and all serious adverse events regardless of causality. Mental health outcomes

	Diabetes distress (Type 1 Diabetes Distress Scale). Awareness of hypoglycaemia Clarke Survey. Quality of life measured by validated tools General quality of life (PROMIS Global Health Short Form; National Institutes of Health [NIH] Toolbox [http://www.nihtoolbox.org] Emotion Battery). Hypoglycaemia fear (Hypoglycaemia Fear Survey II–Worry subscale).
Number of participants	Continuous glucose monitoring N=103 Intermittent capillary blood glucose monitoring N=100
Type of insulin delivery system	Multiple daily injections Insulin pump
Duration of follow-up	6 months
Additional comments	Each participant completeda2-week pre-randomisation period using a masked CGM on which sensor glucose concentrations were not visible to participants. To be eligible for randomisation, participants were required to have at least 10 of 14 days (240 hours) of data available with an average of at least 1.8 calibrations per day using the study-provided blood glucose meter (Bayer Contour NextUSB; Ascensia Diabetes Care). Type of insulin regimen was not reported.

Study arms

Continuous glucose monitoring (N = 103)

Loss to follow-up	Lost to follow-up (n=1)

Use of continuous glucose monitoring (CGM) (Dexcom G5, Dexcom) with a study blood glucose meter as needed.

Intermittent capillary blood glucose monitoring (N = 100)

Loss to follow-up	Lost to follow-up (n=1) Requested to withdraw from study (n=3) Discontinued intervention (n=2; these participants in the standard BGM group initiated real-time CGM before completing the 26-week visit).
Methods of analysis	

Use of standard capillary blood glucose monitoring (BGM) with the study blood glucose meter without CGM.

Characteristics

Arm-level characteristics

Characteristic	**Continuous glucose monitoring (N = 103)**	**Intermittent capillary blood glucose monitoring (N = 100)**
% Female Nominal	59	44
Mean age (SD) (years) Median (IQR)	68 (65 to 72)	67 (64 to 71)
Time since diabetes diagnosis (years) Median (IQR)	39 (24 to 49)	36 (25 to 47)
Past but not current Sample size	n = 53 ; % = 51	n = 40 ; % = 40
Never Sample size	n = 50 ; % = 49	n = 60 ; % = 60

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*

Section	Question	Answer
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 *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
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 *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study.)*
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	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions. Unblinded nature of studies not marked down, nature of each outcomes usefulness RE: measurement and objectivity will be discussed with committee.)*
Overall bias and Directness	Overall Directness	Directly applicable

1

2 Reddy, 2018

Bibliographic Reference	Reddy, M; Jugnee, N; El Laboudi, A; Spanudakis, E; Anantharaja, S; Oliver, N; A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with Type 1 diabetes and impaired awareness of hypoglycaemia.; Diabetic medicine : a journal of the British Diabetic Association; 2018; vol. 35 (no. 4); 483-490

3

4 Study details

Secondary publication of another	Avari, P., Moscardo, V., Jugnee, N. et al. (2019) Glycemic Variability and Hypoglycemic Excursions With Continuous Glucose Monitoring Compared to Intermittently Scanned Continuous Glucose Monitoring in Adults With Highest Risk Type 1 Diabetes. Journal of Diabetes Science and Technology

included study- see primary study for details	

Reddy, 2018

Bibliographic Reference	Reddy, Monika; Jugnee, Narvada; Anantharaja, Sinthuka; Oliver, Nick; Switching from Flash Glucose Monitoring to Continuous Glucose Monitoring on Hypoglycemia in Adults with Type 1 Diabetes at High Hypoglycemia Risk: The Extension Phase of the I HART CGM Study.; Diabetes technology & therapeutics; 2018; vol. 20 (no. 11); 751-757

Study details

Secondary publication of another included study- see primary study for details	Avari, P., Moscardo, V., Jugnee, N. et al. (2019) Glycemic Variability and Hypoglycemic Excursions With Continuous Glucose Monitoring Compared to Intermittently Scanned Continuous Glucose Monitoring in Adults With Highest Risk Type 1 Diabetes. Journal of Diabetes Science and Technology

Riveline, 2012

Bibliographic Reference	Riveline, Jean-Pierre; Schaepelynck, Pauline; Chaillous, Lucy; Renard, Eric; Sola-Gazagnes, Agnes; Penfornis, Alfred; Tubiana-Rufi, Nadia; Sulmont, Veronique; Catargi, Bogdan; Lukas, Celine; Radermecker, Regis P; Thivolet, Charles; Moreau, Francois; Benhamou, Pierre-Yves; Guerci, Bruno; Leguerrier, Anne-Marie; Millot, Luc; Sachon, Claude; Charpentier, Guillaume; Hanaire, Helene; EVADIAC Sensor Study, Group; Assessment of patient-led or physician-driven continuous glucose monitoring in patients with poorly controlled type 1 diabetes using basal-bolus insulin regimens: a 1-year multicenter study.; Diabetes care; 2012; vol. 35 (no. 5); 965-71

Study details

Trial registration number and/or trial name	Capteur Evadiac; NCT00726440
Study type	Randomised controlled trial (RCT)
Study location	France
Study setting	19 diabetes care centres
Study dates	May 2008 to June 2009
Sources of funding	This study was supported by the Association Française des Diabétiques and the Leon Fredericq Foundation of the University of Liège (for the Belgian part of this trial).
Inclusion criteria	People with T1D Duration of diabetes >12 months Treated with either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDI) Age between 8 and 60 years HbA1c level ≥8.0% SMBG performed at least twice daily
Intervention(s)	**Continuous glucose monitoring patient-led** The use of the CGM device was managed entirely by the participants themselves. Participants were advised to use CGM continuously throughout the study, as they would with a glucose meter, especially if glucose targets were not achieved. **Continuous glucose monitoring physician-prescribed** The use of the CGM device was prescribed by the participant's physician, who asked the participant to use the sensors intermittently according to guidelines based on glucose outcomes: 2 weeks' sensor use per month during the first 3 months, thereafter continuing either in the same manner or with more intensive use during the following 3 months if at any visit the participant presented one of the following criteria: HbA1c 7.5%, greater than four mild hypoglycaemic episodes per week, or at least one severe hypoglycaemic episode. Thus, use of the sensors could be gradually increased every 3 months to 20, 25, or even 30 days/month. **Intermittent capillary blood glucose monitoring** Participants were asked to carry out standard home SMBG.
Comparator	

Outcome measures	HBA1C Reduction in HbA1c at 12 months versus baseline. A 0.5% change in HbA1c value was considered clinically meaningful. Hypoglycaemia Mild hypoglycaemia (defined as an SMBG value <70 mg/dL or symptoms of low BG) during the preceding week, severe hypoglycaemia (defined as an event requiring assistance from another person). Glycaemic variability Diabetic ketoacidosis % of CGM data captured In both CGM groups, the glucose data were downloaded from the device memory and the amount of actually used sensors was recorded. Adverse events Adverse events included mild hypoglycaemia, severe hypoglycaemia, ketoacidosis, unexpected study- or device-related events, and any serious adverse event, regardless of cause. Quality of life measured by validated tools Diabetes Quality of Life (DQoL) and SF-36 questionnaires.
Number of participants	Continuous glucose monitoring patient-led N=62 Continuous glucose monitoring physician-prescribed N=55 Intermittent capillary blood glucose monitoring N=61
Type of insulin delivery system	Multiple daily injections Continuous subcutaneous insulin infusion
Duration of follow-up	12 months
Loss to follow-up	7.4%
Additional comments	Before inclusion, participants were instructed in the technical use of the study CGM device and were required to wear it during a 10-day test period to confirm their ability and willingness to use CGM. At the time of inclusion, all participants received intensive education about target glucose values, insulin dose management, and insulin-to-carbohydrate ratios and correction factors, and they

	were asked to perform SMBG at least three times daily. Participants in the CGM arms received specific training in how to analyse and make use of the CGM data and to confirm glucose values using the meter included in the Navigator device before making therapeutic decisions. Type of insulin regimen was not reported. In the final included participants, less than 15% were aged <19 years.

Study arms

Continuous glucose monitoring patient-led (N = 62)

Patient-led use of continuous glucose monitoring with FreeStyle Navigator glucose needle-type sensor system (Abbott Diabetes Care, Alameda, CA).

Continuous glucose monitoring physician-prescribed (N = 55)

Physician-prescribed continuous glucose monitoring with FreeStyle Navigator glucose needle-type sensor system (Abbott Diabetes Care, Alameda, CA).

Intermittent capillary blood glucose monitoring (N = 61)

Participants were asked to carry out standard home self-monitoring of blood glucose (Abbott Diabetes Care provided the home glucose meters and test strips).

Characteristics

Arm-level characteristics

Characteristic	**Continuous glucose monitoring patient-led (N = 62)**	**Continuous glucose monitoring physician-prescribed (N = 55)**	**Intermittent capillary blood glucose monitoring (N = 61)**
% Female Nominal	50	54.5	36.1
Mean age (SD) (years) Mean (SD)	*empty data*	*empty data*	37.8 (13.9)

Characteristic	Continuous glucose monitoring patient-led (N = 62)	Continuous glucose monitoring physician-prescribed (N = 55)	Intermittent capillary blood glucose monitoring (N = 61)
BMI (kg/m²) Mean (SD)	24.1 (3.9)	24.7 (3.2)	25.3 (3.6)
Time since diabetes diagnosis (years) Mean (SD)	*empty data*	*empty data*	18.8 (10.6)

1

2

3 Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*
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 *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
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 *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study.)*
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	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Less than 15% participants were aged <19 years.)*

1

2 Seyed Ahmadi, 2020

Bibliographic Reference	Seyed Ahmadi, Shilan; Westman, Klara; Pivodic, Aldina; Olafsdottir, Arndis F; Dahlqvist, Sofia; Hirsch, Irl B; Hellman, Jarl; Ekelund, Magnus; Heise, Tim; Polonsky, William; Wijkman, Magnus; Schwarcz, Erik; Lind, Marcus; The Association Between HbA1c and Time in Hypoglycemia During CGM and Self-Monitoring of Blood Glucose in People With Type 1 Diabetes and Multiple Daily Insulin Injections: A Randomized Clinical Trial (GOLD-4).; Diabetes care; 2020; vol. 43 (no. 9); 2017-2024

3

4 Study details

Trial registration number and/or trial name	GOLD-4; NCT02092051
Study type	Cross-over randomised controlled trial
Study location	Sweden
Study setting	15 sites
Study dates	From 24 February 2014 to 1 June 2016
Sources of funding	The study was financed by grants from Swedish State (ALF agreement). CGM sensors and CGM systems were received from Dexcom for carrying out the GOLD trial.
Inclusion criteria	People with T1D Age ≥18 years Duration of diabetes >1 year HbA1c ≥7.5% (≥58 mmol/mol) Fasting C-peptide levels <0.91 ng/mL (<0.3 nmol/L).
Exclusion criteria	Treated with insulin pumps

	Used continuous glucose monitoring within the preceding 4 months
Intervention(s)	All participants were given basic instructions on insulin dosing, such as bolus correction, food choices, and the effect of physical activity on glucose control. All patients had the possibility to contact the responsible staff member for the trial at each site for additional support between the visits if needed, e.g., for technical problems with SMBG meters or the Dexcom G4 system. **Continuous glucose monitoring** Participants used the Dexcom G4 Platinum stand-alone system (Dexcom, Inc., San Diego, CA). **Intermittent capillary blood glucose monitoring** Participants used conventional therapy with regular capillary SMBG. Participants were encouraged to measure blood glucose levels according to guidelines (i.e., at least four times daily) and adjust insulin dosages according to those values.
Comparator	
Outcome measures	HBA1C Time in range Percentage of time with glucose levels 3.9–10.0 mmol/L (70–180 mg/dL) (time in range). Time spent above/below target glucose range Amount of time (expressed as percentage) spent in hypoglycaemia per day using two different cut-offs: <3.9 mmol/L (<70 mg/dL) and <3.0 mmol/L (<54 mg/dL). Corresponding analyses were performed between mean glucose level estimated by masked CGM and time spent in hypoglycaemia. Additionally, the percentage of patients who reached the target for time spent in hypoglycaemia was evaluated according to guidelines issued by the American Diabetes Association in 2019 for HbA1c <7.0% (<53 mmol/mol) and <7.5% (<58mmol/mol).
Number of participants	Continuous glucose monitoring N=131 Intermittent capillary blood glucose monitoring N=127
Type of insulin delivery system	Multiple daily injections

Duration of follow-up	16 months
Loss to follow-up	Not reported
Additional comments	Each participant wore a masked CGM using the Dexcom G4 Platinum (Dexcom, Inc., San Diego, CA) for 2 weeks during a 6-week run-in phase. Afterward, participants were excluded if they either did not believe they would wear the CGM sensor >80% of the time or did not perform adequate calibrations on their CGM system during the run-in phase (on average ≥12 of 14 during a 7-day period). Participants were randomized 1:1 to either CGM or SMBG for the first treatment period of 26 weeks, with a 17-week washout period between treatment phases. During the conventional treatment phase (SMBG), masked CGM was performed during 2 of the last 4 weeks to evaluate the total time spent in hypoglycaemia, time in range, hyperglycaemia, and glycaemic variability. Patients could then not see their CGM data, but the data were collected for comparisons with CGM treatment data. Type of insulin regimen was not reported.

Study arms

Continuous glucose monitoring (N = 131)

Participants used the Dexcom G4 Platinum stand-alone system. The number of participants with data included in the analyses of time on hypoglycaemia and HbA1c was the same as number of participants with data included in analyses of time on hypoglycaemia and mean glucose (N=131).

Intermittent capillary blood glucose monitoring (N = 127)

Participants used conventional therapy with regular capillary self-monitoring of blood glucose (SMBG). Participants with data included in the analyses of time on hypoglycaemia and HbA1c (N=125). Participants with data included in analyses of time on hypoglycaemia and mean glucose (N=127).

Characteristics

Study-level characteristics

Characteristic	Study (N = 137)
% Female Nominal	43.1
Mean age (SD) (years) Mean (SD)	44.6 (12.9)
Time since diabetes diagnosis (years) Mean (SD)	22.3 (11.8)

161 patients were included in the study, of whom 137 (85.1%) had either valid masked CGM data during the first 14 days of the run-in period or at the end of the SMBG treatment or valid CGM data during 14 days at the end of CGM treatment. The numbers of participants in the arms varied between 125 and 132.

Speight, 2019

Bibliographic Reference	Speight, J.; Holmes-Truscott, E.; Little, S.A.; Leelarathna, L.; Walkinshaw, E.; Tan, H.K.; Bowes, A.; Kerr, D.; Flanagan, D.; Heller, S.R.; Evans, M.L.; Shaw, J.A.M.; Satisfaction with the use of different technologies for insulin delivery and glucose monitoring among adults with long-standing type 1 diabetes and problematic hypoglycemia: 2-Year follow-up in the HypoCOMPaSS randomized clinical trial; Diabetes Technology and Therapeutics; 2019; vol. 21 (no. 11); 619-626

Study details

Secondary publication of another included study- see primary study for details	Little, Stuart A, Speight, Jane, Leelarathna, Lalantha et al. (2018) Sustained Reduction in Severe Hypoglycemia in Adults With Type 1 Diabetes Complicated by Impaired Awareness of Hypoglycemia: Two-Year Follow-up in the HypoCOMPaSS Randomized Clinical Trial. Diabetes care 41(8): 1600-1607

Tanenberg, 2004

Bibliographic Reference	Tanenberg, Robert; Bode, Bruce; Lane, Wendy; Levetan, Claresa; Mestman, Jorge; Harmel, Anne Peters; Tobian, Janet; Gross, Todd; Mastrototaro, John; Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial.; Mayo Clinic proceedings; 2004; vol. 79 (no. 12); 1521-6

1

2 Study details

Trial registration number and/or trial name	
Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	7 diabetes centres
Study dates	January to September 2000
Sources of funding	Medtronic MiniMed, Northridge, Calif.
Inclusion criteria	Insulin-treated diabetes Aged 19 to 76 years Inadequate metabolic control HbA1c >7.9%
Intervention(s)	**Continuous glucose monitoring** Participants in the CGM arm were instructed to perform capillary blood glucose measurements at least 4 times per day and in response to symptoms of hypoglycaemia for the duration of the study. In addition, they wore the monitors for 3 days during week 1. The GCM system was used again for 3 days during week 3. **Intermittent capillary blood glucose monitoring** Participants in the SMBG arm were instructed to perform capillary blood glucose measurements at least 4 times per day (i.e. before meals and at bed time) and in response to symptoms of hypoglycaemia for the duration (12 weeks) of the study.
Outcome measures	HBA1C Time spent above/below target glucose range Duration of hypoglycaemia (defined as sensor glucose values of 60 mg/dL or less, and the end of a hypoglycaemic event was defined as the absence

	of hypoglycaemic sensor readings for 30 minutes or longer) and hyperglycaemia (defined as sensor glucose values of 200 mg/dL or higher, and the end of a hyperglycaemic event was defined as the absence of hyperglycaemic sensor readings for 30 minutes or longer). Hypoglycaemia Defined as sensor glucose values of 60 mg/dL or less, and the end of a hypoglycaemic event was defined as the absence of hypoglycaemic sensor readings for 30 minutes or longer. Severe hypoglycaemia. Adverse events
Number of participants	Continuous glucose monitoring N=62 Intermittent capillary blood glucose monitoring N=66
Type of insulin delivery system	Multiple daily injections Continuous subcutaneous insulin infusion
Duration of follow-up	12 weeks
Loss to follow-up	
Additional comments	To test for differences in the frequency and duration of hypoglycaemia and hyperglycaemia between arms, all participants used the CGM system for 3 consecutive days during week 12. Type of insulin regimen was not reported.

Study arms

Continuous glucose monitoring (N = 51)

Duration of follow-up	
Loss to follow-up	11 discontinued intervention: • 5 non-compliance • 3 participant request • 1 insufficient sensor data • 1 moved out of state • 1 therapy changes in the first week only

CGM system (Medtronic MiniMed, Northridge, Calif)

Intermittent capillary blood glucose monitoring (N = 58)

Loss to follow-up	8 discontinued intervention: • 2 non-compliance • 2 participant request • 1 insufficient sensor data • 1 pregnancy • 1 family illness • 1 hospitalised

SMBG using a home blood glucose metre (OneTouch FastTake, Lifescan, a Johnson & Johnson Company, Milpitas, Calif)

Characteristics

Arm-level characteristics

Characteristic	**Continuous glucose monitoring (N = 51)**	**Intermittent capillary blood glucose monitoring (N = 58)**
% Female Nominal	62.7	56.9
Mean age (SD) (years) Mean (SD)	44 (10.2)	44.5 (12.6)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

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)	High *(The consort diagram shows that analyses were done in participants who continued with the intervention and without missing data on HbA1c.)*
Domain 2b: Risk of bias due to deviations from	Risk of bias judgement for deviations from the	High *(No information on whether an*

Section	Question	Answer
the intended interventions (effect of adhering to intervention)	intended interventions (effect of adhering to intervention)	*appropriate analysis was used to estimate the effect of adhering to the interventions.)*
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	High *(The consort diagram shows that analyses were done in participants who continued with the intervention and without missing data on HbA1c. No information on whether an appropriate analysis was used to estimate the effect of adhering to the interventions.)*
Overall bias and Directness	Overall Directness	Partially applicable *(<10% had type 2 diabetes)*

1

2 Tansey, 2011

Bibliographic Reference	Tansey, M; Laffel, L; Cheng, J; Beck, R; Coffey, J; Huang, E; Kollman, C; Lawrence, J; Lee, J; Ruedy, K; Tamborlane, W; Wysocki, T; Xing, D; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group; Satisfaction with continuous glucose monitoring in adults and youths with Type 1 diabetes.; Diabetic medicine : a journal of the British Diabetic Association; 2011; vol. 28 (no. 9); 1118-22

3

4 Study details

Secondary publication of another included study- see primary study for details	Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Tamborlane, William V, Beck, Roy W et al. (2008) Continuous glucose monitoring and intensive treatment of type 1 diabetes. The New England journal of medicine 359(14): 1464-76

1

2

3 Tumminia, 2015

Bibliographic Reference	Tumminia, Andrea; Crimi, Salvatore; Sciacca, Laura; Buscema, Massimo; Frittitta, Lucia; Squatrito, Sebastiano; Vigneri, Riccardo; Tomaselli, Letizia; Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled crossover trial.; Diabetes/metabolism research and reviews; 2015; vol. 31 (no. 1); 61-8

4

5 Study details

Trial registration number and/or trial name	Not reported
Study type	Cross-over randomised controlled trial
Study location	Italy
Study setting	Diabetes Centre
Study dates	From January to March 2012
Sources of funding	Medtronic (Tolochenaz, Switzerland) provided insulin pumps, CGM systems (Mini-Med Paradigm real-time and iPro2 CGM systems) and the diabetes management software (CareLink Therapy Management System for Diabetes-Clinical).
Inclusion criteria	Duration of diabetes >1 year 18 to 60 years old HbA1c >8.0% (64 mmol/mol)
Exclusion criteria	Pregnant or planning pregnancy Concomitant chronic illness Poor compliance to diet, insulin therapy and/or glucose monitoring (plasma glucose had to be measured at least 4 to 5 times a day, correcting the insulin dose when required)
Intervention(s)	All participants underwent a structured educational programme by attending 2 initials meetings 1 month before starting the study. Each meeting dealt with self-management of blood glucose monitoring, dietary, education, carbohydrate counting and training for the electronic devices

	(glucometers, CGM system). Participants were also given the basic rules to prevent and correct hypoglycaemia and hyperglycaemia episodes (by using carbohydrates and insulin, respectively) and to intervene in case of CGM alerts (set a threshold level for blood glucose at 70 and 200 mg/dL, respectively). All participants had their knowledge and capacity assessed monthly with the support of a dietician and a nurse.
Outcome measures	HBA1C Decrease during the two study periods. Time spent above/below target glucose range Risk of either hyperglycaemia or hypoglycaemia, measured on the basis of the area under the curve (AUC) calculated from CGM for glucose>200 mg/dL/day or <70 mg/dL/day, respectively, which are measurements of the frequency, severity and duration of time spent in hyperglycaemia or hypoglycaemia. Glycaemic variability Day-to-day variation was calculated using the mean of the daily serum glucose differences, defined as the mean of the absolute differences between glucose values on day 2 and the corresponding values on day 1, at the same time of day. Intraday glucose variability was measured according to the standard deviation (SD) of daily glucose values, the coefficient of variation (calculated as the SD divided by the mean of all of the glucose values) and the mean amplitude of glycaemic excursions procedure, as a marker of the amplitude of glycaemic excursions. Diabetic ketoacidosis
Number of participants	Continuous glucose monitoring N=10 Intermittent capillary blood glucose monitoring N=10
Type of insulin delivery system	Multiple daily injections Continuous subcutaneous insulin infusion
Duration of follow-up	6 months in each period
Loss to follow-up	0
Additional comments	After the first period of intervention (6 months), participants had 2-month wash-out period and then crossed over to the other arm. During the wash-out period, the patients continued the same treatment and monitored diabetes by using only SMBG; no control visit was performed. CGM was performed for 1 week at the beginning and at the end of each study period, using a system in which participants were blinded to glycaemic values

	(iPro2 CGM; Medtronic, Tolochenaz, Switzerland). During each visit, data from the devices were uploaded to a computer using diabetes management software (CareLink Therapy Management System for Diabetes-Clinical; Medtronic, Tolochenaz, Switzerland). Type of insulin regimen was not reported. Baseline characteristics were reported by type of insulin delivery system rather than by arm.

Study arms

Continuous glucose monitoring (N = 10)

Using real-time continuous glucose monitoring (RT-CGM) with Guardian real-time Clinical; Medtronic, Tolochenaz, Switzerland. Participants were advised to use the device at least 2 to 3 weeks per month.

Intermittent capillary blood glucose monitoring (N = 10)

Using self-monitoring of blood glucose (SMBG).

Characteristics

Study-level characteristics

Characteristic	Study (N = 20)
% Female Nominal	70

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) T1 Cross-over trial

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low *(2 months long enough to lose CGM learning effect? Committee opinion. Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)	High *(The paper reports that their data indicated that CGM use greater than 40% was sufficient to obtain a benefit from the device. This cut-off was generated considering the regression curve of the HbA1c decrease on the basis of the CGM utilisation rate. Fourteen participants (70%, eight MDI and six CSII) used the RT-CGM at least 40% of the total time.)*
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	High *(The paper reports that their data indicated that CGM use greater than 40% was sufficient to obtain a benefit from the device. This cut-off was generated considering the regression curve of the HbA1c decrease on the basis of the CGM utilisation rate. Fourteen participants (70%, eight MDI and six CSII) used the RT-CGM at least 40% of the total time.)*
Overall bias and Directness	Overall Directness	Directly applicable

1

1 van Beers, 2017

Bibliographic Reference	van Beers, Cornelis A J; de Wit, Maartje; Kleijer, Susanne J; Geelhoed-Duijvestijn, Petronella H; DeVries, J Hans; Kramer, Mark H H; Diamant, Michaela; Serne, Erik H; Snoek, Frank J; Continuous Glucose Monitoring in Patients with Type 1 Diabetes and Impaired Awareness of Hypoglycemia: Also Effective in Patients with Psychological Distress?.; Diabetes technology & therapeutics; 2017; vol. 19 (no. 10); 595-599

2

3 Study details

Secondary publication of another included study- see primary study for details	van Beers, Cornelis A J, DeVries, J Hans, Kleijer, Susanne J et al. (2016) Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. The lancet. Diabetes & endocrinology 4(11): 893-902

4

5

6 van Beers, 2016

Bibliographic Reference	van Beers, Cornelis A J; DeVries, J Hans; Kleijer, Susanne J; Smits, Mark M; Geelhoed-Duijvestijn, Petronella H; Kramer, Mark H H; Diamant, Michaela; Snoek, Frank J; Serne, Erik H; Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial.; The lancet. Diabetes & endocrinology; 2016; vol. 4 (no. 11); 893-902

7

8 Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this	van Beers, Cornelis A J, de Wit, Maartje, Kleijer, Susanne J et al. (2017) Continuous Glucose Monitoring in Patients with Type 1 Diabetes and Impaired Awareness of Hypoglycemia: Also Effective in Patients with Psychological Distress?. Diabetes technology & therapeutics 19(10): 595-599

study included in review	
Trial registration number and/or trial name	IN CONTROL; NCT01787903
Study type	Cross-over randomised controlled trial
Study location	Netherlands
Study setting	Two medical centres
Study dates	March 4, 2013, to Feb 9, 2015
Sources of funding	This research was supported by funding from Eli Lilly and Sanofi. Medtronic provided continuous glucose monitoring devices.
Inclusion criteria	People with T1D Based on American Diabetes Association (ADA) criteria. Impaired awareness of hypoglycaemia Defined by Gold criteria with a Gold score ≥4 18 to 75 years Treated with either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDI) Undertaking at least three SMBG measurements per day
Exclusion criteria	Pregnancy History of renal, liver, or heart disease Current malignancy Current use of non-selective β blockers Current psychiatric disorders Current substance abuse or alcohol abuse Current use of CGM other than for a short period (3 consecutive months) Any hearing or vision impairment that could hinder perception of the glucose display and alarms Poor command of the Dutch language or any disorder that precluded full understanding of the purpose and instructions of the study

	Participation in another clinical study Any known or suspected allergy to trial-related products
Intervention(s)	The (re)education about diabetes management given to all participants before randomisation covered the basic principles of SMBG, hyperglycaemia and hypoglycaemia, glucose fluctuations, insulin and carbohydrates, impaired awareness of hypoglycaemia, and safe and effective use of CGM. No education about the technique of carbohydrate counting was given, in case patients did not practise this technique before enrolment. Participants were equipped with a masked CGM system consisting of an iPro 2 continuous glucose monitor and an Enlite glucose sensor (Medtronic, Northridge, CA, USA), for 2 weeks. This masked CGM system does not display real time CGM data or glucose trends or allow alarms to be set. The Enlite sensors have a mean absolute relative difference between sensor and reference values of less than 20%. Participants were eligible for randomisation if the maximum number of sensor values per day (288) for at least 4 days per week had been obtained, three to four valid calibrations per day had been done, and a daily mean absolute difference less than 18% (in case of a difference between the highest and the lowest calibration value <5.6 mmol/L) or a daily mean absolute difference ess than 28% (in case of a difference between the highest and the lowest calibration value ≥5.6 mmol/L) was noted. These cut-off values are used in our clinical practice, and were based on CGM manufacturers' advice (Medtronic, personal communication). In case of low quality or missing CGM data, the run-in phase was extended until satisfactory CGM data for at least 4 days per week had been obtained. **Continuous glucose monitoring** The CGM system used during the intervention phase consisted of the Paradigm Veo system used solely as a monitor with a MiniLink transmitter (Medtronic, Northridge, CA, USA for both), and the Enlite glucose sensor. Participants were encouraged to use CGM continuously, although this use was not mandatory. **Intermittent capillary blood glucose monitoring** During the SMBG phase, participants wore the masked CGM system continuously throughout the intervention phase and uploaded the masked CGM data each week. Because of frequent issues with uploading data from the masked CGM device, the quality of the CGM data was assessed and included these data in the analysis if at least 4 days per week's worth of satisfactory CGM data, based on the same criteria as in the run-in phase, were obtained. In case of low quality or missing CGM data, the intervention phase was extended until at least 2 weeks of satisfactory CGM data in a 4-week period had been obtained.
Outcome measures	HBA1C Baseline and 16-week HbA1c measurements.

	Time in range Mean difference in the percentage of time that participants spent in normoglycaemia (4.0–10.0 mmol/L) between CGM and SMBG calculated over the total intervention periods. Time spent in normoglycaemia each month to show an effect over time. Time spent above/below target glucose range Percentage of time participants spent in a hypoglycaemic state (blood glucose ≤3.9 mmol/L) and a hyperglycaemic state (>10.0 mmol/L). Duration (min per episode) of CGM-derived hypoglycaemic episodes (≥three sequential sensor values ≤3.9 mmol/L), frequency (episode per night) and duration of CGM derived hypoglycaemic episodes at night-time (0000–0600 h). Hypoglycaemia Severe hypoglycaemia (defined as a hypoglycaemic event requiring third-party assistance). Glycaemic variability Within-day and between-day glucose variability calculated as within-day SD of glucose concentration, coefficient of variation, mean absolute change in glucose concentration, mean of daily differences, and continuous overall net glycaemic action. Adverse events Mental health outcomes Psychological distress scores (World Health Organisation Well-being Index 5 [WHO-5], Problem Areas in Diabetes 5 [PAID-5], and Hypoglycaemia Fear Survey [HFS] Worry). Awareness of hypoglycaemia Self-reported hypoglycaemia awareness (based on Gold and Clarke methods). Quality of life measured by validated tools Diabetes-specific measures of quality of life (PAID-5, HFS, CIDS, EQ5D, and WHO-5), and satisfaction with use of CGM assessed by the CGM-SAT questionnaire.
Number of participants	Continuous glucose monitoring N=26 Intermittent capillary blood glucose monitoring N=26

Type of insulin delivery system	Multiple daily injections Continuous subcutaneous insulin infusion
Duration of follow-up	16 weeks in each intervention period
Loss to follow-up	
Additional comments	After the first intervention period, participants entered a 12-week washout phase, during which they only received telephone consultations for taking recent medical history and monitoring of potential adverse events every 2 weeks. At the end of the washout period, the general diabetes education was repeated and participants wore a masked CGM device again for 2 weeks to gather baseline data for the second intervention period.

Study arms

Continuous glucose monitoring (N = 26)

Loss to follow-up	**Period 1** Discontinued treatment (n=3) Withdrew consent (n=3) **Period 2** None lost to follow-up

Real-time CGM system consisting of a Paradigm Veo system with a MiniLink transmitter and an Enlite glucose sensor (Medtronic, CA, USA).

Intermittent capillary blood glucose monitoring (N = 26)

Loss to follow-up	**Period 1** Discontinued treatment (n=2) Withdrew consent (n=2) **Period 2** Discontinued treatment (n=1 Withdrew consent (n=1)

Self-monitoring of blood glucose (SMBG).

1 Characteristics

2 Study-level characteristics

Characteristic	Study (N = 52)
% Female Nominal	46
Mean age (SD) (years) Mean (SD)	48.6 (11.6)
BMI (kg/m²) Mean (SD)	25 (3.8)
Time since diabetes diagnosis (years) Median (IQR)	30.5 (18.5 to 40.8)

3 Intention-to-treat population

4

5

6 Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) T1 Cross-over trial

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low *(12 weeks long enough to lose CGM learning effect? Committee opinion. Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
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 *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study.)*
Overall bias and Directness	Overall Directness	Directly applicable

1

2

3

4 Visser, 2021

Bibliographic Reference	Visser MM; Charleer S; Fieuws S; De Block C; Hilbrands R; Van Huffel L; Maes T; Vanhaverbeke G; Dirinck E; Myngheer N; Vercammen C; Nobels F; Keymeulen B; Mathieu C; Gillard P; Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial.; Lancet (London, England); 2021; vol. 397 (no. 10291)

5

6 Study details

Secondary publication of another included study- see primary study for details	
Trial registration number and/or trial name	NCT03772600
Study type	Randomised controlled trial (RCT)
Study location	Belgium
Study setting	6 hospitals
Study dates	January - June 2019
Sources of funding	Dexcom

Inclusion criteria	People with T1D Age ≥18 years Duration of diabetes >= 6 months Treatment with MDI or insulin pump HbA1c 10% or less Exclusive isCGM use for 6 months
Exclusion criteria	planned pregnancy severe cognitive impairment limiting CGM usage, use of systemic corticosteroids, or concomitant pathology that could cause oedema at anticipated CGM insertion sites
Intervention(s)	
Comparator	
Outcome measures	HBA1C 6 months Time in range 3.9 - 10 mmol/L 3.9 - 7.8 mmol/L Time spent above/below target glucose range < 3.9, >10, >13.9 mmol/l Glycaemic variability CV, SD, number of low glucose events Quality of life measured by validated tools HFS-Worry
Number of participants	254
Type of insulin delivery system	Multiple daily injections rtCGM: 81%, isCGM: 80% Continuous subcutaneous insulin infusion

	rtCGM: 19%, isCGM: 20%
Duration of follow-up	6 months
Loss to follow-up	rtCGM: 3 isCGM: 5
Additional comments	The trial was subdivided in a baseline phase of 4–7 weeks (hereafter referred to as baseline) and a study phase of 6 months.

Study arms

rtCGM (N = 127)

Dexcom G6 (10-day wear)

isCGM (N = 127)

FreeStyle Libre; (14-day wear)

Characteristics

Arm-level characteristics

Characteristic	**rtCGM (N = 127)**	**isCGM (N = 127)**
% Female (%) Nominal	36	40
Mean age (SD) Mean (SD)	42.8 (13.8)	43 (14.5)
BMI Median (IQR)	25.6 (23.2 to 28.4)	24.8 (22.4 to 27.2)
Time since diabetes diagnosis Median (IQR)	18 (10 to 30)	17 (8 to 28)
Length of time with CGM monitor Median (IQR)	29 (25 to 31)	27 (22 to 31)
HBA1C (%) Mean (SD)	7.4 (0.9)	7.4 (0.9)

1

2 Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T1

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 *(Unmasked data but CGM masking not possible due to patient reading, thus marked low as other studies.)*
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 bias and Directness	Overall Directness	Directly applicable

4

5

6

Appendix F – Forest plots

rtCGM vs isCGM

Figure 1: Time in range (%) (3.9 - 10 mmol/l) <= 3 months

Study or Subgroup	rtCGM Mean	rtCGM SD	rtCGM Total	isCGM Mean	isCGM SD	isCGM Total	Weight	Mean Difference IV, Fixed, 95% CI
Haskova 2020	0	14.7018	30	-8.14	14.7018	30	49.8%	8.14 [0.70, 15.58]
IHARTCGM Avari 2019	9.6	15	20	6.6	7.8	20	50.2%	3.00 [-4.41, 10.41]
Total (95% CI)			50			50	100.0%	**5.56 [0.31, 10.81]**

Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)

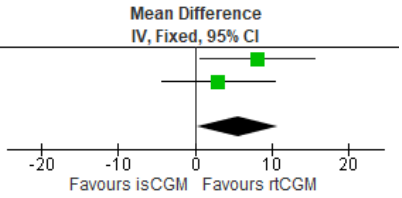


Figure 2: Time below range (%) <3.9 mmol/l <= 3 months

Study or Subgroup	rtCGM Mean	rtCGM SD	rtCGM Total	isCGM Mean	isCGM SD	isCGM Total	Weight	Mean Difference IV, Fixed, 95% CI
Haskova 2020	0	3.6952	30	2.03	3.6952	30	81.4%	-2.03 [-3.90, -0.16]
IHARTCGM Avari 2019	-3.1	5.4	20	1.8	7.1	20	18.6%	-4.90 [-8.81, -0.99]
Total (95% CI)			50			50	100.0%	**-2.56 [-4.25, -0.88]**

Heterogeneity: Chi² = 1.68, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 2.98 (P = 0.003)

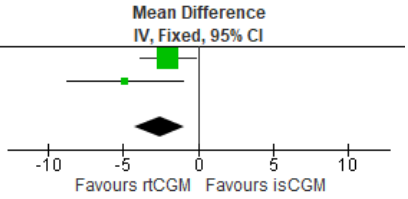
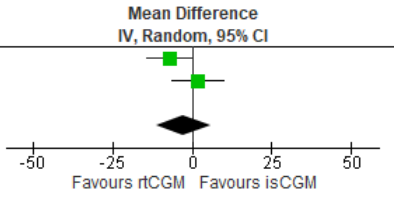


Figure 3: Time above range (%) (>10 mmol/l) <= 3 months

Study or Subgroup	rtCGM Mean	rtCGM SD	rtCGM Total	isCGM Mean	isCGM SD	isCGM Total	Weight	Mean Difference IV, Random, 95% CI
Haskova 2020	0	14.3066	30	6.96	14.3066	30	52.2%	-6.96 [-14.20, 0.28]
IHARTCGM Avari 2019	-6.5	14.2	20	-8.4	11.8	20	47.8%	1.90 [-6.19, 9.99]
Total (95% CI)			50			50	100.0%	**-2.72 [-11.40, 5.95]**

Heterogeneity: Tau² = 23.91; Chi² = 2.56, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 0.61 (P = 0.54)



rtCGM vs SMBG

Figure 4: Change from baseline HBA1C (%) <= 6 months

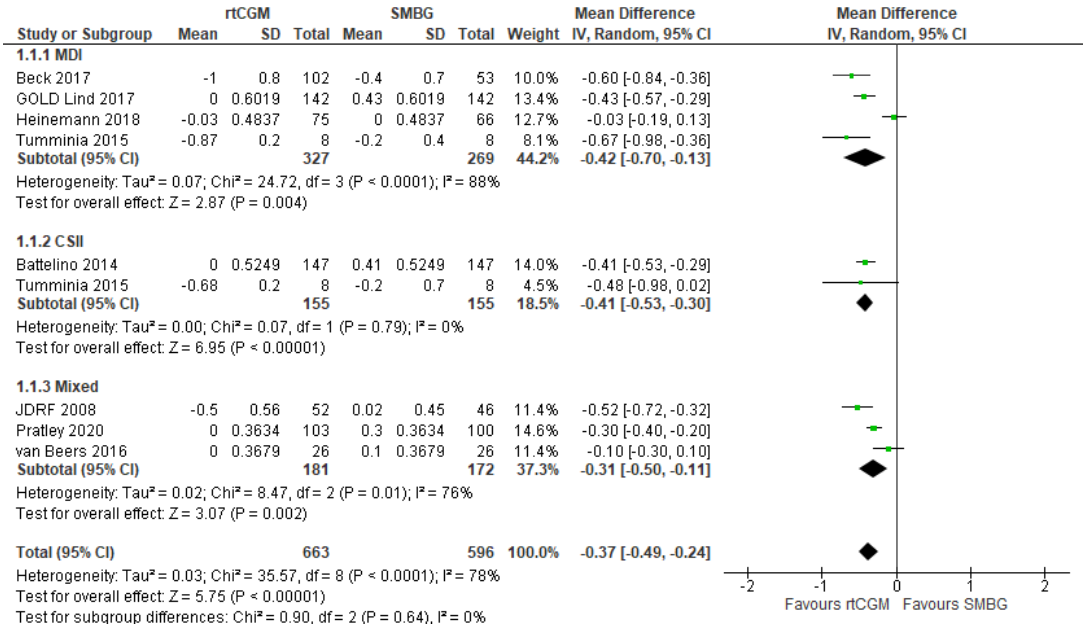


Figure 5: Change from baseline HbA1c (%) - <= 3 months

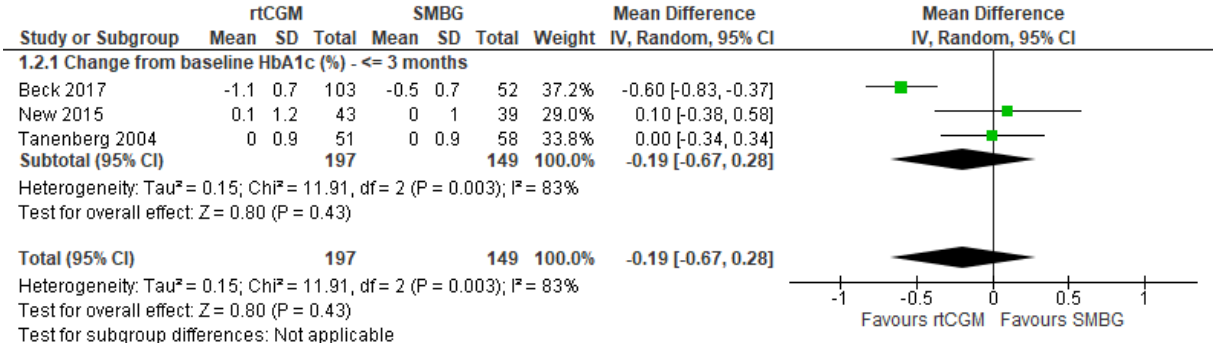


Figure 6: Change in HbA1c (mmol/mol) <= 6 months

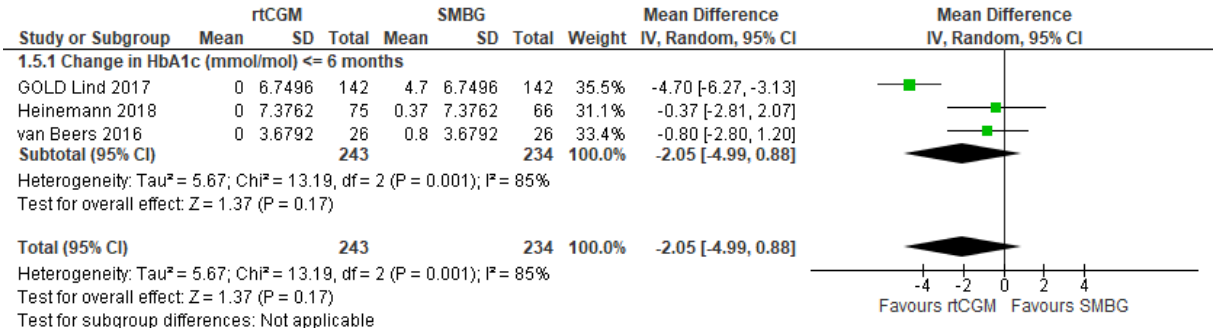


Figure 7: Time in range (%) [3.9/4 - 10 mmol/l] <= 6 months

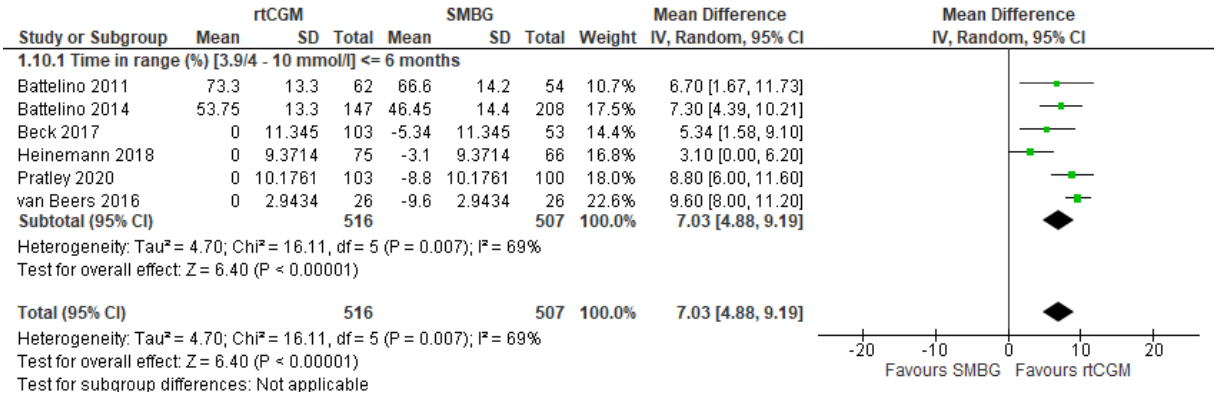


Figure 8: Time below range (%) <3.9 mmol/l <= 6 months

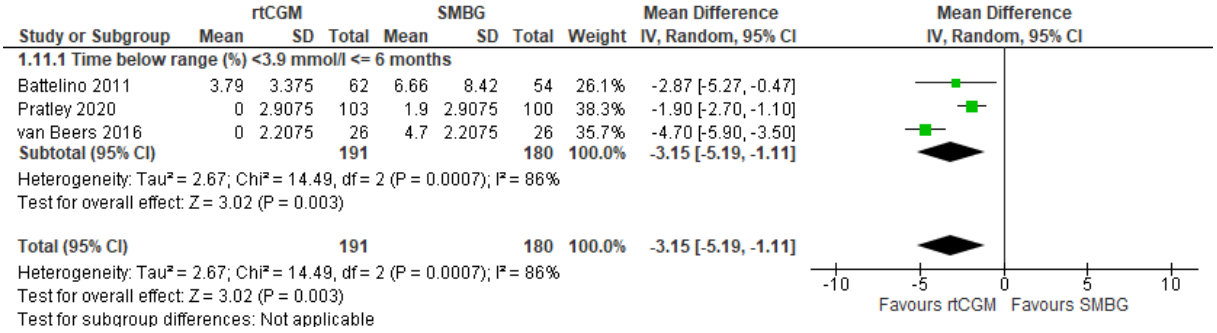


Figure 9: Time above range (%)>10mmol/l <= 6 months

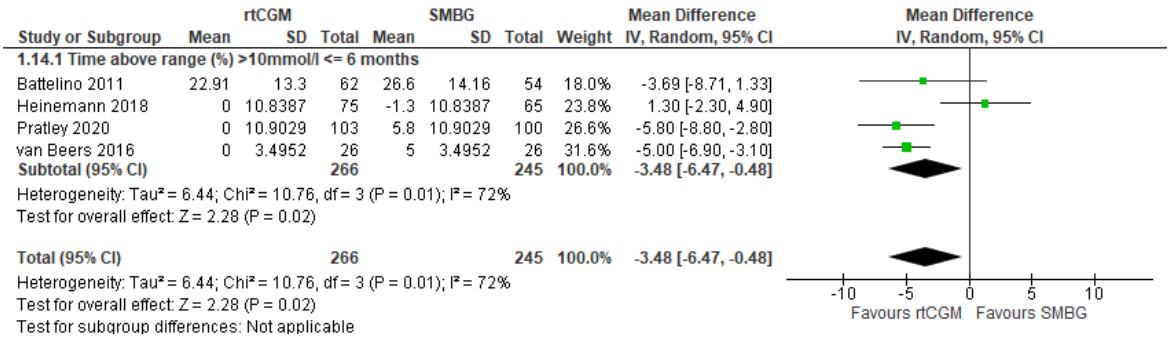


Figure 10: Time above range (%) >13.9 mmol/l <= 6 months

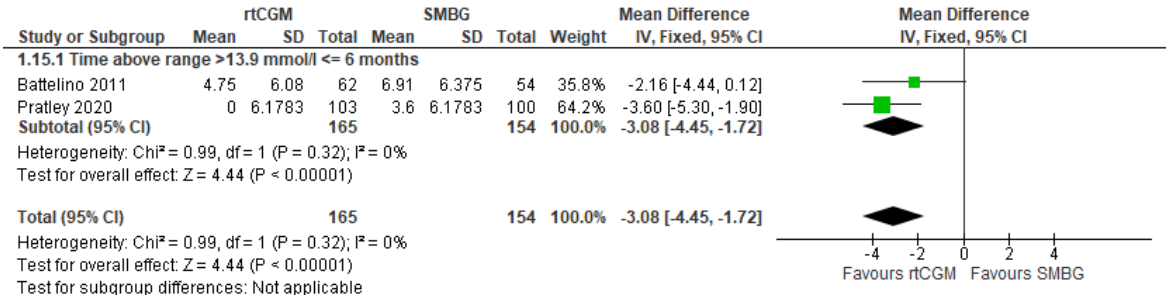


Figure 11: Glycemic variability: SD <= 6 months

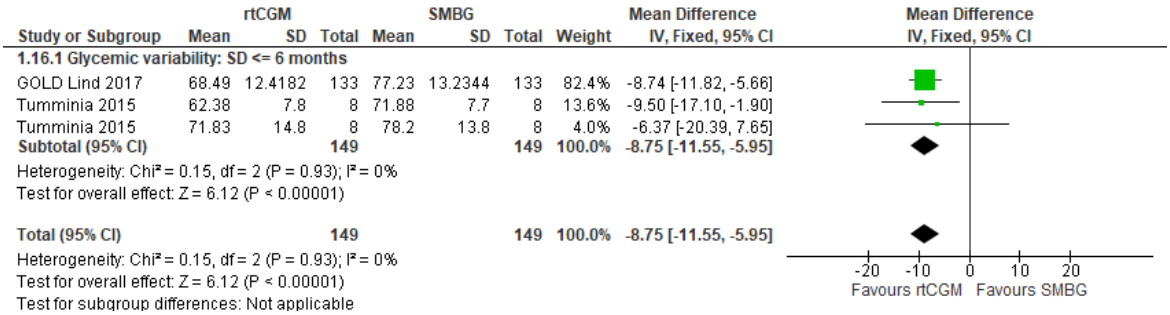


Figure 12: Glycemic variability: coefficient of variation <= 6 months

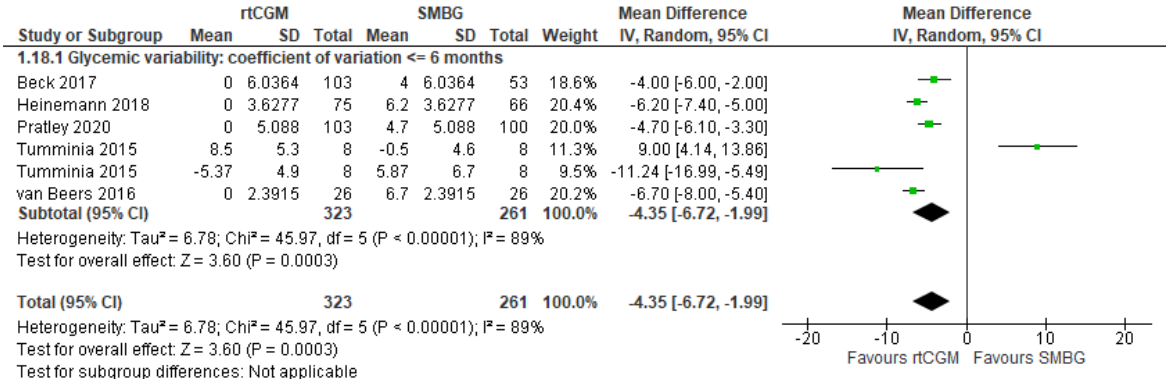


Figure 13: Glycemic variability: MAGE <= 6 months

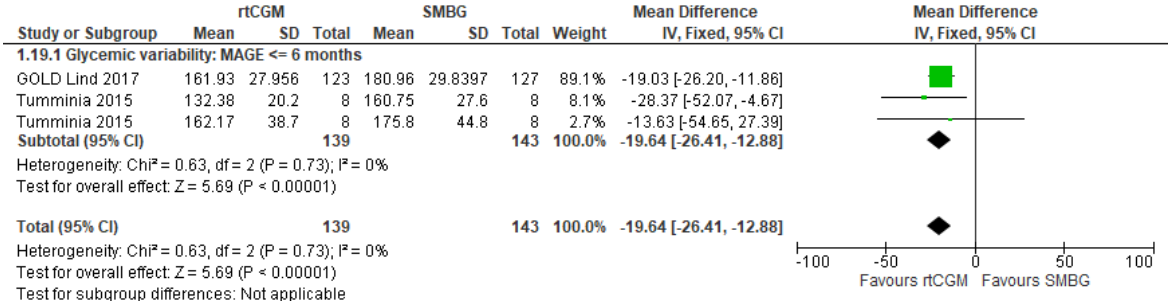


Figure 14: Hypoglycaemia (events/week) <3.9 mmol/l <= 6 months

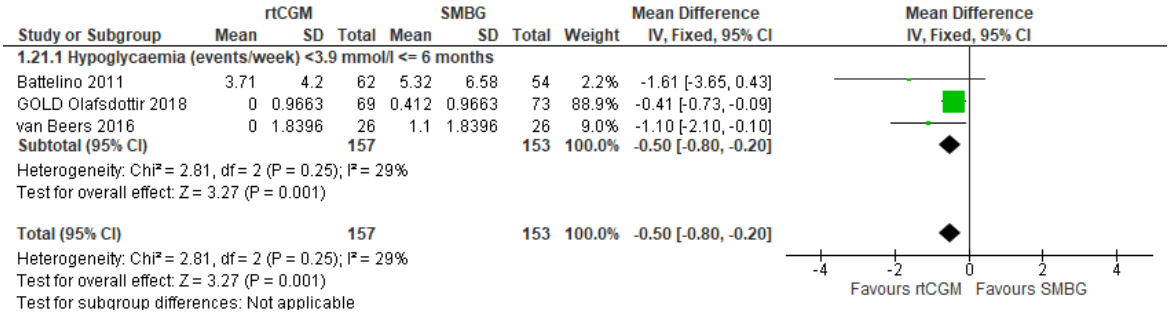


Figure 15: Hypoglycaemia (events/week) <3 mmol/l <= 6 months

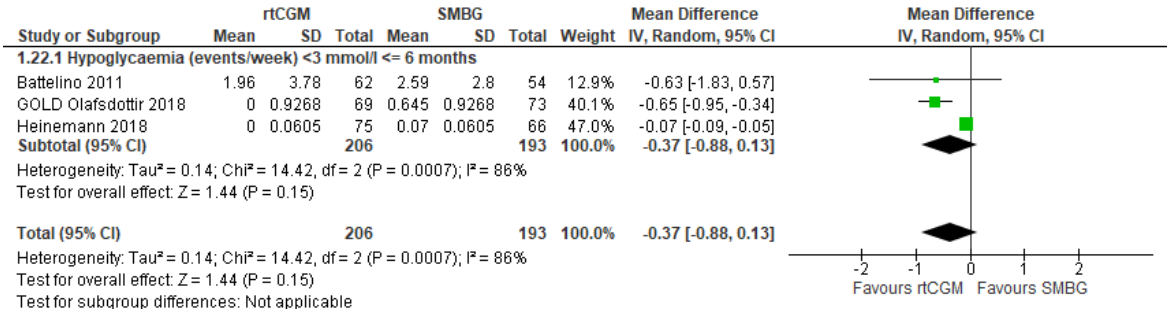


Figure 16: Severe hypoglycaemia <= 6 months

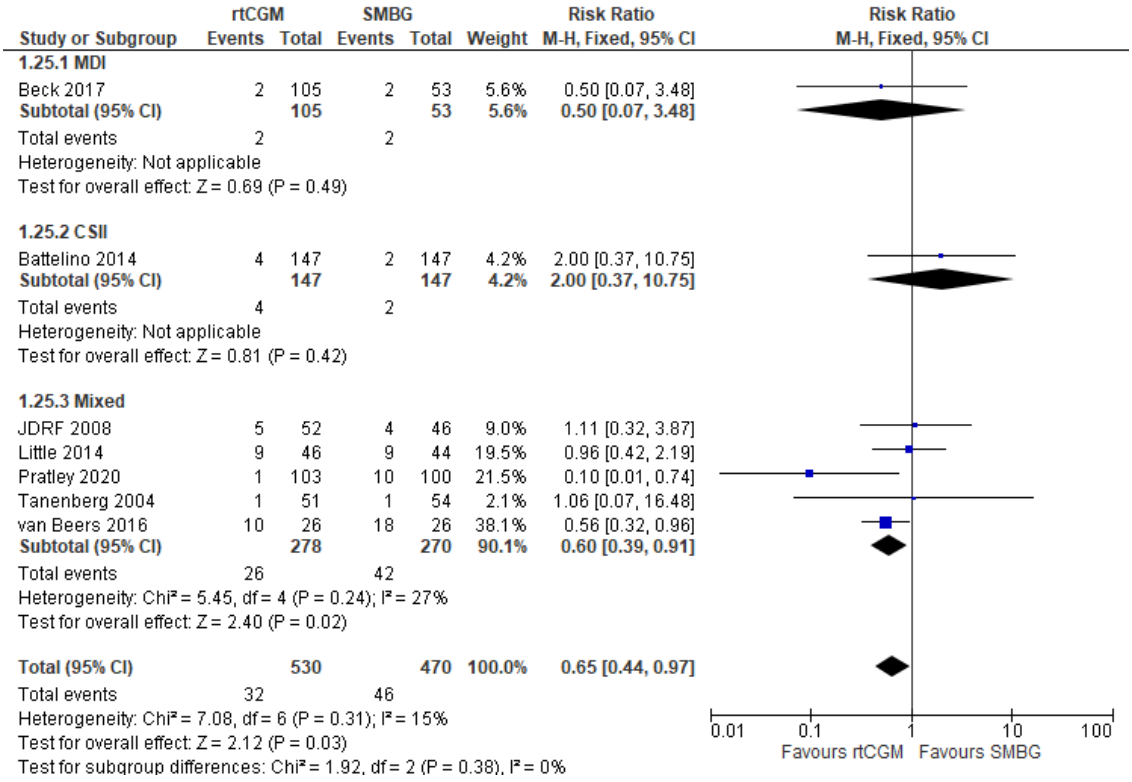


Figure 17: Nocturnal hypoglycaemia (% of time) <3.9 mmol/l <= 6 months

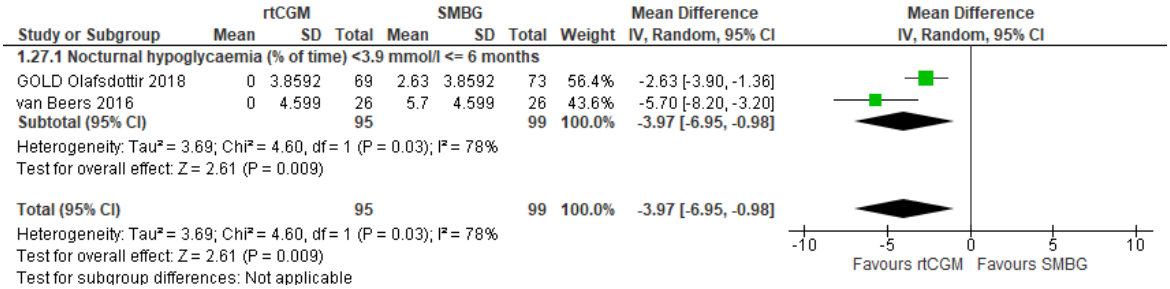


Figure 18: Nocturnal hypoglycaemia number of events / night <3.9 mmol/l <= 6 months

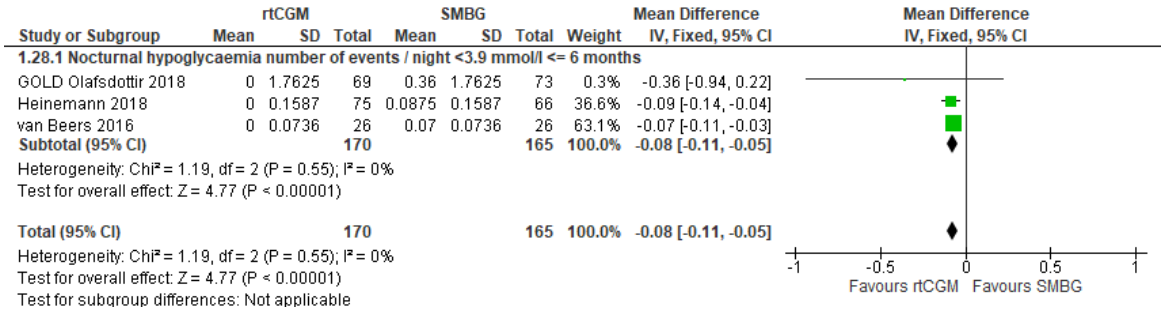


Figure 19: DKA <= 6 months

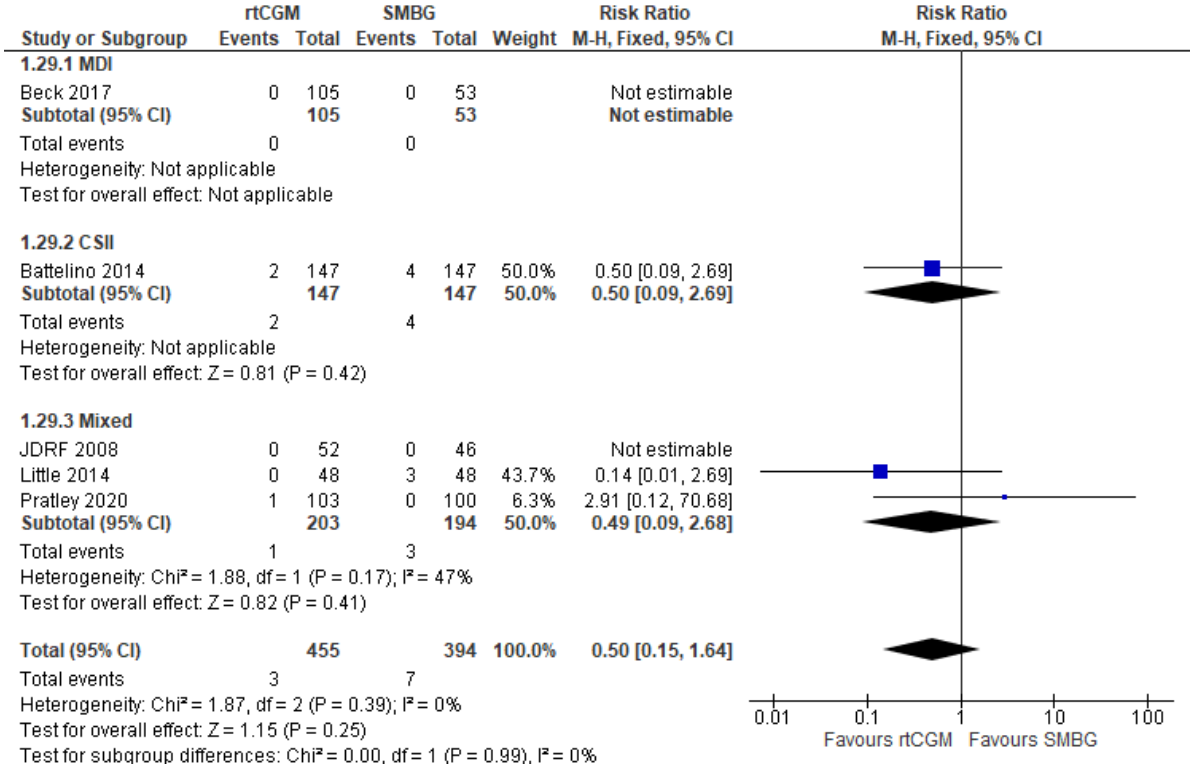


Figure 20: Hypoglycaemia awareness - Clarke score <= 6 months

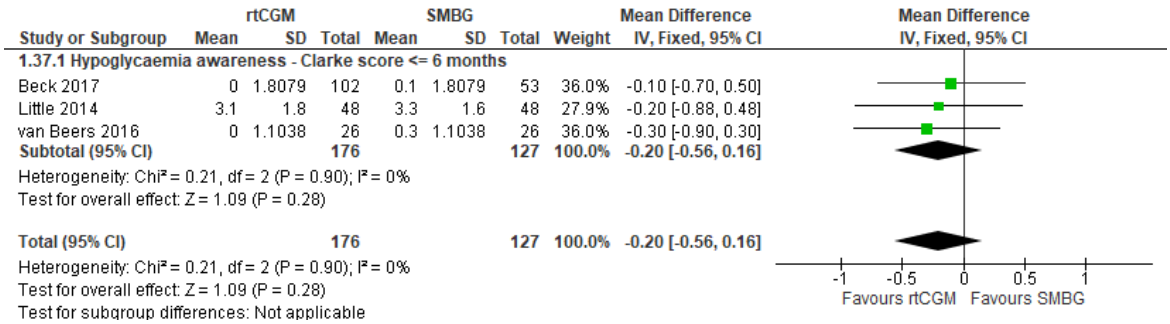


Figure 21: Hypoglycaemia awareness - GOLD score

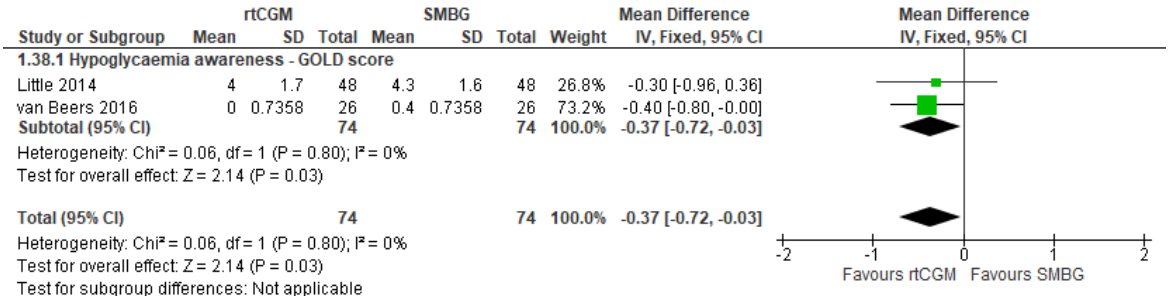
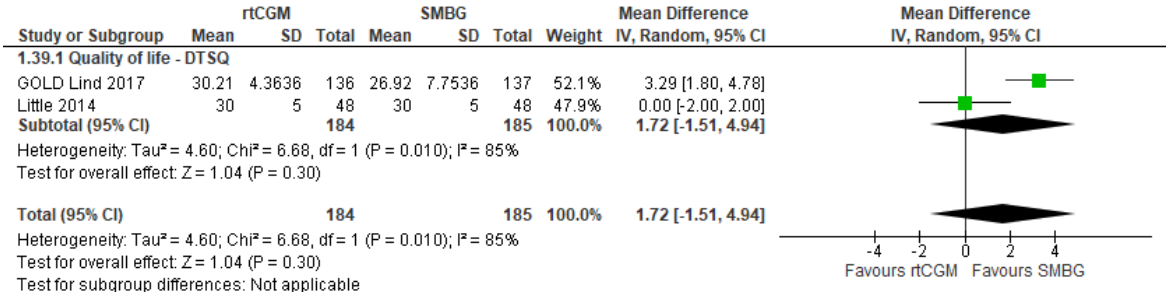


Figure 22: Quality of life - DTSQ



isCGM vs SMBG

No outcomes featured more than 1 study and thus are not presented here, for results see GRADE and summary of GRADE tables.

Appendix G - GRADE tables for pairwise data

rtCGM vs isCGM

No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
HbA1c (%) <= 6 months											
1 (Visser 2021)	Parallel RCT	254	+/- 0.50	MD -0.36 (-0.48, -0.24)	-	-	Not serious	Not serious	NA2	Not serious	High
HbA1c <7% <= 6 months											
1 (Visser 2021)	Parallel RCT	254	0.80 , 1.25	RR 1.50 (1.09, 2.06)	31 per 100	16 more per 100 (3 more to 33 more)	Not serious	Not serious	NA2	Serious4	Moderate
Time in range (%) [3.9/4 - 10 mmol/l] <= 3 months											
2	Parallel RCT	100	+/- 5.00	MD 5.56 (0.31, 10.81)	-	-	Serious 1	Not serious	Not serious	Serious4	Low
Time in range (%) [3.9/4 - 10 mmol/l] <= 6 months											
1 (Visser 2021)	Parallel RCT	254	+/- 5.00	MD 6.85 (4.36, 9.34)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Time below range <3.9 mmol/l <= 3 months											
2	Parallel RCT	100	+/- 3.55	MD -2.56 (-4.25, -0.88)	-	-	Not serious	Not serious	Serious3	Serious4	Low
Time below range <3.0 mmol/l <= 3 months											
1 (Haskova 2020)	Parallel RCT	60	+/- 0.87	MD -0.82 (-1.70, 0.06)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Time below range <3.0 mmol/l <= 6 months											
1 (Visser 2021)	Parallel RCT	254	+/- 0.53	MD -0.35 (-0.61, -0.09)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Time above range >10 mmol/l <= 3 months											

2	Parallel RCT	100	+/- 7.15	MD -2.72 (-11.40, 5.95)	-	-	Serious 1	Not serious	Serious3	Serious4	Very low
Time above range >13.9 mmol/l <= 3 months											
1 (Haskova 2020)	Parallel RCT	60	+/- 3.76	MD -4.19 (-8.00, -0.38)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Glycemic variability: SD <= 3 months											
1 (Haskova 2020)	Parallel RCT	60	+/- 0.41	MD -0.29 (-0.70, 0.12)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Glycemic variability: SD <= 6 months											
1 (Visser 2021)	Parallel RCT	254	+/- 0.24	MD -0.33 (-0.45, -0.21)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Glycemic variability: coefficient of variation <= 3 months											
1 (Haskova 2020)	Parallel RCT	60	+/- 0.09	MD -0.01 (-0.10, 0.08)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Glycemic variability: coefficient of variation <= 6 months											
1 (Visser 2021)	Parallel RCT	254	+/- 1.87	MD -1.38 (-2.30, -0.46)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Glycemic variability: mean amplitude of glucose excursions (MAGE) <= 3 months											
1 (Haskova 2020)	Parallel RCT	60	+/- 0.88	MD -0.61 (-1.50, 0.28)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Nocturnal hypoglycemia [0000 - 0600] <3.9 mmol/l <= 3 months											
1 (Haskova 2020)	Parallel RCT	60	+/- 3.30	MD -3.96 (-7.30, -0.62)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Nocturnal hypoglycemia [0000-0600] <3.0 mmol/l <= 3 months											
1 (Haskova 2020)	Parallel RCT	60	+/- 2.08	MD -2.79 (-4.90, -0.68)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Quality of life - physical health <= 3 months											
1 (Haskova 2020)	Parallel RCT	60	+/- 0.85	MD 0.10 (-0.71, 0.91)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Quality of life - psychological health <= 3 months											

1 (Haskova 2020)	Parallel RCT	60	+/- 0.80	MD -0.20 (-1.04, 0.64)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Quality of life - social relationships <= 3 months											
1 (Haskova 2020)	Parallel RCT	60	+/- 1.40	MD 0.50 (-0.92, 1.92)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Quality of life - environment <= 3 months											
1 (Haskova 2020)	Parallel RCT	60	+/- 0.90	MD -0.60 (-1.59, 0.39)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Hypoglycemia fear scale (worry) <= 6 months											
1 (Visser 2021)	Parallel RCT	254	+/- 3.86	MD -2.62 (-4.52, -0.72)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
DTSQ - status <= 6 months											
1 (Visser 2021)	Parallel RCT	254	+/- 2.42	MD 2.34 (1.15, 3.53)	-	-	Not serious	Not serious	NA2	Serious4	Moderate
Severe hypoglycemia (events) <= 6 months											
1 (Visser 2021)	Parallel RCT	254	0.80 , 1.25	RR 0.08 (0.03, 0.25)	30 per 100	28 fewer per 100 (29 fewer to 22 fewer)	Not serious	Not serious	NA2	Not serious	High

1

2 1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias

3 2. Only one study so no inconsistency

4 3. I2 between 33.3% and 66.7%

5 4. 95% confidence intervals cross one end of the defined MIDs

6 # rtCGM vs SMBG

No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Change from baseline HbA1c (%) - <= 6 months											

8	RCT and crossover	1259	+/- 0.50	MD -0.37 (-0.49, -0.24)	-	-	Serious1	Not serious	Very serious4	Not serious	Very low
Change from baseline HbA1c (%) - <= 3 months											
3	RCT	346	+/- 0.50	MD -0.19 (-0.67, 0.28)	-	-	Very serious2	Serious3	Very serious4	Serious6	Very low
Change from baseline HbA1c (%) - > 6 months											
1 (Riveline 2012)	RCT	123	+/- 0.50	MD -0.52 (-0.80, -0.24)	-	-	Serious1	Serious3	NA5	Serious6	Very low
HbA1c (mmol/mol) <= 3 months											
1 (New 2015)	RCT	82	+/- 5.50	MD 2.00 (-3.23, 7.23)	-	-	Very serious2	Serious3	NA5	Serious6	Very low
Change in HbA1c (mmol/mol) <= 6 months											
3	RCT and Crossover	477	+/- 5.50	MD -2.05 (-4.99, 0.88)	-	-	Not serious	Not serious	Very serious4	Not serious	Low
HbA1c achieved target <7.5% <= 3 months											
1 (Beck 2017)	RCT	155	0.80 , 1.25	RR 1.77 (0.61, 5.10)	8 per 100	6 more per 100 (3 fewer to 32 more)	Serious1	Not serious	NA5	Very serious7	Very low
HbA1c achieved target <7.5% <= 6 months											
1 (Beck 2017)	RCT	155	0.80 , 1.25	RR 2.02 (1.18, 3.46)	23 per 100	24 more per 100 (4 more to 57 more)	Serious1	Not serious	NA5	Serious6	Low
HbA1c achieved target <7.0% <= 3 months											
1 (Beck 2017)	RCT	155	0.80 , 1.25	RR 2.34 (0.83, 6.56)	8 per 100	10 more per 100	Serious1	Not serious	NA5	Serious6	Low

						(1 fewer to 42 more)					
HbA1c achieved target <7.0% <= 6 months											
1 (Beck 2017)	RCT	155	0.80 , 1.25	RR 1.80 (1.00, 3.22)	21 per 100	17 more per 100 (0 more to 46 more)	Serious1	Not serious	NA5	Serious6	Low
Time in range (%) [3.9/4 - 10 mmol/l] <= 6 months											
6	RCT and Crossover	1023	+/- 5.00	MD 7.03 (4.88, 9.19)	-	-	Serious1	Not serious	Very serious4	Serious6	Very low
Time below range (%) <3.9 mmol/l <= 6 months											
3	RCT and Crossover	371	+/- 4.21	MD -3.15 (-5.19, -1.11)	-	-	Serious1	Not serious	Very serious4	Serious6	Very low
Time below range (%) <55mg/dL <= 6 months											
1 (Battelino 2011)	RCT	116	+/- 3.23	MD -3.12 (-4.88, -1.37)	-	-	Serious1	Serious3	NA5	Serious6	Very low
Time below range (%) <63mg/dL <= 6 months											
1 (Battelino 2011)	RCT	116	+/- 3.23	MD -2.04 (-3.86, -0.22)	-	-	Serious1	Serious3	NA5	Serious6	Very low
Time above range >10mmol/l <= 6 months											
4	RCT and Crossover	511	+/- 7.08	MD -3.48 (-6.47, -0.48)	-	-	Serious1	Not serious	Very serious4	Not serious	Very low
Time above range >13.9 mmol/l <= 6 months											
2	RCT	319	+/- 3.19	MD -3.08 (-4.45, -1.72)	-	-	Serious1	Serious3	Not serious	Serious6	Very low
Glycemic variability: SD <= 6 months											

3	RCT and Crossover	298	+/- 6.90	MD -8.75 (-11.55, -5.95)	-	-	Not serious	Not serious	Not serious	Serious6	Moderate
Glycemic variability: SD > 6 months											
1 (Riveline 2012)	RCT	123	+/- 16.20	MD -8.70 (-21.21, 3.81)	-	-	Serious1	Serious3	NA5	Serious6	Very low
Glycemic variability: coefficient of variation <= 6 months											
6	RCT and Crossover	584	+/- 3.35	MD -4.35 (-6.72, -1.99)	-	-	Serious1	Not serious	Very serious4	Serious6	Very low
Glycemic variability: MAGE <= 6 months											
3	RCT and Crossover	282	+/- 22.40	MD -19.64 (-26.41, -12.88)	-	-	Not serious	Not serious	Not serious	Serious6	Moderate
Hypoglycaemia (events/day) <3.9 mmol/l <= 3 months											
1 (Tanenberg 2004)	RCT	109	+/- 0.60	MD -0.30 (-0.73, 0.13)	-	-	Very serious2	Serious3	NA5	Serious6	Very low
Hypoglycaemia (events/week) <3.9 mmol/l <= 6 months											
3	RCT and Crossover	310	+/- 3.29	MD -0.50 (-0.80, -0.20)	-	-	Not serious	Not serious	Not serious	Not serious	High
Hypoglycaemia (events/week) <3 mmol/l <= 6 months											
3	RCT and Crossover	399	+/- 1.40	MD -0.37 (-0.88, 0.13)	-	-	Not serious	Not serious	Very serious4	Not serious	Low
Hypoglycaemia event duration (minutes) <= 3 months											
1 (Tanenberg 2004)	RCT	109	+/- 30.55	MD -31.60 (-50.90, -12.30)	-	-	Very serious2	Serious3	NA5	Serious6	Very low
Hypoglycaemia event duration (minutes) <= 6 months											

1 (van Beers 2016)	Crossover RCT	52	+/- 6.25	MD -37.80 (-44.60, -31.00)	-	-	Not serious	Not serious	NA5	Not serious	High
Severe hypoglycaemia <= 6 months											
7	RCT and Crossover	1000	0.80 , 1.25	RR 0.65 (0.44, 0.97)	10 per 100	3 fewer per 100 (5 fewer to 0 more)	Serious1	Not serious	Not serious	Serious6	Low
Severe hypoglycaemia >= 6 months											
1 (Riveline 2012)	RCT	123	0.80 , 1.25	RR 2.46 (1.02, 5.92)	10 per 100	14 more per 100 (0 more to 48 more)	Serious1	Serious3	NA5	Serious6	Very low
Nocturnal Hypoglycaemia (% of time) <3.9 mmol/l <= 6 months											
2	Crossover RCT	194	+/- 2.30	MD -3.97 (-6.95, -0.98)	-	-	Not serious	Not serious	Very serious4	Serious6	Very low
Nocturnal hypoglycaemia number of events / night <3.9 mmol/l <= 6 months											
3	RCT and Crossover	335	+/- 0.88	MD -0.08 (-0.11, -0.05)	-	-	Not serious	Not serious	Not serious	Not serious	High
DKA <= 6 months											
5	RCT and Crossover	849	0.80 , 1.25	RR 0.50 (0.15, 1.64)	2 per 100	1 fewer per 100 (2 fewer to 1 more)	Very serious2	Not serious	Not serious	Very serious7	Very low
DKA > 6 months											
1 (Riveline 2012)	RCT	123	0.80 , 1.25	RR 0.98 (0.14, 6.76)	3 per 100	0 fewer per 100 (3 fewer to 19 more)	Serious1	Serious3	NA5	Very serious7	Very low
Hospitalisation <= 6 months											
1 (Pratley 2020)	RCT	203	0.80 , 1.25	RR 1.46 (0.25, 8.53)	2 per 100	1 more per 100 (2 fewer to 15 more)	Serious1	Not serious	NA5	Very serious7	Very low

Serious adverse events <= 6 months											
1 (Beck 2017)	RCT	158	0.80 , 1.25	RR 2.55 (0.12, 52.12)	0 per 100	0 fewer per 100 (0 more to 0 more)	Serious1	Not serious	NA5	Very serious7	Very low
Diabetes distress - PAID - <= 6 months											
1 (JDRF 2010)	RCT	226	+/- 7.30	MD -0.10 (-3.85, 3.65)	-	-	Serious1	Not serious	NA5	Not serious	Moderate
Fear of hypoglycaemia (HFS) <= 6 months											
1 (JDRF 2010)	RCT	226	+/- 6.80	MD -2.70 (-6.01, 0.61)	-	-	Serious1	Not serious	NA5	Not serious	Moderate
Fear of hypoglycaemia (HFS-II) <= 6 months											
1 (Little 2014)	RCT	96	+/- 12.00	MD 0.00 (-9.80, 9.80)	-	-	Very serious2	Not serious	NA5	Not serious	Low
Fear of hypoglycaemia (HFS-SWE) <= 6 months											
1 (Lind 2017)	Crossover RCT	280	+/- 0.30	MD 0.02 (-0.12, 0.16)	-	-	Not serious	Not serious	NA5	Not serious	High
Hypoglycaemia awareness - Clarke score <= 6 months											
3	RCT and Crossover	303	+/- 0.90	MD -0.20 (-0.56, 0.16)	-	-	Serious1	Not serious	Not serious	Not serious	Moderate
Hypoglycaemia awareness - GOLD score											
2	RCT and Crossover	148	+/- 0.80	MD -0.37 (-0.72, -0.03)	-	-	Not serious	Not serious	Not serious	Not serious	High
Quality of life - DTSQ											
2	RCT and Crossover	369	+/- 3.88	MD 1.72 (-1.51, 4.94)	-	-	Very serious2	Not serious	Very serious4	Serious6	Very low

Quality of life - Sf-8 physical - 3 months											
1 (New 2015)	RCT	82	+/- 4.33	MD 0.30 (-3.45, 4.05)	-	-	Very serious2	Serious3	NA5	Not serious	Very low
Quality of life - Sf-8 mental - 3 months											
1 (New 2015)	RCT	82	+/- 4.70	MD 3.60 (-0.47, 7.67)	-	-	Very serious2	Serious3	NA5	Serious6	Very low
Quality of life - Who-5 general wellbeing index - 6 months											
1 (Lind 2017)	Crossover RCT	279	+/- 7.66	MD 3.39 (-0.66, 7.44)	-	-	Not serious	Not serious	NA5	Not serious	High
Quality of life -Sf 12 physical - 6 months											
1 (JDRF 2010)	RCT	226	+/- 5.00	MD 1.40 (-0.70, 3.50)	-	-	Serious1	Not serious	NA5	Not serious	Moder ate
Quality of life - Sf-12 mental - 6 months											
1 (JDRF 2010)	RCT	226	+/- 4.80	MD -0.30 (-2.87, 2.27)	-	-	Serious1	Not serious	NA5	Not serious	Moder ate

1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
2. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
3. >33.3% of the weight in a meta-analysis came from partially direct or indirect studies
4. I2 > 66.7%
5. Only one study so no inconsistency
6. 95% confidence intervals cross one end of the defined MIDs
7. 95% confidence intervals cross both ends of the defined MIDs

1 # isCGM vs SMBG

No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Change from baseline HbA1c (%)											
1 (Bolinder 2016)	RCT	238	+/- 0.50	MD 0.00 (-0.01, 0.01)	-	-	Serious 1	Not serious	NA2	Not serious	Moderate
Change from baseline HbA1c (mmol/mol)											
1 (Bolinder 2016)	RCT	238	+/- 5.50	MD 0.00 (-0.17, 0.17)	-	-	Serious 1	Not serious	NA2	Not serious	Moderate
Time in range (%) [3.9/4 - 10 mmol/l]											
1 (Bolinder 2016)	RCT	238	+/- 5.00	MD 4.16 (3.84, 4.48)	-	-	Serious 1	Not serious	NA2	Not serious	Moderate
Time below range (%) <3.9 mmol/l											
1 (Bolinder 2016)	RCT	238	+/- 0.50	MD -5.17 (-5.42, -4.91)	-	-	Serious 1	Not serious	NA2	Not serious	Moderate
Time below range (%) <3.1 mmol/l											
1 (Bolinder 2016)	RCT	238	+/- 2.81	MD -3.42 (-4.85, -1.99)	-	-	Serious 1	Not serious	NA2	Serious3	Very low
Time below range (%) <2.5 mmol/l											
1 (Bolinder 2016)	RCT	238	+/- 0.29	MD -2.29 (-2.44, -2.14)	-	-	Serious 1	Not serious	NA2	Not serious	Moderate
Time below range (%) <2.2 mmol/l											
1 (Bolinder 2016)	RCT	238	+/- 0.25	MD -1.92 (-2.05, -1.79)	-	-	Serious 1	Not serious	NA2	Not serious	Moderate
Time above range >13.9 mmol/l											
1 (Bolinder 2016)	RCT	238	+/- 0.34	MD -1.54	-	-	Serious 1	Not serious	NA2	Not serious	Moderate

				(-1.71, -1.37)							
Glycemic variability: SD											
1 (Bolinder 2016)	RCT	238	+/- 0.58	MD -5.00 (-5.29, -4.71)	-	-	Serious 1	Not serious	NA2	Not serious	Moderate
Glycemic variability: coefficient of variation											
1 (Bolinder 2016)	RCT	238	+/- 0.31	MD -4.40 (-4.56, -4.24)	-	-	Serious 1	Not serious	NA2	Not serious	Moderate
Glycemic variability: MAGE											
1 (Bolinder 2016)	RCT	238	+/- 1.50	MD -8.00 (-8.76, -7.24)	-	-	Serious 1	Not serious	NA2	Not serious	Moderate
Hypoglycaemia <3.1 mmol/l											
1 (Bolinder 2016)	RCT	241	0.80 , 1.25	RR 0.20 (0.01, 4.16)	2 per 100	1 fewer per 100 (2 fewer to 5 more)	Serious 1	Not serious	NA2	Very serious4	Very low
Severe hypoglycaemia											
1 (Bolinder 2016)	RCT	241	0.80 , 1.25	RR 0.67 (0.11, 3.95)	2 per 100	1 fewer per 100 (2 fewer to 7 more)	Serious 1	Not serious	NA2	Very serious4	Very low
Nocturnal hypoglycaemia [2300-0600] (time in h) <3.1mmol/l											
1 (Bolinder 2016)	RCT	238	+/- 0.04	MD -0.30 (-0.32, -0.28)	-	-	Serious 1	Not serious	NA2	Not serious	Moderate
Discontinuation											
1 (Bolinder 2016)	RCT	241	0.80 , 1.25	RR 6.05 (0.74, 49.50)	1 per 100	4 more per 100 (0 more to 40 more)	Serious 1	Not serious	NA2	Very serious4	Very low
Serious adverse events											

1 (Bolinder 2016)	RCT	241	0.80 , 1.25	RR 1.01 (0.30, 3.39)	4 per 100	0 more per 100 (3 fewer to 10 more)	Serious 1	Not serious	NA2	Very serious4	Very low
CGM monitor malfunction											
1 (Bolinder 2016)	RCT	241	0.80 , 1.25	RR 21.17 (1.25, 357.32)	0 per 100	0 fewer per 100 (0 more to 0 more)	Serious 1	Not serious	NA2	Not serious	Moderate

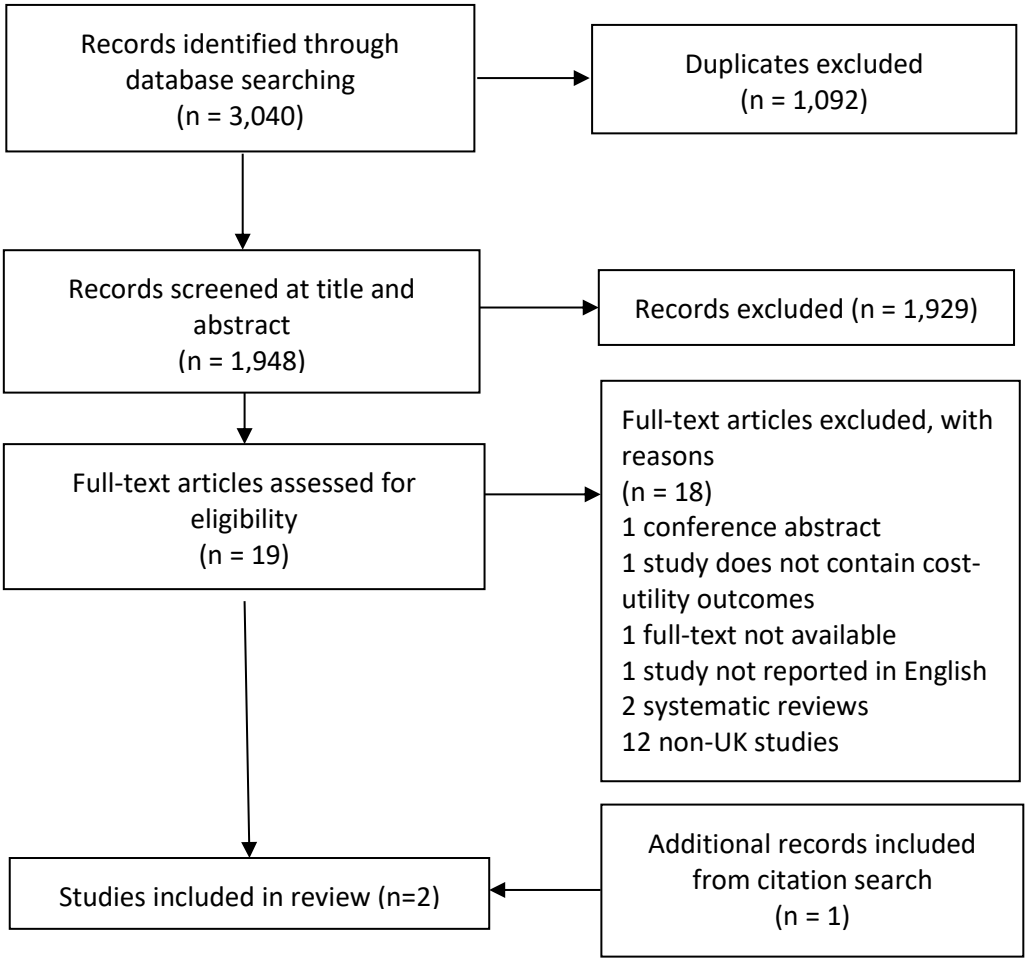
1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias

2. Only one study so no inconsistency

3. 95% confidence intervals cross one end of the defined MIDs

4. 95% confidence intervals cross both ends of the defined MIDs

Appendix H – Economic evidence study selection



1 Appendix I – Economic evidence tables

2 Healthcare Improvement Scotland (2018)

Healthcare Improvement Scotland (2018). What is the clinical and cost effectiveness of Freestyle Libre flash glucose monitoring for patients with diabetes mellitus treated with intensive insulin therapy?[1]

Study details	**Analysis** Cost-utility analysis **Approach to analysis:** a simple two state Markov structure separated into two sub-models, one for each of the diabetes types (T1 DM and T2 DM). A patient can be either alive or dead, with transition determined by a diabetes-specific mortality rate. One year of living with diabetes is associated with a direct resource use linked to the consumables involved in monitoring blood glucose, but also an indirect resource use due to severe hypoglycaemic events. **Diabetes related complications considered:** Hypoglycaemic events **Perspective:** Scottish National Health Service **Time horizon:** Lifetime **Discounting:** 3.5%
Interventions	**Intervention:** Freestyle Libre flash glucose monitoring **Comparator:** Self-monitoring of blood glucose (SMBG)
Population	**Population:** Adults with type 1 and type 2 diabetes **Characteristics:** Mean age: 43.7(T1DM); 59.2(T2DM); Male: 56.9%(T1DM); 67%(T2DM); Duration of diabetes (years): 22(T1DM); 17(T2DM); BMI (kg/m^2): 25(T1DM); 33.2(T2DM); HbA1c (% points): 6.78%(T1DM); 8.68%(T2DM); Weight (kg): NR
Data sources	**Resource use:** Data on the number of blood tests per day were based on the findings from the IMPACT and REPLACE trials[2, 3]. **Baseline/natural history:** The cohort characteristics were set to reflect the populations in the IMPACT and REPLACE trials[2, 3]. **Effectiveness:** Outcome data on the testing frequency of blood glucose and the frequency of hypoglycaemic events were withdrawn from the findings from the IMPACT and REPLACE trials[2, 3]. Due to a lack of evidence, the model did not consider the impact of Freestyle Libre on HbA1c and other intermediate outcomes. **Costs:** Consumables costs involved in SMBG were estimated from Scottish National Procurement data by taking a weighted average that accounts for the distribution of quantities of various brands purchased. The price for a single Freestyle Libre sensor used is the list price included on the Scottish Drug Tariff Part IX2. The scanners involved in both types of monitoring were assumed to be offered at no cost by the manufacturers. The healthcare resource implications of hypoglycemia-related hospital admissions were investigated in a retrospective record-linked cohort study in England[4]. Costs were all inflated to the current price, but the price year was not stated. **QoL:** Utilities of various hypoglycaemic events were derived from published literature[5,6].
Base-case results	Two different model structures were used: 1) Restricted model, only taking into account the relative cost of monitoring and the direct impact of the device on health utility scores; 2) Full model, building on the restricted model and also incorporating hypoglycaemic events and the associated impact on utility scores and NHS resource use. **Type 1 diabetes patients:**

Full model					
Treatments	**Absolute**		**Incremental**		
	Costs	**QALYs**	**Costs**	**QALYs**	**ICER**
Freestyle Libre	18,074	9.73			
SMBG	12,860	7.61	5,214	2.12	UK £2,459/ QALY
Restricted model					
Treatments	**Absolute**	**Incremental**			
	Costs	**QALYs**	**Costs**	**QALYs**	**ICER**
Freestyle Libre	17,010	13.20			
SMBG	10,496	12.67	6,514	0.53	UK £12,340/ QALY

Type 2 diabetes patients:

Full model					
Treatments	**Absolute**		**Incremental**		
	Costs	**QALYs**	**Costs**	**QALYs**	**ICER**

Healthcare Improvement Scotland (2018). What is the clinical and cost effectiveness of Freestyle Libre flash glucose monitoring for patients with diabetes mellitus treated with intensive insulin therapy?[1]

	Freestyle Libre	10,450	6.14			
	SMBG	5,535	5.04	4,916	1.09	UK £4,498/ QALY
	Restricted model					
	Treatments	**Absolute**	**Incremental**			
		Costs	**QALYs**	**Costs**	**QALYs**	**ICER**
	Freestyle Libre	9,837	7.51			
	SMBG	4,241	7.20	5,596	0.31	UK £18,125/ QALY
	**Notes: The base case results were presented differently in the main report and the appendix. We agreed that the results in the appendix were the correct ones, so the results above were based on the appendix version.*					
Sensitivity analyses	**Deterministic:** One-way sensitivity analyses were performed by varying the key model inputs across their 95% CI range where available, or by ±20% where confidence interval were not available. ICER is most sensitive to: annual number of hypoglycaemic events; reduction in blood tests used; hypoglycaemia disutilities; Freestyle Libre utility; and consumables costs. Various other scenarios and parameter values identified as relevant by the panel of clinical experts were also explored. Freestyle Libre remained cost-effective across these scenarios. **Probabilistic:** A probabilistic sensitivity analysis (PSA) was conducted by assigning a specific probability distribution for each of the key model inputs and running 1,000 simulations of the model results. It showed a high probability of Freestyle Libre being cost-effective compared with SMBG at various levels of the willingness-to-pay threshold. For type 1 diabetes, the probability of flash monitoring being cost-effective at £20,000/QALY was 98% in the restricted model and 99% in the full model. For type 2 diabetes, the probability of flash monitoring being cost-effective at £20,000/QALY was 72% in the restricted model and 99% in the full model.					
Comments	**Source of funding:** Healthcare Improvement Scotland **Applicability:** Partially applicable **Limitations:** Potentially serious limitations					

1

Category	Rating	Comments
Applicability		
1.1 Is the study population appropriate for the review question?	Partly	The cohort characteristics were set to reflect the populations in the IMPACT and REPLACE trials[2, 3], however, the trial populations may not accurately reflect the overall UK diabetes population, especially the T1 DM population in the IMPACT trial which had well-controlled diabetes.
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).	Yes	
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Partly	The model used a simple two state structure that only allowed patients to be in alive or dead states, and therefore only considers the quality of life associated

Category	Rating	Comments
		with hypoglycaemic events and direct utility benefits of monitoring.
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	The model does not take into account HbA1c or other intermediate outcomes.
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	The baseline outcome data were drawn from the IMPACT and REPLACE trials[2, 3], which might not fully reflect the UK diabetes population.
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	Absolute effect of the interventions assumed constant throughout the time horizon of the analysis
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
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?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

1 Roze et al. (2020)

Roze et al (2020). Long-term Cost-Effectiveness of Dexcom G6 Real-time Continuous Glucose Monitoring Versus Self-Monitoring of Blood Glucose in Patients With Type 1 Diabetes in the U.K[7]	
Study details	**Analysis:** Cost-utility analysis **Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Include mild/ moderate and severe hypoglycaemic events, cardiovascular, ophthalmic, and renal complications are included in the CDM as well as peripheral neuropathy, foot ulcer, and amputation. **Perspective:** U.K. health care payer (National Health Service and personal social services) **Time horizon:** lifetime **Discounting:** 3.5%
Interventions	**Intervention:** Real-time continuous glucose monitoring (RT-CGM) **Comparator:** Self-monitoring of blood glucose (SMBG)
Population	**Population:** Adults with type 1 diabetes **Characteristics:** Mean age: 48; Male: 55%; Duration of diabetes (years): 20; BMI (kg/m2): 27.09; HbA1c (% points): 8.6; BMI (kg/m^2): 27.9
Data sources	**Resource use:** Data on SMBG usage per day was based on the findings from the DIAMOND trial[8]. **Baseline/natural history:** Baseline demographics and cohort characteristics were based on patients with T1D in the DIAMOND trial[8]. **Effectiveness:** The treatment effects in terms of change in HbA1c from baseline and hypoglycemic event rates were both sourced from the 24-week data from the DIAMOND trial[8]. **Costs:** Direct costs associated with treatment and management of complications were taken from the published literature[9-21]. All costs were inflated to 2018 GBP using the consumer price index health component. **QoL:** Baseline utility values derived from the DIAMOND trial[8]. Disutility from hypoglycaemic events were sourced from published literature[5,22]. Disutilities from other diabetes related complications were obtained from a literature review[23]. A utility benefit associated with reduced Fear of Hypoglycemia (FoH) was derived from the worry subscale of the Hypoglycemia Fear Survey (HFS-II) measured in the DIAMOND trial mapped to

Roze et al (2020). Long-term Cost-Effectiveness of Dexcom G6 Real-time Continuous Glucose Monitoring Versus Self-Monitoring of Blood Glucose in Patients With Type 1 Diabetes in the U.K[7]	
	EuroQol 5-dimension questionnaire (EQ-5D)[24]. An additional utility benefit owing to avoiding fingerstick SMBG testing multiple times per day was sourced from a published study[6].
Base-case results	<table><tr><th rowspan="2">Treatments</th><th colspan="2">Absolute</th><th colspan="3">Incremental</th></tr><tr><th>Costs</th><th>QALYs</th><th>Costs</th><th>QALYs</th><th>ICER</th></tr><tr><td>CGM</td><td>102,468</td><td>11.47</td><td></td><td></td><td></td></tr><tr><td>SMBG</td><td>88,234</td><td>9.99</td><td>14,234</td><td>1.49</td><td>UK£ 9,558/ QALY</td></tr></table>
Sensitivity analyses	**Deterministic:** Sensitivity analysis showed that when no QoL benefit with RT-CGM was assumed, ICER increased to GBP 28,225 per QALY gained. When this same analysis (no direct QoL benefit with RT-CGM) was limited to patients with baseline HbA1c ≥8.5%, the corresponding ICER was GBP 34,287 per QALY gained, which is above the commonly cited upper limit of GBP 30,000 per QALY gained for the WTP threshold in the U.K. In an analysis where SMBG use was assumed to be 10 strips per day, the ICER was reduced to GBP 2,798 per QALY gained. Sensitivity analysis in the cohort with baseline HbA1c ≥8.5% produced results analogous to those reported in the overall cohort. However, in this cohort the ICER was more sensitive to changes in HbA1c treatment effect, driven by the larger difference in absolute HbA1c values.
Comments	**Source of funding:** Dexcom **Applicability**: Partly applicable **Limitations:** Potentially serious limitations

1

Category	Rating	Comments
Applicability		
1.1 Is the study population appropriate for the review question?	Partly	Type 1 diabetes patients from the US
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).	Yes	
1.8 OVERALL JUDGEMENT	**PARTIALLY 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?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	The baseline outcome data were drawn from a US trial, which might not fully reflect the diabetes population in the UK.
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	Absolute effect of the interventions assumed constant throughout the time horizon of the analysis
2.6 Are all important and relevant costs included?	Yes	

Category	Rating	Comments
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
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?	No	Probabilistic sensitivity analysis not conducted
2.11 Has no potential financial conflict of interest been declared?	No	The study was funded by the Dexcom, who produce the CGM device being evaluated
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

References

1. Healthcare Improvement Scotland (2018). "What is the clinical and cost effectiveness of Freestyle Libre flash glucose monitoring for patients with diabetes mellitus treated with intensive insulin therapy?" Advice on health technologies Retrieved 11 July, 2021.
2. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet. 2016;388(10057):2254-63.
3. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline J-P, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. Diabetes Therapy. 2017;8(1):55-73.
4. McEwan P, Thorsted BL, Wolden M, Jacobsen J, Evans M. Healthcare resource implications of hypoglycemia-related hospital admissions and inpatient hypoglycemia: retrospective record-linked cohort studies in England. BMJ Open Diabetes Res care. 2015;3(1):e000057.
5. Evans M, Khunti K, Mamdani M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. Health Qual Life Outcomes 2013;11:90
6. Matza LS, Stewart KD, Davies EW, Hellmund R, Polonsky WH, Kerr D. Health State Utilities Associated with Glucose Monitoring Devices. Value Health. 2017;20(3):507-11.
7. Roze, S., et al. (2020). "Long-term Cost-Effectiveness of Dexcom G6 Real-time Continuous Glucose Monitoring Versus Self-Monitoring of Blood Glucose in Patients With Type 1 Diabetes in the U.K." Diabetes care **43**(10): 2411.
8. Beck, R. W., et al. (2017). "Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial." Jama **317**(4): 371-378.
9. National Institute for Health and Care Excellence. NICE guideline NG17: Type 1 diabetes in adults: diagnosis and management [Internet]. Available from https://www.nice.org.uk/guidance/ng17/. Accessed 09 July 2021
10. The East of England Priorities Advisory Committee. Guidance Statement: FreeStyle Libre Glucose Monitoring System 1.0, PrescQIPP, 2017. Available from http://www.southstaffordshirejointformulary.nhs.uk/docs/CDD/PrescQiPP%20freestyle%20libre%20Sept%202017.pdf. Accessed 09 July 2021
11. Walker S, Asaria M, Manca A, et al. Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). Eur Heart J Qual Care Clin Outcomes 2016;2:125–140
12. Beaudet A, Palmer JL, Timlin L, et al. Cost-utility of exenatide once weekly compared with insulin glargine in patients with type 2 diabetes in the UK. J Med Econ 2011;14:357–366
13. Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabet Med 2015;32:459–466
14. Xu XM, Vestesson E, Paley L, et al. The economic burden of stroke care in England, Wales and Northern Ireland: using a national stroke register to estimate and report patient-level health economic outcomes in stroke. Eur Stroke J 2018;3:82–91
15. UK Government. UK Government National tariff payment system: BZ23Z: Vitreous Retinal Procedures - category 1; Outpatient Procedure tariff [Internet], 2015. Available from https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015. Accessed 09 July 2021
16. Meads C, Hyde C. What is the cost of blindness? Br J Ophthalmol 2003;87:1201–1204
17. MIMS Online. Duloxetine 60 mg daily (first-line treatment of Neuropathy in Diabetes [NICE CG87]) [Internet], 2016. Available from https://www.mims.co.uk/drugs/pain/pain-fever/duloxetine. Accessed 09 July 2021
18. Kerr M, Rayman G, Jeffcoate WJ. Cost of diabetic foot disease to the National Health Service in England. Diabet Med 2014;31:1498–1504
19. Zimny S, Voigt A, Schatz H, Pfohl M. Prediction of wound radius reductions and healing times in neuropathic diabetic foot ulcers. Diabetes Care 2003;26:959–960
20. Ghatnekar O, Willis M, Persson U. Cost-effectiveness of treating deep diabetic foot ulcers with Promogran in four European countries. J Wound Care 2002;11:70–74

21. Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T. Cost-effectiveness of insulin degludec compared with insulin glargine for patients with type 2 diabetes treated with basal insulin - from the UK health care cost perspective. Diabetes Obes Metab 2014;16:366–375

22. Lauridsen JT, Lønborg J, Gundgaard J, Jensen HH. Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries. Qual Life Res 2014;23:2645–2650

23. Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modelling in type 2 diabetes. Value Health 2014;17:462–470

24. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin 2006;22:1523–1534

Appendix J – Health economic model

Full details of the health economic model are shown in the economic model report.

Appendix K – Excluded studies

Clinical

Study	Reason for exclusion
Akturk, HK, Acciaroli, G, Parker, AS et al. (2020) Rebound hyperglycemia and the effects of continuous glucose monitoring in the hypode clinical study. Diabetes technology & therapeutics 22: A39-A40	- Conference abstract
Avari, P, Moscardo, V, Jugnee, N et al. (2019) Ambulatory glucose profiling and glycaemic outcomes when switching flash to continuous glucose monitoring: the i-hart cgm study. Diabetes technology & therapeutics 21: A108-A109	- Conference abstract
Babu, R. Naresh, Pravallika, M. Yoshitha Lakshmi, Kumar, N. Doondi Phani et al. (2020) Continuous glucose monitoring devices: A systematic review. Journal of Global Trends in Pharmaceutical Sciences 11(2): 7562-7568	- Not a relevant study design *Not a proper sys rev just summarises treatments*
Beck, Roy W, Riddlesworth, Tonya D, Ruedy, Katrina J et al. (2017) Effect of initiating use of an insulin pump in adults with type 1 diabetes using multiple daily insulin injections and continuous glucose monitoring (DIAMOND): a multicentre, randomised controlled trial. The lancet. Diabetes & endocrinology 5(9): 700-708	- Comparator is not CGM/FLASH/SMBG *Study comparing insulin regimens not CGM*
Bode, Bruce, Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group et al. (2009) Sustained benefit of continuous glucose monitoring on A1C, glucose profiles, and hypoglycemia in adults with type 1 diabetes. Diabetes care 32(11): 2047-9	- Comparator is not CGM/FLASH/SMBG *2ndary study examining 1 arm only*
Bronstone, Amy and Graham, Claudia (2016) The Potential Cost Implications of Averting Severe Hypoglycemic Events Requiring Hospitalization in High-Risk Adults With Type 1 Diabetes Using Real-Time Continuous Glucose Monitoring. Journal of diabetes science and technology 10(4): 905-13	- HE study
Charleer, Sara, Mathieu, Chantal, Nobels, Frank et al. (2018) Effect of Continuous Glucose Monitoring on Glycemic Control, Acute	- Not a relevant study design *Prospective cohort study, we now have RCT data [QoL]*

Study	Reason for exclusion
Admissions, and Quality of Life: A Real-World Study. The Journal of clinical endocrinology and metabolism 103(3): 1224-1232	
Chaugule, Shraddha and Graham, Claudia (2017) Cost-effectiveness of G5 Mobile continuous glucose monitoring device compared to self-monitoring of blood glucose alone for people with type 1 diabetes from the Canadian societal perspective. Journal of medical economics 20(11): 1128-1135	- HE study
Dicembrini, Ilaria, Caliri, Mariasmeralda, Minardi, Silvia et al. (2020) Combined continuous glucose monitoring and subcutaneous insulin infusion versus self-monitoring of blood glucose with optimized multiple injections in people with type 1 diabetes: A randomized crossover trial. Diabetes, Obesity and Metabolism 22(8): 1286-1291	- Comparator is not CGM/FLASH/SMBG *it looks at CSII + CGM followed by MDI+SMBG compared to MDI followed by CSII +CGM. Doesn't answer our question.*
Elbalshy, Mona, Boucher, Sara, Galland, Barbara et al. (2020) The MiaoMiao study: can do-it-yourself continuous glucose monitoring technology improve fear of hypoglycaemia in parents of children affected by type 1 diabetes?. Journal of Diabetes and Metabolic Disorders 19(2): 1647-1658	- Does not contain population with T1D *CYP population, moved to CYP*
Eleftheriadou, I., Didangelos, T., Pappas, A.C. et al. (2019) Improvement of metabolic control after 3-month use of real-time continuous glucose monitoring in patients with type 1 diabetes: a multicenter study in Greece. Hormones	- Not a relevant study design *prospective, multicentre, non-randomized, post-market release study, no comparison*
Garg, SK, Voelmle, MK, Beatson, CR et al. (2011) Use of continuous glucose monitoring in subjects with type 1 diabetes on multiple daily injections versus continuous subcutaneous insulin infusion therapy: a prospective 6-month study. Diabetes care 34(3): 574-579	- Not a relevant study design *non randomized prospective cohort study*
Gordon, Ian, Rutherford, Carolyn, Makarounas-Kirchmann, Kelly et al. (2020) Meta-analysis of average change in laboratory-measured HbA1c among people with type 1 diabetes mellitus using the 14 day Flash Glucose Monitoring System. Diabetes research and clinical practice 164: 108158	- Not a relevant study design *MA of non-randomised data*

Study	Reason for exclusion
Guo, Lixin (2020) Improved time-in-range and glycemic variability in adults with type 1 diabetes: an analysis of 12-week flash glucose monitoring data from a multicenter prospective trial. Diabetes 69	- Conference abstract
Hanes, S, Wadwa, RP, Weber, I et al. (2020) Continuous glucose monitoring (CGM) initiation at diagnosis versus six months later: which is best?. Diabetes technology & therapeutics 22: A128-A129	- Conference abstract
Haskova, A, Radovnicka, L, Parkin, C et al. (2020) Continuous glucose monitoring is more effective than flash glucose monitoring in preventing hypoglycemia in patients with type 1 diabetes and normal awareness of hypoglycemia. Diabetes technology & therapeutics 22: A-129	- Conference abstract
Haskova, Aneta, Horova, Eva, Navratilova, Vendula et al. (2020) Real-time cgm is superior to flash glucose monitoring for glucose control in type 1 diabetes: The corrida randomized controlled trial. Diabetes Care 43(11): 2744-2750	- Duplicate reference
Hermanns, N, Kulzer, B, Gulde, C et al. (2009) Short-term effects on patient satisfaction of continuous glucose monitoring with the GlucoDay with real-time and retrospective access to glucose values: a crossover study. Diabetes technology & therapeutics 11(5): 275-81	- Comparator is not CGM/FLASH/SMBG *comparison of CGM real-time vs CGM retrospective which isn't the focus of our review.*
Hermanns, Norbert, Schumann, Beatrix, Kulzer, Bernhard et al. (2014) The impact of continuous glucose monitoring on low interstitial glucose values and low blood glucose values assessed by point-of-care blood glucose meters: results of a crossover trial. Journal of diabetes science and technology 8(3): 516-22	- Retrospective (blinded) CGM examined *This is blind CGM vs real time CGM*
Huang, Elbert S, O'Grady, Michael, Basu, Anirban et al. (2010) The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. Diabetes care 33(6): 1269-74	- HE study
Jensen, Morten Hasselstrom, Hejlesen, Ole, Vestergaard, Peter et al. (2020) Use of Personal Continuous Glucose Monitoring Device Is	- Not a relevant study design

Study	Reason for exclusion
Associated With Reduced Risk of Hypoglycemia in a 16-Week Clinical Trial of People With Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion. Journal of Diabetes Science and Technology	*Randomisation not based on CGM/No CGM but insulin therapy*
Kanapka, L, Miller, K, Rickels, M et al. (2020) Older adults with type 1 diabetes demonstrate high utilization of CGM and high confidence in CGM data. Diabetes technology & therapeutics 22: A-71	- Conference abstract
Klonoff, David C; Ahn, David; Drincic, Andjela (2017) Continuous glucose monitoring: A review of the technology and clinical use. Diabetes research and clinical practice 133: 178-192	- Not a relevant study design *literature review*
Langeland, L B L, Salvesen, O, Selle, H et al. (2012) Short-term continuous glucose monitoring: effects on glucose and treatment satisfaction in patients with type 1 diabetes mellitus; a randomized controlled trial. International journal of clinical practice 66(8): 741-747	- Comparator is not CGM/FLASH/SMBG *Not SMBG regimen*
Langendam, M.W., Hooft, L., De Vries, H. et al. (2009) Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews: cd008101	- More recent systematic review included that covers the same topic
Lind, M, Olafsdottir, AF, Hirsch, IB et al. (2020) Sustained intensive treatment and long-term effects on A1c reduction (silver study) by CGM in persons with t1d treated with MDI. Diabetes 69	- Conference abstract
Lind, Marcus, Dahlqvist, Sofia, Olafsdottir, Arndis F et al. (2021) Sustained Intensive Treatment and Long-term Effects on HbA1c Reduction (SILVER Study) by CGM in People With Type 1 Diabetes Treated With MDI. Diabetes care 44(1): 141-149	- Not a relevant study design *Single arm extension study*
Little, Stuart, Chadwick, Thomas, Choudhary, Pratik et al. (2012) Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (the Hypo COMPaSS trial). BMC endocrine disorders 12: 33	- Secondary publication of an included study that does not provide any additional relevant information *Protocol for Little 2018*
Logtenberg, Susan J J, Kleefstra, Nanne, Groenier, Klaas H et al. (2009) Use of short-	- <1 week duration

Study	Reason for exclusion
term real-time continuous glucose monitoring in type 1 diabetes patients on continuous intraperitoneal insulin infusion: a feasibility study. Diabetes technology & therapeutics 11(5): 293-9	*4-5 days CGM*
Miller (2020) Benefit of continuous glucose monitoring (CGM) in reducing hypoglycemia is sustained through 12 months of use among older adults with type 1 diabetes (T1D). Diabetes technology & therapeutics 22: A21-A22	- Conference abstract
Moreno-Fernandez, Jesus, Pazos-Couselo, Marcos, Gonzalez-Rodriguez, Maria et al. (2018) Clinical value of Flash glucose monitoring in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion. Endocrinologia, diabetes y nutricion 65(10): 556-563	- Not a relevant study design *retrospective cohort study*
Mostrom, P., Ahlen, E., Imberg, H. et al. (2017) Adherence of self-monitoring of blood glucose in persons with type 1 diabetes in Sweden. BMJ Open Diabetes Research and Care 5(1): e000342	- Not a relevant study design *survey*
Olafsdottir, Arndis F., Ahlen, Elsa, Lind, Marcus et al. (2021) The majority of people with type 1 diabetes and multiple daily insulin injections benefit from using continuous glucose monitoring: An analysis based on the GOLD randomized trial (GOLD-5). Diabetes, Obesity and Metabolism 23(2): 619-630	- Duplicate reference
Oliver, Nick, Gimenez, Marga, Calhoun, Peter et al. (2020) Continuous Glucose Monitoring in People With Type 1 Diabetes on Multiple-Dose Injection Therapy: The Relationship Between Glycemic Control and Hypoglycemia. Diabetes care 43(1): 53-58	- Comparator is not CGM/FLASH/SMBG *DAIMOND study doesn't compare BGM types*
Olson, Darin E (2020) In older adults with type 1 diabetes, continuous glucose monitoring reduced hypoglycemia over 6 months. Annals of internal medicine 173(10): jc54	- Not a relevant study design *Commentary*
Priesterroth, Lilli, Grammes, Jennifer, Clauter, Mona et al. (2021) Diabetes technologies in people with type 1 diabetes mellitus and disordered eating: A systematic review on	- Study does not contain CGM/ FLASH / SMBG *Study not focused on CGM vs non-CGM*

Study	Reason for exclusion
continuous subcutaneous insulin infusion, continuous glucose monitoring and automated insulin delivery. Diabetic medicine : a journal of the British Diabetic Association: e14581	
Radermecker, RP, Saint Remy, A, Scheen, AJ et al. (2010) Continuous glucose monitoring reduces both hypoglycaemia and HbA1c in hypoglycaemia-prone type 1 diabetic patients treated with a portable pump. Diabetes & metabolism 36(5): 409-413	- Not a relevant study design *observational*
Ranjan, Ajenthen G., Rosenlund, Signe V., Hansen, Tine W. et al. (2020) Improved time in range over 1 year is associated with reduced albuminuria in individuals with sensor-augmented insulin pump- treated type 1 diabetes. Diabetes Care 43(11): 2882-2885	- Secondary publication of an included study that does not provide any additional relevant information *sub analysis of Rosenlund 2015*
Reddy, Monika and Oliver, Nick (2019) Self-monitoring of Blood Glucose Requirements with the Use of Intermittently Scanned Continuous Glucose Monitoring. Diabetes technology & therapeutics	- Secondary publication of an included study that does not provide any additional relevant information *post-hoc of impact with no new outcomes of interest*
Secher, A, Almdal, T, Dorflinger, L et al. (2020) Optimizing glycemic control in T1D treated with mdi-intermittently scanned continuous glucose monitoring, carbohydrate counting with automated bolus calculation, or both?. Diabetes technology & therapeutics 22: A243-A244	- Conference abstract
Secher, Anna Lilja, Pedersen-Bjergaard, Ulrik, Svendsen, Ole Lander et al. (2020) Study protocol for optimising glycaemic control in type 1 diabetes treated with multiple daily insulin injections: intermittently scanned continuous glucose monitoring, carbohydrate counting with automated bolus calculation, or both? A randomised controlled trial. BMJ open 10(4): e036474	- study protocol *isCGM and standard care arms*
Seibold, Alexander (2021) Real-time cgm is superior to flash glucose monitoring for glucose control in type 1 diabetes: The corrida randomized controlled trial. Diabetes care 2020;43:2744-2750. Diabetes Care 44(4): e75-e76	- Not a relevant study design *comment on Huskova*
Sequeira, Paola A, Montoya, Lucy, Ruelas, Valerie et al. (2013) Continuous glucose	- No primary outcomes of interest

Study	Reason for exclusion
monitoring pilot in low-income type 1 diabetes patients. Diabetes technology & therapeutics 15(10): 855-8	*Primary outcome has no variance data and secondary outcome only (unclear if validated)*
Soupal, J, Haskova, A, Grunberger, G et al. (2020) Is real-time CGM superior to flash glucose monitoring? Results of the type 1 diabetes CORRIDA randomized control trial. Diabetes 69	- Conference abstract
Soupal, J, Petruzelkova, L, Flekac, M et al. (2016) Comparison of Different Treatment Modalities for Type 1 Diabetes, Including Sensor-Augmented Insulin Regimens, in 52 Weeks of Follow-Up: a COMISAIR Study. Diabetes technology & therapeutics 18(9): 532-538	- Not a relevant study design
Speight, J, Holmes-Truscott, E, Little, S et al. (2019) Satisfaction with the use of different technologies for insulin delivery and glucose monitoring among adults with long-standing type 1 diabetes and problematic hypoglycaemia: 2-year follow-up in the HypoCOMPaSS Randomised Clinical Trial. Diabetes technology & therapeutics	- Duplicate reference
Tanenbaum, Molly L, Hanes, Sarah J, Miller, Kellee M et al. (2017) Diabetes Device Use in Adults With Type 1 Diabetes: Barriers to Uptake and Potential Intervention Targets. Diabetes care 40(2): 181-187	- Not a relevant study design *Qualitative survey*
van Beers, Cornelis A J, Caris, Martine G, DeVries, J Hans et al. (2018) The relation between HbA1c and hypoglycemia revisited; a secondary analysis from an intervention trial in patients with type 1 diabetes and impaired awareness of hypoglycemia. Journal of diabetes and its complications 32(1): 100-103	- Secondary publication of an included study that does not provide any additional relevant information *secondary analysis looking at outcome relationship, not raw outcome results as captured in earlier papers*
Vloemans, A F, van Beers, C A J, de Wit, M et al. (2017) Keeping safe. Continuous glucose monitoring (CGM) in persons with Type 1 diabetes and impaired awareness of hypoglycaemia: a qualitative study. Diabetic medicine : a journal of the British Diabetic Association 34(10): 1470-1476	- Not a relevant study design *qualitative*

Study	Reason for exclusion
Waldenmaier, Delia, Freckmann, Guido, Pleus, Stefan et al. (2021) Therapy adjustments in people with type 1 diabetes with impaired hypoglycemia awareness on multiple daily injections using real-time continuous glucose monitoring: A mechanistic analysis of the HypoDE study. BMJ Open Diabetes Research and Care 9(1): 1848	- Secondary publication of an included study that does not provide any additional relevant information *HYPO-DE secondary no outcomes of interest*
Walker, Tomas C and Yucha, Carolyn B (2014) Continuous glucose monitors: use of waveform versus glycemic values in the improvements of glucose control, quality of life, and fear of hypoglycemia. Journal of diabetes science and technology 8(3): 488-93	- Comparator is not CGM/FLASH/SMBG *CGM numbers vs CGM waveform*
Wan, Wen, Skandari, M Reza, Minc, Alexa et al. (2018) Cost-effectiveness of Continuous Glucose Monitoring for Adults With Type 1 Diabetes Compared With Self-Monitoring of Blood Glucose: The DIAMOND Randomized Trial. Diabetes care 41(6): 1227-1234	- HE study
Wilhelm, Birgit, Forst, Senait, Weber, Matthias M et al. (2006) Evaluation of CGMS during rapid blood glucose changes in patients with type 1 diabetes. Diabetes technology & therapeutics 8(2): 146-55	- Not a relevant study design *protocol*
Zhou, Yongwen, Deng, Hongrong, Liu, Hongxia et al. (2020) Effects of novel flash glucose monitoring system on glycaemic control in adult patients with type 1 diabetes mellitus: protocol of a multicentre randomised controlled trial. BMJ open 10(12): e039400	- study protocol
Study	Code [Reason]
Battelino, Tadej and Bolinder, Jan (2008) Clinical use of real-time continuous glucose monitoring. Current diabetes reviews 4(3): 218-22	- Not a relevant study design summary of trials
Bidonde, Julia, Fagerlund, Beate Charlotte, Fronsdal, Katrine B. et al. (2017) FreeStyle Libre Flash Glucose Self-Monitoring System: A Single-Technology Assessment.	- Not a relevant study design STA

Study	Reason for exclusion
Billings, Liana K; Parkin, Christopher G; Price, David (2018) Baseline Glycated Hemoglobin Values Predict the Magnitude of Glycemic Improvement in Patients with Type 1 and Type 2 Diabetes: Subgroup Analyses from the DIAMOND Study Program. Diabetes technology & therapeutics 20(8): 561-565	- Study does not contain a relevant intervention DIAMOND focuses on insulin delivery not CGM
Chico, A, Vidal-Rios, P, Subira, M et al. (2003) The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes care 4: 1153-1157	- Study does not contain a relevant intervention Mixed op and 3 day CGM under week requirement
Dunn, Timothy C, Xu, Yongjin, Hayter, Gary et al. (2018) Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests. Diabetes research and clinical practice 137: 37-46	- Not a relevant study design database analysis not RCT
Golden, Sherita Hill, Brown, Todd, Yeh, Hsin-Chieh et al. (2012) Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. Comparative Effectiveness Review.	- Secondary publication of an included study that does not provide any additional relevant information More recent paper with same data (YEh 2012)
John M. Eisenberg Center for Clinical Decisions and Communications, Science (2007) Insulin Delivery and Glucose Monitoring Methods for Diabetes Mellitus: Comparative Effectiveness.	- Secondary publication of an included study that does not provide any additional relevant information Yeh 2012 more recent
McGill, Janet B and Ahmann, Andrew (2017) Continuous Glucose Monitoring with Multiple Daily Insulin Treatment: Outcome Studies. Diabetes technology & therapeutics 19(s3): 3-s12	- 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	- Not a relevant study design HTA

Study	Reason for exclusion
Medical Advisory, Secretariat (2011) Continuous glucose monitoring for patients with diabetes: an evidence-based analysis. Title to be Checked	- Not a relevant study design HTA
New, JP, Ajjan, R, Pfeiffer, AFH et al. (2016) Continuous glucose monitoring in people with diabetes: the randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). Diabetes technology & therapeutics 18: S11-S12	- Duplicate reference Already in T1/T2 CGM
Rubin, Richard R and Peyrot, Mark (2010) Patient-reported outcomes and diabetes technology: a systematic review of the literature. Pediatric endocrinology reviews : PER 7suppl3: 405-12	- More recent systematic review included that covers the same topic No MA and more recent SLRs
Ruxer, J, Mozdzan, M, Loba, J et al. (2005) Usefulness of continuous glucose monitoring system in detection of hypoglycaemic episodes in patients with diabetes in course of chronic pancreatitis. Polskie archiwum medycyny wewnetrznej 114(4): 953-957	- Study not reported in English Polish
Yeoh, Ester, Lim, Boon Khim, Fun, Sharon et al. (2018) Efficacy of self-monitoring of blood glucose versus retrospective continuous glucose monitoring in improving glycaemic control in diabetic kidney disease patients. Nephrology (Carlton, Vic.) 23(3): 264-268	- Study does not contain a relevant intervention short episodic CGM not continuous wear as in scope

Study	Code [Reason]
Alva, Shirdhara (2020) Accuracy of a 14-Day Factory-Calibrated Continuous Glucose Monitoring System With Advanced Algorithm in Pediatric and Adult Population With Diabetes. Journal of diabetes science and technology	- No relevant outcomes *Only outcomes are algorithm accuracy*
Benkhadra, Khalid, Alahdab, Fares, Tamhane, Shrikant et al. (2017) Real-time continuous glucose monitoring in type 1 diabetes: a systematic review and individual patient data meta-analysis. Clinical endocrinology 86(3): 354-360	- Irrelevant SLR *Did not give individual study data in sys review/ meta-analysis*

Study	Code [Reason]
Chetty, V T, Almulla, A, Odueyungbo, A et al. (2008) The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HbA1c) levels in Type I diabetic patients: a systematic review. Diabetes research and clinical practice 81(1): 79-87	- Duplicate reference
Hanes, S, Wadwa, RP, Clay, SM et al. (2019) CGM at diagnosis of type 1 diabetes: impact on glycemic and psychosocial outcomes. Diabetes technology & therapeutics 21: A24	- Conference abstract
Hirsch, Irl B (2009) Clinical review: Realistic expectations and practical use of continuous glucose monitoring for the endocrinologist. The Journal of clinical endocrinology and metabolism 94(7): 2232-8	- Not a relevant study design *review not an SLR*
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group (2010) Prolonged nocturnal hypoglycemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes. Diabetes care 33(5): 1004-8	- Not a relevant study design *single arm study*
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group (2010) Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. Diabetes care 33(1): 17-22	- Duplicate reference *duplicate of other 2010 study*
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Beck, Roy W, Buckingham, Bruce et al. (2009) Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. Diabetes care 32(11): 1947-53	- Not a relevant study design *association study*
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Beck, Roy W, Hirsch, Irl B et al. (2009) The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes care 32(8): 1378-83	- Does not contain a population of people with XXX *does not present adult/c CYP subgroups and unclear what % of people over under 18*
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group,	- Not a relevant study design

Study	Code [Reason]
Fiallo-Scharer, Rosanna, Cheng, Jing et al. (2011) Factors predictive of severe hypoglycemia in type 1 diabetes: analysis from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized control trial dataset. Diabetes care 34(3): 586-90	*assocation study*
Kanapka, L (2019) Adolescents and young adults with type 1 diabetes (T1D) experience substantial glycemic variability. Diabetes technology & therapeutics 21: A25-A26	- Conference abstract
Laffel, Lori M, Kanapka, Lauren G, Beck, Roy W et al. (2020) Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes: A Randomized Clinical Trial. JAMA 323(23): 2388-2396	- Does not contain a population of people with XXX *Population not divided in a way that can be split between >18 and <18*
Messer, L H, Johnson, R, Driscoll, K A et al. (2018) Best friend or spy: a qualitative meta-synthesis on the impact of continuous glucose monitoring on life with Type 1 diabetes. Diabetic medicine : a journal of the British Diabetic Association 35(4): 409-418	- Not a relevant study design *qualitative*
Roze, S, Saunders, R, Brandt, A-S et al. (2015) Health-economic analysis of real-time continuous glucose monitoring in people with Type 1 diabetes. Diabetic medicine 32(5): 618-626	- CE study
Thabit, H, Mubita, WM, Fullwood, C et al. (2020) Comparison of dexcom G6 CGM with self-monitoring blood glucose in young adults with type 1 diabetes: the millennial study. Diabetes 69	- Conference abstract
Wilson, Darrell M, Xing, Dongyuan, Cheng, Jing et al. (2011) Persistence of individual variations in glycated hemoglobin: analysis of data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Trial. Diabetes care 34(6): 1315-7	- Secondary publication of an included study that does not provide any additional relevant information *secondary associations not important for review*

Study	Code [Reason]
Alva, Shirdhara (2020) Accuracy of a 14-Day Factory-Calibrated Continuous Glucose Monitoring System With Advanced Algorithm in Pediatric and Adult Population With Diabetes. Journal of diabetes science and technology	- No relevant outcomes *Only outcomes are algorithm accuracy*
Benkhadra, Khalid, Alahdab, Fares, Tamhane, Shrikant et al. (2017) Real-time continuous glucose monitoring in type 1 diabetes: a systematic review and individual patient data meta-analysis. Clinical endocrinology 86(3): 354-360	- Irrelevant SLR *Did not give individual study data in sys review/ meta-analysis*
Chetty, V T, Almulla, A, Odueyungbo, A et al. (2008) The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HbA1c) levels in Type I diabetic patients: a systematic review. Diabetes research and clinical practice 81(1): 79-87	- Duplicate reference
Hanes, S, Wadwa, RP, Clay, SM et al. (2019) CGM at diagnosis of type 1 diabetes: impact on glycemic and psychosocial outcomes. Diabetes technology & therapeutics 21: A24	- Conference abstract
Hirsch, Irl B (2009) Clinical review: Realistic expectations and practical use of continuous glucose monitoring for the endocrinologist. The Journal of clinical endocrinology and metabolism 94(7): 2232-8	- Not a relevant study design *review not an SLR*
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group (2010) Prolonged nocturnal hypoglycemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes. Diabetes care 33(5): 1004-8	- Not a relevant study design *single arm study*
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group (2010) Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. Diabetes care 33(1): 17-22	- Duplicate reference *duplicate of other 2010 study*
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Beck, Roy W, Buckingham, Bruce et al. (2009)	- Not a relevant study design *association study*

Study	Code [Reason]
Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. Diabetes care 32(11): 1947-53	
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Beck, Roy W, Hirsch, Irl B et al. (2009) The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes care 32(8): 1378-83	- Does not contain a population of people with XXX *does not present adult/ CYP subgroups and unclear what % of people over under 18*
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Group, Fiallo-Scharer, Rosanna, Cheng, Jing et al. (2011) Factors predictive of severe hypoglycemia in type 1 diabetes: analysis from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized control trial dataset. Diabetes care 34(3): 586-90	- Not a relevant study design *assocation study*
Kanapka, L (2019) Adolescents and young adults with type 1 diabetes (T1D) experience substantial glycemic variability. Diabetes technology & therapeutics 21: A25-A26	- Conference abstract
Laffel, Lori M, Kanapka, Lauren G, Beck, Roy W et al. (2020) Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes: A Randomized Clinical Trial. JAMA 323(23): 2388-2396	- Does not contain a population of people with XXX *Population not divided in a way that can be split between >18 and <18*
Messer, L H, Johnson, R, Driscoll, K A et al. (2018) Best friend or spy: a qualitative meta-synthesis on the impact of continuous glucose monitoring on life with Type 1 diabetes. Diabetic medicine : a journal of the British Diabetic Association 35(4): 409-418	- Not a relevant study design *qualitative*
Roze, S, Saunders, R, Brandt, A-S et al. (2015) Health-economic analysis of real-time continuous glucose monitoring in people with Type 1 diabetes. Diabetic medicine 32(5): 618-626	- CE study
Thabit, H, Mubita, WM, Fullwood, C et al. (2020) Comparison of dexcom G6 CGM with self-monitoring blood glucose in young adults with type 1 diabetes: the millennial study. Diabetes 69	- Conference abstract

Study	Code [Reason]
Wilson, Darrell M, Xing, Dongyuan, Cheng, Jing et al. (2011) Persistence of individual variations in glycated hemoglobin: analysis of data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Trial. Diabetes care 34(6): 1315-7	- Secondary publication of an included study that does not provide any additional relevant information *secondary associations not important for review*

Health economics

Study	Reason for exclusion
Clua Espuny J L, P. J. J. Q. T. M. L. P. G. A. (2000). "[Cost-effectiveness analysis of self-monitoring of blood glucose in type 2 diabetics]." Gaceta Sanitaria 14(6): 442-448.	- Study not reported in English
Gil-Ibanez, M. T. and G. R. Aispuru (2019). "Cost-effectiveness analysis of glycaemic control of a glucose monitoring system (FreeStyle Libre) for patients with type 1 diabetes in primary health care of Burgos." Enfermeria clinica.	- Full text not available
Li, H., et al. (2014). "Cost Effectiveness Analysis of Flash Glucose Monitoring for Type 2 Diabetes Patients Receiving Insulin Treatment In The Uk." Value Health 17(7): a351.	- Conference abstract
Medical Advisory, S. (2011). Continuous glucose monitoring for patients with diabetes. Canada, Medical Advisory Secretariat (MAS).	- Not a cost-utility study
Ontario Health (Quality) (2019). "Flash Glucose Monitoring System for People with Type 1 or Type 2 Diabetes: A Health Technology Assessment." Ont Health Technol Assess Ser 19(8): 1-108.	- Systematic review
Zomer, E., et al. (2020). "Cost-effectiveness of health technologies in adults with type 1 diabetes: A systematic review and narrative synthesis." Systematic Reviews 9(1): 171.	- Systematic review
Bilir, S. P., et al. (2018). "Cost-effectiveness Analysis of a Flash Glucose Monitoring System for Patients with Type 1 Diabetes Receiving Intensive Insulin Treatment in Sweden." European endocrinology 14(2): 73-79.	- Non-UK study: Sweden
Bilir, S. P., et al. (2018). "The Cost-effectiveness of a Flash Glucose Monitoring System for Management of Patients with Type 2 Diabetes Receiving Intensive Insulin Treatment in Sweden." European endocrinology 14(2): 80-85.	- Non-UK study: Sweden
Roze, S., et al. (2015). "Health-economic analysis of real-time continuous glucose monitoring in people with Type 1 diabetes." Diabetic medicine : a journal of the British Diabetic Association 32(5): 618-626.	- Non-UK study: Sweden

Study	Reason for exclusion
Roze, S., et al. (2021). "Long-Term Cost-Effectiveness the Dexcom G6 Real-Time Continuous Glucose Monitoring System Compared with Self-Monitoring of Blood Glucose in People with Type 1 Diabetes in France." Diabetes Therapy 12(1): 235-246.	- Non-UK study: France
Garcia-Lorenzo, B., et al. (2018). "Cost-effectiveness analysis of real-time continuous monitoring glucose compared to self-monitoring of blood glucose for diabetes mellitus in Spain." J Eval Clin Pract 24(4): 772-781.	- Non-UK study: Spain
Chaugule, S. and C. Graham (2017). "Cost-effectiveness of G5 Mobile continuous glucose monitoring device compared to self-monitoring of blood glucose alone for people with type 1 diabetes from the Canadian societal perspective." Journal of Medical Economics 20(11): 1128-1135.	- Non-UK study: Canada
Fonda, S. J., et al. (2016). "The Cost-Effectiveness of Real-Time Continuous Glucose Monitoring (RT-CGM) in Type 2 Diabetes." Journal of diabetes science and technology 10(4): 898-904.	- Non-UK study: US
Herman, W. H., et al. (2018). "The 30-year cost-effectiveness of alternative strategies to achieve excellent glycemic control in type 1 diabetes: An economic simulation informed by the results of the diabetes control and complications trial/epidemiology of diabetes interventions and complications (DCCT/EDIC)." Journal of diabetes and its complications 32(10): 934-939.	- Non-UK study: US
Huang, E. S., et al. (2010). "The cost-effectiveness of continuous glucose monitoring in type 1 diabetes." Diabetes care 33(6): 1269-1274.	- Non-UK study: US
McQueen, R., et al. (2011). "Cost-effectiveness of continuous glucose monitoring and intensive insulin therapy for type 1 diabetes." Cost Effectiveness and Resource Allocation 9(13).	- Non-UK study: US
Wan, W., et al. (2018). "Cost-effectiveness of Continuous Glucose Monitoring for Adults With Type 1 Diabetes Compared With Self-Monitoring of Blood Glucose: The DIAMOND Randomized Trial." Diabetes care 41(6): 1227-1234.	- Non-UK study: US
Tsuji, S., et al. (2020). "Cost-Effectiveness of a Continuous Glucose Monitoring Mobile App for Patients With Type 2 Diabetes Mellitus: Analysis Simulation." J Med Internet Res 22(9): e16053.	- Non-UK study: Japan

Appendix L - Research recommendations – full details

L.1 Research recommendation

What is the effectiveness and cost effectiveness of CGM devices to improve glycaemic control using routinely collected real-world data?

L.2 Why this is important

A lot of clinical trial data on CGM in diabetes has been collected, but this does not fully reflect the picture of the real world data on how CGM is being used. This is a large potential resource of specific real-time outcome data that could be used for decision making at both personal and system wide levels in diabetes management strategies.

L.3 Rationale for research recommendation

Importance to 'patients' or the population	If routine healthcare data is collected it can show the direct effect of implemented technology on the population, rather than it being interpreted through the results of clinical trials.
Relevance to NICE guidance	NICE is using more routine real-world healthcare data to assess the effectiveness of interventions, resolve gaps in knowledge and drive forward access to innovations for patients.
Relevance to the NHS	With increasing numbers of people with diabetes of different demographics, and different devices recording data, this could enable the NHS to access a powerful resource of personalised management of diabetes through CGM and routine data.
National priorities	High
Current evidence base	NICE does not have a current evidence base for CGM using routine healthcare data.
Equality considerations	Increased monitoring of routine healthcare data will ensure a broader population is captured, rather than just those eligible for clinical trials.

L.4 Modified PICO table

Population	Adults with type 1 diabetes using CGM devices
Intervention	CGM device
Comparator	Self-monitoring of blood glucose
Outcome	Any metric/ outcome measuring CGM effectiveness (study/ data must compare multiple outcomes)
Study design	Routine healthcare data Registries/ audits

Timeframe	Long term
Additional information	None

1