National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: diagnosis and management

[A] Evidence reviews for continuous glucose monitoring in adults with type 2 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 Update Team

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1 Continuous glucose monitoring in adults with type 2 diabetes

1.1 Review question

In adults with type 2 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

Recommendations from the 2015 version of this guideline 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. The 2015 version of this guideline does not recommend continuous monitoring of interstitial fluid glucose levels using a continuous glucose monitor, although this can be considered for some people.

New studies identified during routine surveillance of evidence for continuous glucose monitoring (CGM) for type 2 diabetes, and the possibility of decreasing cost and increasing access to CGM technologies, suggests the evidence should be reviewed to ascertain the effectiveness of real time CGM (rtCGM) and intermittently scanned continuous glucose monitoring (isCGM – commonly known as flash) versus standard blood glucose monitoring (SMBG) techniques. It should also be considered whether routine rtCGM/isCGM use is now more appropriate for certain populations of people with diabetes.

Table 1:Summary of the protocol

PICO Table	
Population	Adults with type 2 diabetes Adult is defined as aged 18 years and above.
Intervention	• Continuous glucose monitoring (rtCGM) • Flash glucose monitoring (isCHM) • Intermittent capillary blood glucose monitoring (SMBG)
Comparator	Compared to each other

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)

PICO Table	
	• % of data captured **Secondary outcomes** • Other adverse events (dichotomous) limited to: ○ Diabetes related hospitalisation ○ malfunction of CGM monitor ○ hypersmolar hyperglycemic state ○ 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.

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 (see Appendix C for the search strategy and Appendix D for the study selection process).

Following title and abstract screening, 288 studies were included for full text screening to see if they were relevant to any of the CGM questions that were included in this update (CGM for people with type 1 diabetes, CGM for people with type 2 diabetes and CGM for children and young people with type 1 diabetes).

Of the 288 included studies, 42 were potentially relevant for the type 2 diabetes question. The other 246 were assessed for relevance for the other CGM questions (for more information on the included studies for the other questions see Evidence review X: CGM for type 1 diabetes and Evidence review X: CGM for children and young people).

The 42 studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A). Overall, 13 publications were included of 11 studies, along with 7 systematic reviews that were checked for references. No additional studies were identified from the systematic reviews and so these were not used as part of the review. All studies were parallel RCTs. After discussion with the committee it was decided that there was sufficient evidence from these RCTs and so a search for prospective cohort studies was not required.

Most studies compared rtCGM against SMBG but some compared isCGM to SMBG. No studies compared the effectiveness of rtCGM with isCGM. Different populations were included in the studies, with some including people who used insulin, some including a mixed population and others including people who did not use insulin. Results were therefore stratified by these populations, as specified in the review protocol. The number of studies for each comparison and each population is outlined in Table 2. Further information about these studies is shown in Table 3.

Table 2: List of comparisons and associated studies/trials

	Insulin only	Mixed pop	No insulin
rtCGM vs SMBG	• Ajjan 2019 • Beck 2017 • Tildesley 2016 (Tang 2014)	• Ehrhardt 2011 (Vigersky 2012) • Isaacson 2020 • Taylor 2019 • Yoo 2008	• Cox 2020
isCGM vs SMBG	• Haak 2017 • Wang 2021	•	• Wada 2020

See **Error! Reference source not found.** for evidence tables and the reference list in section 1.1.10 References – included studies.

1.1.3.2 Excluded studies

Overall, 22 studies were excluded at full text screening stage. 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 self blood glucose monitoring (SMBG)

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes
Ajjan 2019	45	• People with T2D • Age >18 • Duration of diabetes • MDI at least 6 months prior • HbA1c: 7.5 - 12 % • Can use rtCGM device	Freestyle navigator - The intervention group used unmasked FSN with the low, high and projected alarms switched off (data loss and calibration alarms were still active).	standard SMBG (FreeStyle Freedom Lite; Abbott Diabetes Care Ltd, Witney, UK) and used another masked FSN for the final 15-day period of the study	100 days	• HbA1c • Time above/below target glucose range [<70 mg/dL, >180 mg/dL
Beck 2017	158	• People with T2D • Age: >25 • Insulin treatment: Treated with MDI for at least 1 year + Stable diabetes medication for prior 3 months • HbA1c: 7.5% - 10% • BG testing: Averaging more than 2 times a day • Glomerular filtration weight 45 mL/min/1.73m2	Dexcom G4	Asked to monitor BG at least 4 times daily	24 weeks	• HBA1C ○ (change in %) ○ proportion below 7/7.5% ○ relative reduction of 10% ○ absolute reduction of 1% ○ 1% reduction in HbA1c <7% cases • Time in range • 70 to 180 mg/dL

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes

						• Time above below target glucose range
						  ○ (<70, <60, <50 mg/dL,
						  ○ >180, >250, > 300 mg/dL
						• Glycemic variability
						• coefficient of variation
						• Awareness of hypoglycemiaQoL (validated tools)
						• EuroQoL-5D, WHO wellbeing index
						• HFS, DDS, Hypoglycemic confidence scale
						• CGM satisfaction scale

Cox 2020	30	People with T2D Age 30 - 80 Duration of diabetes <11 years Insulin treatment None	The 2-month GEMCGM intervention period involved meeting in groups of 8 to 10 for 90 minutes on 4 occasions, with 1 week between sessions 1 and 2 and 3 weeks between sessions 2 and 3 and 3 and 4 (Fig. 1). At each session, participants were given a 7-day Dexcom G5 sensor, and 1 month after session 4, a fifth	All participants continued their usual care in consultation with their treating physician, who adjusted medication as clinically indicated throughout the 5-month study	3 months	• HBA1C • QoL (validated tools) • WHOQoL

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes
		HbA1c >= 7% able to walk for 30 mins	sensor was given. This timing was intended to diminish reliance on CGM and group support and to encourage autonomy following the conclusion of the intervention. Follow-up assessment occurred three months after session 4.			
Ehrhardt 2011 (Vigersky 2012)	100	• People with T2D • military care beneficiaries • Age: >18 • Duration of diabetes: >=3 months • Insulin treatment: All therapies except prandial insulin, including basal insulin • HbA1c: >= 7% but <12% • BG testing: 4 times daily	Dexcom SEVEN	Perform SMBG before each meal and at bedtime. They were provided with and instructed in the use of the AccuChek® Aviva glucometer (Roche Diagnostics Corp., Indianapolis, IN)	12 months	HbA1c Time in range (70-180mg/dL) Time above below target glucose range (% time) <50mg/dl <70mg/dl >180mg/dl >240 mg/dl % of CGM data captured QoL (validated tools) Paid, SUS

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes
						SMBG frequency rtcgm 2.9 ○ SMBG 2.4
Isaacson 2017		• People with T2D • Type 1 or type 2 • Age: 18-80 • HbA1c: >= 6.5% • BG testing	Dexcom G6	Standard of care finger stick glucometer	6 months	• HBA1C (median) • Hypoglycemia • glycemic excursion odds (%) • Glycemic variability • MAGE
Taylor 2019	20	• Age: “Adult” • Weight: “obese”	All participants wore the MedtronicTM Guardian Connect device with the Harmony glucose sensor (Medtronic, Los Angeles, CA). The minimally invasive glucose sensor was inserted into subcutaneous tissue on the body (usually on the abdomen) to continuously and automatically measure interstitial glucose levels at 5-minute interviews, 24 h a day 288 glucose readings every 24 h) throughout the study. At the first insertion all participants were	**SMBG**	12 weeks	○ HBA1C ○ QoL (validated tools) ○ PSS

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes
			instructed to conduct a calibration finger-stick (capillary blood) at 2 h and again at 6 h post insertion, then 12-hourly for the duration of the sensor wear. Sensors were removed and replaced with a new sensor every 10 days.			
Tildesley 2016 (Tang 2014)	57	• Insulin treatment: Alone or in combination with oral antihyperglycemic agents • HbA1c: recent >= 7% • BG testing • prior training • Internet access	Guardian REAL-Time Continuous Glucose Monitoring System (Medtronic MiniMed, Inc., Northridge, CA).	Patients randomized to the IBGMS group were trained by the research coordinator to upload their glucose readings every 2 weeks to a secure, commercially available website (ALR Technologies, Inc., Atlanta, GA). Glucose levels were presented in table and graph formats according to the time of day, with automatic	6 months	• HBA1C • QoL (validated tools) • DTSQ (Tang)

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes
				calculations showing the mean, standard deviation and range for specific time periods. The system allowed patients to input medications, view summaries of readings and contact their endocrinologist. The endocrinologist reviewed the readings and sent feedback through the ALR messaging system.		
Yoo 2008		• People with T2D • Age • 20-80 • Insulin treatment • Use of oral hypoglycemia gents or insulin for at least 1 year • a stable insulin or OHA regimen for the prior 2 months • a stable dose of antihypertensive or lipid-	**rtCGM** Guardian real-time The Guardian RT group underwent real time continuous glucose monitoring once a month for 3 days (due to the life span of the RT-CGM sensor)	SMBG group was instructed to continue to check their blood glucose level at least four times a week, including fasting blood glucose and	3 months	• HBA1C (HbA1c reduction) • Time in range (80 - 250 mg/dL) • Time above below target glucose range (>250 mg/dL, <60 mg/dL) • Glycemic variability: MAGE

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes
		lowering drugs for at least 4 weeks	for 12 weeks. Sensor placement was done by a certified diabetes educator nurses and the alarm thresholds were set for hyperglycemia (>300 mg/dL) and hypoglycemia (<60 mg/ dL).	postprandial 2 h blood glucose levels for 3 months continuously. The testing frequency of blood glucose in the SMBG group (four times a week) was the median frequency of their usual practice prior to the study. Standard diabetes education was also performed for the SMBG group before the beginning of the study, based on the Diabetes Education Guideline of Korea Diabetes Association and Staged Diabetes Management		

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes
				Guidelines in Korea		

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2 **Table 4: Intermittently scanned continuous glucose monitoring (isCGM) vs self blood glucose monitoring (SMBG)**

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes
Haak 2017	224	• People with T2D • Age • >18 • Insulin treatment • at least 6 months and on their current regimen (prandial only or prandial and basal • intensive insulin therapy or CSII therapy) for 3 months or more • HbA1c • 7.5 - 12% • BG testing • self-reported more than 10 a week for 2 months	**isCGM** Abbott Sensor Based Glucose Monitoring System	**SMBG** Abbott Blood Glucose Monitoring System (standard blood glucose meter)	6 months	HBA1C mmol/mol & % Time in range 3.9 - 10 Time above below target glucose range < 3.9 & <3.1 & <2.5 & <2.2 Hypoglycemia < 3.9 & <3.1 & <2.5 & <2.2 Glycemic variability

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes
						CV, MAGE, SD Adverse events SAE, DKA, hypersmolar QoL (validated tools) DTSQ & DQoL ○ SMBG frequency
Wada 2020	100	• People with T2D • Age: (>= 20 and <70) • HbA1c (>= 7.5%)	Flash glucose monitoring Free Style Libre Pro; Abbott Diabetes Care, Alameda, California, USA	SMBG device (Free Style Precision Neo; Abbott Diabetes Care).	24 weeks	HBA1C Time in range time in sensor glucose 70–180 mg/dL (3.9–10.0 mmol/L) Time above below target glucose range time in hypoglycemia (<70 mg/dL (3.9 mmol/L), <55 mg/dL (3.1 mmol/L) and <45 mg/dL (2.5 mmol/L)

Study	Sample size	Population	Intervention	Comparator	Follow up	Outcomes
						time in hyperglycemia >180 mg/dL (10.0 mmol/L) and >240 mg/dL (13.3 mmol/L) and >300 mg/dL (16.7 mmol/L)) Glycemic variability coefficient of variation, MAGE QoL (validated tools) ○ DTSQ
Wang 2012	80	• "People with T2D"	**isCGM** Freestyle Libre Flash Glucose Monitoring System (Abbott Laboratories, USA)	**SMBG** blood glucose was detected through collection of fingertip blood for multiple times in control group	2 weeks	• Time in range (<7.0 mmol/l so technically not "in range" no hypo level) • Hypoglycemia (event n) ○ QoL (validated tools): SAS, SDS, GCQ, PSQI, WHOQolBREF

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1.1.5 Summary of the effectiveness evidence

Evidence in meta-analysis

Table 5: Summary of GRADE: rtCGM vs SMBG

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
HbA1c (% change from baseline) <= 3 months	**404**	**MD -0.80 (-1.39, -0.22)**	**+/- 0.50**	**Very low**	**Effect (favouring rtCGM)**
HbA1c (% change from baseline) 3-6 months	302	MD -0.34 (-0.52, -0.16)	+/- 0.50	Moderate	Effect less than MID (favouring rtCGM)
HbA1c (% change from baseline) >6 months	100	MD -0.40 (-0.89, 0.09)	+/- 0.50	Very low	Could not differentiate
HbA1c level <7% (%) <= 3 months	152	MD 10.00 (-2.00, 22.00)	+/- 18.87	Moderate	Could not differentiate
HbA1c level <7% (%) 3-6 months	152	MD 3.00 (-9.00, 15.00)	+/- 18.87	High	No meaningful difference
HbA1c level <7.5% (%) <= 3 months	152	MD 17.00 (-3.00, 37.00)	+/- 31.45	Moderate	Could not differentiate
HbA1c level <7.5% (%) 3-6 months	152	MD 8.00 (-11.00, 27.00)	+/- 29.88	High	No meaningful difference
Relative reduction HbA1c >= 10 % (%) <=3 months	152	MD 25.00 (3.00, 47.00)	+/- 34.59	Moderate	Effect less than MID (favouring rtCGM)
Relative reduction HbA1c >= 10% (%) 3-6 months	152	MD 22.00 (-0.00, 44.00)	+/- 34.59	Moderate	Could not differentiate
Reduction HbA1c >= 1% (%) <= 3 months	152	MD 20.00 (-1.00, 41.00)	+/- 33.02	Moderate	Could not differentiate
Reduction HbA1c >= 1% (%) 3-6 months	152	MD 12.00 (-7.00, 31.00)	+/- 29.88	Moderate	Could not differentiate
Reduction HbA1c >= 0.5% (%) <= 3 months	152	MD 31.00 (5.00, 57.00)	+/- 40.88	Moderate	Effect less than MID (favouring rtCGM)
Reduction HbA1c >= 0.5% (%) 3-6 months	152	MD 26.00 (-0.00, 52.00)	+/- 40.88	Moderate	Could not differentiate
Time in hypoglycemia (<70 mg/dL) (minutes) <=3 months	45	MD -0.13 (-0.55, 0.29)	+/- 0.34	Moderate	Could not differentiate

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Time in hyperglycemia (>180 md/dL) (minutes) <= 3 months	45	MD -0.42 (-2.69, 1.85)	+/- 1.83	Low	Could not differentiate
Change in BMI <= 3 months	157	MD -0.03 (-1.49, 1.44)	+/- 2.68	Very low	No meaningful difference
Change in BMI 3-6 months	32	MD 1.27 (-2.12, 4.66)	+/- 0.59	Very low	Could not differentiate
Change in BMI >6 months	100	MD 0.50 (-2.06, 3.06)	+/- 3.55	Low	No meaningful difference
Change in weight (kg) <= 3 months	165	MD -1.49 (-3.43, 0.46)	+/- 2.02	Moderate	Could not differentiate
Change in weight (kg) >6 months	100	MD -0.95 (-8.02, 6.12)	+/- 9.98	Low	No meaningful difference
Weight loss >3 pounds - <3 months	**100**	**RR 2.22 (1.12, 4.40)**	**0.80 , 1.25**	**Very low**	**Effect (favouring rtCGM)**
Weight loss >3 pounds - >6 months	100	RR 1.35 (0.83, 2.21)	0.80 , 1.25	Very low	Could not differentiate
Weight gain >3 pounds - <3 months	100	RR 0.50 (0.20, 1.23)	0.80 , 1.25	Very low	Could not differentiate
Weight gain >3 pounds - >6 months	100	RR 0.61 (0.32, 1.16)	0.80 , 1.25	Very low	Could not differentiate
Serious adverse events 3-6 months	158	RR Not estimable	0.80 , 1.25	High	Not estimable
Severe hypoglycemia 3-6 months	207	RR Not estimable	0.80 , 1.25	High	Not estimable
DKA 3-6 months	157	RR Not estimable	0.80 , 1.25	High	Not estimable
Quality of life: DTSQ 3-6 months	**32**	**MD -8.61 (-12.42, -4.80)**	**+/- 1.32**	**Low**	**Effect (favouring SMBG)**
Quality of life: PHQ-9 <=3 months	30	MD -0.90 (-5.62, 3.82)	+/- 3.35	Very low	Could not differentiate
Quality of life: WHO-QoL physiological <=3 months	30	MD 0.00 (-1.22, 1.22)	+/- 0.85	Very low	Could not differentiate
Quality of life: WHO-QoL psychological <=3 months	**30**	**MD 1.20 (0.26, 2.14)**	**+/- 0.50**	**Low**	**Effect (favouring rtCGM)**
Quality of life: glucose monitor satisfaction survey <= 3 months	30	MD 0.40 (-0.06, 0.86)	+/- 0.30	Low	Could not differentiate

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Quality of life: diabetes empowerment scale <=3 months	30	MD 2.50 (-0.48, 5.48)	+/- 1.70	Low	Could not differentiate
Quality of life: diabetes distress scale (emotional) <=3 months	30	MD -0.70 (-1.53, 0.13)	+/- 0.55	Low	Could not differentiate
Quality of life: diabetes distress scale (regimen) <=3 months	**30**	**MD -0.80 (-1.45, -0.15)**	**+/- 0.35**	**Low**	**Effect (favouring rtCGM)**
Quality of life (PAID) <= 3 months	100	MD 1.00 (-6.79, 8.79)	+/- 10.25	Low	No meaningful difference
Quality of life (PAID) 3-6 months	100	MD -0.60 (-8.85, 7.65)	+/- 10.73	Low	No meaningful difference
Quality of life: Perceived stress scale <= 3 months	20	MD 0.80 (-2.80, 4.40)	+/- 1.56	Low	Could not differentiate

Table 6: Summary of GRADE: isCGM vs SMBG

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
HbA1c (% change from baseline) <= 3 months	93	MD -0.13 (-0.35, 0.09)	+/- 0.50	High	No meaningful difference
HbA1c (% change from baseline) 3-6 months	317	MD -0.12 (-0.44, 0.19)	+/- 0.50	Very low	No meaningful difference
HbA1c (% change from baseline) 3-6 months Subgroup: On insulin	224	MD 0.03 (-0.19, 0.25)	+/- 0.50	Moderate	No meaningful difference
HbA1c (% change from baseline) 3-6 months Subgroup: No insulin	93	MD -0.29 (-0.54, -0.04)	+/- 0.50	Moderate	Effect less than MID (favouring isCGM)
Time in range (70 – 180 mg/dL) (hours) 3-6 months	300	MD 1.27 (0.46, 2.08)	+/- 5.00	Very low	Effect less than MID (favouring isCGM)
Time in range (70 – 180 mg/dL) (hours) 3-6 months Subgroup: On insulin	224	MD 0.20 (-0.94, 1.34)	+/- 5.00	Moderate	No meaningful difference
Time in range (70 – 180 mg/dL) (hours) 3-6 months Subgroup: No insulin	76	MD 2.36 (1.21, 3.51)	+/- 5.00	High	No meaningful difference
Time in hypoglycemia (<70 mg/dL) (hours) 3-6 months	300	MD -0.18 (-0.77, 0.41)	+/- 0.41	Very low	Could not differentiate

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Time in hypoglycemia (<70 mg/dL) (hours) 3-6 months Subgroup: On insulin	224	MD -0.47 (-0.73, -0.21)	+/- 0.47	Low	Effect less than MID (favouring isCGM)
Time in hypoglycemia (<70 mg/dL) (hours) 3-6 months Subgroup: No insulin	76	MD 0.13 (-0.19, 0.45)	+/- 0.35	Moderate	Could not differentiate
Time in hypoglycemia (<55 mg/dL) (hours) 3-6 months	300	MD -0.05 (-0.39, 0.30)	+/- 0.21	Very low	Could not differentiate
Time in hypoglycemia (<55 mg/dL) (hours) 3-6 months Subgroup: On insulin	224	MD -0.22 (-0.35, -0.09)	+/- 0.24	Low	Effect less than MID (favouring isCGM)
Time in hypoglycemia (<55 mg/dL) (hours) 3-6 months Subgroup: No insulin	76	MD 0.13 (-0.03, 0.29)	+/- 0.18	Moderate	Could not differentiate
Time in hypoglycemia (<45 mg/dL) (hours) 3-6 months	300	MD -0.02 (-0.26, 0.21)	+/- 0.13	Very low	Could not differentiate
Time in hypoglycemia (<45 mg/dL) (hours) 3-6 months Subgroup: On insulin	224	MD -0.14 (-0.22, -0.06)	+/- 0.14	Low	Effect less than MID (favouring isCGM)
Time in hypoglycemia (<45 mg/dL) (hours) 3-6 months Subgroup: No insulin	76	MD 0.10 (0.00, 0.20)	+/- 0.11	Moderate	Effect less than MID (Favouring SMBG)
Time in hypoglycemia (<40 mg/dL) (hours) 3-6 months	224	MD -0.10 (-0.16, -0.04)	+/- 0.11	Low	Effect less than MID (Favouring isCGM)
Time in hyperglycemia (<180 mg/dL) (hours) 3-6 months	300	MD -1.18 (-4.09, 1.72)	+/- 1.77	Very low	Could not differentiate
Time in hyperglycemia (<180 mg/dL) (hours) 3-6 months Subgroup: On insulin	224	MD 0.30 (-0.93, 1.53)	+/- 2.22	Moderate	No meaningful difference
Time in hyperglycemia (<180 mg/dL) (hours) 3-6 months Subgroup: No insulin	**76**	**MD -2.66 (-3.85, -1.47)**	**+/- 1.32**	**High**	**Effect (Favouring isCGM)**
Time in hyperglycemia (<240 mg/dL) (hours) 3-6 months	300	MD -0.62 (-1.92, 0.68)	+/- 1.09	Very low	Could not differentiate
Time in hyperglycemia (<240 mg/dL) (hours) 3-6 months Subgroup: On insulin	224	MD 0.10 (-0.80, 1.00)	+/- 1.62	Moderate	No meaningful difference
Time in hyperglycemia (<240 mg/dL) (hours) 3-6 months Subgroup: No insulin	**76**	**MD -1.23 (-1.73, -0.73)**	**+/- 0.55**	**High**	**Effect (Favouring isCGM)**
Time in hyperglycemia (<300 mg/dL) (hours) 3-6 months	300	MD -0.23 (-0.65, 0.20)	+/- 0.54	Very low	Could not differentiate
Time in hyperglycemia (<300 mg/dL) (hours) 3-6 months Subgroup: On insulin	224	MD 0.06 (-0.43, 0.55)	+/- 0.88	Moderate	No meaningful difference

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Time in hyperglycemia (<300 mg/dL) (hours) 3-6 months Subgroup: No insulin	**76**	**MD -0.39 (-0.57, -0.21)**	**+/- 0.20**	**High**	**Effect (Favouring isCGM)**
Events in hypoglycemia (<70 mg/dL) 3-6 months	224	MD -0.16 (-0.29, -0.03)	+/- 0.23	Low	Effect less than MID (Favouring isCGM)
Events in hypoglycemia (<55 mg/dL) 3-6 months	224	MD -0.12 (-0.19, -0.05)	+/- 0.13	Low	Effect less than MID (Favouring isCGM)
Events in hypoglycemia (<45 mg/dL) 3-6 months	224	MD -0.06 (-0.10, -0.02)	+/- 0.07	Low	Effect less than MID (Favouring isCGM)
Events in hypoglycemia (<40 mg/dL) 3-6 months	224	MD -0.05 (-0.09, -0.01)	+/- 0.07	Low	Effect less than MID (Favouring isCGM)
Nocturnal time in hypoglycemia (<70 mg/dL) (hours) 3-6 months	**224**	**MD -0.29 (-0.45, -0.13)**	**+/- 0.28**	**Low**	**Effect (Favouring isCGM)**
Nocturnal Time in hypoglycemia (<55 mg/dL) (hours) 3-6 months	224	MD -0.12 (-0.20, -0.04)	+/- 0.14	Low	Effect less than MID (Favouring isCGM)
Nocturnal Time in hypoglycemia (<45 mg/dL) (hours) 3-6 months	224	MD -0.08 (-0.14, -0.02)	+/- 0.11	Low	Effect less than MID (Favouring isCGM)
Nocturnal Time in hypoglycemia (<40 mg/dL) (hours) 3-6 months	224	MD -0.10 (-0.16, -0.04)	+/- 0.11	Low	Effect less than MID (Favouring isCGM)
Nocturnal Events in hypoglycemia (<70 mg/dL) 3-6 months	**224**	**MD -0.12 (-0.18, -0.06)**	**+/- 0.11**	**Low**	**Effect (Favouring isCGM)**
Nocturnal Events in hypoglycemia (<55 mg/dL) 3-6 months	224	MD -0.07 (-0.11, -0.03)	+/- 0.07	Low	Effect less than MID (Favouring isCGM)
Nocturnal Events in hypoglycemia (<45 mg/dL) 3-6 months	224	MD -0.04 (-0.08, -0.00)	+/- 0.07	Low	Effect less than MID (Favouring isCGM)
Nocturnal Events in hypoglycemia (<40 mg/dL) 3-6 months	224	MD -0.05 (-0.09, -0.01)	+/- 0.07	Low	Effect less than MID (Favouring isCGM)
Change in BMI <=3 months	76	MD -0.30 (-0.69, 0.09)	+/- 0.43	Moderate	Could not differentiate
Change in BMI 3-6 months	76	MD -0.20 (-0.59, 0.19)	+/- 0.43	Moderate	Could not differentiate
Glycemic variability: SD 3-6 months	300	MD -3.30 (-6.56, -0.04)	+/- 4.22	Very low	Effect less than MID (Favouring isCGM)
Glycemic variability: SD 3-6 months Subgroup: On insulin	224	MD -1.67 (-4.51, 1.17)	+/- 5.12	Moderate	No meaningful difference

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Glycemic variability: SD 3-6 months Subgroup: No insulin	76	MD -5.00 (-8.00, -2.00)	+/- 3.33	Moderate	Effect (Favouring isCGM)
Glycemic variability: CV 3-6 months	300	MD -1.03 (-3.44, 1.38)	+/- 2.03	Very low	Could not differentiate
Glycemic variability: CV 3-6 months Subgroup: On insulin	224	MD -2.26 (-3.65, -0.87)	+/- 2.51	Low	Effect less than MID (Favouring isCGM)
Glycemic variability: CV 3-6 months Subgroup: No insulin	76	MD 0.20 (-1.20, 1.60)	+/- 1.55	Moderate	Could not differentiate
Glycemic variability: MAGE 3-6 months	300	MD -10.43 (-23.17, 2.31)	+/- 9.71	Very low	Could not differentiate
Glycemic variability: MAGE 3-6 months Subgroup: On insulin	224	MD -4.00 (-10.47, 2.47)	+/- 11.65	Moderate	No meaningful difference
Glycemic variability: MAGE 3-6 months Subgroup: No insulin	**76**	**MD -17.00 (-24.00, -10.00)**	**+/- 7.76**	**High**	**Effect (Favouring isCGM)**
Serious adverse events 3-6 months	324	RR 0.69 (0.35, 1.36)	0.80 , 1.25	Very low	Could not differentiate
Severe hypoglycemia 3-6 months	224	RR 1.51 (0.16, 14.27)	0.80 , 1.25	Very low	Could not differentiate
Hypoglycemia events 3-6 months	324	RR 0.85 (0.36, 1.98)	0.80 , 1.25	Very low	Could not differentiate
Device related AEs 3-6 months	100	RR 7.29 (0.93, 57.07)	0.80 , 1.25	Moderate	Could not differentiate
DKA 3-6 months	224	RR 0.00 (0.00, 0.00)	0.80 , 1.25	Moderate	Not estimable
Hyposmolar hypoglycemic state 3-6 months	224	RR 0.00 (0.00, 0.00)	0.80 , 1.25	Moderate	Not estimable
DTSQ - Total score 3-6 months	**300**	**MD 3.70 (2.57, 4.83)**	**+/- 2.41**	**Moderate**	**Effect (Favouring isCGM)**
DQOL - 3-6 months	224	MD -0.20 (-0.34, -0.06)	+/- 0.26	Low	Effect less than MID (Favouring SMBG)
Self-rating anxiety scale <=3 months	**80**	**MD -6.18 (-8.89, -3.47)**	**+/- 3.11**	**Low**	**Effect (Favouring isCGM)**
Self-rating depression scale <=3 months	**80**	**MD -6.24 (-8.88, -3.60)**	**+/- 3.02**	**Low**	**Effect (Favouring isCGM)**
General comfort questionairre <=3 months	**80**	**MD 10.61 (6.94, 14.28)**	**+/- 3.98**	**Low**	**Effect (Favouring isCGM)**

Outcome	Sample size	Effect estimate	MIDs	Quality	Interpretation of effect
Pittsburgh Sleep Quality Index <=3 months	80	MD -2.17 (-3.26, -1.08)	+/- 1.25	Very low	Effect (Favouring isCGM)
WHOQoLBREF - physiology <=3 months	80	MD 6.56 (3.95, 9.17)	+/- 2.96	Low	Effect (Favouring isCGM)
WHOQoLBREF - psychology <=3 months	80	MD 6.30 (3.78, 8.82)	+/- 2.86	Low	Effect (Favouring isCGM)
WHOQoLBREF - environment <=3 months	80	MD 5.87 (3.62, 8.12)	+/- 2.54	Low	Effect (Favouring isCGM)
WHOQoLBREF - social relations <=3 months	80	MD 7.27 (4.92, 9.62)	+/- 2.62	Low	Effect (Favouring isCGM)

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) rtCGM; 2) isCGM; 3) intermittent capillary blood glucose monitoring. Only one UK study was included in this evidence review in full as the most relevant evidence for people with type 2 diabetes in the UK. 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

Healthcare Improvement Scotland (2018) assessed the Freestyle Libre isCGM device for type 2 diabetes patients, and found this device is likely to be cost effective compared with self-monitoring of blood glucose (SMBG).

Table 7: Summary of economic evidence

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 the T2DM population are reported 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 isCGM Comparator: self-monitoring of blood glucose (SMBG)	NHS Lifetime	Base case: 1) Restricted analysis: ICER=£18,125/QALY for T2DM 2) Full analysis: ICER=£4,498/QALY for T2DM 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

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 2 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 2 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:

- rtCGM
- isCGM
- self-monitoring of blood glucose

Analyses of rtCGM versus self-monitoring of blood glucose, and isCGM versus self-monitoring of blood glucose 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 2 diabetes patients were defined using patient demographics, racial characteristics, baseline risk factors, and baseline complications to reflect an adult type 2 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

The base case results showed that isCGM was cost-effective compared with SMBG at a threshold of £20,000 per QALY, while rtCGM was not cost-effective even if we increased the threshold to £30,000 per QALY.

Table 8: Base-case deterministic cost–utility results

Treatments	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (vs SMBG)
SMBG	16,364	7.489			
rtCGM	34,424	7.887	18,078	0.398	45,479
isCGM	22,015	7.957	5,669	0.468	12,109

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 were important for measuring a person's blood sugar levels over time. HbA1c is limited as a specific outcome to define the effectiveness of a monitoring technique by it reflecting the previous 3 months of therapy, whereas time in range is a measurement over a shorter time period. The committee considered time in range to be a better measure than HbA1c as it captures variation over time and can be used to highlight hypoglycaemia and hyperglycaemia, whereas HbA1c gives an average value and does not indicate how often hypoglycaemia or hyperglycaemia occurs. The committee thought that time in range was an important measure when assessing the clinical effectiveness of CGM interventions. However, while there was evidence for both HbA1c and time in range for comparisons between isCGM and SMBG, there was no evidence for time in range for comparisons between rtCGM and SMBG.

Hypoglycaemia events, severe hypoglycaemia events, and nocturnal hypoglycaemia were also considered to be important outcomes. These are often highlighted by people living with type 2 diabetes as key due to the fear these events generate and the impact they can have on quality of life (e.g. 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. Outcomes relating to hypoglycaemic events and quality of life were therefore both considered important. Evidence was available for all of these outcomes for comparisons between isCGM and SMBG, but only severe hypoglycaemic events were reported for comparisons between rtCGM and SMBG.

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

The quality of the evidence

Real time CGM (rtCGM) vs self-monitoring of blood glucose (SMBG)

Ten studies examined the use of rtCGM in comparison to SMBG. Outcomes ranged from high to very low quality and the quality of some of the evidence for these outcomes was downgraded for indirectness because it came from studies that were partially applicable to the review question. Reasons for studies being judged as partially applicable included not all people in the study being given insulin and some including people with type 1, as well as those with type 2 diabetes, in the study. Some studies also provided limited information about their inclusion criteria, making it difficult to establish what specific population was included in the study. This is potentially important, as people who have had type 2 diabetes for a long period of time often present with similar characteristics to those with type 1 diabetes. The effects of rtCGM may therefore differ depending on how long the participants in each study have had type 2 diabetes. However, with limited information about study inclusion criteria it is difficult to determine whether this affected the results. The effectiveness of rtCGM may also vary between people who use insulin and those who do not. These differences in populations may have led to the high levels of heterogeneity that were seen between studies for many of the outcomes. This led to wide confidence intervals for many of the pooled estimates, resulting in uncertainty about the effects of rtCGM.

Studies which compared rtCGM to SMBG were published between 2008 and 2020. The committee discussed how even some of the most recently published studies could be considered out of date due to recent, rapid advances in the technology used for CGM. Advances include improvements in the sensors that are used and people no longer needing to calibrate the equipment. As a result, the committee took the evidence into consideration, but also used their clinical knowledge and experience when deciding on recommendations.

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.

Intermittently scanned CGM (isCGM) vs self-monitoring of blood glucose (SMBG)

Only 3 studies compared the use of isCGM and SMBG. Although there were few studies, they reported on a number of the outcomes stated in the protocol and one had a larger sample size than any of the studies for rtCGM. Outcomes ranged from high to very low quality and all studies were directly applicable to the review question. One study (Wada 2020) included a different population to the other studies, stating that participants were not currently using insulin. Similar issues were raised to the rtCGM comparisons, where the age of the studies meant that they may no longer reflect very recent advances in CGM technology. This was thought to be particularly important for isCGM, which the committee noted had advanced even within a few months prior to this review. Combining the evidence with the committee's knowledge and experience was therefore important when discussing recommendations for this intervention. isCGM was also included within the research recommendation to investigate the effectiveness of CGM devices using real-world data. This

will provide evidence to help determine how effective the newest versions of CGM devices are for people with type 2 diabetes.

Overall summary

For both rtCGM and isCGM, the contrasting results between the studies which included people who used insulin, and those who did not, impacted on many of the pooled estimates. Many of the pooled estimates had wide confidence intervals which could not differentiate between the intervention and control arms. As a result, the committee considered the effects of CGM separately, based on whether people do or do not use insulin.

Benefits and harms

The committee discussed how CGM could potentially be useful for many people with type 2 diabetes. It was noted that for many of the outcomes, the evidence suggested that there was a difference in the effectiveness of using CGM depending on whether or not participants were using insulin. In addition, where the evidence favoured either isCGM or SMBG, many of the statistical outcomes were less than the minimally important differences (MIDs), suggesting that there were limited effects of the different types of glucose monitoring. Where there was a difference, the greater effect for CGM than SMBG was often seen up to 3 months, but beyond 3 months the evidence could not differentiate between the different monitoring techniques. However, the committee highlighted that, in their experience, in current practice there are people with type 2 diabetes who use isCGM and have good outcomes, including those who use insulin and those who do not. The committee thought that the difference between the evidence and their experience was likely due to the age of some of the studies and the rapid advancements in technology which means that most of the studies do not reflect the most recent versions of CGM devices. As such, they based most of their decisions about the benefits of isCGM for people with type 2 diabetes on their clinical knowledge and experience. It was also noted that while many of the clinical outcomes did not greatly favour the use of CGM, outcomes relating to quality of life and anxiety showed improvements with CGM, particularly for isCGM.

Although the committee were confident that people who have type 2 diabetes can benefit from the use of isCGM, they were aware that with the large number of people who have type 2 diabetes, a recommendation offering everyone the use of CGM would result in high costs to the NHS. As a result, the committee discussed who is likely to gain the most benefit from its use. In addition, isCGM appeared to be more cost-effective than rtCGM and so, with no evidence that rtCGM is more effective than isCGM for people with type 2 diabetes, it was decided that isCGM should be offered more widely than rtCGM.

The committee decided that recommendations should be aimed at people who use insulin to manage their diabetes, particularly those who use multiple daily insulin injections. Although CGM can also provide useful information for people who do not use insulin, this group may not receive as much benefit as those who do. For instance, while people would be aware that they have a spike in blood glucose, they would not be able to respond to the information in the same way as people who use insulin. One of the groups expected to benefit the most from CGM are people who have recurrent or severe hypoglycaemia. Hypoglycaemic events were raised as one of the most important and concerning outcomes for people who have type 2 diabetes, and so the potential to reduce these events is crucial. The evidence showed reductions in nocturnal hypoglycaemic events and nocturnal time spent in hypoglycaemia with isCGM, although it only showed small reductions in the number of total hypoglycaemic events, with effects less than the MIDs. However, in the committee's experience, advances in isCGM technology that have taken place since the evidence was published mean that the use of isCGM is a good way to monitor and reduce the number of hypoglycaemic events. Recurrent or severe hypoglycaemia was considered a better indicator of someone who will benefit from isCGM than specific HbA1c target values, as target values can vary between different people. Whereas number of hypoglycaemic episodes reflects individual variability of

HbA1c. In addition, the evidence suggested that isCGM had minimal effects on HbA1c values. The evidence also showed that the use of isCGM can reduce the number of hyperglycaemic episodes in comparison to self-monitoring. However, the committee thought that hypoglycaemic events are the more concerning outcome for people with type 2 diabetes, and so they decided that it was most important to highlight these in the recommendations.

In the committee's experience, isCGM is an effective method for people with impaired hypoglycaemic awareness to monitor their blood glucose levels, and so this group were also listed as people who should be offered isCGM. Although no evidence was identified for this specific group, the committee thought that it was important to include people with impaired hypoglycaemic awareness in the recommendations because of the potential serious effects of hypoglycaemic episodes. isCGM will make it easier for these people to monitor their blood glucose levels, potentially reducing their time spent in hypoglycaemia. The committee also recommended that isCGM should be offered to people who cannot self-monitor their blood glucose levels, such as those with a physical or cognitive impairment. There was no specific evidence for this group but the committee thought that by giving this group of people access to isCGM, they will no longer have to rely on others to monitor their diabetes, potentially increasing their independence. An additional group who were named as people who should be offered isCGM are people who are advised to self-test (SMBG) over 8 times per day. This aligns with the funding requirements for the NHS England National Arrangements of Funding for Flash Glucose Monitoring which states that people must agree to scan their glucose levels no less than 8 times per day when using isCGM for funding to be obtained. Therefore, although isCGM will still require people to monitor their blood glucose levels multiple times per day, using isCGM rather than self-testing will reduce the amount of time that this takes.

The committee decided to recommend that either isCGM should also be offered to people who need help from a carer or other healthcare professional to monitor their blood glucose levels, even if they only use once-daily insulin injections. The use of isCGM should enable carers to help people record their blood glucose levels more quickly than if self-monitoring is used. In addition, where people have multiple nurse or health visitors per day, blood glucose levels can be recorded at each visit. This should help to provide sufficient, reliable, recordings against which a person's insulin schedule can be adjusted. This will help healthcare professionals to develop a treatment plan to ensure that the person is given insulin at the most effective times, reducing the risk of hypoglycaemic events between home visits.

In addition to recommending who should be offered isCGM, the committee also thought it was important to highlight that it should be provided by a team who have expertise in its use. There can be many benefits to isCGM, but the committee noted that the use of the technology itself is not sufficient to ensure it is effective. Healthcare professionals must also have the skills to interpret and communicate the data effectively, understanding the importance of information such as time in range, and having the skills to discuss and explain this information with the person using isCGM.

The committee thought that the recommendations should also highlight the importance of people being given education about the use of isCGM. This will help them to understand how isCGM works and the benefits it can provide. Ensuring that people understand isCGM will increase the likelihood that they will use it correctly, such as scanning frequently and reporting the results so that no important data is missed. This will help people gain the greatest benefit from the use of this technology and be able to manage their diabetes effectively. Furthermore people using isCGM with language difficulties or learning disabilities will particularly benefit from support from their diabetes care team.

The committee discussed the practicalities of isCGM, including how it does not always need to be a permanent solution. The committee discussed how temporary, rather than permanent, use of CGM may actually be useful for some people. Using CGM for a short period of time may help people to understand when they have hypoglycaemic episodes,

thereby helping them to develop a more effective treatment plan. By developing this understanding of their blood glucose patterns, they can still benefit from CGM even if is decided that they do not want to use the monitor on a long-term basis. For other people, the use of CGM may lead to them feeling overwhelmed by the additional information it provides. By making people aware from the outset that the effectiveness of CGM will be assessed based on discussions between themselves and clinicians, mutual decisions can be made over whether to pause the use of CGM. This will avoid the risk of conflict that might be present if a clinician were to decide that the use of the device should be stopped without discussions with the person who is using the device.

In addition to isCGM being a more convenient and accessible option for monitoring blood glucose than self-monitoring, the committee discussed the time-saving benefits for the NHS. Health care professionals do not have to meet with people who have diabetes as often when isCGM is used, meaning that time is saved by people requiring fewer appointments.

Cost effectiveness and resource use

The committee noted that the published UK cost-effectiveness study (in isCGM) found it to be cost-effective compared to intermittent capillary blood glucose monitoring. They agreed it was generally well conducted analyses, with the key limitations being it was based on a single European multi-centre RCT rather than all available evidence on clinical effectiveness (clinical effectiveness data from the trial were included as part of the clinical evidence review, and 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 2 diabetes. This model uses HbA1c rather than the committee's preferred measure of time in range to predict future outcomes, in the absence of time in range data being available from the clinical review, the committee were confident this was not a substantial limitation. The modelling found that isCGM appeared to be cost-effective compared with SMBG among people with type 2 diabetes using insulin, whilst rtCGM was not cost-effective at £20,000-£30,000 per QALY. They noted that whilst the base-case did not contain any benefits on hypoglycaemia for rtCGM, even when those benefits were included (by extrapolating from the benefits found with isCGM) rtCGM was not cost-effective. The primary reasons for rtCGM being less cost-effective in type 2 diabetes than in type 1 diabetes are the lower baseline rates of hypoglycaemic events (meaning there is less potential benefit, even if the same proportional reduction in events were to be found) and the lack of evidence on fear of hypoglycaemia in type 2 diabetes. However, the committee also acknowledged the uncertainty around the cost-effectiveness results for isCGM since the clinical inputs for hypoglycaemic events were based on only one single published study.

The committee recognised the fact that all the clinical evidence used to population the model for isCGM was drawn from people who were on insulin treatments, and there was considerably less relevant clinical data available on people not using insulin, and therefore agreed it was important to restrict the recommendation to that population (as it would be expected this would be the most cost-effective population, as people using insulin are likely to have higher rates of hypoglycaemic events than those not on insulin). Due to the large number of people with type 2 diabetes in the UK, offering the devices to everyone will lead to a significant increase in health care cost for the NHS. In addition, people who are not on insulin treatment have less short-term control over their glucose levels, and therefore less ability to respond to the information provided by the devices. The committee therefore agreed they could not make any recommendations for people with type 2 diabetes not using insulin.

The committee noted that the key benefits of isCGM were patient preference for it as a monitoring device, and reduced rates of hypoglycaemia. They therefore agreed to focus their recommendations on people who would have the most potential to benefit. These would be

people with problematic hypoglycaemia (either due to recurrent events, severe events or impaired awareness) and people having to self-monitory frequently. The committee agreed that, given the large population of people with type 2 diabetes, it was appropriate to focus the recommendations down to these groups, rather than making a blanket recommendation to cover all people with type 2 diabetes using insulin.

The committee noted it was important to future proof the recommendations to potential changes in prices of the devices, and suggested that rtCGM should still be considered as a potential alternative to isCGM, since its acquisition cost might become lower in the future. Given that the marketplace for rtCGM is rapidly changing and there are a number of manufacturers competing in the market, they agreed it was plausible that its price will decrease and become as cheap as isCGM at some point. They agreed that if the prices were to be equivalent, they would find it unlikely that isCGM would be significantly clinically superior to rtCGM, and therefore if such circumstances were to arise it would be appropriate to consider rtCGM as an alternative to isCGM.

The recommendations on education and monitoring for people using isCGM were not expected to require substantial additional resources. This is because both education and monitoring are already recommended for all people with type 2 diabetes and would be necessary whether a person was using isCGM or not. 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 discussed whether there should be a threshold for when to consider stopping the use of isCGM. One scenario where isCGM use could be reviewed is when someone is not scanning their monitor frequently enough, or not sharing the data routinely. This was recommended in the 2015 version of the guideline for type 1 diabetes, but this was at a time when CGM was considerably more expensive than it is now. Although the committee understood the reasoning behind this recommendation, they were also aware that there is no evidence to support how frequently a monitor should be scanned, or how often the results should be reported for it to be effective. It was also noted that there may be a range of reasons why someone is not routinely using their isCGM, and this is something that they should be able to discuss with a healthcare professional, instead of one rule for everyone irrespective of their circumstances. The committee therefore decided against adding a stopping criterion to the recommendations for people with type 2 diabetes.

Although the committee were confident that CGM will be beneficial for many people, particularly those with physical or cognitive impairments, or those who rely on carers to monitor blood glucose levels, they were also aware that there are some people who may not be able to benefit from the technology. This includes people from lower socio-economic groups who 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).

The committee noted that people who have type 2 diabetes for a long time are often clinically similar to those who have type 1 diabetes, in the way they respond to insulin treatment. The amount of insulin that people with long-standing type 2 diabetes produce tends to decrease over time, and so they use insulin to control their blood glucose levels in the same way as people with type 1 diabetes. Given that people with type 1 diabetes are able to access isCGM, the committee considered it was important that people who have type 2 diabetes and use insulin are also offered access to isCGM. The similarities between these populations means that people with type 2 diabetes who use insulin should experience similar benefits from isCGM as those who have type 1 diabetes.

Recommendations supported by this evidence review

This evidence review supports the updated recommendations 1.6.17 to 1.6.22 and the research recommendation for the effectiveness of CGM devices for people with type 2 diabetes (see Appendix L).

1.1.10 References – included studies

1.1.10.1 Effectiveness *(systematic reviews in italics)*

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Taylor, P J, Thompson, C H, Luscombe-Marsh, N D et al. (2019) Tolerability and acceptability of real-time continuous glucose monitoring and its impact on diabetes management behaviours in individuals with Type 2 Diabetes - A pilot study. Diabetes research and clinical practice 155: 107814

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Wang, Jinxia (2021) Role of Flash Glucose Monitoring System Combined with Insulin Pump in Blood Glucose Treatment of Patients with Type 2 Diabetes Mellitus. Indian Journal of Pharmaceutical Sciences 83: 102-105

Yoo, H J, An, H G, Park, S Y et al. (2008) Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes research and clinical practice 82(1): 73-9

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.

Appendices

Appendix A – Review protocols

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

ID	Field	Content	Developer comments (delete before publication)	QA comments (delete before publication)
0.	PROSPERO registration number	1. [Complete this section with the PROSPERO registration number once allocated]		
1.	Review title	Glucose monitoring in adults with type 2 diabetes		
2.	Review question	***Guideline:*** Type 2 diabetes in adults: management (NG28) ***Question***: In adults with type 2 diabetes prescribed insulin, what is the most effective method of glucose monitoring to improve glycaemic control: • continuous glucose monitoring • flash glucose monitoring • intermittent capillary blood glucose monitoring?	It may be worth noting that the intervention of glucose monitoring alone does not change the glycaemic control. It is a combination of the data provided by the glucose monitoring method and the ability to act on that data or the decision that is made as a result	

3.	Objective	To determine the clinical and cost effectiveness of different glucose monitoring methods in improving glycaemic control in adults with type 2 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 2 diabetes in adults.		
6.	Population	Adults with type 2 diabetes Adult is defined as aged 18 years and above.	**Note**: An adult with type 2 diabetes can also be defined as aged 19 years and above if paediatric best practice tariff definitions are applied. 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. The committee also highlighted that it was important to look at the use of CGM in women with T2DM who are pregnant or planning a pregnancy as well as in children with T2DM. These populations are not covered as part of this guideline update.	
7.	Intervention	• Continuous glucose monitoring	The committee highlighted that continuous glucose monitoring and	

		• 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	flash glucose monitoring examine interstitial fluid and not blood glucose levels; therefore, question is incorrect. Secondly, they highlighted that term glycaemic control is a better term than diabetic control. Further committee comments: The committee were further consulted about the definitions of the different glucose monitoring devices. The committee highlighted that with continuous GM it was important to highlight that data can be downloaded to smart phones and that all continuous GMs allow users to set alerts. The committee highlighted that in some articles flash glucose monitoring may be referred to as intermittently scanned CGM. Also, smart phones can also be used as display devices. The committee also noted that there are alternate sites for blood testing.	

		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.	Review protocol from the previous update highlighted that comparison groups should be on similar insulin regimens as the treatment group. Committee agreed with this, however noted that in most RCTs regimens should be the same.	

9.	Types of study to be included	• RCTs • Systematic review of RCTs • If insufficient[1] RCT evidence is identified for individual comparisons, prospective cohort studies ○ If no comparative prospective observational 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.	The review protocol from the previous update specified that only studies that randomised individual patients would be included. Question was raised about the inclusion of cluster trials and committee agreed that they were not aware of specific cluster trials and therefore we did not need to specify the exclusion of such studies. The review protocol from the previous update stated that that evidence from non-randomised, non-comparative and observational studies would be considered if there was no/ insufficient RCT evidence. Question was also raised about the inclusion of observational studies. The committee noted that there is good observational data however there is likely to be enough RCT evidence for this question. Further comments: General view among committee was that observational studies should be examined if there is insufficient evidence. Insufficient can be judged as a lack of quantity of evidence. Quality of studies is covered by the tiered system of study design and	

			study quality of outcomes that form part of evidence review. Quantity will be main factor here but unwise to specify a number at this stage. Cannot stratify at intervention level as only looking at comparative evidence. Won't be pooling two different study types that vary by intervention. To extrapolate from that, unlikely then to include observational studies just because they have a single outcome not reported in RCT evidence, RCT outcome evidence will be of such a higher quality to render observational evidence of less use.	
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 children o ≤50% of people are aged >18 years	Committee agreed with the exclusion criteria applied in the previous update. During the development of the framework with early members, retrospective glucose monitoring was removed. Further discussions with the committee highlighted that retrospective (blinded) monitoring should be excluded as this is not used in practice and is predominantly used in research.	

		• 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:
		  ○ data has not been reported for the subgroup of type 1 diabetes patients, in which case this subgroup data will be used OR,
		  ○ the population contains ≤70% of type 1 diabetes patients
		• Non-English language studies
		• Conference abstracts
		• Studies which examine retrospective (blinded) glucose monitoring
			May need more definition on rare forms of diabetes but cystic fibrosis will fall into that.	

11.	Context	This review is part of an update of the NICE guideline on Type 2 diabetes in adults: diagnosis and management (NG28). https://www.nice.org.uk/guidance/ng28 This update		

		covers continuous glucose monitoring in adults with type 2 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
		
		• Mortality
		
		• Diabetic ketoacidosis
			Time in range: percentage of readings in the range of 70-180 mg/L (3.9-10.0 mmol/L) per unit of time. This can be expressed as the percentage of CGM readings or average hours and minutes spent.
			
			The same range applies for older and or high-risk individuals (those with higher risk of complications, comorbid conditions e.g., cognitive deficits, renal disease, joint disease, osteoporosis, fracture, and/or cardiovascular disease, and those requiring assisted care)
			
			Source: Clinical Targets For Continuous Glucose Monitoring Data Interpretation: Recommendations From The International Consensus Of Time In Range
			
			Hypoglycaemia: A hypoglycaemic event can be defined as CGM readings below the threshold	

		• Glycaemic variability • Change in BMI/ weight • Heart failure • % of data captured	(defined below) for at least 15 minutes: • (Level 1) a hypoglycaemic alert glucose value of < 70 – 54 mg/dL (3.9 -3.0 mmol/L). • (Level 2) A glucose concentration <54 mg/dL (3.0 mmol/L) with or without symptoms. This should be considered clinically significant hypoglycaemia requiring immediate action. **Severe hypoglycaemia:** (Level 3) Severe event characterised by cognitive impairment requiring external assistance for recovery. Source: *International Consensus On Use Of Continuous Glucose Monitoring* **Time in hypoglycaemia:** Percentage of readings and time per day below target glucose range 54-69 mg/dL (Level 1) or < 54 mg/dL (Level 2). A range of <70 mg/dL (<3.9 mmol/ L) applies for older and or high-risk individuals (those with higher risk of complications, comorbid conditions e.g. cognitive deficits, renal disease, joint disease, osteoporosis, fracture,	

			and/or cardiovascular disease, and those requiring assisted care) Source: *Clinical Targets For Continuous Glucose Monitoring Data Interpretation: Recommendations From The International Consensus Of Time In Range* **Glycaemic variability:** Process characterised by the amplitude, frequency, and duration of the fluctuations in blood glucose levels. Outcome can be expressed as standard deviation, coefficient of variation (CV) and mean amplitude of glucose excursions. Standard glucose levels: CV <36% Unstable glucose levels: CV ≥ 36% Source: *International Consensus On Use Of Continuous Glucose Monitoring*	
13.	Secondary outcomes (important outcomes)	• Other adverse events (dichotomous) limited to: ○ Diabetes related hospitalisation ○ malfunction of CGM monitor ○ hypersmolar hyperglycaemic state (HHS)	Definitions of AEs match T1 protocol, apart from: HHS	

		○ serious adverse events • Mental health outcomes: ○ Diabetes distress (including fear of hypoglycaemia and diabetes burnout) ○ Diabetes related depression ○ Body image issues due to diabetes ○ 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))	Will include all evidence that looks at these outcomes and assess the applicability of these studies against the definitions they have used. **Hyperosmolar hyperglycaemic state**: A metabolic complication of diabetes mellitus characterized by severe hyperglycemia, extreme dehydration, hyperosmolar plasma, and altered consciousness. Blood glucose levels are often over 40 mmol/L) . Sources: Diabetes UK, MSD Manual **Diabetes distress:** Same definition as the one used in T1DM protocol. Source: *Diabetes UK* **Diabetes burnout:** Same definition as the one used in T1DM protocol. Source: *Diabetes UK*	
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 committee also wanted to retain the other factors identified for subgroup analysis. Retrospective CGM was also discussed with the committee. The committee highlighted that there was a difference between blinded retrospective CGM and retrospective CGM. In retrospective CGM, data is collected continuously and can be analysed in real-time or older data can be viewed.	

		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)	Further comments: Committee noted that all CGMs are real time and retrospective. Committee also noted that by duration of diabetes they were referring to was long duration of diabetes.	
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery		

		☐ Other (please specify)				
19.	Language	English				
20.	Country	England				
21.	Anticipated or actual start date	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 2 diabetes, glycaemic control		
33.	Details of existing review	None		

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

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Appendix B – Methods

Priority screening

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

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

Evidence of effectiveness of interventions

Quality assessment

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

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

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

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

Methods for combining intervention evidence

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

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

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

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

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

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

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

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

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

Minimal clinically important differences (MIDs)

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

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

MIDs found through this process and used to assess imprecision in the guideline are given in Table 9. For other continuous outcomes not specified in the table below, no MID was defined.

Table 9: Identified MIDs

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

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For dichotomous outcomes, such as relative risks where no other MID was available, default MIDS of 0.8,1.25 were used.

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

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from randomised controlled trials, non-randomised controlled trials and cohort studies were initially rated as high quality while data from other study types were originally rated as low quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 10.

Table 10: Rationale for downgrading quality of evidence for intervention studies

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

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

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

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

Appendix C – Literature search strategies

Clinical 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

1

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,kw	19
#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

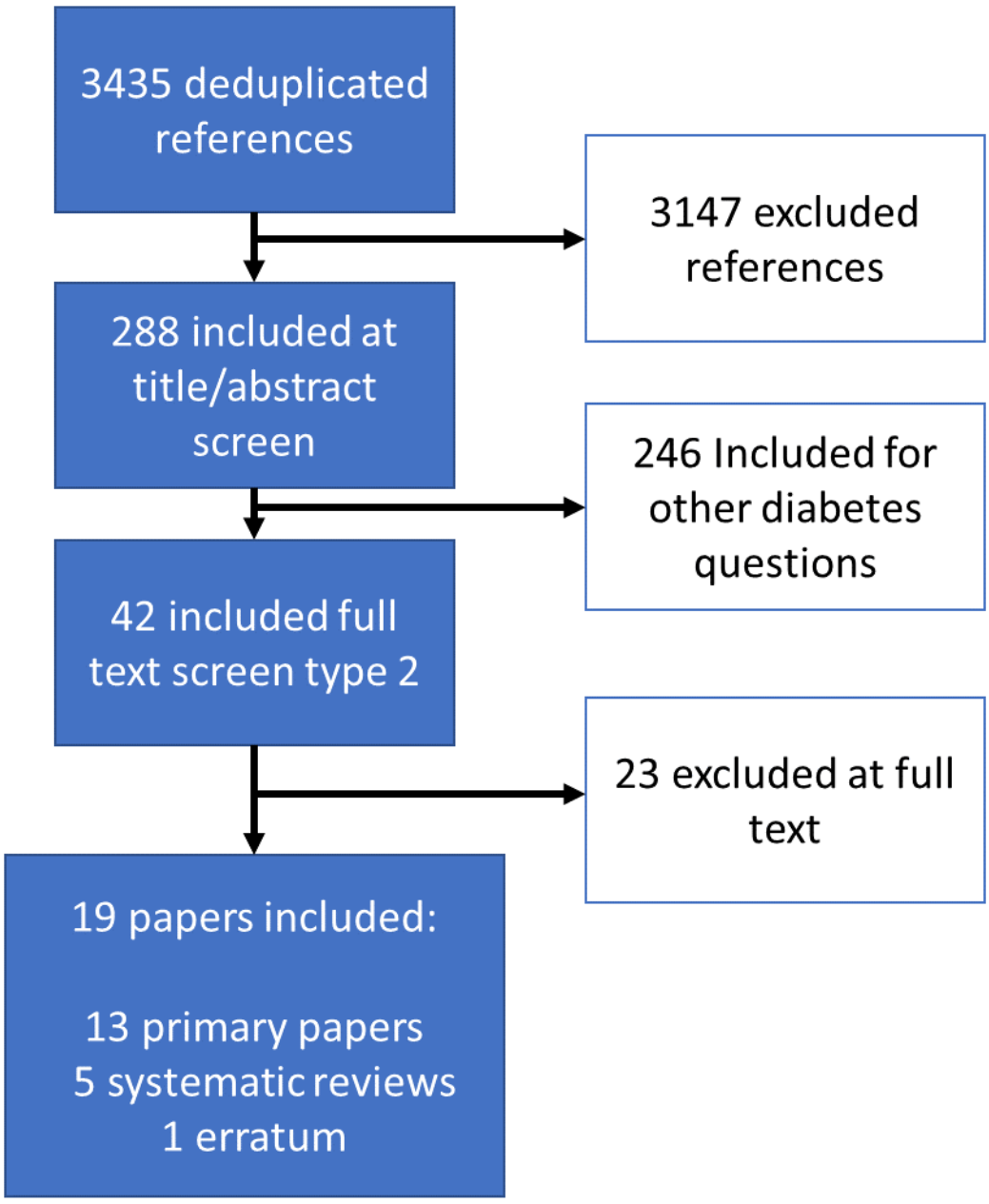
	7	(((dm2 or t2d* or mody or niddm)))	83
	8	(((DM near4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II))))	4
	9	((DM near4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)))	0
	10	(((DM near4 onset* near4 (maturit* or adult* or slow*))))	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



Appendix E – Evidence tables for included studies

Ajjan, 2019

Bibliographic Reference	Ajjan, Ramzi A; Jackson, Neil; Thomson, Scott A; Reduction in HbA1c using professional flash glucose monitoring in insulin-treated type 2 diabetes patients managed in primary and secondary care settings: A pilot, multicentre, randomised controlled trial.; Diabetes & vascular disease research; 2019; vol. 16 (no. 4); 385-395

Study details

Trial registration number and/or trial name	NCT01713348
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	9 UK hospitals
Study dates	October 2012 - May 2013
Sources of funding	Abbott Diabetes Care
Inclusion criteria	People with T2D Age >18 Duration of diabetes MDI at least 6 months prior HbA1c

	7.5 - 12 % Can us RtCGM device
Exclusion criteria	Previous CGM use within 6 months of study Comorbidity Coronary heart disease, CF, serious psychiatric disorder, uncontrolled chronic condition Pregnancy PRegnant or planning to be Insulin treatment CSII/ basal insulin only In another CGM study
Outcome measures	HBA1C internal arm only no comparative Time above below target glucose range < 3.9 > 10.0
Number of participants	45

Type of insulin delivery system	MDI
Duration of follow-up	
Loss to follow-up	0
Additional comments	TIR internal comparison no 2 arm data

Study arms

rtCGM (N = 30)

Freestyle navigator - The intervention group used unmasked FSN with the low, high and projected alarms switched off (data loss and calibration alarms were still active). Patients were instructed to leave the alarms turned off for the duration of the study to avoid interference, and to better understand the effect of reviewing glucose profile on hyper- and hypoglycaemia. Patients in both groups were allowed to make changes to their insulin doses using their existing diabetes knowledge. Study-related adjustments to insulin doses were made on days 30 and 45 only in the presence of the health care practitioner (HCP) who reviewed the glucose data with the patient.

SMBG (N = 15)

The control group managed their BG with standard SMBG (FreeStyle Freedom Lite; Abbott Diabetes Care Ltd, Witney, UK) and used another masked FSN for the final 15-day period of the study

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes

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 *(CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)*
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

Beck, 2017

Bibliographic Reference	Beck, Roy W; Riddlesworth, Tonya D; Ruedy, Katrina; Ahmann, Andrew; Haller, Stacie; Kruger, Davida; McGill, Janet B; Polonsky, William; Price, David; Aronoff, Stephen; Aronson, Ronnie; Toschi, Elena; Kollman, Craig; Bergenstal, Richard; DIAMOND Study, Group; Continuous Glucose Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections: A Randomized Trial.; Annals of internal medicine; 2017; vol. 167 (no. 6); 365-374

1 ## Study details

Trial registration number and/or trial name	NCT02282397
Study type	Randomised controlled trial (RCT)
Study location	North america (US and Canada)
Study setting	25 endocrinology practices (22 US, 3 Canada 19 community based, 6 academic centres
Sources of funding	DEXCOM funded - dexcom employee on steering committee
Inclusion criteria	People with T2D Age >25 Insulin treatment Treated with MDI for at least 1 year + Stable diabetes medication for prior 3 motnhs HbA1c 7/5% - 10% BG testing Averaging more than 2 times a day Glomerular filtration weight >45 mL/min/1.73m2
Intervention(s)	

Outcome measures	HBA1C change in % proportion below 7/7.5% relative reduction of 10% absoloute reduction of 1% 1% reduction in HbA1c <7% cases Time in range 70 to 180 mg/dL Time above below target glucose range <70, <60, <50 mg/dL >180, >250, > 300 mg/dL Glycemic variability coefficient of variation Awareness of hypoglycemia clarke

	QoL (validated tools) EuroQoL-5D, WHO wellbeing index HFS, DDS, Hypoglycemic confidence scale CGM satisfaction scale
Number of participants	158
Type of insulin delivery system	MDI
SMBG checks per day	4 minimum
CGM use per day	
Duration of follow-up	24 weeks
Methods of analysis	
Additional comments	USe of blinded cgm device 2 weeks all participants before randomisation control group had blinded CGM 85% CGM wear required for eligibility + 2 calibration / day (10 did not) insulin adjustments not prescriptive in protocol but made at clinician discretion at clinical sites

Study arms

rtCGM (N = 79)

Dexcom G4

SMBG (N = 79)

Asked to monitor bg at least 4 times daily

Characteristics

Arm-level characteristics

Characteristic	rtCGM (N = 79)	SMBG (N = 79)
% Female (%) Nominal	62	51
Mean age (SD) Mean (SD)	60 (11)	60 (9)
BMI Mean (SD)	35 (8)	37 (7)
Time since diabetes diagnosis Median (IQR)	17 (11 to 23)	18 (12 to 23)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Probably yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
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	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
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 (CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)
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

Cox, 2020

Bibliographic Reference	Cox, Daniel J.; Banton, Tom; Moncrief, Matthew; Diamond, Anne; Conaway, Mark; McCall, Anthony L.; Minimizing glucose excursions (GEM) with continuous glucose monitoring in type 2 diabetes: A randomized clinical trial; Journal of the Endocrine Society; 2020; vol. 4 (no. 11)

1 Study details

Trial registration number and/or trial name	NCT03207893
Study type	Randomised controlled trial (RCT)
Study location	Virginia, USA
Study setting	University of virginia hospital
Study dates	July 2018 - January 2020
Sources of funding	This work was supported by Dexcom, Inc (Grant IIS-2017-047 for equipment and financial support) and the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (Grant DK108957). The funding sources were not involved in the design or conduct of the study, nor in the preparation of this manuscript.
Inclusion criteria	People with T2D Age 30 - 80 Duration of diabetes <11 years

	Insulin treatment None HbA1c >= 7% able to walk for 30 mins
Exclusion criteria	Insulin treatment Any insulin treatment or
Intervention(s)	or nondiabetic medications that could affect BG control (eg, prednisone)
Outcome measures	HBA1C QoL (validated tools) WHOQoL
Number of participants	30
Additional comments	The following week participants wore a blinded activity monitor (Fitbit Charge 2), and were interviewed over the telephone on 2 workdays and 1 weekend day to complete the automated

	self-administered 24-hour dietary recall dietary recall [14]. Ten RC and 12 GEMCGM participants also wore a blinded CGM (Dexcom Platinum G4). This assessment was repeated a second time 5 months later—3 months after the conclusion of GEMCGM. Also involved coaching and work sessions so not purely CGM treatment.

Study arms

rtCGM (N = 20)

The 2-month GEMCGM intervention period involved meeting in groups of 8 to 10 for 90 minutes on 4 occasions, with 1 week between sessions 1 and 2 and 3 weeks between sessions 2 and 3 and 3 and 4 (Fig. 1). At each session, participants were given a 7-day Dexcom G5 sensor, and 1 month after session 4, a fifth sensor was given. This timing was intended to diminish reliance on CGM and group support and to encourage autonomy following the conclusion of the intervention. Follow-up assessment occurred three months after session 4.

SMBG (N = 10)

All participants continued their usual care in consultation with their treating physician, who adjusted medication as clinically indicated throughout the 5-month study

Characteristics

Arm-level characteristics

Characteristic	rtCGM (N = 20)	SMBG (N = 10)
% Female Nominal	50	80
Mean age (SD) Mean (SD)	54.6 (12.2)	50.8 (14.2)
BMI Mean (SD)	35.6 (8.4)	35.6 (8.4)
Time since diabetes diagnosis Mean (SD)	5.4 (2.7)	5.9 (2.5)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

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

Section	Question	Answer
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 (CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)
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 *(Question marks over lack of insulin use)*

Ehrhardt, 2011

Bibliographic Reference	Ehrhardt, Nicole M; Chellappa, Mary; Walker, M Susan; Fonda, Stephanie J; Vigersky, Robert A; The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus.; Journal of diabetes science and technology; 2011; vol. 5 (no. 3); 668-75

Study details

Other publications associated with this study included in review	Vigersky 2012

Trial registration number and/or trial name	Walter reed medical centre trial
Study type	Randomised controlled trial (RCT)
Study location	Washington DC, USA
Study setting	Army medical centre
Study dates	NR
Sources of funding	DexCom, Inc. provided financial and in-kind support for this investigator-initiated study.
Inclusion criteria	People with T2D military care beneficiaries Age >18 Duration of diabetes >=3 months Insulin treatment All therapies except prandial insulin, including basal insulin HbA1c >= 7% but <12%

	BG testing 4 times daily
Exclusion criteria	Comorbidity glucocorticoids, amphetamines, anabolic, or weightreducing medications Pregnancy pregnant or lactating or attempting pregnancy
Outcome measures	HBA1C Time in range 70-180 Time above below target glucose range % time <50mg/dl <70mg/dl >180mg/dl >240 mg/dl

	% of CGM data captured QoL (validated tools) Paid, SUS SMBG frequency rtcgm 2.9 SMBG 2.4
Number of participants	100
Type of insulin delivery system	Other Diet and excercise only C: 4/50 I: 3/50 oral medications only C: 27/50 I: 24/50 oral medications/byetta C: 5/50 I: 4/50 basal insulin alone or in combo C: 14/50 I: 19/50
Duration of follow-up	12 weeks/12 months
Loss to follow-up	

Additional comments	Check whether blinded CGM was used in control arm: Don't think it was so unsure how TIR etc. can be relied on...

Study arms

rtCGM (N = 50)

Dexcom SEVEN

SMBG (N = 50)

perform SMBG before each meal and at bedtime. They were provided with and instructed in the use of the AccuChek® Aviva glucometer (Roche Diagnostics Corp., Indianapolis, IN)

Characteristics

Arm-level characteristics

Characteristic	rtCGM (N = 50)	SMBG (N = 50)
% Female (n (%)) Nominal	33	22
Mean age (SD) Mean (SD)	55.5 (9.6)	60 (11.9)
BMI Mean (SD)	31.9 (5.8)	32.7 (7.7)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Very little info on randomisation)*
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	Some concerns *(Some concerns for TIR outcomes as not based on masked CGM readings in SMBG arm but SMBG readings.)*
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 *(Very little information on randomisation, for range of glucose outcomes no masked CGM counterpart in control arm.)*
Overall bias and Directness	Overall Directness	Partially applicable *(not all patients on insulin.)*

Haak, 2017

Bibliographic Reference	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; vol. 8 (no. 1); 55-73

1 **Study details**

Trial registration number and/or trial name	NCT02082184
Study type	Randomised controlled trial (RCT)
Study location	Europe
Study setting	26 European diabetes centres (MAjority UK)
Study dates	
Sources of funding	Thomas Haak reports personal fees from Abbott Diabetes Care outside the submitted work. Gerry Rayman reports personal fees from Abbott Diabetes Care outside the submitted work. He´le`ne Hanaire reports personal fees from Abbott Diabetes Care and Medtronic, and grants from Johnson and Johnson outside the submitted work. Ramzi Ajjan reports other funding from Abbott Diabetes Care during the conduct of the study

	and personal fees from Abbott Diabetes Care outside the submitted work. Norbert Hermanns reports grants and personal fees from Abbott Diabetes Care Germany, grants from Dexcom, grants and personal fees from Berlin-Chemie, grants from Ypsomed, personal fees and non-financial support from Novo Nordisk, and grants from Lilly International, outside the submitted work. Jean-Pierre Riveline reports grants outside the submitted work.
Inclusion criteria	People with T2D Age >18 Insulin treatment at least 6 months and on their current regimen (prandial only or prandial and basal intensive insulin therapy or CSII therapy) for 3 months or more HbA1c

	7.5 - 12% BG testing self-reported more than 10 a week for 2 months
Exclusion criteria	Previous CGM use within 4 months Comorbidity severe hypo requiring 3rd party assisstance, diabetic ketoacidosis, or hyperosmolar-hyperglycemic state in the preceding 6 months Insulin treatment any other insulin regimen to that described above, a total daily dose of insulin C1.75 units/kg on study entry
Intervention(s)	
Outcome measures	HBA1C mmol/mol & % Time in range 3.9 - 10 Time above below target glucose range

	< 3.9 & <3.1 & <2.5 & <2.2 Hypoglycemia < 3.9 & <3.1 & <2.5 & <2.2 Glycemic variability CV, MAGE, SD Adverse events SAE, DKA, hypersmolar QoL (validated tools) DTSQ & DQoL SMBG frequency
Number of participants	224
Type of insulin delivery system	MDI "intensive insulin therapy" insulin pen device: I: 94%, C: 95%

	insulin syringe: I: 1% C: 0% CSII I: 5%, C: 5%
SMBG checks per day	I: 3.6 +/- 1.28 C: 3.9 +/- 1.33
CGM use per day	2 weeks blinded sensor wear
Duration of follow-up	6 months
Loss to follow-up	I: 10 C: 13
Methods of analysis	
Additional comments	

Study arms

isCGM (N = 149)

Abbott Sensor Based Glucose Monitoring System

SMBG (N = 75)

Abbott Blood Glucose Monitoring System (standard blood glucose meter)

Characteristics

Arm-level characteristics

Characteristic	isCGM (N = 149)	SMBG (N = 75)
% Female Nominal	94	56
Mean age (SD) Mean (SD)	59 (9.9)	59.5 (11)
BMI Mean (SD)	33.1 (6.2)	33.3 (5.5)
Time since diabetes diagnosis Mean (SD)	17 (8)	18 (8)
HBA1C Mean (SD)	72 (10.6)	73.5 (11.3)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

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	Some concerns *(Mild concern about high rate of dropout in control group despite being half the size of int. Reasons for dropout seem unclear.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)
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 *(Mild concerns around dropout number across 2:1 arms.)*
Overall bias and Directness	Overall Directness	Directly applicable

Isaacson, 2020

Bibliographic Reference	Isaacson, Brad; Kaufusi, Stephanie; Joy, Elizabeth; Jones, Christopher; Ingram, Valerie; Mark, Nickolas; Phillips, Mike; Briesacher, Mark; Sorensen, Jeff; Demonstrating the Clinical Impact of Continuous Glucose Monitoring Within an Integrated Healthcare Delivery System; Journal of Diabetes Science and Technology; 2020

Study details

Study type	Randomised controlled trial (RCT)
Study location	Utah, USA
Study setting	Four primary care clinics
Study dates	December 2018 to May 2019
Sources of funding	The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Intermountain Ventures, a wholly owned subsidiary of Intermountain Healthcare.
Inclusion criteria	People with T2D Type 1 or Type 2 Age 18-80 HbA1c >= 6.5% BG testing
Exclusion criteria	Previous CGM use not currently using

	Pregnancy or planning to
Outcome measures	HBA1C median Hypoglycemia glycemic excursion odds (%) Glycemic variability MAGE
Duration of follow-up	
Loss to follow-up	14 (79% dropped out on assignment to control arm)
Additional comments	"The availability of real-time, continuous glucose information was educational and transformative for 70% of the CGM users" suggests not blinded! YEs they talk about diabetes self-management

Study arms

rtCGM (N = 50)

Dexcom G6

SMBG (N = 49)

Standard of care finger stick glucometer

Characteristics

Study-level characteristics

Characteristic	Study (N =)
18-24 Nominal	0
25-34 Nominal	6
35-44 Nominal	6
45-54 Nominal	13
55-64 Nominal	26
65-74 Nominal	38
75-80 Nominal	10

1 **Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Allocation clearly revealed to patients pre-randomisation)*
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 *(Non-blinding resulted in large dropout specifically control cases.)*
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 (CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)
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 *(Lack of blinding at randomization led to large control arm dropout pre randomisation creating large risk of bias.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Contains some T1 patients.)*

3
4

Tang, 2014

Bibliographic Reference	Tang, Tricia S; Digby, Erica M; Wright, Anthony M; Chan, Jeremy H M; Mazanderani, Adel B; Ross, Stuart A; Tildesley, Hamish G; Lee, Augustine M; White, Adam S; Tildesley, Hugh D; Real-time continuous glucose monitoring versus internet-based blood glucose monitoring in adults with type 2 diabetes: a study of treatment satisfaction.; Diabetes research and clinical practice; 2014; vol. 106 (no. 3); 481-6

Study details

Secondary publication of another included study- see primary study for details	Tildesley 2013
Other publications associated with this study included in review	

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

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 *(7 immediate dropouts from CGM arm not included in ITT analysis despite the fact they'd already been randomised.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Missing outcome data corresponded to desire to participate in intervention.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)
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 *(7 patients ignored in intervention arm despite the fact they dropped out based on knowledge of intervention post randomisation.)*
Overall bias and Directness	Overall Directness	Directly applicable

Taylor, 2019

Bibliographic Reference	Taylor, P J; Thompson, C H; Luscombe-Marsh, N D; Wycherley, T P; Wittert, G; Brinkworth, G D; Zajac, I; Tolerability and acceptability of real-time continuous glucose monitoring and its impact on diabetes management behaviours in individuals with Type 2 Diabetes - A pilot study.; Diabetes research and clinical practice; 2019; vol. 155; 107814

Study details

Trial registration number and/or trial name	ANZTR: 372898
Study type	Randomised controlled trial (RCT)
Study location	Adelaide, Australia

Study setting	health and nutrition research unit
Study dates	June - September 2017
Sources of funding	Grant funding was received for the delivery of the clinical trial only, by the Diabetes Australia Research Trust (DART). No funding was received for preparation or publication of this article, these were funded by the authors
Inclusion criteria	Age Adult Weight obese
Exclusion criteria	People without T1d T1D Comorbidity proteinuria (urinary albumin-to-creatinine ratio C 30 mg/mmol), abnormal liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST) or gamma-glutamyl transferase (GGT) C 2.5 times the normal upper limit], impaired renal function (eGFR \ 60 ml/min), any abnormal or significant clinical history including current

	malignancy, liver, respiratory, gastrointestinal, cardiovascular disease or pregnancy/lactation, eating disorder or clinical depression; any significant endocrinopathy (other than stable treated thyroid disease); have taken/or taking glucocorticoids (oral/inhaled or topical) within last 3 months, psychotropics other than a stable dose of a selective serotonin reuptake inhibitor; illicit drugs, medications which affect gastrointestinal motility or hunger/appetite (e.g. metoclopramide, domperidone and cisapride, anticholinergic drugs (e.g. atropine), erythromycin) or past history of gastrointestinal surgery which may affect study outcomes
Outcome measures	HBA1C QoL (validated tools) PSS
Duration of follow-up	12 weeks
Loss to follow-up	0

Additional comments	In addition to wearing the glucose monitors all participants were provided a prescriptive low carbohydrate, high protein and unsaturated fat diet (LC diet) and exercise plan incorporating moderate intensity aerobic and resistance exercises in the form of a commercial publication At week 3, participants were provided a 30-minute group-based education session on food exchanges, which informed the participant of food groups and proportions of foods that are matched for the benchmark food (i.e. 1 slice of bread can be exchanged for 3 regular sized crispbreads). A food exchange booklet, to assist participants in making informed food exchanges, to maintain the prescribed energy level and macronutrient profile was provided at visit 2

1

Study arms

rtCGM (N = 10)

All participants wore the MedtronicTM Guardian Connect device with the Harmony glucose sensor (Medtronic, Los Angeles, CA). The minimally invasive glucose sensor was inserted into subcutaneous tissue on the body (usually on the abdomen) to continuously and automatically measure interstitial glucose levels at 5-minute interviews, 24 h a day 288 glucose readings every 24 h) throughout the study. At the first insertion all participants were instructed to conduct a calibration finger-stick (capillary blood) at 2 h and again at 6 h post insertion, then 12-hourly for the duration of the sensor wear. Sensors were removed and replaced with a new sensor every 10 days.

SMBG (N = 10)

with blinded CGM

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

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

Section	Question	Answer
		(CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)
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 *(Consider fact a diet intervention was also used.)*

Tildesley, 2016

Bibliographic Reference	Tildesley, HD; Wright, AM; Chan, JHM; Mazanderani, AB; Ross, SA; Tildesley, HG; Lee, AM; Tang, TS; White, AS; A Comparison of Internet Monitoring with Continuous Glucose Monitoring in Insulin-Requiring Type 2 Diabetes Mellitus; Canadian journal of diabetes; 2016; vol. 40 (no. 1); 24-27

Study details

Other publications associated with this study included in review	Tang 2014
Study type	Randomised controlled trial (RCT)
Study location	Vancouver, Canada
Study setting	NR
Study dates	October 2010 - January 2012

Inclusion criteria	Age Insulin treatment Alone or in combination with oral antihyperglycemic agents HbA1c recent >= 7% BG testing proir training Internet access
Intervention(s)	
Outcome measures	HBA1C QoL (validated tools) DTSQ (Tang)
Number of participants	57
Type of insulin delivery system	MDI i; 5, C; 7 Other single injection I: 2, C: 6

	twice injection I: 16, C: 14
Duration of follow-up	6 months
Loss to follow-up	I: 7
Additional comments	Question marks over internet based GM as a comparator. Also Qs over 7 patients dropped out after rnaodmisation they reckon don't need to go into ITT analysis...

Study arms

rtCGM (N = 32)

Guardian REAL-Time Continuous Glucose Monitoring System (Medtronic MiniMed, Inc., Northridge, CA).

SMBG (Internet based glucose management system) (N = 25)

Patients randomized to the IBGMS group were trained by the research coordinator to upload their glucose readings every 2 weeks to a secure, commercially available website (ALR Technologies, Inc., Atlanta, GA). Glucose levels were presented in table and graph formats according to the time of day, with automatic calculations showing the mean, standard deviation and range for specific time periods. The system allowed patients to input medications, view summaries of readings and contact their endocrinologist. The endocrinologist reviewed the readings and sent feedback through the ALR messaging system.

Characteristics

Arm-level characteristics

Characteristic	rtCGM (N = 32)	SMBG (Internety based glucose management system) (N = 25)
% Female (n (%)) Nominal	9	9
Mean age (SD) Mean (SD)	58 (8.8)	59.5 (10.7)

Characteristic	rtCGM (N = 32)	SMBG (Internety based glucose management system) (N = 25)
BMI Mean (SD)	34.9 (6.9)	34.7 (5.7)
Time since diabetes diagnosis Mean (SD)	17.4 (7.9)	17 (7.1)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

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 *(7 immediate dropouts from CGM arm not included in ITT analysis despite the fact they'd already been randomised.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Missing outcome data corresponded to desire to participate in intervention.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (*CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)*

Section	Question	Answer
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 *(7 patients ignored in intervention arm despite the fact they dropped out based on knowledge of intervention post randomisation.)*
Overall bias and Directness	Overall Directness	Directly applicable

Vigersky, 2012

Bibliographic Reference	Vigersky, Robert A; Fonda, Stephanie J; Chellappa, Mary; Walker, M Susan; Ehrhardt, Nicole M; Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes.; Diabetes care; 2012; vol. 35 (no. 1); 32-8

Study details

Secondary publication of another included study- see primary study for details	Erhardt 2011

Wada, 2020

Bibliographic Reference	Wada, Eri; Kobayashi, Tomoko; Handa, Tomoko; Hayase, Ayaka; Ito, Masaaki; Furukawa, Mariko; Okuji, Takayuki; Okada, Norio; Iwama, Shintaro; Sugiyama, Mariko; Tsunekawa, Taku; Takagi, Hiroshi; Hagiwara, Daisuke; Suga, Hidetaka; Goto, Motomitsu; Onoue, Takeshi; Ito, Yoshihiro; Banno, Ryoichi; Kuwatsuka, Yachiyo; Ando, Masahiko; Arima, Hiroshi; Flash

glucose monitoring helps achieve better glycemic control than conventional self-monitoring of blood glucose in non-insulin-treated type 2 diabetes: a randomized controlled trial; BMJ open diabetes research & care; 2020; vol. 8 (no. 1)

Study details

Trial registration number and/or trial name	UMIN000026452
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	5 hospitals
Study dates	July 2017 - November 2018
Sources of funding	This study was supported by the Nagoya University Hospital Funding for Clinical Development.
Inclusion criteria	People with T2D Age >= 20 and < 70 HbA1c >= 7.5%
Exclusion criteria	Previous CGM use any Comorbidity

	dialysis, severe renal failure, preproliferative diabetic retinopathy or proliferative diabetic retinopathy Insulin treatment any Other could not properly operate the devices were judged by their physicians to be unsuitable for participation in the study.
Intervention(s)	
Outcome measures	HBA1C Time in range time in sensor glucose 70–180 mg/dL (3.9–10.0 mmol/L) Time above below target glucose range time in hypoglycemia (<70 mg/dL (3.9 mmol/L), <55 mg/dL (3.1 mmol/L) and <45 mg/dL (2.5 mmol/L)

	time in hyperglycemia >180 mg/dL (10.0 mmol/L) and >240 mg/dL (13.3 mmol/L) and >300 mg/dL (16.7 mmol/L)) Glycemic variability coefficient of variation, MAGE QoL (validated tools) DTSQ
Number of participants	100
Duration of follow-up	24 weeks
Loss to follow-up	I: 1 (disc) C: 6 (5 disc, 1 LTFU)
Additional comments	The participants in each group were instructed on how to use each device and how to adjust their diet and lifestyle based on the blood glucose levels. The target fasting and postprandial blood glucose levels were set at <130 mg/dL (7.2 mmol/L) and <180 mg/dL (10.0 mmol/L), respectively, based on the 'Japanese Clinical Practice Guideline for Diabetes'

	of the Japan Diabetes Association18 and the 'Standards of Medical Care in Diabetes' of the American Diabetes Association.19 The devices were provided for 12 weeks. Participants in the SMBG group wore a blinded sensor (Free Style Libre Pro) again for the last 2 weeks of the 12-week period.

Study arms

isCGM (N = 49)

Flash glucose monitoring Free Style Libre Pro; Abbott Diabetes Care, Alameda, California, USA

SMBG (N = 51)

SMBG device (Free Style Precision Neo; Abbott Diabetes Care).

Characteristics

Arm-level characteristics

Characteristic	isCGM (N = 49)	SMBG (N = 51)
% Female Nominal	15	17

Characteristic	isCGM (N = 49)	SMBG (N = 51)
Mean age (SD) Mean (SD)	58.1 (9.8)	58.7 (10)
BMI Mean (SD)	27.5 (6.5)	26.1 (4.1)
HbA1c (%) Mean (SD)	7.83 (0.25)	7.84 (0.27)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

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

Section	Question	Answer
		(CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)
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

Wang, 2021

Bibliographic Reference	Wang, Jinxia; Role of Flash Glucose Monitoring System Combined with Insulin Pump in Blood Glucose Treatment of Patients with Type 2 Diabetes Mellitus; Indian Journal of Pharmaceutical Sciences; 2021; vol. 83; 102-105

Study details

Other publications associated with this study included in review	
Study type	Randomised controlled trial (RCT)
Study location	Nanjing, China
Study setting	Hospital
Study dates	September 2019 to Septermber 2020
Sources of funding	NR

Inclusion criteria	People with T2D
Outcome measures	Time in range <7.0 mmol/l so technically not "in range" no hypo level Hypoglycemia event n QoL (validated tools) SAS, SDS, GCQ, PSQI, WHOQolBREF
Number of participants	80
Type of insulin delivery system	CSII 100%
SMBG checks per day	NR
CGM use per day	NR
Duration of follow-up	2 weeks
Loss to follow-up	0
Methods of analysis	Unclear often
Additional comments	Suspicious of reporting and inclusion criteria in this paper or lack thereof

1

Study arms

isCGM (N = 40)

Freestyle Libre Flash Glucose Monitoring System (Abbott Laboratories, USA)

SMBG (N = 40)

blood glucose was detected through collection of fingertip blood for multiple times in control group

Characteristics

Arm-level characteristics

Characteristic	isCGM (N = 40)	SMBG (N = 40)
% Female (n (%)) Nominal	18	19
Mean age (SD) Mean (SD)	71.68 (9.32)	71.43 (9.14)
Time since diabetes diagnosis Mean (SD)	4.98 (1.4)	4.85 (1.42)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

Warning: There are 8 unanswered questions

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)	Some concerns *(almost no reporting on patient flow so risk of unseen bias despite short study time)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
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	4.1 Was the method of measuring the outcome inappropriate?	No

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	*Low* *(CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(Overall reporting of characteristics, criteria and methodology is very poor.)*
Overall bias and Directness	Risk of bias judgement	High *(Concerns around lack of info on patient flow and overall poor reporting of inclusions criteria methodology, and baseline characteristics to ensure balance.)*
Overall bias and Directness	Overall Directness	Directly applicable

Yoo, 2008

Bibliographic Reference	Yoo, H J; An, H G; Park, S Y; Ryu, O H; Kim, H Y; Seo, J A; Hong, E G; Shin, D H; Kim, Y H; Kim, S G; Choi, K M; Park, I B; Yu, J M; Baik, S H; Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes.; Diabetes research and clinical practice; 2008; vol. 82 (no. 1); 73-9

Study details

Secondary publication of another included study- see primary study for details	

Study type	Randomised controlled trial (RCT)
Study location	Seoul, Korea
Study setting	four general hospitals
Study dates	enrollment January 2007 - June 2007
Sources of funding	This study was supported by a grant from the Korean Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (A050463).
Inclusion criteria	People with T2D Age 20-80 Insulin treatment Use of oral hypoglycemia gents or insulin for at least 1 year a stable insulin or OHA regimen for the prior 2 months a stable dose of antihypertensive or lipid-lowering drugs for at least 4 weeks
Exclusion criteria	Comorbidity severe diabetic complications, croticosteroid use in previous 3 months, liver disease (aspartate aminotransferase or alanine aminotransferase levels >2.5 times the reference level), renal insufficiency with a serum creatinine level >=2.0 mg/dL, and other medical problems that affected study results or trial participation
Outcome measures	HBA1C

	HbA1c reduction Time in range 80 - 250 mg/dL Time above below target glucose range >250 mg/dL <60 mg/dL Glycemic variability MAGE
Number of participants	65
Type of insulin regimen	Mixed insulin I: 13.8% Insulin alone, 37.9% insulin + OHA C: 17.9% insulin alone, 42.9% insulin + OHA
SMBG checks per day	BG test 4 times a day
Duration of follow-up	3 months
Loss to follow-up	I: 3 C: 5
Additional comments	Only used CGM 3 days once per month (intermittent)

	Advocated self-management not clinician based Time in range range different to most other studies

Study arms

Guardian RT (N = 32)

SMBG (N = 33)

Characteristics

Arm-level characteristics

Characteristic	Guardian RT (N = 32)	SMBG (N = 33)
% Female Nominal	34.5	50
Mean age (SD) Mean (SD)	54.6 (6.8)	57.5 (9)
BMI Mean (SD)	25 (3)	25.7 (3.5)
Time since diabetes diagnosis Mean (SD)	11.7 (5.8)	13.3 (4.9)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT T2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 *(per protocol analysis not appropriate, should've imputed data for study dropouts.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing outcome data could be linked to true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(CGM outcomes cannot be blinded due to open nature of intervention, and thus this domain has not been marked down.)*
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 inappropriate as dropouts have no reason given and should've been imputed, missing outcome data could be dependent on missing data's true value.)*
Overall bias and Directness	Overall Directness	Directly applicable *(Question mark around amount of CGM 3 days per month)*

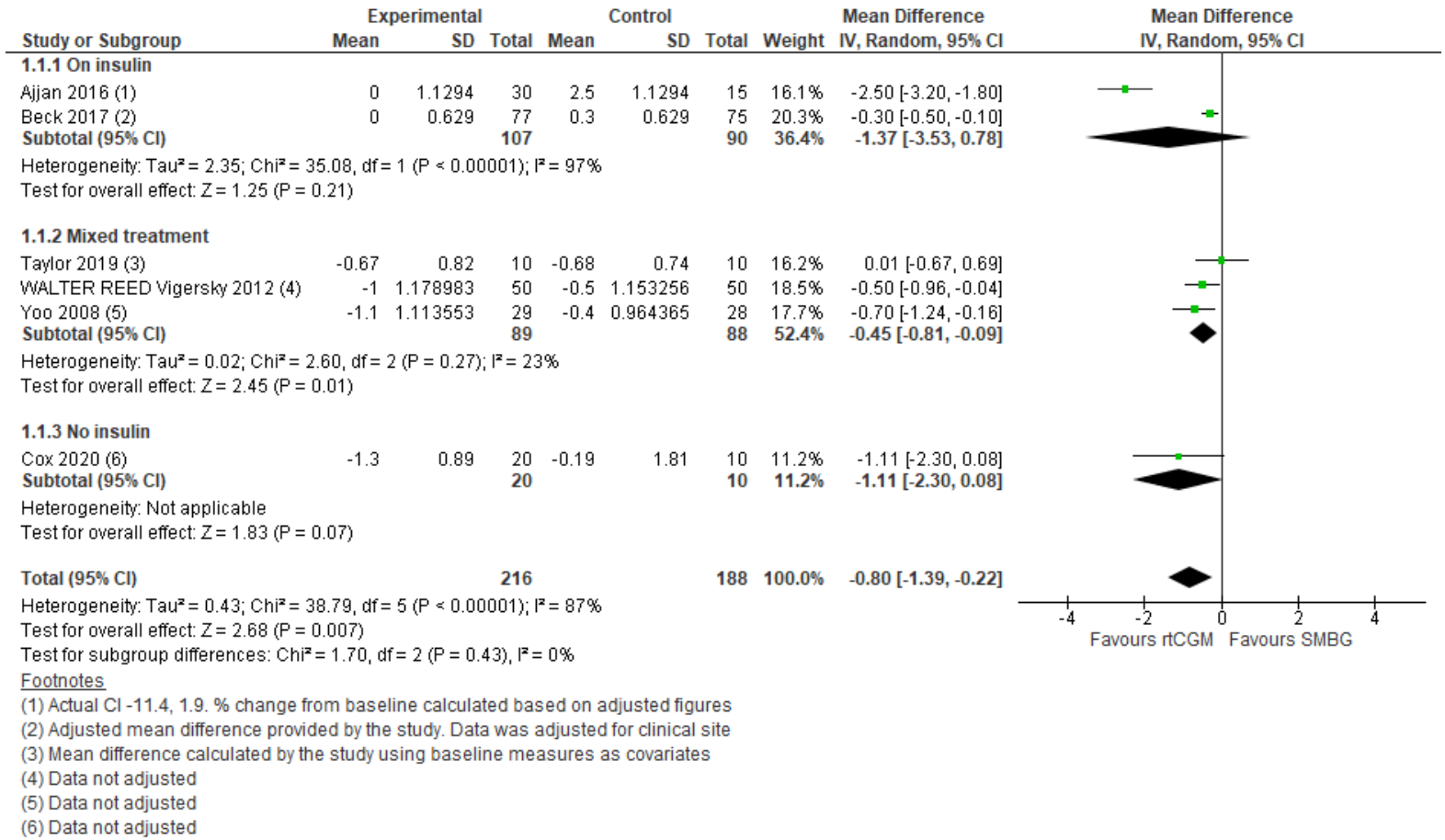
1

2

Appendix F – Forest plots

rtCGM vs SMBG

Figure 1: HbA1c (% change from baseline) <= 3 months (MD<0 favours rtCGM)



Footnotes

(1) Actual CI -11.4, 1.9. % change from baseline calculated based on adjusted figures
(2) Adjusted mean difference provided by the study. Data was adjusted for clinical site
(3) Mean difference calculated by the study using baseline measures as covariates
(4) Data not adjusted
(5) Data not adjusted
(6) Data not adjusted

Figure 2: HbA1c (% change from baseline) 3-6 months (MD<0 favours rtCGM)

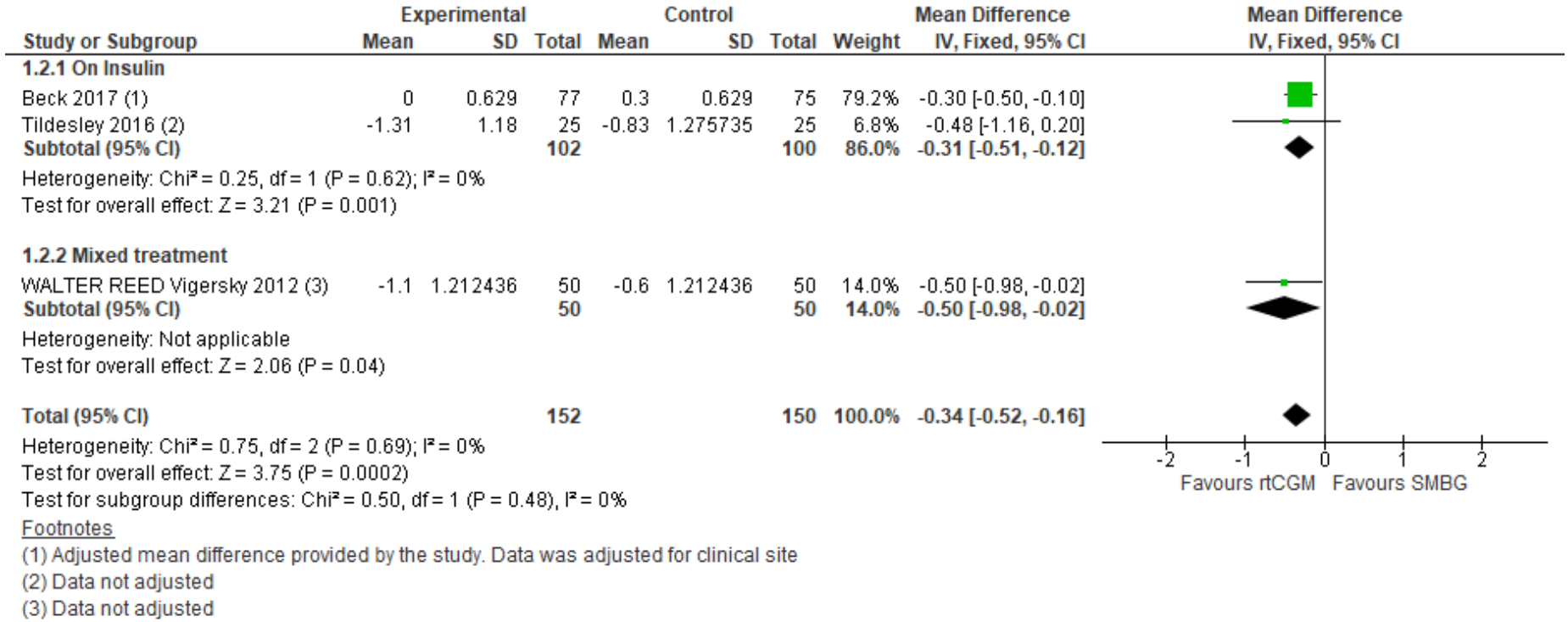


Figure 3: Change in BMI<= 3 months (MD<0 favours rtCGM)

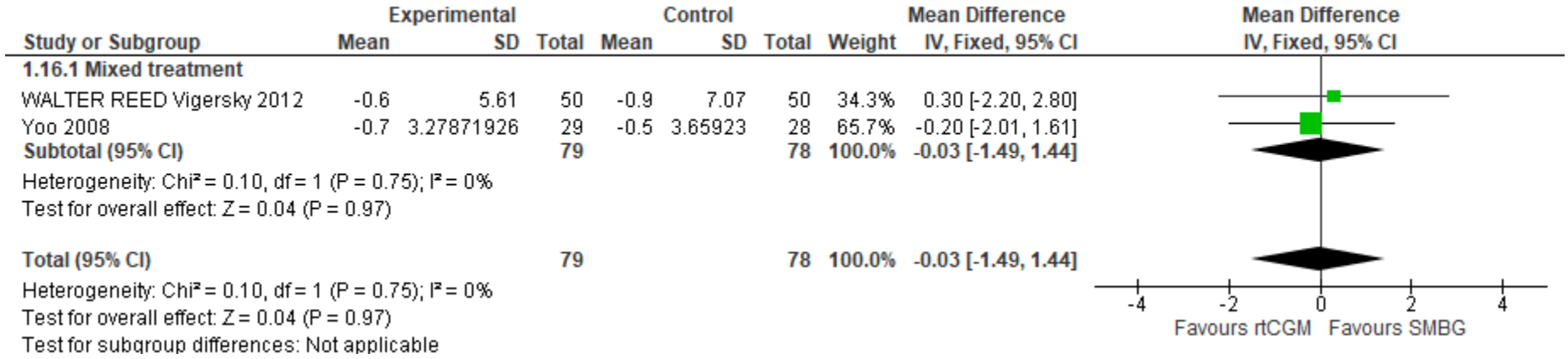


Figure 4: Change in weight (Kg) <= 3 months (MD<0 favours rtCGM)

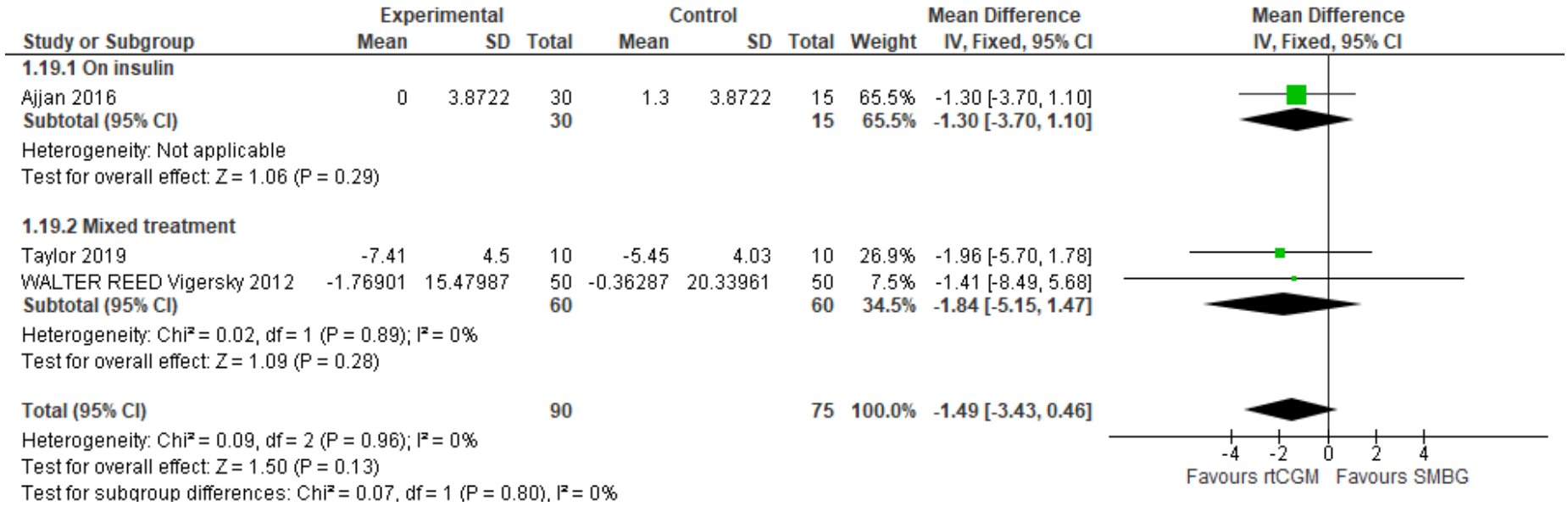
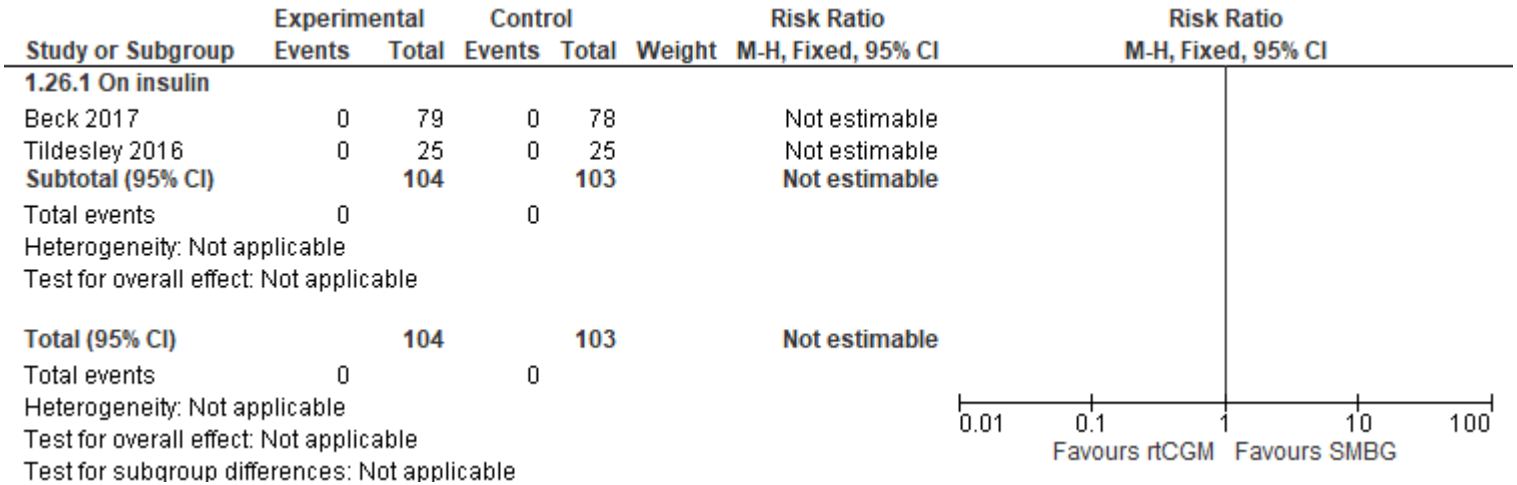
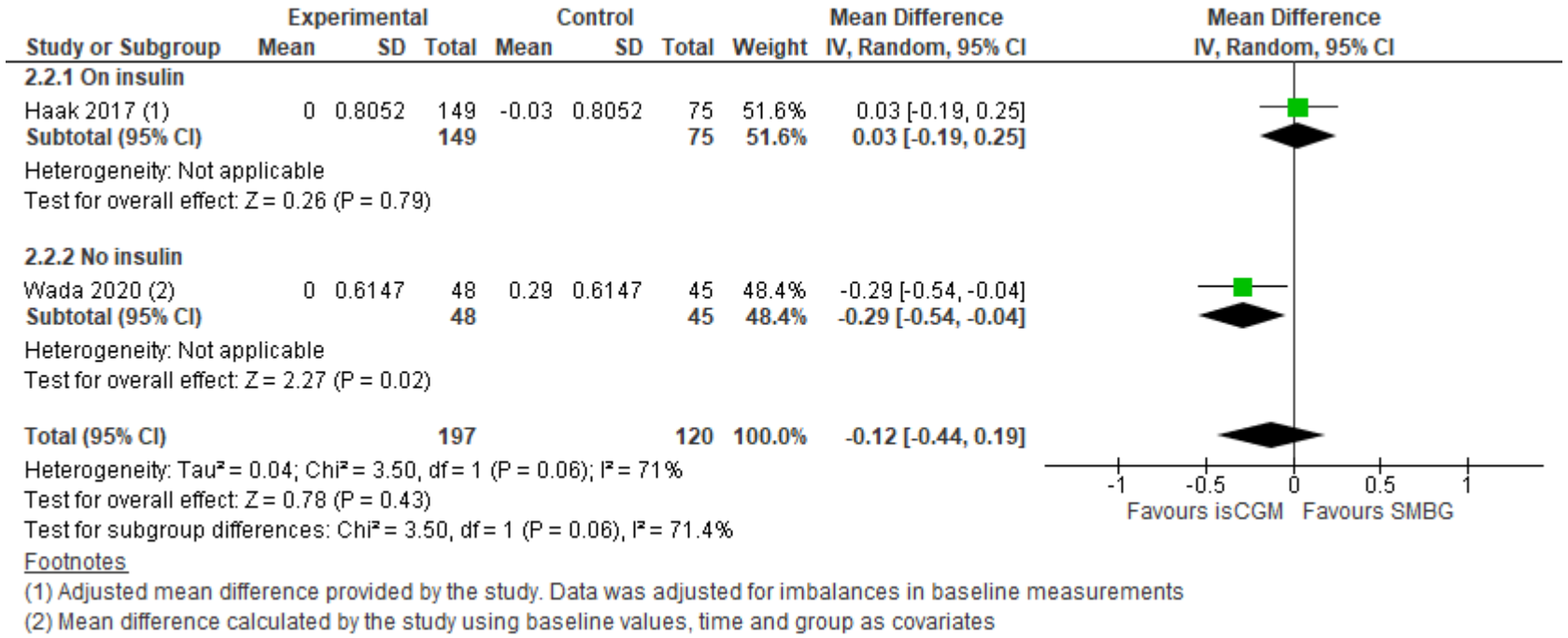


Figure 5: Severe hypoglycemia 3-6 months (RR<1 favours rtCGM)



isCGM vs SMBG

Figure 6: HbA1c (% change from baseline) 3-6 months (MD<0 favours isCGM)

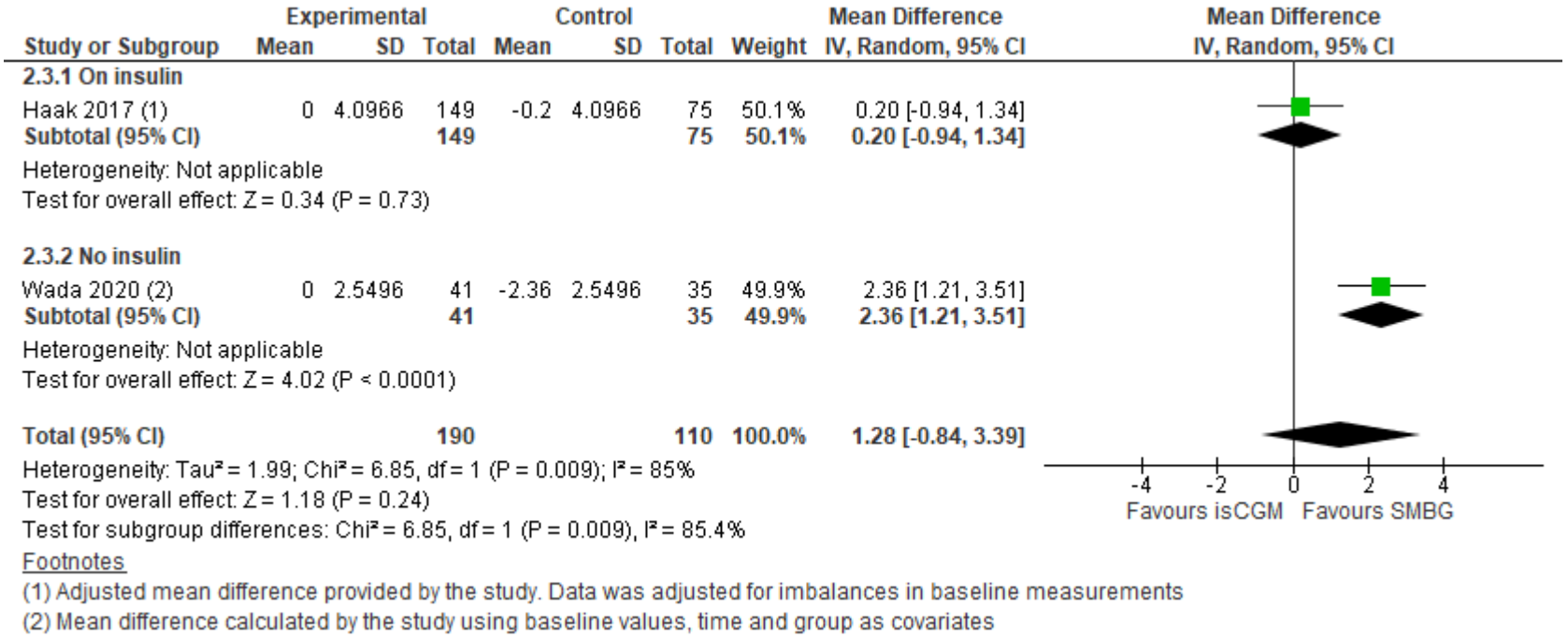


Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 7: Time in range (70 - 180 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)

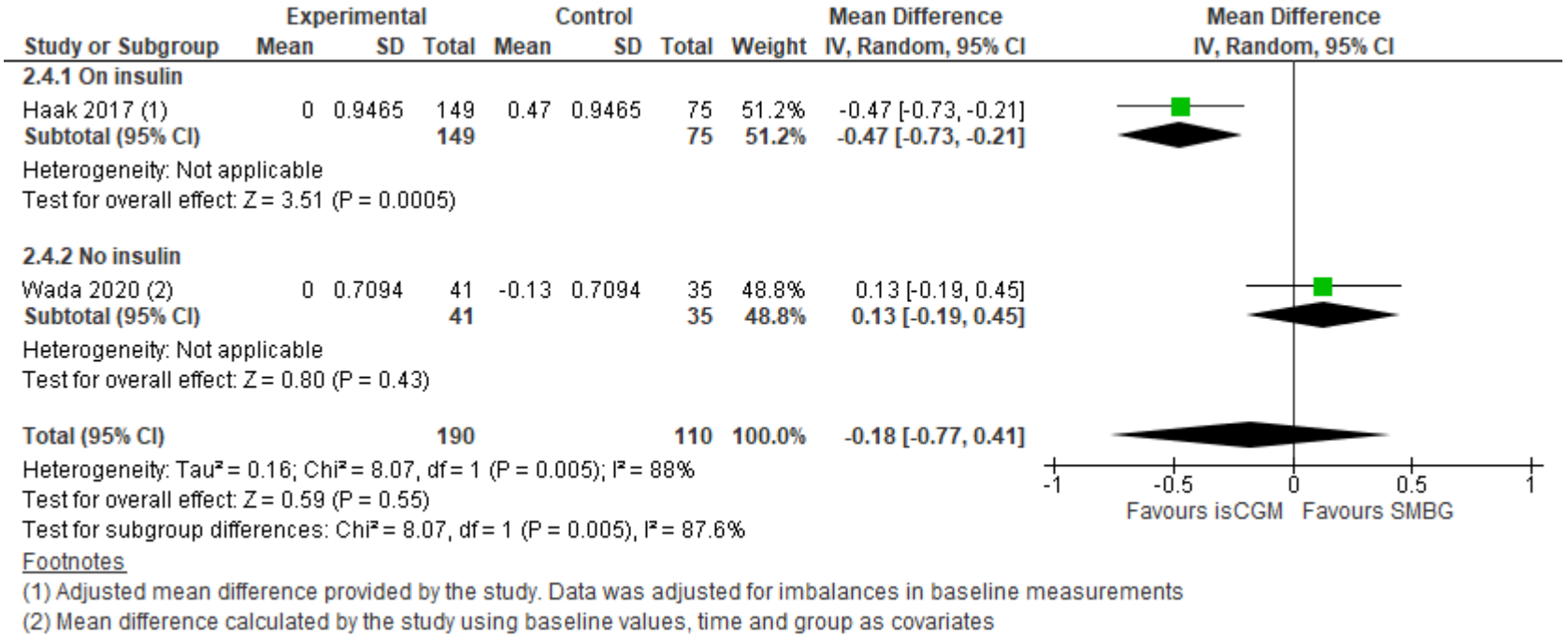


Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 8: Time in hypoglycemia (<70 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)

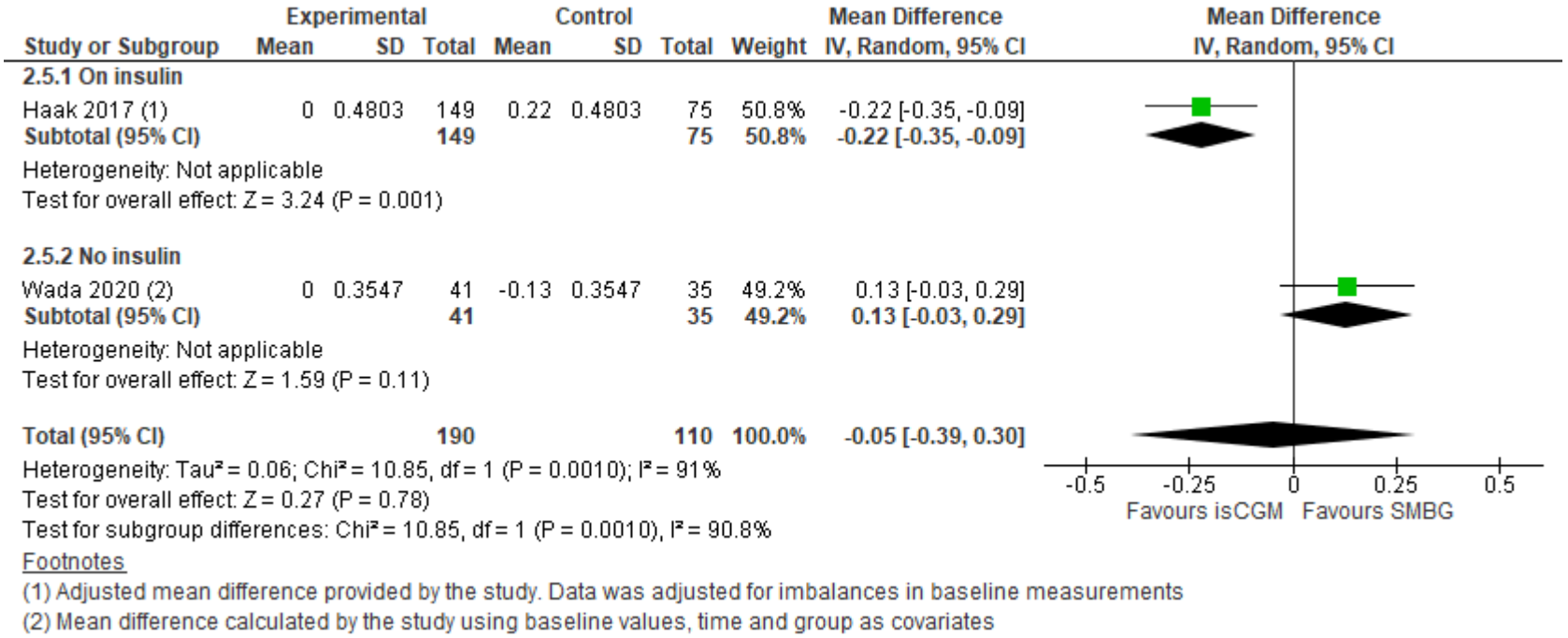


Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 9: Time in hypoglycemia (<55 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)

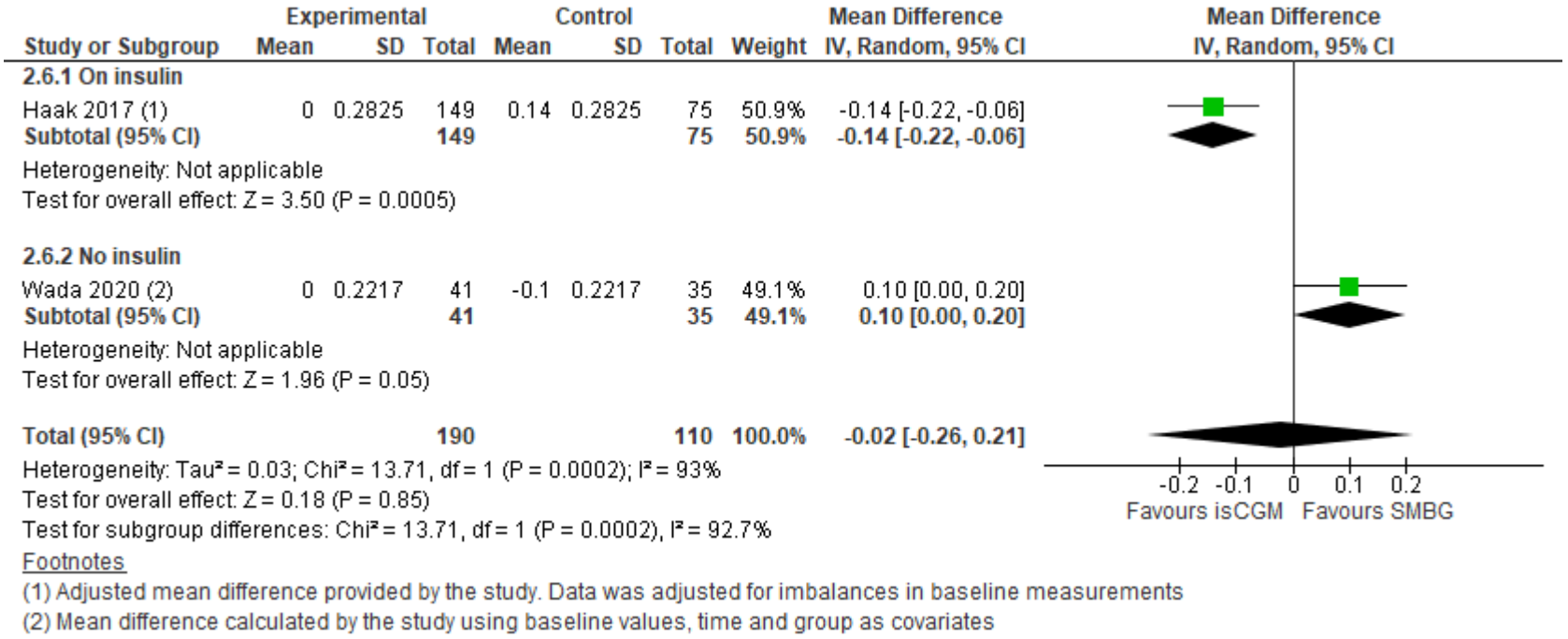


Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 10: Time in hypoglycemia (<45 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)

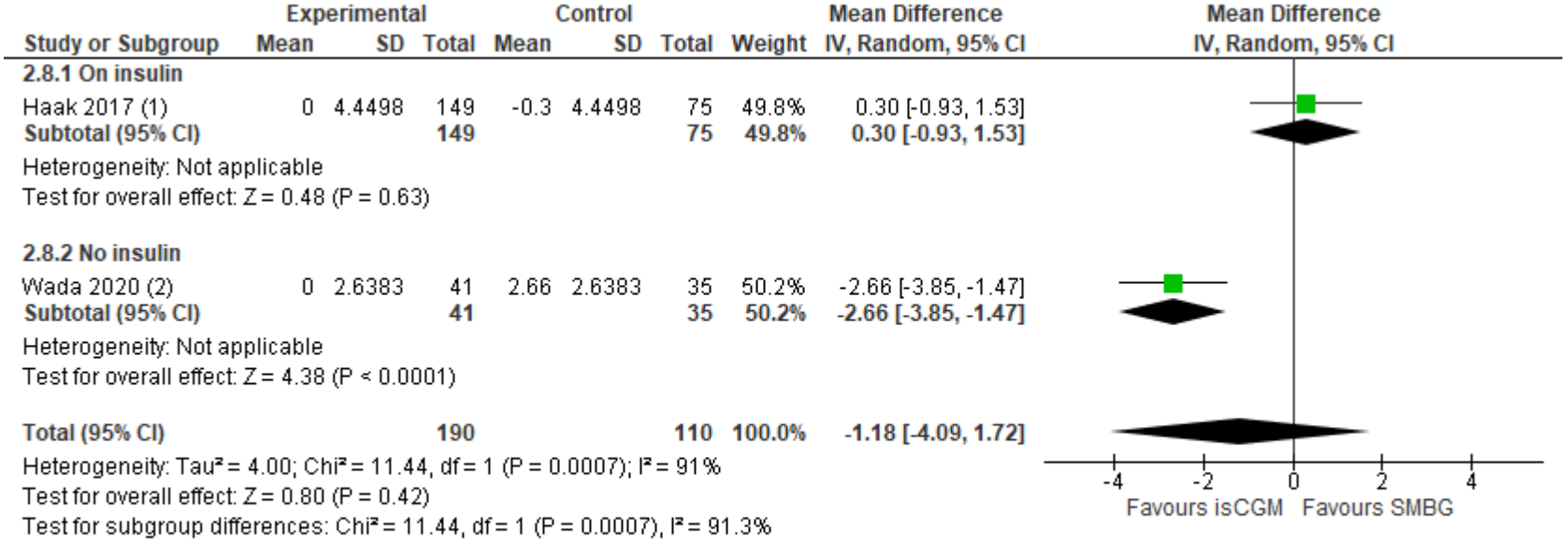


Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 11: Time in hyperglycemia (>180 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)

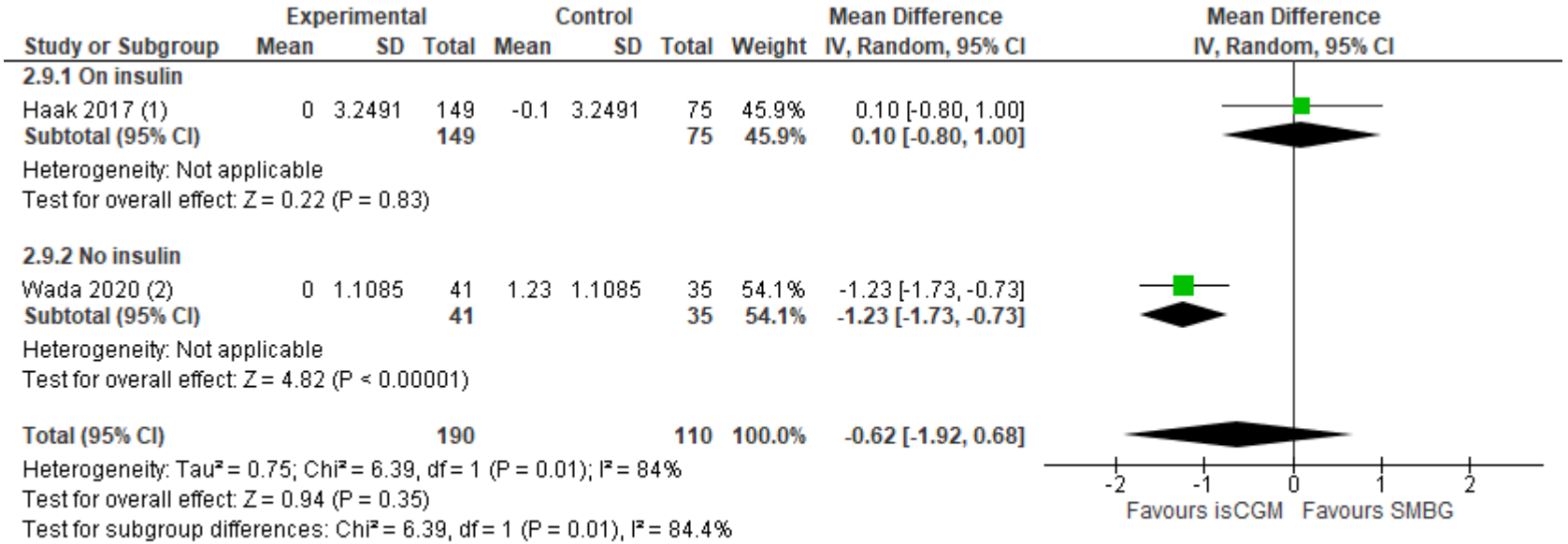


Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 12: Time in hyperglycemia (>240 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)

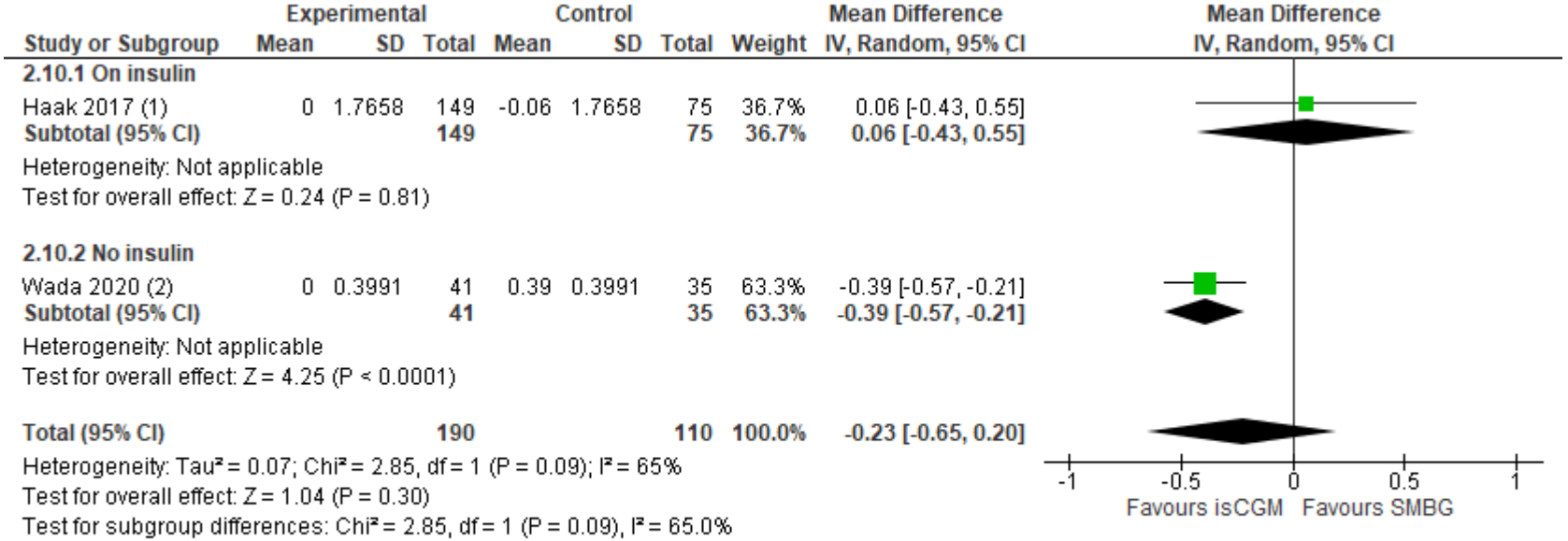


Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 13: Time in hyperglycemia (>300 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)

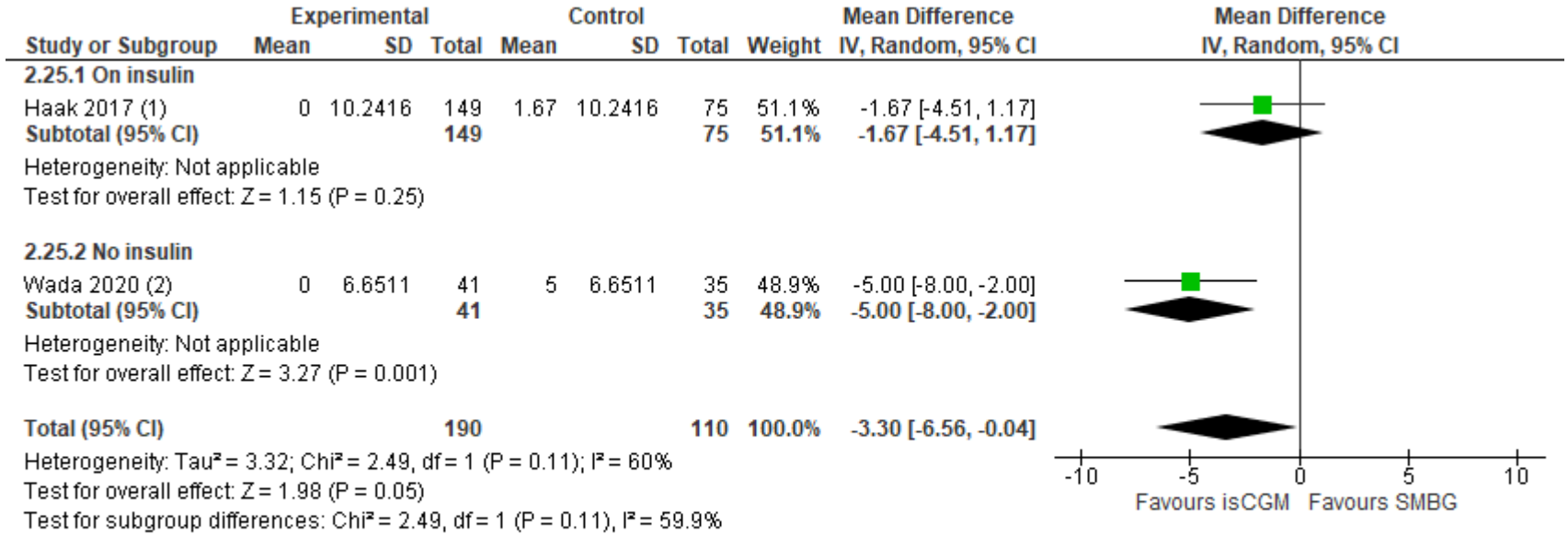


Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 14: Glycemic variability: SD 3-6 months (MD<0 favours isCGM)

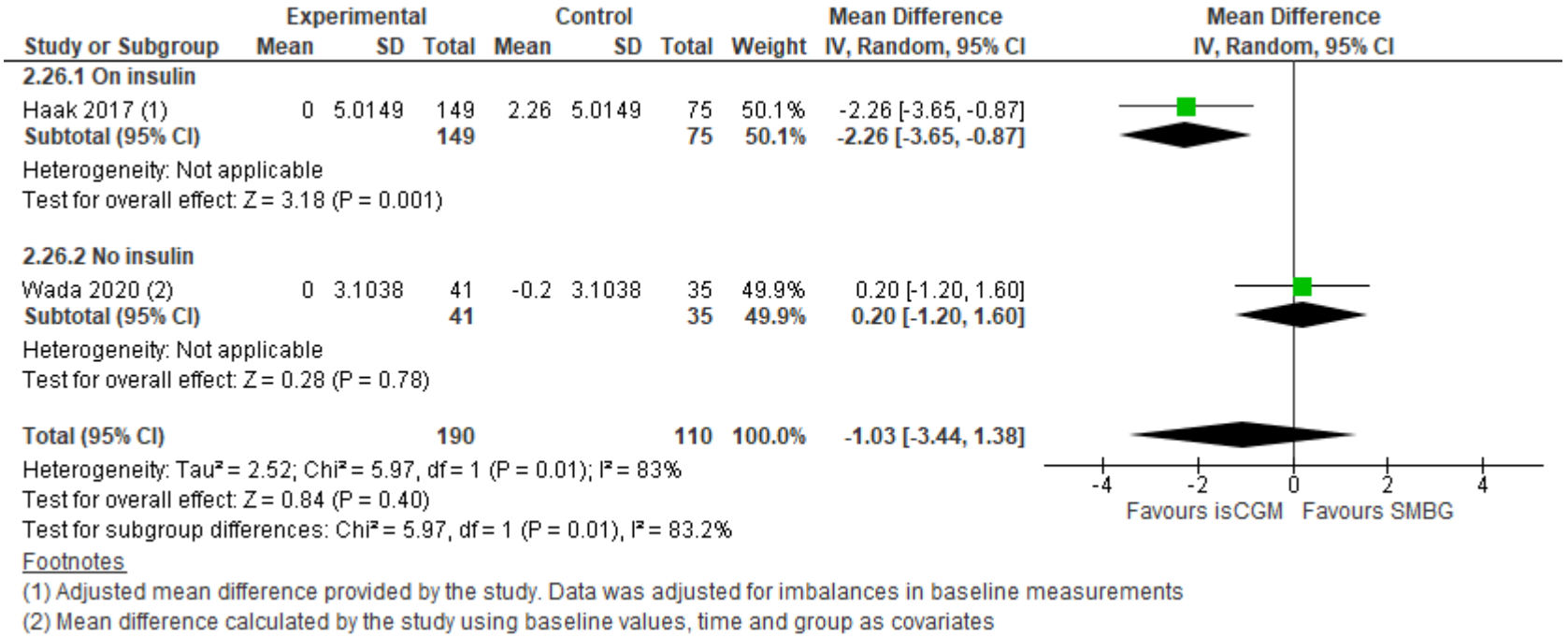


Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 15: Glycemic variability: CV 3-6 months (MD<0 favours isCGM)

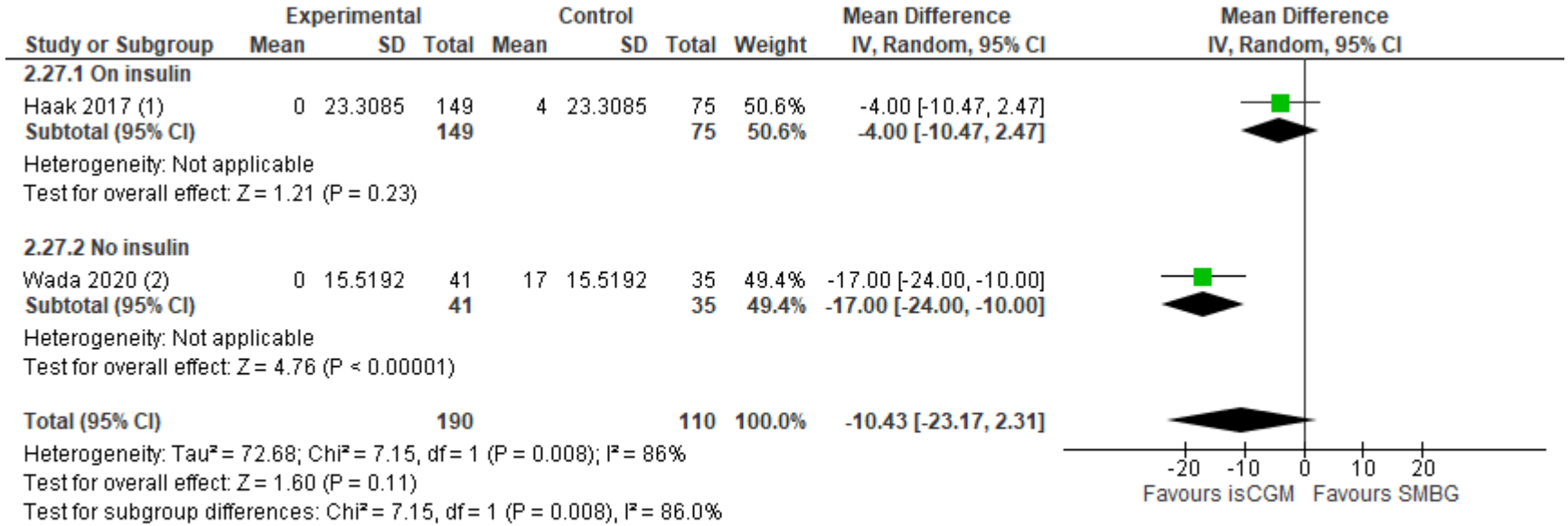


Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 16: Glycemic variability: MAGE 3-6 months (MD<0 favours isCGM)



Footnotes

(1) Adjusted mean difference provided by the study. Data was adjusted for imbalances in baseline measurements

(2) Mean difference calculated by the study using baseline values, time and group as covariates

Figure 17: Serious adverse events 3-6 months (RR<1 favours isCGM)

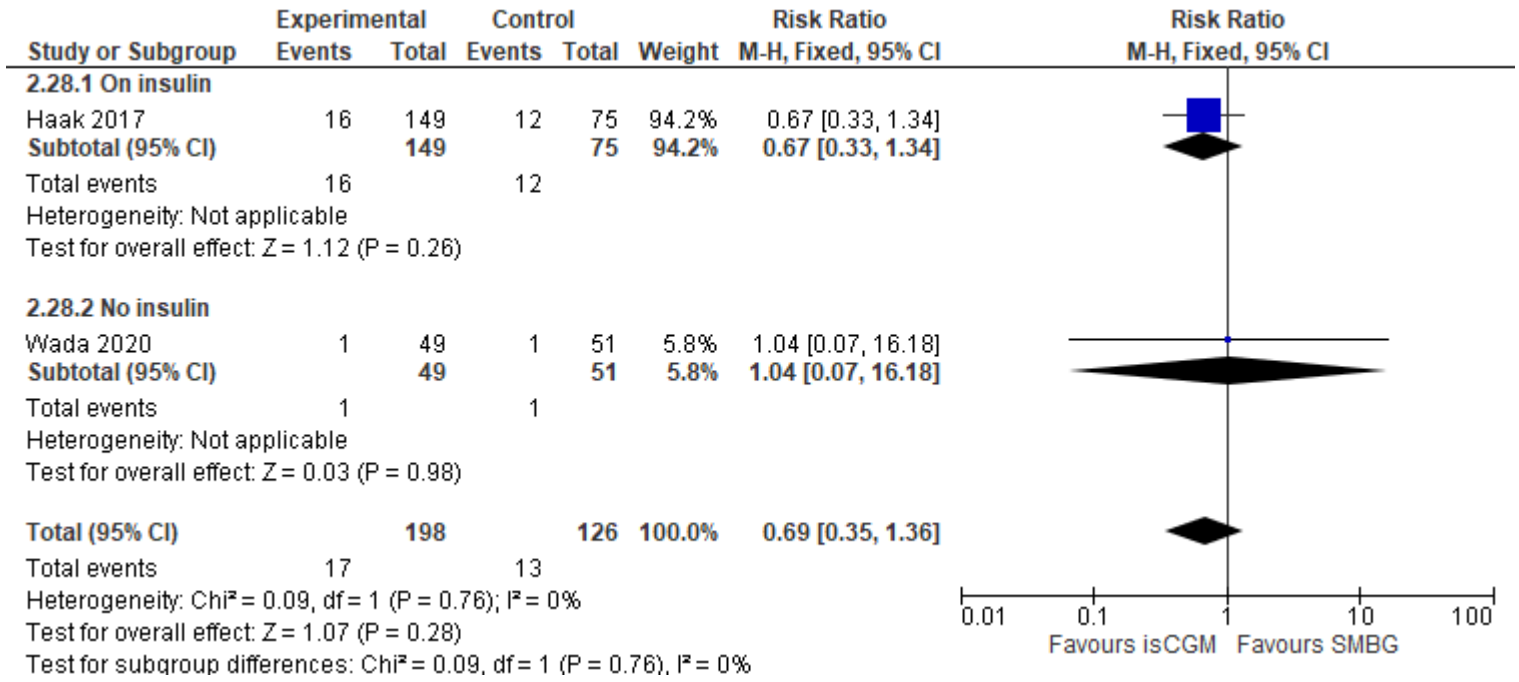


Figure 18: Hypoglycemia events 3-6 months (RR<1 favours isCGM)

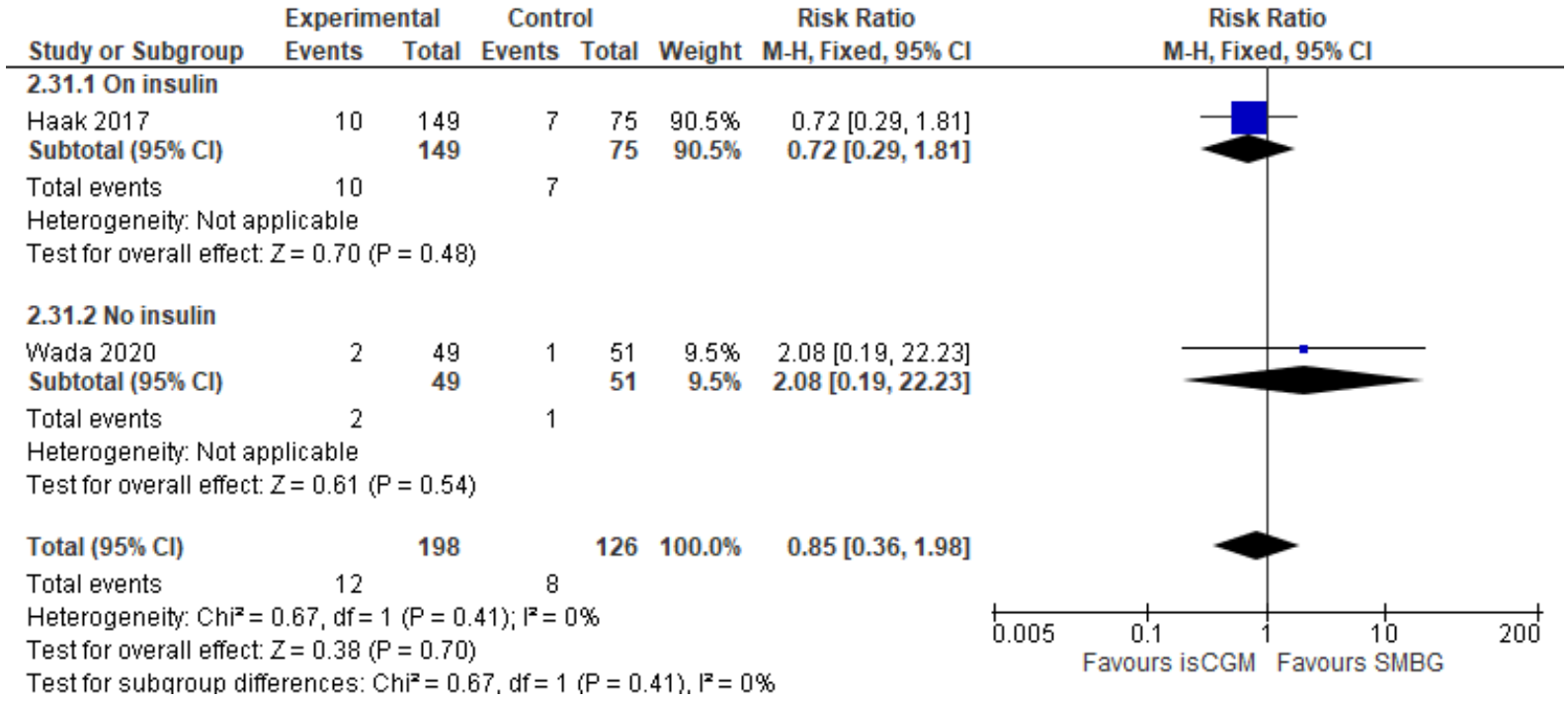
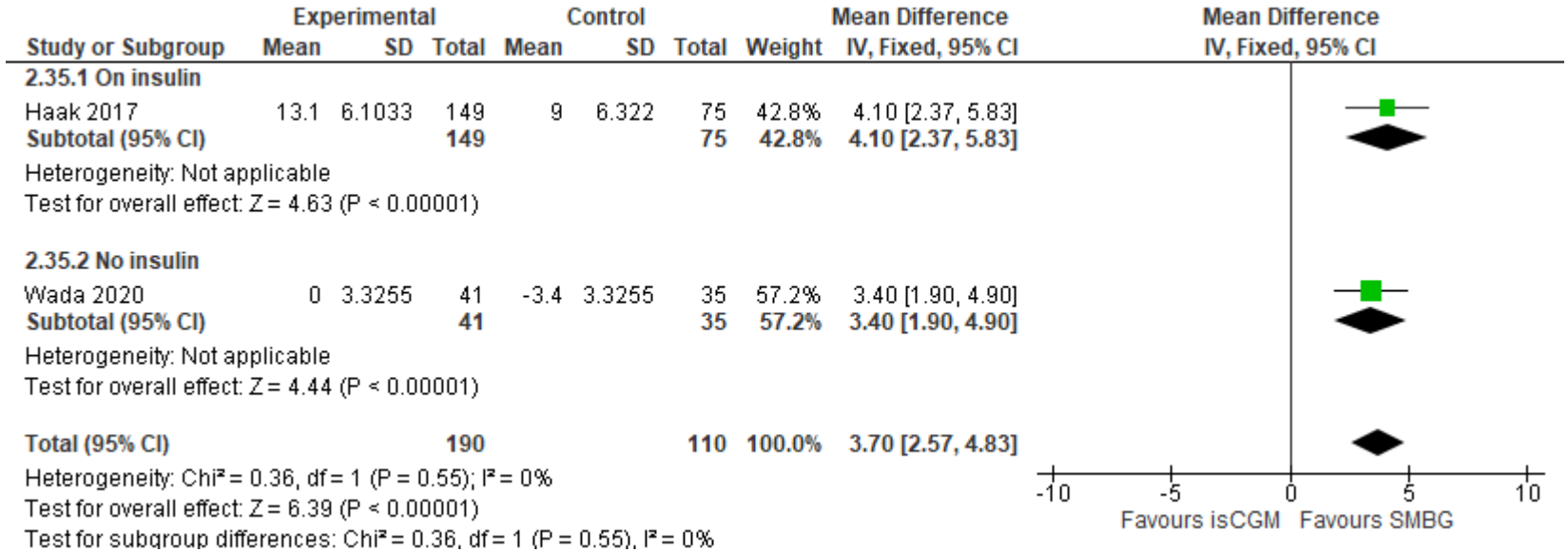


Figure 19: DTSQ - Total score 3-6 months (MD<0 favours isCGM)



Appendix G - GRADE tables for pairwise data

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
HbA1c (% change from baseline)<= 3 months (MD<0 favours rtCGM)											
6	PRCT	404	+/- 0.50	MD -0.80 (-1.39, -0.22)	-	-	Serious1	Not serious	Very serious4	Serious6	Very low
HbA1c (% change from baseline) 3-6 months (MD<0 favours rtCGM)											
3	PRCT	302	+/- 0.50	MD -0.34 (-0.52, -0.16)	-	-	Not serious	Not serious	Not serious	Serious6	Moderate
HbA1c (% change from baseline) >6 months (MD<0 favours rtCGM)											
1 (Vigersky 2012)	PRCT	100	+/- 0.50	MD -0.40 (-0.89, 0.09)	-	-	Serious1	Serious3	NA5	Serious6	Very low
HbA1c level <7% (%) <= 3 months (MD<0 favours rtCGM)											
1 (Beck 2017)	PRCT	152	+/- 18.87	MD 10.00 (-2.00, 22.00)	-	-	Not serious	Not serious	NA5	Serious6	Moderate
HbA1c level <7% (%) 3-6 months (MD<0 favours rtCGM)											
1 (Beck 2017	PRCT	152	+/- 18.87	MD 3.00 (-9.00, 15.00)	-	-	Not serious	Not serious	NA5	Not serious	High
HbA1c level <7.5% (%) <= 3 months (MD<0 favours rtCGM)											
1 (Beck 2017	PRCT	152	+/- 31.45	MD 17.00 (-3.00, 37.00)	-	-	Not serious	Not serious	NA5	Serious6	Moderate
HbA1c level <7.5% (%) 3-6 months (MD<0 favours rtCGM)											
1 (Beck 2017	PRCT	152	+/- 29.88	MD 8.00 (-11.00, 27.00)	-	-	Not serious	Not serious	NA5	Not serious	High
Relative reduction HbA1c >= 10 % (%) <=3 months (MD<0 favours rtCGM)											

1 (Beck 2017	PRCT	152	+/- 34.59	MD 25.00 (3.00, 47.00)	-	-	Not serious	Not serious	NA5	Serious6	Moderate
Relative reduction HbA1c >= 10% (%) 3-6 months (MD<0 favours rtCGM)											
1 (Beck 2017	PRCT	152	+/- 34.59	MD 22.00 (-0.00, 44.00)	-	-	Not serious	Not serious	NA5	Serious6	Moderate
Reduction HbA1c >= 1% (%) <= 3 months (MD<0 favours rtCGM)											
1 (Beck 2017	PRCT	152	+/- 33.02	MD 20.00 (-1.00, 41.00)	-	-	Not serious	Not serious	NA5	Serious6	Moderate
Reduction HbA1c >= 1% (%) 3-6 months (MD<0 favours rtCGM)											
1 (Beck 2017	PRCT	152	+/- 29.88	MD 12.00 (-7.00, 31.00)	-	-	Not serious	Not serious	NA5	Serious6	Moderate
Reduction HbA1c >= 0.5% (%) <= 3 months (MD<0 favours rtCGM)											
1 (Beck 2017	PRCT	152	+/- 40.88	MD 31.00 (5.00, 57.00)	-	-	Not serious	Not serious	NA5	Serious6	Moderate
Reduction HbA1c >= 0.5% (%) 3-6 months (MD<0 favours rtCGM)											
1 (Beck 2017	PRCT	152	+/- 40.88	MD 26.00 (-0.00, 52.00)	-	-	Not serious	Not serious	NA5	Serious6	Moderate
Time in hypoglycemia (<70 mg/dL) (minutes) <=3 months (MD<0 favours rtCGM)											
1 (Beck 2017	PRCT	45	+/- 0.34	MD -0.13 (-0.55, 0.29)	-	-	Not serious	Not serious	NA5	Serious6	Moderate
Time in hyperglycemia (>180 md/dL) (minutes) <= 3 months (MD<0 favours rtCGM)											
1 (Beck 2017	PRCT	45	+/- 1.83	MD -0.42 (-2.69, 1.85)	-	-	Not serious	Not serious	NA5	Very serious7	Low
Change in BMI <= 3 months (MD<0 favours rtCGM)											
2	PRCT	157	+/- 2.68	MD -0.03 (-1.49, 1.44)	-	-	Very serious2	Serious3	Not serious	Not serious	Very low
Change in BMI 3-6 months (MD<0 favours rtCGM)											
1 (Tang 2014)	PRCT	32	+/- 0.59	MD 1.27 (-2.12, 4.66)	-	-	Very serious2	Not serious	NA5	Very serious7	Very low
Change in BMI >6 months (MD<0 favours rtCGM)											

1 (Vigersky 2012)	PRCT	100	+/- 3.55	MD 0.50 (-2.06, 3.06)	-	-	Serious1	Serious3	NA5	Not serious	Low
Change in weight (kg) <= 3 months (MD<0 favours rtCGM)											
3	PRCT	165	+/- 2.02	MD -1.49 (-3.43, 0.46)	-	-	Not serious	Not serious	Not serious	Serious6	Moderate
Change in weight (kg) >6 months (MD<0 favours rtCGM)											
1 (Vigersky 2012)	PRCT	100	+/- 9.98	MD -0.95 (-8.02, 6.12)	-	-	Serious1	Serious3	NA5	Not serious	Low
Weight loss >3 pounds - <3 months (RR>1 favours rtCGM)											
1 (Vigersky 2012)	PRCT	100	0.80 , 1.25	RR 2.22 (1.12, 4.40)	18 per 100	22 more per 100 (2 more to 61 more)	Serious1	Serious3	NA5	Serious6	Very low
Weight loss >3 pounds - >6 months (RR>1 favours rtCGM)											
1 (Vigersky 2012)	PRCT	100	0.80 , 1.25	RR 1.35 (0.83, 2.21)	34 per 100	12 more per 100 (6 fewer to 41 more)	Serious1	Serious3	NA5	Serious6	Very low
Weight gain >3 pounds - <3 months (RR>1 favours rtCGM)											
1 (Vigersky 2012)	PRCT	100	0.80 , 1.25	RR 0.50 (0.20, 1.23)	24 per 100	12 fewer per 100 (19 fewer to 5 more)	Serious1	Serious3	NA5	Serious6	Very low
Weight gain >3 pounds - >6 months (RR>1 favours rtCGM)											
1 (Vigersky 2012)	PRCT	100	0.80 , 1.25	RR 0.61 (0.32, 1.16)	36 per 100	14 fewer per 100 (24 fewer to 6 more)	Serious1	Serious3	NA5	Serious6	Very low
Serious adverse events 3-6 months (RR>1 favours rtCGM)											
1 (Beck 2017	PRCT	158	0.80 , 1.25	Not estimable[8]	Not estimable	Not estimable	Not serious	Not serious	NA5	Not estimable	High
Severe hypoglycemia 3-6 months (RR>1 favours rtCGM)											
2	PRCT	207	0.80 , 1.25	Not estimable[8]	Not estimable	Not estimable	Not serious	Not serious	NA5	Not estimable	High
DKA 3-6 months (RR>1 favours rtCGM)											
1 (Beck 2017)	PRCT	157	0.80 , 1.25	Not estimable[8]	Not estimable	Not estimable	Not serious	Not serious	NA5	Not estimable	High
Quality of life: DTSQ 3-6 months (MD<0 favours rtCGM)											

1 (Tang 2014)	PRC T	32	+/- 1.32	MD -8.61 (-12.42, -4.80)	-	-	Very serious2	Not serious	NA5	Not serious	Low
Quality of life: PHQ-9 <=3 months (MD<0 favours rtCGM)											
1 (Cox 2020)	PRC T	30	+/- 3.35	MD -0.90 (-5.62, 3.82)	-	-	Not serious	Serious3	NA5	Very serious7	Very low
Quality of life: WHO-QoL physiological <=3 months (MD<0 favours rtCGM)											
1 (Cox 2020)	PRC T	30	+/- 0.85	MD 0.00 (-1.22, 1.22)	-	-	Not serious	Serious3	NA5	Very serious7	Very low
Quality of life: WHO-QoL psychological <=3 months (MD<0 favours rtCGM)											
1 (Cox 2020)	PRC T	30	+/- 0.50	MD 1.20 (0.26, 2.14)	-	-	Not serious	Serious3	NA5	Serious6	Low
Quality of life: glucose monitor satisfaction survey <= 3 months (MD<0 favours rtCGM)											
1 (Cox 2020)	PRC T	30	+/- 0.30	MD 0.40 (-0.06, 0.86)	-	-	Not serious	Serious3	NA5	Serious6	Low
Quality of life: diabetes empowerment scale <=3 months (MD<0 favours rtCGM)											
1 (Cox 2020)	PRC T	30	+/- 1.70	MD 2.50 (-0.48, 5.48)	-	-	Not serious	Serious3	NA5	Serious6	Low
Quality of life: diabetes distress scale (emotional) <=3 months (MD<0 favours rtCGM)											
1 (Cox 2020)	PRC T	30	+/- 0.55	MD -0.70 (-1.53, 0.13)	-	-	Not serious	Serious3	NA5	Serious6	Low
Quality of life: diabetes distress scale (regimen) <=3 months (MD<0 favours rtCGM)											
1 (Cox 2020)	PRC T	30	+/- 0.35	MD -0.80 (-1.45, -0.15)	-	-	Not serious	Serious3	NA5	Serious6	Low
Quality of life (PAID) <= 3 months (MD<0 favours rtCGM)											
1 (Vigersky 2012)	PRC T	100	+/- 10.25	MD 1.00 (-6.79, 8.79)	-	-	Serious1	Serious3	NA5	Not serious	Low
Quality of life (PAID) 3-6 months (MD<0 favours rtCGM)											
1 (Vigersky 2012)	PRC T	100	+/- 10.73	MD -0.60 (-8.85, 7.65)	-	-	Serious1	Serious3	NA5	Not serious	Low
Quality of life: Perceived stress scale <= 3 months (MD<0 favours rtCGM)											

1 (Taylor 2019)	PRCT	20	+/- 1.56	MD 0.80 (-2.80, 4.40)	-	-	Not serious	Not serious	NA5	Very serious7	Low

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

PRCT = Parallel RCT

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
HbA1c (% change from baseline) <= 3 months (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	93	+/- 0.50	MD -0.13 (-0.35, 0.09)	-	-	Not serious	Not serious	N/A3	Not serious	High
HbA1c (% change from baseline) 3-6 months (MD<0 favours isCGM)											
2 (see subgroups below_	PRCT	317	+/- 0.50	MD -0.12 (-0.44, 0.19)	-	-	Serious1	Not serious	Very serious4	Not serious	Very low
HbA1c (% change from baseline) 3-6 months Subgroup: On insulin (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.50	MD 0.03 (-0.19, 0.25)	-	-	Serious1	Not serious	N/A3	Not serious	Moderate

HbA1c (% change from baseline) 3-6 months Subgroup: No insulin (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	93	+/- 0.50	MD -0.29 (-0.54, -0.04)	-	-	Not serious	Not serious	N/A3	Serious6	Moderate
Time in range (70 - 180 mg/dL) (hours) 3-6 months (MD>0 favours isCGM)											
2	PRCT	300	+/- 5.00	MD 1.28 (0.84, 3.39)	-	-	Serious1	Not serious	Very serious4	Not serious	Very low
Time in range (70 - 180 mg/dL) (hours) 3-6 months Subgroup: On insulin (MD>0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 5.00	MD 0.20 (-0.94, 1.34)	-	-	Serious1	Not serious	N/A3	Not serious	Moderate
Time in range (70 - 180 mg/dL) (hours) 3-6 months Subgroup: No insulin (MD>0 favours isCGM)											
1 (Wada 2020)	PRCT	76	+/- 5.00	MD 2.36 (1.21, 3.51)	-	-	Not serious	Not serious	N/A3	Not serious	High
Time in hypoglycemia (<70 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)											
2	PRCT	300	+/- 0.41	MD -0.18 (-0.77, 0.41)	-	-	Serious1	Not serious	Very serious4	Serious6	Very low
Time in hypoglycemia (<70 mg/dL) (hours) 3-6 months Subgroup: On insulin (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.47	MD -0.47 (-0.73, -0.21)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Time in hypoglycemia (<70 mg/dL) (hours) 3-6 months Subgroup: No insulin (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	76	+/- 0.35	MD 0.13 (-0.19, 0.45)	-	-	Not serious	Not serious	N/A3	Serious6	Moderate
Time in hypoglycemia (<55 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)											
2	PRCT	300	+/- 0.21	MD -0.05 (-0.39, 0.30)	-	-	Serious1	Not serious	Very serious4	Very serious7	Very low
Time in hypoglycemia (<55 mg/dL) (hours) 3-6 months Subgroup: On insulin (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.24	MD -0.22 (-0.35, -0.09)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Time in hypoglycemia (<55 mg/dL) (hours) 3-6 months Subgroup: No insulin (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	76	+/- 0.18	MD 0.13 (-0.03, 0.29)	-	-	Not serious	Not serious	N/A3	Serious6	Moderate
Time in hypoglycemia (<45 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)											

2	PRCT	300	+/- 0.13	MD -0.02 (-0.26, 0.21)	-	-	Serious1	Not serious	Very serious4	Very serious7	Very low
Time in hypoglycemia (<45 mg/dL) (hours) 3-6 months Subgroup: On insulin (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.14	MD -0.14 (-0.22, -0.06)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Time in hypoglycemia (<45 mg/dL) (hours) 3-6 months Subgroup: No insulin (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	76	+/- 0.11	MD 0.10 (0.00, 0.20)	-	-	Not serious	Not serious	N/A3	Serious6	Moderate
Time in hypoglycemia (<40 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.11	MD -0.10 (-0.16, -0.04)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Time in hyperglycemia (<180 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)											
2	PRCT	300	+/- 1.77	MD -1.18 (-4.09, 1.72)	-	-	Serious1	Not serious	Very serious4	Serious6	Very low
Time in hyperglycemia (<180 mg/dL) (hours) 3-6 months Subgroup: On insulin (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 2.22	MD 0.30 (-0.93, 1.53)	-	-	Serious1	Not serious	N/A3	Not serious	Moderate
Time in hyperglycemia (<180 mg/dL) (hours) 3-6 months Subgroup: No insulin (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	76	+/- 1.32	MD -2.66 (-3.85, -1.47)	-	-	Not serious	Not serious	N/A3	Not serious	High
Time in hyperglycemia (<240 mg/dL) (hours) 3-6 months (effect size >0 favours control)											
2	PRCT	300	+/- 1.09	MD -0.62 (-1.92, 0.68)	-	-	Serious1	Not serious	Very serious4	Serious6	Very low
Time in hyperglycemia (<240 mg/dL) (hours) 3-6 months Subgroup: On insulin (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 1.62	MD 0.10 (-0.80, 1.00)	-	-	Serious1	Not serious	N/A3	Not serious	Moderate
Time in hyperglycemia (<240 mg/dL) (hours) 3-6 months Subgroup: No insulin (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	76	+/- 0.55	MD -1.23 (-1.73, -0.73)	-	-	Not serious	Not serious	N/A3	Not serious	High
Time in hyperglycemia (<300 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)											

2	PRCT	300	+/- 0.54	MD -0.23 (-0.65, 0.20)	-	-	Serious1	Not serious	Serious5	Serious6	Very low
Time in hyperglycemia (<300 mg/dL) (hours) 3-6 months Subgroup: On insulin (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.88	MD 0.06 (-0.43, 0.55)	-	-	Serious1	Not serious	N/A3	Not serious	Moderate
Time in hyperglycemia (<300 mg/dL) (hours) 3-6 months Subgroup: No insulin (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	76	+/- 0.20	MD -0.39 (-0.57, -0.21)	-	-	Not serious	Not serious	N/A3	Not serious	High
Events in hypoglycemia (<70 mg/dL) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.23	MD -0.16 (-0.29, -0.03)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Events in hypoglycemia (<55 mg/dL) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.13	MD -0.12 (-0.19, -0.05)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Events in hypoglycemia (<45 mg/dL) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.07	MD -0.06 (-0.10, -0.02)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Events in hypoglycemia (<40 mg/dL) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.07	MD -0.05 (-0.09, -0.01)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Nocturnal time in hypoglycemia (<70 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.28	MD -0.29 (-0.45, -0.13)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Nocturnal Time in hypoglycemia (<55 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.14	MD -0.12 (-0.20, -0.04)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Nocturnal Time in hypoglycemia (<45 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.11	MD -0.08 (-0.14, -0.02)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Nocturnal Time in hypoglycemia (<40 mg/dL) (hours) 3-6 months (MD<0 favours isCGM)											

1 (Haak 2017)	PRCT	224	+/- 0.11	MD -0.10 (-0.16, -0.04)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Nocturnal Events in hypoglycemia (<70 mg/dL) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.11	MD -0.12 (-0.18, -0.06)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Nocturnal Events in hypoglycemia (<55 mg/dL) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.07	MD -0.07 (-0.11, -0.03)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Nocturnal Events in hypoglycemia (<45 mg/dL) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.07	MD -0.04 (-0.08, -0.00)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Nocturnal Events in hypoglycemia (<40 mg/dL) 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.07	MD -0.05 (-0.09, -0.01)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Change in BMI <=3 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	76	+/- 0.43	MD -0.30 (-0.69, 0.09)	-	-	Not serious	Not serious	N/A3	Serious6	Moderate
Change in BMI 3-6 months (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	76	+/- 0.43	MD -0.20 (-0.59, 0.19)	-	-	Not serious	Not serious	N/A3	Serious6	Moderate
Glycemic variability: SD 3-6 months (MD<0 favours isCGM)											
2	PRCT	300	+/- 4.22	MD -3.30 (-6.56, -0.04)	-	-	Serious1	Not serious	Serious5	Serious6	Very low
Glycemic variability: SD 3-6 months Subgroup: On insulin (MD<0 favours isCGM))											
1 (Haak 2017)	PRCT	224	+/- 5.12	MD -1.67 (-4.51, 1.17)	-	-	Serious1	Not serious	N/A3	Not serious	Moderate
Glycemic variability: SD 3-6 months Subgroup: No insulin (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	76	+/- 3.33	MD -5.00 (-8.00, -2.00)	-	-	Not serious	Not serious	N/A3	Serious6	Moderate
Glycemic variability: CV 3-6 months (MD<0 favours isCGM)											

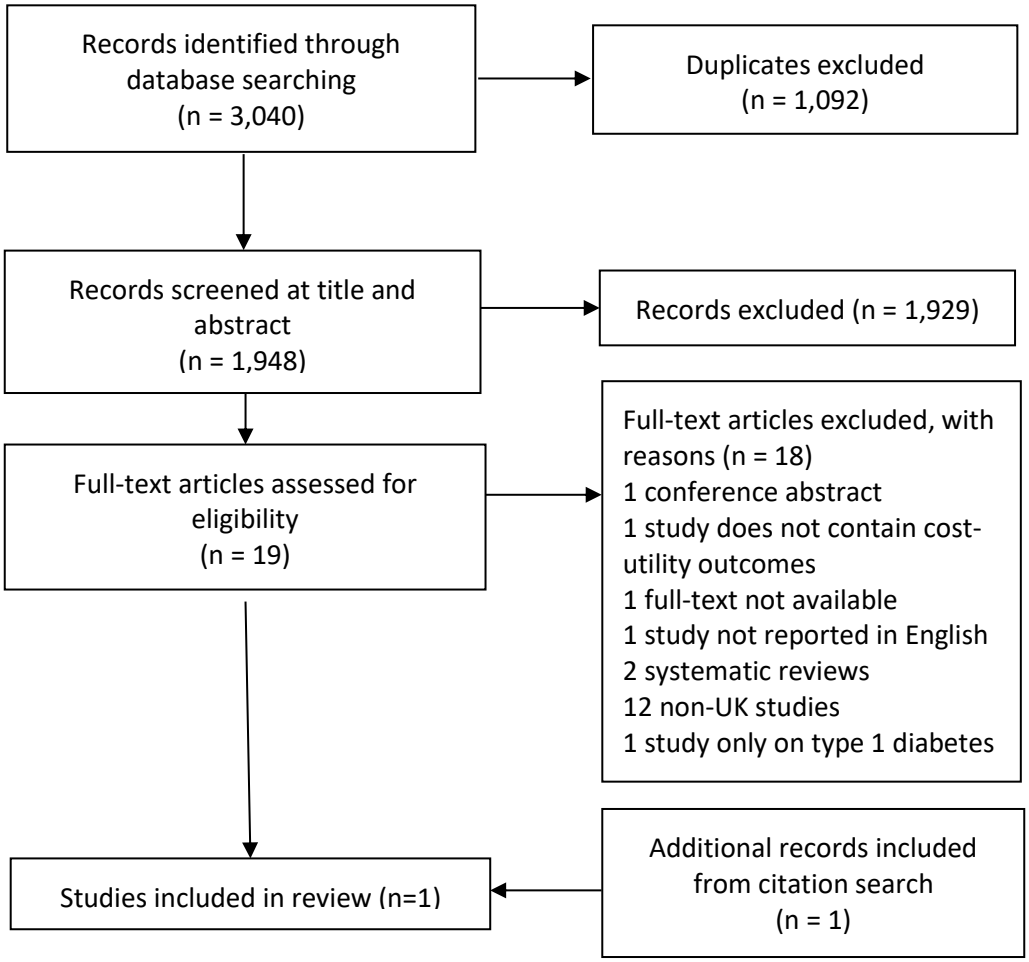
2	PRCT	300	+/- 2.03	MD -1.03 (-3.44, 1.38)	-	-	Serious1	Not serious	Very serious4	Serious6	Very low
Glycemic variability: CV 3-6 months Subgroup: On insulin (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 2.51	MD -2.26 (-3.65, -0.87)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Glycemic variability: CV 3-6 months Subgroup: No insulin (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	76	+/- 1.55	MD 0.20 (-1.20, 1.60)	-	-	Not serious	Not serious	N/A3	Serious6	Moderate
Glycemic variability: MAGE 3-6 months (MD<0 favours isCGM)											
2	PRCT	300	+/- 9.71	MD -10.43 (-23.17, 2.31)	-	-	Serious1	Not serious	Very serious4	Serious6	Very low
Glycemic variability: MAGE 3-6 months Subgroup: On insulin (MD<0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 11.65	MD -4.00 (-10.47, 2.47)	-	-	Serious1	Not serious	N/A3	Not serious	Moderate
Glycemic variability: MAGE 3-6 months Subgroup: No insulin (MD<0 favours isCGM)											
1 (Wada 2020)	PRCT	76	+/- 7.76	MD -17.00 (-24.00, -10.00)	-	-	Not serious	Not serious	N/A3	Not serious	High
Serious adverse events 3-6 months (RR<1 favours isCGM)											
2	PRCT	324	0.80 , 1.25	RR 0.69 (0.35, 1.36)	10 per 100	3 fewer per 100 (7 fewer to 4 more)	Serious1	Not serious	Not serious	Very serious7	Very low
Severe hypoglycemia 3-6 months (RR<1 favours isCGM)											
1 (Haak 2017)	PRCT	224	0.80 , 1.25	RR 1.51 (0.16, 14.27)	1 per 100	1 more per 100 (1 fewer to 18 more)	Serious1	Not serious	N/A3	Very serious7	Very low
Hypoglycemia events 3-6 months (RR<1 favours isCGM)											
2	PRCT	324	0.80 , 1.25	RR 0.85 (0.36, 1.98)	6 per 100	1 fewer per 100 (4 fewer to 6 more)	Serious1	Not serious	Not serious	Very serious7	Very low
Device related AEs 3-6 months (RR<1 favours isCGM)											
1 (Wada 2020)	PRCT	100	0.80 , 1.25	RR 7.29 (0.93, 57.07)	2 per 100	12 more per 100 (0 more to 110 more)	Not serious	Not serious	N/A3	Serious6	Moderate
DKA 3-6 months (RR<1 favours isCGM)											

1 (Haak 2017)	PRCT	224	0.80 , 1.25	Not estimable	Not estimable	Not estimable	Serious1	Not serious	N/A3	Not estimable	Moderate
Hyposmolar hypoglycemic state 3-6 months (RR<1 favours isCGM)											
1 (Haak 2017)	PRCT	224	0.80 , 1.25	Not estimable	Not estimable	Not estimable	Serious1	Not serious	N/A3	Not estimable	Moderate
DTSQ - Total score 3-6 months (MD>0 favours isCGM)											
2	PRCT	300	+/- 2.41	MD 3.70 (2.57, 4.83)	-	-	Serious1	Not serious	Not serious	Not serious	Moderate
DQOL - 3-6 months (MD>0 favours isCGM)											
1 (Haak 2017)	PRCT	224	+/- 0.26	MD -0.20 (-0.34, -0.06)	-	-	Serious1	Not serious	N/A3	Serious6	Low
Self-rating anxiety scale <=3 months (MD<0 favours isCGM)											
1 (Wang 2021)	PRCT	80	+/- 3.11	MD -6.18 (-8.89, -3.47)	-	-	Very serious2	Not serious	N/A3	Not serious	Low
Self-rating depression scale <=3 months (MD<0 favours isCGM)											
1 (Wang 2021)	PRCT	80	+/- 3.02	MD -6.24 (-8.88, -3.60)	-	-	Very serious2	Not serious	N/A3	Not serious	Low
General comfort questionnaire <=3 months (MD>0 favours isCGM)											
1 (Wang 2021)	PRCT	80	+/- 3.98	MD 10.61 (6.94, 14.28)	-	-	Very serious2	Not serious	N/A3	Not serious	Low
Pittsburgh Sleep Quality Index <=3 (MD<0 favours isCGM)											
1 (Wang 2021)	PRCT	80	+/- 1.25	MD -2.17 (-3.26, -1.08)	-	-	Very serious2	Not serious	N/A3	Serious6	Very low
WHOQoLBREF - physiology <=3 months (MD<0 favours isCGM)											
1	PRCT	80	+/- 2.96	MD 6.56 (3.95, 9.17)	-	-	Very serious2	Not serious	N/A3	Not serious	Low
WHOQoLBREF - psychology <=3 months (MD<0 favours isCGM)											
1	PRCT	80	+/- 2.86	MD 6.30 (3.78, 8.82)	-	-	Very serious2	Not serious	N/A3	Not serious	Low

WHOQoLBREF - environment <=3 months (MD<0 favours isCGM)											
1	PRCT	80	+/- 2.54	MD 5.87 (3.62, 8.12)	-	-	Very serious2	Not serious	N/A3	Not serious	Low
WHOQoLBREF - social relations <=3 months (MD<0 favours isCGM)											
1	PRCT	80	+/- 2.62	MD 7.27 (4.92, 9.62)	-	-	Very serious2	Not serious	N/A3	Not serious	Low

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. Only one study so no inconsistency
4. I2 > 66.7%
5. I2 between 33.3% and 66.7%
6. 95% confidence intervals cross one end of the defined MIDs
7. 95% confidence intervals cross both ends of the defined MIDs

Appendix H – Economic evidence study selection



1 Appendix I – Economic evidence tables

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**
Freestyle Libre	10,450	6.14			
SMBG	5,535	5.04	4,916	1.09	UK £4,498/ QALY

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]

	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.
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 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	

Category	Rating	Comments
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**	

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Appendix J – Health economic model

Full details of the modelling are available in the economic model report.

Appendix K – Excluded studies

Clinical

Study	Reason for exclusion
Everett, Colin C, Reynolds, Catherine, Fernandez, Catherine et al. (2020) Rationale and design of the LIBERATES trial: Protocol for a randomised controlled trial of flash glucose monitoring for optimisation of glycaemia in individuals with type 2 diabetes and recent myocardial infarction. Diabetes & vascular disease research 17(5): 1479164120957934	- study protocol
Fonda, SJ, Salkind, SJ, Walker, MS et al. (2014) Heterogeneity of responses to real-time continuous glucose monitoring (RT-CGM) in patients with type 2 diabetes and its implications for application. Diabetes technology & therapeutics 16(suppl1): 13	- Secondary publication of an included study that does not provide any additional relevant information *Erhardt 2011, no relevant outcomes*
Fonda, Stephanie J, Graham, Claudia, Munakata, Julie 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	- Cost-effectiveness study
Fonda, Stephanie J, Salkind, Sara J, Walker, M Susan et al. (2013) Heterogeneity of responses to real-time continuous glucose monitoring (RT-CGM) in patients with type 2 diabetes and its implications for application. Diabetes care 36(4): 786-92	- Secondary publication of an included study that does not provide any additional relevant information *Erhardt 2011 no extra outcomes of interest*
Fortmann, Addie L., Bagsic, Samantha R. Spierling, Talavera, Laura et al. (2020) Glucose as the fifth vital sign: A randomized controlled trial of continuous glucose monitoring in a non-ICU hospital setting. Diabetes Care 43(11): 2873-2877	- Blinded retrospective CGM *CFGM data not given to patients*
Furler, John, O'Neal, David, Speight, Jane et al. (2020) Use of professional-mode flash glucose monitoring, at 3-month intervals, in adults with type 2 diabetes in general practice (GP-OSMOTIC): a pragmatic, open-label, 12-month, randomised controlled trial. The lancet. Diabetes & endocrinology 8(1): 17-26	- Study does not contain a relevant intervention *CGM data available to clinician only*

Study	Reason for exclusion
Gallieni, Maurizio, De Salvo, Cristina, Sabiu, Gianmarco et al. (2021) Continuous glucose monitoring in patients with type 2 diabetes on hemodialysis. Acta Diabetologica	- Study does not contain a relevant intervention
Haak, T., Hanaire, H., Ajjan, R. et al. (2017) Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes. Diabetes Therapy 8(3): 573-586	- Secondary publication of an included study that does not provide any additional relevant information *Open label only not RCT*
Heinrich E, Schaper NC, de Vries NK (2010) Self-management interventions for type 2 diabetes: a systematic review. European Diabetes Nursing 7(2): 71-76	- Study does not contain a relevant intervention *CGM included but sys rev focuses mostly on other self-management interventions, other sys revs for CGM specifically*
Khoja, Adeel, Zheng, Mingyue, Yang, Shenqiao et al. (2020) Comparing effects of continuous glucose monitoring systems (CGMs) and self-monitoring of blood glucose (SMBG) amongst adults with type 2 diabetes mellitus: A systematic review protocol. Systematic Reviews 9(1): 120	- study protocol
Levy, JC; Davies, MJ; Holman, RR (2017) Continuous glucose monitoring detected hypoglycaemia in the Treating to Target in Type 2 Diabetes Trial (4-T). Diabetes research and clinical practice 131: 161-168	- Blinded retrospective CGM *Blinded CGM*
Lind, Nanna, Norgaard, Kirsten, Lindqvist Hansen, Dorte et al. (2021) Real-time continuous glucose monitoring versus self-monitoring of blood glucose in adults with insulin-treated type 2 diabetes: A protocol for a randomised controlled single-centre trial. BMJ Open 11(1): 039760	- Duplicate reference *Duplicate form T1*
McGeoch G, Derry S, Moore RA (2007) Self-monitoring of blood glucose in type-2 diabetes: what is the evidence?. Diabetes/Metabolism Research and Reviews 23(6): 423-440	- Study does not contain a relevant intervention *No CGM SMBG only*
McMorrow, R, Manski-Nankervis, J-A, Thuraisingam, S et al. (2019) Is the use of retrospective continuous glucose monitoring associated with increased health service utilisation in people with type 2 diabetes? A secondary analysis of the GP-OSMOTIC Study. Australian journal of primary health 25(3): xxxvi	- Conference abstract

Study	Reason for exclusion
Meade, Lisa T (2012) The use of continuous glucose monitoring in patients with type 2 diabetes. Diabetes technology & therapeutics 14(2): 190-5	- Not a relevant study design *Not an SR*
Sato, Junko, Kanazawa, Akio, Ikeda, Fuki et al. (2016) Effect of treatment guidance using a retrospective continuous glucose monitoring system on glycaemic control in outpatients with type 2 diabetes mellitus: A randomized controlled trial. The Journal of international medical research 44(1): 109-21	- Blinded retrospective CGM *retrospective CGM*
Sato, Shuichi, Shimono, Dai, Sumiyoshi, Shusaku et al. (2020) Changes in psychological behavior accompanied by the short-term usage of flash glucose monitoring for newly diagnosed type 2 diabetes mellitus. Therapeutic Research 41(7): 577-586	- Data not reported in an extractable format *No outcomes have enough data to be extractable*
Schapira Wajman, D, Nunes Salles, JE, Marques Naldi, M et al. (2019) Accuracy of flash glucose monitoring system in hospitalized patients with type 2 diabetes mellitus-pilot study. Diabetes technology & therapeutics 21: A99	- Conference abstract
Singh, Lakshmi G., Scott, William H., Pinault, Lillian F. et al. (2020) Reducing inpatient hypoglycemia in the general wards using real-time continuous glucose monitoring: The glucose telemetry system, a randomized clinical trial. Diabetes Care 43(11): 2736-2743	- Blinded retrospective CGM *CGM vs blinded CGM*
Thielen, V, Scheen, A, Bringer, J et al. (2010) Attempt to improve glucose control in type 2 diabetic patients by education about real-time glucose monitoring. Diabetes & metabolism 36(3): 240-3	- Does not contain a relevant population *4 patients only who passed treatment*
Tildesley, Hugh D, Wright, Anthony M, Chan, Jeremy H M et al. (2013) A comparison of internet monitoring with continuous glucose monitoring in insulin-requiring type 2 diabetes mellitus. Canadian journal of diabetes 37(5): 305-8	- Full text paper not available *paper withdrawn*
Vigersky, RA, Fonda, SJ, Chellapta, M et al. (2013) Short- and long-term effects of real-time continuous glucose monitoring on patients with type 2 diabetes. Diabetes technology & therapeutics 15(suppl1): 20	- Duplicate reference *vigersky 2012 same paper*

Study	Reason for exclusion
Yaron, M, Roitman, E, Aharon-Hananel, G et al. (2019) Effect of Flash Glucose Monitoring Technology on Glycemic Control and Treatment Satisfaction in Patients With Type 2 Diabetes. Diabetes care	- Retrospective CGM (Data downloaded weeks after use)

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
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.	- People with type 1 diabetes only

Appendix L - Research recommendations – full details

L.1.1 Research recommendation

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

L.1.2 Why this is important

There is some evidence on the effectiveness and cost-effectiveness of CGM devices to improve glycaemic control in people with type 2 diabetes. However, this is based on RCT evidence with limited evaluation of how well these devices work on a daily basis in normal life. By using real-world data, it will be possible to identify how effective different CGM devices are to a wide range of people from different ages and backgrounds. This may lead to an increased understanding of CGM devices and make it possible to produce recommendations about their use for a wider range of people in future.

L.1.3 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 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	Understanding which CGM device is the most effective at improving glycaemic control will help to improve people's control of their diabetes. This may help to improve patient outcomes, such as reducing the number of hypoglycaemic episodes, as well as reducing time and costs for the NHS that are associated with treating people with less well controlled diabetes.
National priorities	High
Current evidence base	There are currently 13 RCTs on the use of CGM devices for people with type 2 diabetes. 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.1.4 Modified PICO table

Population	Adults with type 2 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