National Institute for Health and Care Excellence

Final

Type 1 diabetes in children and young people: diagnosis and management

[B] Evidence reviews for continuous glucose monitoring in children and young people with type 1 diabetes

NICE guideline NG18

Evidence reviews underpinning recommendations 1.2.60 to 1.2.70 and research recommendations in the NICE guideline

March 2022

Final

These evidence reviews were developed by the Guideline Development Team

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1 Continuous glucose monitoring in children and young people with type 1 diabetes

1.1 Review question

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

- continuous glucose monitoring (rtCGM)
- flash glucose monitoring (isCGM)
- intermittent capillary blood glucose monitoring? (SMBG)

1.1.1 Introduction

NICE guidelines state that people with diabetes should be empowered to self-monitor their blood glucose levels, and be educated about how to measure and interpret the results. Routine blood glucose testing is typically done using a finger-prick capillary blood sample. In the 2015 guidance, continuous monitoring of interstitial fluid glucose levels using a continuous glucose monitor is not recommended for routine use but can be considered for some people.

New studies identified by NICE's surveillance team and the possibility of decreasing cost and increasing access to continuous glucose management technologies suggests the evidence should be reviewed to ascertain the effectiveness of real-time continuous glucose monitoring (rtCGM) and intermittently scanned continuous glucose monitoring (isCGM), commonly referred to as "Flash" glucose monitoring versus standard self-monitoring of blood glucose (SMBG) techniques and each other. This review also aims to consider whether routine rtCGM/isCGM use is now more appropriate for certain populations of people with diabetes.

Please be aware that isCGM devices are not licensed for children under 4.

Table 1:Summary of the protocol

PICO Table	
Population	Children and young people with type 1 diabetes (<18 years old)
Intervention	• Continuous glucose monitoring (rtCGM) • Flash glucose monitoring (isCGM) • Intermittent capillary blood glucose monitoring (self-monitoring of blood glucose [SMBG])
Comparator	Compared to each other
Outcomes	• HbA1c • Time in target glucose range ○ Time above/below target glucose range • Hypoglycemia (severe/nocturnal) • Glycemic variability • Mortality • Satisfaction with CGM • Diabetic ketoacidosis (DKA) • % of data captured • Other adverse events

PICO Table	
	○ diabetes related hospitalisation; ○ serious adverse events; ○ severe monitor malfunction) • Mental health outcomes ○ Diabetes distress (including fear of hypoglycaemia and diabetes burnout) ○ Diabetes related depression ○ Body image issues related to device • Awareness of hypoglycemia • Adherence • Attendance to care services • Educational attainment • Quality of life (validated and continuous)

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 in more detail in the methods section appendix B.

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

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the minimally important difference (MID) (i.e. the point estimate is not in the zone of equivalence, see appendix B for details). In such cases, we state that the evidence showed that there is **an effect**.

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an **effect, but it is less than the defined MID.**

- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is **no meaningful difference**.

- Where the 95% CI crosses the line of no effect, and it is not completely between the MID, (i.e., it crosses one or both MIDs) the evidence **could not differentiate** between the comparators.

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

No significant subgroup differences followed our methodology outlined in appendix B were identified, so no subgroup analysis were reported in appendix G.

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 3,435 RCTs and systematic reviews were screened at title and abstract stage after deduplication.

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 adults with type 1 diabetes, CGM for adults with type 2 diabetes and CGM for children and young people with type 1 diabetes).

Of the 288 included studies, 70 were potentially relevant for the type 1 diabetes children and young people question. The other 218 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 type 2 diabetes).

The 70 studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A). Overall, 6 studies were included, along with 8 systematic reviews that were checked for additional references. No additional studies were identified from the systematic reviews.

Most studies compared rtCGM against SMBG but some compared isCGM to SMBG. The number of studies for each comparison is outlined in Table 2. Further information about these studies is shown in Table 3.

Table 2: List of comparisons and associated studies/trials

Comparison	Study
rtCGM vs SMBG (6 studies)	• Burckhardt 2018 • Deiss 2006 • JDRF 2008 • JDRF 2010 • Laffel 2020 • Hommel 2014
isCGM vs SMBG (2 studies)	• Boucher 2020 • Xu 2021

Regarding rtCGM vs isCGM, a check for observational studies and propensity matched cohort studies was carried out and nothing was identified. The committee therefore felt they had enough evidence to make recommendations.

See Appendix E for evidence tables and the reference list in section 1.1.8 References – included studies.

1.1.3.2 Excluded studies

Overall, 56 studies were excluded. 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: Summary of all included primary study characteristics

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes

Boucher 2020	RCT	64	• Age: 13-20 years
			• Duration of diabetes: >= 12 months
			• HbA1c level: >=9% 6 months prior to enrolment
				isCGM
				FreeStyle Libre system; Abbott Diabetes Care - 1 additional visit with sensor education
					SMBG
					Self-monitored blood glucose concentrations using their usual glucometer.
					(Mean 1.9 +/- 3.6 measures a day at baseline)
						6 months	• HbA1c (%) (mmol/mol)
							• % of CGM data captured
							• Number of Glucose monitor checks / day
							• Adverse events
							• DKA
							• Severe hypoglycemia
							• Hospitalisations
							• QoL (validated tools)
							  ○ PedsQL generic
							  ○ PedsQL Diabetes
							  ○ HFS
							  ○ DTSQ

Burckhardt 2018	Crossover RCT	49	• Age: 2 – 12 years
			• Duration of diabetes: More than 1 year
			• No previous CGM use in last 6 months
			• +1 parent per child
				rtCGM
				Dexcom G5 mobile CGM system
					SMBG
					Conventional blood glucose monitoring
					(Mean 6.2 measures / day at 3 months)
						3 months	• QoL (validated tools)
							  ○ Parental HFS
							  ○ PedsQL generic
							  ○ PedsQL diabetes
							  ○ DASS
							  ○ STAI
							  ○ PSQI

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
Deiss 2006	RCT	30	No details given beyond "children and adolescents" with T2D [Age range 2 to 16]	**rtCGM (n = 15)** A continuous glucose monitoring system (CGMS, Medtronic MiniMed Inc., Northridge, CA, USA)	**SMBG (N=15)** No data on measures/ day	3 months	• HbA1c (%) • Hypoglycaemia >180 • % of CGM data captured • Adverse events (mild local side effects)
Hommel 2014	Crossover RCT	72	People with T1D Duration of diabetes: >1 year Age: <= 18 years Treatment with continuous subcutaneous insulin infusion (CSII) therapy with rapid-acting insulin analogues for more than 6 months HbA1c between 7.5% and 9.5% (58.5 and 80.3 mmol/mol) Naive to CGM Had successfully completed a five-question multiple choice test concerning pump therapy and general understanding of diabetes	**rtCGM (n = 41)** Guardian REAL-Time Clinical; Medtronic, Tolochenaz, Switzerland	**SMBG (N = 41)** Sensor off Mean 5.2 +/- 0.2 measures /day	6 months	• PEDs-QL (children and parents) • DTSQ
JDRF 2008 JDRF 2010	RCT	114	• Aged 8 years and older • Duration of diabetes ≥1 year • Using an insulin pump or receiving at least three daily insulin injections • HbA1c 7.0 to 10.0% • Not used continuous glucose monitoring at home in the 6 months leading up to the trial	**rtCGM** DexCom Seven or the FreeStyle Navigator	**SMBG** Blood glucose meters and test strips Mean 7 +/- 2.5 measures/day	6 months	• HbA1c • Time in range ○ Amount of time per day the glucose level was 71 to 180 mg per decilitre (3.9 to 10.0 mmol per litre) • Time spent above/below target glucose range

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
							○ Amount of time per day the glucose level was - hypoglycaemic (≤70 mg per decilitre or ≤50 mg per decilitre [≤3.9 or ≤2.8 mmol per litre]) - hyperglycaemic (>180 mg per decilitre or >250 mg per decilitre [10.0 or 13.9 mmol per litre]) • Hypoglycaemia • Severe hypoglycaemia • Glycaemic variability • Diabetic ketoacidosis • Adverse events • Quality of life ○ Participants ≥18 years old completed the Hypoglycaemia Fear Survey (HFS) and Social Functioning Health Survey (SF-12) version 2 ○ Continuous Glucose Monitoring Satisfaction Scale (CGM-SAT)
Laffel 2020	RCT	153	• Age: 14 – 24 years • No previous CGM use for 3 months • Insulin regimen: total daily insulin of at least 0.4 units/kg/d • HbA1c level: >7.5% to <11%	**rtCGM (n = 74)** Dexcom G5, Dexcom, Inc	**(SMBG n = 79)** Continue BGM with a blood glucose meter without CGM	6 months	• HbA1c (%) • Time in range: 70 to 180mg/dL • Time in hyperglycemia(>180 / >250 mg/dL) • Time in hypoglycemia • Glycemic variability: CV

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
					Mean baseline 3.5 measures a day (95% CI 3,4.5)		• % of CGM data captured • CGM use days/week • hours of CGm data • Adverse events • Severe hypoglycemia • DKA • SAE • QoL (validated tools) ○ PAID-P ○ GMSS ○ Hypoglycemia confidence ○ Sleep quality
Xu 2021	RCT	80	• Age: 10-19 years • Duration of diabetes: >1 year • No previous CGM use 3 months before study • Use of multiple daily insulin (MDI) and continuous subcutaneous insulin infusion (CSII) for at least 3 months, • stable diabetes medication regimen for 3 months before study entry (change in insulin <= 20%), • previous documentation of blood glucose level self-monitoring regularly for 2 months (at least three times per day) and willingness to continue for at least 6 months • HbA1c level: >7 - <10 % • Willingness to wear CGM • Can speak, read, and write chinese • Ability to use WeChat program	**isCGM (n = 25)** (Libre 1, Abbott Diabetes Care) - A specialist applied the flash glucose monitor to the back of the upper arm through a simple disposable applicator: a thin wire (flexible probe) was subcutaneously implanted, and the sensor was fixed to the	**SMBG (N=30)** a conventional home glucometer was used to monitor blood glucose ≥ three times a day, and the blood glucose monitoring values were uploaded to the Wenjuan survey platform. “at least 3 measures a day” in	6 months	• HbA1c (%) • Hypoglycaemia • number of episodes <3.9mmol • QoL (validated tools) ○ DMTSQ ○ DQoL ○ CHFSII

Study	Study type	N	Population	Intervention	Comparator	Follow up	Outcomes
				application site with an adhesive film. It recorded the blood glucose value at 15-minute intervals automatically, and the blood glucose value can be determined at any time from the display	inclusion criteria		

1.1.5 Summary of the effectiveness evidence

Evidence in meta-analysis

Table 4: Summary of GRADE: rtCGM vs SMBG

Outcome	Sample size	Final effect estimate	MIDs	Quality	Interpretation of effect
HbA1c (%) at 3 months	30	MD 0.20 (-0.59, 0.99)	+/- 0.50	Very low	Could not differentiate
HbA1c (mmol/mol) - 6 months	267	MD -0.23 (-0.42, -0.04)	+/- 0.50	Very low	No meaningful difference
HbA1c relative reduction >10% 6 months	**267**	**RR 2.91** **(1.62, 5.23)**	**0.80 , 1.25**	**Low**	**Effect (Favouring rtCGM)**
HbA1c relative reduction >= 5% 6 months	**114**	**RR 1.73** **(1.10, 2.72)**	**0.80 , 1.25**	**Low**	**Effect (Favouring rtCGM)**
HbA1c achieved target <7.0% 3 months	**267**	**RR 1.96** **(1.10, 3.50)**	**0.80 , 1.25**	**Very low**	**Effect (Favouring rtCGM)**
HbA1c achieved target <7.5% 6 months	153	RR 1.37 (0.54, 3.50)	0.80 , 1.25	Very low	Could not differentiate

Outcome	Sample size	Final effect estimate	MIDs	Quality	Interpretation of effect
Time in range (%) [70 - 180 mg/dL] 6 months	**153**	**MD 6.90 (3.10, 10.70)**	**+/- 5.00**	**Low**	**Effect (Favouring rtCGM)**
Time above range (%) >180 mg/dL 6 months	153	MD -5.80 (-10.00, -1.60)	+/- 6.62	Low	Effect less than MID (Favouring rtCGM)
Time above range (%) >250 mg/dL 6 months	**153**	**MD -7.90 (-12.30, -3.50)**	**+/- 6.94**	**Low**	**Effect (Favouring rtCGM)**
Glycemic variability: coefficient of variation 6 months	153	MD -2.20 (-3.90, -0.50)	+/- 2.68	Low	Effect less than MID (Favouring rtCGM)
Severe hypoglycemia (n) <3.9 mmol/l 6 months	267	RR 0.92 (0.34, 2.44)	0.80 , 1.25	Very low	Could not differentiate
Hypoglycemia fear survey - total 3 months	**98**	**MD -8.50 (-12.70, -4.30)**	**+/- 5.30**	**Moderate**	**Effect (Favouring rtCGM)**
Hypoglycemia fear survey - behaviour 3 months	**98**	**MD -3.30 (-5.00, -1.60)**	**+/- 2.15**	**Moderate**	**Effect (Favouring rtCGM)**
Hypoglycemia fear survey - worry 3 months	**98**	**MD -5.20**	**+/- 3.66**	**Moderate**	**Effect (Favouring rtCGM)**

Outcome	Sample size	Final effect estimate	MIDs	Quality	Interpretation of effect
		(-8.10, -2.30)			
Hypoglycemia fear survey - worry 6 months	218	MD -1.60 (2.36, -5.56)	+/- 7.33	High	No meaningful difference
Hypoglycemia fear survey - parents 6 months	218	MD 0.30 (-4.22, 4.82)	+/- 9.32	High	No meaningful difference
Quality of life (PEDS) - generic - 3 months	98	MD 2.60 (-0.90, 6.10)	+/- 4.72	Moderate	Could not differentiate
Quality of life (PEDS) - generic - 6 months	362	MD -0.31 (-1.77, 1.16)	+/- 4.72	Moderate	No meaningful difference
Quality of life (PEDS) - diabetes - 3 months	98	MD 2.60 (-0.20, 5.40)	+/- 5.27	Moderate	Could not differentiate
Quality of life (PEDS) - diabetes - 6 months	218	MD 1.50 (-1.90, 4.90)	+/- 5.27	High	No meaningful difference
Quality of life (PEDS) - family impact - 3 months	98	MD 2.60 (-0.20, 5.40)	+/- 3.54	Moderate	Could not differentiate

Outcome	Sample size	Final effect estimate	MIDs	Quality	Interpretation of effect
Quality of life (PEDS) - generic - parents 6 months	362	MD -2.00 (-6.12, 2.12)	+/- 4.88	Very low	Could not differentiate
Quality of life (PEDS) - diabetes - parents 6 months	218	MD -1.60 (-5.19, 1.99)	+/- 4.54	Moderate	Could not differentiate
DASS - Stress - 3 months	**98**	**MD -2.20** **(-3.80, -0.60)**	**+/- 2.02**	**Moderate**	**Effect (Favouring rtCGM)**
DASS - Anxiety - 3 months	98	MD -1.00 (-2.50, 0.50)	+/- 1.89	Moderate	Could not differentiate
DASS - Depression - 3 months	98	MD -1.10 (-2.40, 0.20)	+/- 1.64	Moderate	Could not differentiate
STAI - state - 3 months	**98**	**MD -3.60** **(-6.40, -0.80)**	**+/- 3.54**	**Moderate**	**Effect (Favouring rtCGM)**
STAI - trait - 3 months	**98**	**MD -3.50** **(-5.40, -1.60)**	**+/- 2.40**	**Moderate**	**Effect (Favouring rtCGM)**
PSQI - 3 months	**98**	**MD -1.50**	**+/- 1.26**	**Moderate**	**Effect (Favouring rtCGM)**

Outcome	Sample size	Final effect estimate	MIDs	Quality	Interpretation of effect
		(-2.50, -0.50)			
PAID-p 6 months	218	MD -0.80 (-4.78, 3.18)	+/- 8.24	High	No meaningful difference
DKA (n) 6 months	267	RR 3.20 (0.34, 30.11)	0.80 , 1.25	Very low	Could not differentiate
SAE 6 months	153	RR 1.07 (0.15, 7.39)	0.80 , 1.25	Very low	Could not differentiate

Table 5: Summary of GRADE: isCGM vs SMBG

Outcome	Sample size	Final effect estimate	MIDs	Quality	Interpretation of effect
HbA1c (%) - <=3 months	64	MD -0.70 (-1.51, 0.11)	+/- 0.50	Low	Could not differentiate
HbA1c (%) >= 6 months	119	MD -0.07 (-0.63, 0.49)	+/- 0.50	Very low	Could not differentiate
HbA1c (mmol/mol) <= 3 months	64	MD -6.60 (-15.29, 2.09)	+/- 5.50	Low	Could not differentiate
HbA1c (mmol/mol) <= 6 months	64	MD -2.10 (-9.60, 5.40)	+/- 5.50	Low	Could not differentiate
Number of glucose checks <= 3 months	**64**	**MD 3.20 (2.97, 3.43)**	**+/- 0.23**	**Moderate**	**Effect (Favouring isCGM)**
Number of glucose checks <= 6 months	**64**	**MD 2.80 (1.72, 3.88)**	**+/- 1.10**	**Moderate**	**Effect (Favouring isCGM)**
Hypoglycemia episodes per month <3.1 mmol/l >= 6 months	55	MD 1.85 (-1.08, 4.78)	+/- 3.50	Very low	Could not differentiate
Quality of life (PEDS) generic - total >= 6 months	64	MD -1.20 (-6.50, 4.10)	+/- 4.72	Low	Could not differentiate
Quality of life (PEDS) diabetes - total >= 6 months	64	MD -1.10 (-6.20, 4.00)	+/- 5.27	Low	Could not differentiate

Hypoglycemia fear survey - behaviour scale >=6 months	64	MD 0.18 (-0.08, 0.44)	+/- 0.27	Low	Could not differentiate
Hypoglycemia fear survey - worry scale >= 6 months	64	MD -0.13 (-0.37, 0.11)	+/- 0.24	Low	Could not differentiate
DTSQ >= 6 months	64	MD 0.47 (0.00, 0.94)	+/- 0.48	Low	Effect less than MID (Favouring is CGM)
DMTSQ >= 6 months	55	MD -2.80 (-7.87, 2.27)	+/- 5.47	Very low	Could not differentiate
DQOL >= 6 months	55	MD 2.55 (-8.20, 13.30)	+/- 11.28	Very low	Could not differentiate
Chinese hypoglycemia fear survey >= 6 months	55	MD 1.25 (-6.57, 9.07)	+/- 5.96	Very low	Could not differentiate
DKA	64	RR 1.13 (0.38, 3.32)	0.80 , 1.25	Very low	Could not differentiate

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. However, none of these studies were in a population of children and young people with type 1 diabetes, and therefore all these studies were excluded from the review. The health economic evidence study selection is presented as a flowchart in appendix H.

1.1.6.2 Excluded studies

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

1.1.6.2 Economic model

No economic modelling was undertaken for this review question. However, the committee did consider the results of the modelling undertaken for adults with type 1 diabetes when making recommendations for children and young people.

1.1.7 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 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.

Hypoglycaemia events, severe hypoglycaemia events, and nocturnal hypoglycaemia were also considered to be important outcomes. These are often highlighted by people living with type 1 diabetes as key due to the fear these events generate and the impact they can have on quality of life. 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.

The committee highlighted that fear of hypoglycaemia was a key quality of life outcome, due to the severity this fear has on children and young people and their parents and carers.

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

The quality of the evidence

All outcomes other than mortality were captured in at least 1 comparison in the data extracted. There was no time in range or glycaemic variability data available for isCGM vs SMBG. Time in range is harder to record in isCGM as this does not continuously capture glycaemic levels in the same way as a rtCGM device.

The committee acknowledged that there was no evidence directly comparing rtCGM and isCGM in children and young people, and found this unsurprising considering the small amount of evidence in the adult population for the same comparison. The committee judged that for type 1 diabetes they had enough evidence to justify the superiority of rtCGM over isCGM in this population, and as a result did not consider there was need for a research recommendation. The committee did note that due to the increasing incidence of type 2 diabetes in children and young people, they should make a research recommendation into clinical effectiveness for this group (see Appendix L.1.1).

The committee also noted that much of the outcome evidence for diabetes in children and young people is now available in routinely collected real-world data, rather than clinical trials. They therefore made another research recommendation to determine effectiveness and cost effectiveness of CGM devices in children and young people using this evidence base (see Appendix L.1.2).

Evidence for rtCGM vs SMBG ranged from very low to high quality and all but one of the studies (Laffel 2020) were directly applicable to the review question. Laffel (2020) was considered partially applicable to the review because it included people with an age range of 14 – 24 years. However, the 14-<19 population made up 64.9% - 67% of the study, and so it still met the criteria in the protocol for >50% of included people being paediatric cases. As the study was at low risk of bias and presented many outcomes, the committee thought it was important to consider as part of the review, The quality of outcome data from some of the other studies were downgraded for risk of bias, mostly due to limited information about randomisation and allocation concealment methods. The committee pointed out that no study was based entirely in the UK. The SWITCH trial (Hommel 2014) had the majority of its centres in the UK, but only reported 2 quality of life outcomes, meaning there was no information to directly show the clinical effectiveness of CGM in UK practice. The committee noted availability and cost of devices would vary considerably across other healthcare systems and data from other countries and this had to be taken into account when making recommendations. The committee did highlight that hypoglycaemia fear survey outcomes were of moderate quality and did show an effect in rtCGM vs SMBG, indicating the effectiveness of rtCGM in this key quality of life outcome.

Only 2 studies compared the use of isCGM to SMBG, and one of these (Boucher 2020) had an inclusion criteria age limit of 13-20 that was only partially applicable to this review. However, as the mean age was within the inclusion criteria for this review, the committee considered that this was still acceptable for inclusion in the analysis. The other study (Xu 2021) was graded as high risk of bias due to limited information about the type of analysis used, and so outcomes containing this study where it was weighted >33.3% were downgraded for very serious risk of bias.. Due to reasons outlined above, the committee did not have full confidence in this evidence alone and used a combination of the evidence, and their clinical knowledge and experience to inform recommendations for the use of CGM for children and young people with type 1 diabetes.

Benefits and harms

The committee considered that the results showing a decrease in HbA1c and an increase in time in target glucose range in rtCGM vs SMBG were promising outcomes, and reflected

their experience from clinical practice. They specifically noted that time in range increased by more than the minimal important difference, they interpreted the increase in time in range to be clinically meaningful (>5%). They acknowledged that only dichotomous HbA1c outcomes were effective, rather than the continuous HbA1c outcomes. However they consider these to be acceptable from their experience and were included in the study protocol as relevant outcomes. The fact that these results were also supported by a reduction of time in hyperglycemia and a reduction in concerns reported in the hypoglycemia fear survey (an important and a moderate quality outcome), both of which the committee noted had clinical importance gave them confidence that the effects shown in the meta-analysis were supportive of rtCGM use in children and young people. The committee did not consider any other quality of life measures to be as important in decision making.

For isCGM, the committee noted that none of the outcomes they deemed informative showed an effect greater than the minimally important difference (MID), and most of the outcomes showed no meaningful difference, or could not differentiate between isCGM or SMBG. There was an effect of an increased number of glucose checks in isCGM users vs SMBG. However the committee considered that this outcome was not informative regarding the effectiveness of isCGM and it did not answer the review question. They explained there were a number of reasons unrelated to its isCGM effectiveness as to why glucose check numbers might increase, particularly in a clinical study where people were likely reminded of the importance of recording data.

Although some outcomes showed no meaningful difference, or could not differentiate between rtCGM or SMBG, where there was an effect it consistently favoured the use of rtCGM.

As the evidence showed key outcomes favoured rtCGM over SMBG, the committee recommended rtCGM use first in all children and young people with type 1 diabetes, only offering isCGM if rtCGM is not preferred or contraindicated. The committee highlighted that the active component of isCGM, of having to “swipe to take a reading” although easier than doing a blood test may be part of the reason adherence may not be as good in some young people more than adults as it requires them to undertake an action. They also highlighted that currently the isCGM device Freestyle Libre does not have a license for children aged under 4 so could not be used in that age group. They also highlighted that the function of sharing readings with parents or carers and is available for both rtCGM and isCGM. This function is important for young children but also for older children as they become more independent at school and start to make their own decisions about meals and insulin doses. Feedback from a CGM device that is provided to both a child and their parents or carers can help to provide remote support and early identification of hypoglycaemia.The committee highlighted that the individual choice element of different CGM devices would be a benefit to children and young people and their parents or carers, as the ‘best’ device for each individual would depend on their preferences, needs and characteristics. They therefore included a summary table in the recommendations outlining the factors to consider when choosing a CGM device. This was adapted from a list of factors that the committee had already decided were important for adults with type 1 diabetes (see evidence review on continuous glucose monitoring in adults with type 1 diabetes). Changes to this list were made based on the committee’s clinical knowledge and experience. They agreed it was important to acknowledge the role of the parent or carer in the decision-making process when deciding on the best method of glucose monitoring for children and young people, so this was added to the list of factors. The recommendations for adults for type 1 diabetes indicates that the ease of use should be considered when choosing the best method of blood glucose monitoring, considering factors such as whether someone has limited dexterity. The committee discussed how other factors should also be considered for children and young people, such as their age and abilities and how this might affect the best choice of monitor. They thought it was also important to consider whether other people would have to take recordings from the device, such as teachers or other people who temporarily care for the child or young person. An additional consideration is how unpredictable their activity patterns are and whether they

take part in sport and exercise. The committee noted that children and young people often have less predictable activity patterns than adults and so it is important for them to be aware of their changing blood glucose levels in response to any changes in activity.

The committee clarified that the child or young person and their families or carers should consult with a member of the diabetes care team with expertise in the use of CGM. Furthermore, children and young people using CGM who have language difficulties or physical or learning disabilities would also benefit from this team's support.

The committee agreed that the recommendations should also highlight the importance of children and young people and their parents or carers being given education about CGM. This will help them understand how CGM works and the benefits it can provide. Improving understanding of CGM will increase the likelihood that it will be used correctly, such as scanning frequently and reporting the results so that no important data is missed. This will help children and young people gain the greatest benefit from the use of this technology and be able to manage their diabetes effectively. Extra effort should be made to ensure that the training is accessible to families where English is not their first language by use of interpreters and providing information in different languages.

The committee highlighted that it was important to use the device consistently to ensure a more positive effect. They therefore made a recommendation for the device to be worn 70% of the time, and for education and support to be provided if this wasn't the case. This recommendation was also made to avoid ongoing prescription of devices that aren't being used, and to give providers an opportunity to address any barriers that may be reducing someone's ability to use the device effectively. The committee justified this 70% figure as this was reported in the JDRF study (2008, 2010) which showed CGM use of on average >= 6 days a week was predictive of positive outcomes. This usage figure from the JDRF study was also considered in the Chase (2010) study, which showed the 17 subjects using CGM >=6 days/week had substantially greater improvement from baseline in HbA1c than did the 63 subjects using CGM <6 days/week. The committee acknowledged that 80% is a high threshold, and that in clinical practice the more lenient threshold of 70% is used, they therefore deferred to current practice and their clinical experience for this value.

The committee emphasised that use of less than 70% should trigger a discussion to assess whether the device is working for them, or steps could be taken to help make use easier. The committee stressed that this should be a positive discussion to encourage and support the use of the device. This could include initially introducing CGM over a trial period and explaining that the benefits will be assessed over the trial period to decide whether it is an appropriate longer-term option. This is useful to assess both clinical benefit, such as reduction in hypoglycaemic episodes, and benefit to the child or young person using it. For instance, while some will find CGM a helpful method to manage their diabetes, others may feel overwhelmed by the additional information it provides. The committee discussed how temporary, rather than permanent, use of CGM may actually be useful for some children and young people. Using CGM for a short period of time may help children and young 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, children and young people can still benefit from CGM even if is decided that they do not want to use the monitor on a long-term basis. By making people aware from the outset that the effectiveness of CGM will be assessed based on discussions between clinicians and children or young people and their families and carers, 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 child or young person.

The committee highlighted that one barrier to adherence to CGM that is a particular area of concern for children and young people is that some children develop skin reactions when wearing a CGM device due to the sensor adhesive. The committee therefore made a

research recommendation (see Appendix L.1.3) to investigate strategies to reduce local skin reactions to promote ease of use of these devices.

Cost effectiveness and resource use

In the absence of any economic evidence specific to children and young people with type 1 diabetes, the committee considered whether the evidence from adults with type 1 diabetes could reasonably be extrapolated to the younger population. They agreed that, assuming the same clinical benefits for a technology were identified in children and young people as in adults, then the technology should be at least as cost-effective in children and young people as in adults. This was because there are some situations where the same outcomes would be expected in children and adults (for example, the direct quality of life impact of a hypoglycaemic event) and some where the benefit might be larger in children (for example fear of hypoglycaemia, where both the child and their parents/guardians may experience this fear), but nothing where the impact in children would be expected to be less. The committee agreed there would be limited value in additional modelling specific to children and young people because of the extra uncertainties in the CORE diabetes model for that population.

The committee agreed the clinical review showed similar benefits for rtCGM in children as in adults, and were therefore comfortable to extrapolate the cost-effectiveness results, concluding that rtCGM was cost-effective in this population. However, since the same clinical benefits were not found for isCGM in children as in adults, the committee agreed those cost-effectiveness findings could not be extrapolated, and therefore were not prepared to conclude that isCGM is a cost-effective technology. They therefore agreed the use of isCGM should be restricted to those people who are unable to or do not want to use rtCGM.

They agreed that this finding (a positive result for rtCGM but not for isCGM) was consistent with their experience of the technologies in children and young people. The committee highlighted the fact that rtCGM has better functionality that makes it more suitable for children and young people. Although some versions of isCGM also have active alerts/alarm functions that warn users of immediate or impending hypoglycaemic events, they still require users to consciously scan the sensor to obtain glucose data. rtCGM, on the other hand, automatically shows a continuous stream of real-time numerical and graphical information on the receiver, so is easier to manage for children and young people, or their parents/guardians. This could lead to a higher adherence rate for rtCGM compared with isCGM among the younger cohorts. They also agreed that if a child or young person expressed a clear preference for using isCGM over rtCGM, their adherence was then likely to be better, meaning the device would be beneficial, as adherence was felt to be the key reason for rtCGM being a more effective technology on average in children and young people.

The committee noted that although the new recommendations are an expansion of the use of rtCGM compared to the previous recommendations for children and young people, the resource impact will be relatively small compared with current practice, as in recent years there has already been a considerable expansion of it's use in this population. Additionally, the population of children and young people with type 1 diabetes is much smaller than the population of adults with type 1 diabetes, and rtCGM is already being used in a considerable proportion of this the paediatric population, meaning the recommendations do not represent a considerable a change in practice as they do for adults. They also noted that there were a number of different rtCGM devices available with considerable overlap in functionality and features, and that therefore if there were multiple different devices available that would meet the person's needs and preferences, the cheapest of those available devices should be used.

The recommendations on education, monitoring and support for people using rtCGM are not expected to require substantial additional resources. This is because education, monitoring and support are al already recommended for all children and young people with type 1

diabetes and would be necessary whether or not a person was using rtCGM. Group training sessions rather than individual training sessions will help reduce the extra resource that maybe required for this purpose.

Other factors the committee took into account

The committee considered extending this recommendation to all children and young people with type 1 diabetes would help remove the observed discrepancies in clinical practice and address known inequalities in access. For example, those from lower socioeconomic groups or those from black, Asian and minority ethnic minority groups who from their clinical experience have been less likely to be prescribed these devices. Despite the positive recommendation for the use of CGM in children and young people with type 1 diabetes, the committee were concerned that inequalities may still occur with uptake of CGM being lower in certain groups. To address this the committee added a recommendation outlining actions to address this. The committee also agreed that capillary blood glucose monitoring is still needed as a back-up in situations such as when blood glucose levels are changing quickly or due to technology failure.

Recommendations supported by this evidence review

This evidence review supports the updated recommendations in NG18: 1.1.2 – 1.1.12 and research recommendations 7 -9.

1.1.8 References – included studies

1.1.12.1 Effectiveness

Systematic reviews (checked for references)

Battelino, T.; Dovc, K.; Bratina, N. (2015) Real-time continuous glucose monitoring in children and adolescents. Front. Diabetes 24: 99-109

Dorando, Elena; Pieper, Dawid; Haak, Thomas (2020) Continuous Glucose Monitoring for Glycemic Control in Children and Adolescents Diagnosed with Diabetes Type 1: A Systematic Review and Meta-Analysis. Experimental and Clinical Endocrinology and Diabetes

Dovc, Klemen; Bratina, Natasa; Battelino, Tadej (2015) A new horizon for glucose monitoring. Hormone research in paediatrics 83(3): 149-56

Golicki, D T, Golicka, D, Groele, L et al. (2008) Continuous Glucose Monitoring System in children with type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetologia 51(2): 233-40

Pieper, Dawid; Dorando, Elena; Haak, Thomas (2021) Erratum: Continuous Glucose Monitoring for Glycemic Control in Children and Adolescents Diagnosed with Diabetes Type 1: A Systematic Review and Meta-Analysis (Journal of Physical Chemistry DOI: 10.1055/a-1268-0967). Experimental and Clinical Endocrinology and Diabetes

Poolsup, N.; Suksomboon, N.; Kyaw, A.M. (2013) Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. Diabetology and Metabolic Syndrome 5(1): 39

Primary studies

Boucher, Sara E., Galland, Barbara C., Tomlinson, Paul A. et al. (2020) Effect of 6 months of flash glucose monitoring in youth with type 1 diabetes and high-risk glycemic control: A randomized controlled trial. Diabetes Care 43(10): 2388-2395

Burckhardt, Marie-Anne, Roberts, Alison, Smith, Grant J et al. (2018) The Use of Continuous Glucose Monitoring With Remote Monitoring Improves Psychosocial Measures in Parents of Children With Type 1 Diabetes: A Randomized Crossover Trial. Diabetes care 41(12): 2641-2643

Deiss, D, Hartmann, R, Schmidt, J et al. (2006) Results of a randomised controlled cross-over trial on the effect of continuous subcutaneous glucose monitoring (CGMS) on glycaemic control in children and adolescents with type 1 diabetes. Experimental and clinical endocrinology & diabetes: official journal, German Society of Endocrinology [and] German Diabetes Association 114(2): 63-7

Hommel E, Olsen B, Battelino T et al. (2014) Impact of continuous glucose monitoring on quality of life, treatment satisfaction, and use of medical care resources: analyses from the SWITCH study. Acta diabetologica 51(5): 845-851

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

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

Xu, Yuejie, Xu, Lei, Zhao, Weijing et al. (2021) Effectiveness of a wechat combined continuous flash glucose monitoring system on glycemic control in juvenile type 1 diabetes mellitus management: Randomized controlled trial. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 14: 1085-1094

MID studies

Little RR, Rohlfing CL. The long and winding road to optimal HbA1c measurement. Clin Chim Acta. 2013 Mar 15;418:63-71. doi: 10.1016/j.cca.2012.12.026. Epub 2013 Jan 11. PMID: 23318564; PMCID: PMC4762213.

Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-1603. doi:10.2337/dci19-0028

Hilliard ME, Lawrence JM, Modi AC, et al. Identification of minimal clinically important difference scores of the PedsQL in children, adolescents, and young adults with type 1 and type 2 diabetes. Diabetes Care. 2013;36(7):1891-1897. doi:10.2337/dc12-1708

1.1.12.2 Economic

No economic studies were included in this review.

Appendices

Appendix A – Review protocols

Review protocol for continuous glucose monitoring in children and young people with type 1 diabetes

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Glucose monitoring in children and young people with type 1 diabetes
2.	Review question	***Guideline:*** Type 1 diabetes in children and young people: diagnosis and management (NG18) ***Question***: In children and young people with type 1 diabetes, what is the most effective method of glucose monitoring to improve glycaemic control: - continuous glucose monitoring - flash glucose monitoring - intermittent capillary blood glucose monitoring
3.	Objective	To determine the clinical and cost effectiveness of different glucose monitoring methods in improving glycaemic control in children and young people with type 1 diabetes
4.	Searches	The following databases will be searched: Clinical searches:

		• Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • DARE • MEDLINE • MEDLINE In Process • MEDLINE ePubs • PsycINFO Economic searches: • Econlit • Embase • HTA • MEDLINE • MEDLINE In Process • MEDLINE ePubs • NHS EED • PsycINFO Searches will be restricted by: • English language

		• Study designs of RCTs, SRs and observational studies will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results There was no date limit set for these searches. Other searches: • N/A The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Type 1 diabetes in children and young people.
6.	Population	Children and young people with type 1 diabetes Children and young people are defined as 18 years and below
7.	Intervention	• Continuous glucose monitoring • Flash glucose monitoring • Intermittent capillary blood glucose monitoring Definitions:

		Continuous glucose monitoring: Consists of a subcutaneous sensor which continuously measures the glucose levels in the interstitial fluid. Data on glucose level and direction/rate of change is automatically sent to a display device (a handheld monitor, smart phones or pump) and the user can obtain real-time data as well as trends. The user can then analyse data and respond to changes in real-time or can make changes to insulin delivery, dose or timing based on retrospective data or trends. CGM models allow users to set alerts for high and low glucose levels, and rapid rate of change of glucose levels. Continuous glucose monitoring can also be referred to as real time CGM (rtCGM). **Flash glucose monitoring:** Consists of a subcutaneous sensor which continuously measures the glucose levels in the interstitial fluid. The user can obtain real-time data as well as trends by scanning the sensor with a reader device (including smart phones). The information provided gives a glucose level and information regarding the rate of change of glucose levels. Flash glucose monitoring can also be referred to as intermittently scanned CGM (isCGM). **Intermittent capillary blood glucose monitoring:** Conventional self-monitoring of blood glucose (SMBG) through 'finger prick' testing. Alternate sites may also be used for testing such as the palm, the upper forearm, the abdomen, the calf or the thigh.
8.	Comparator	Compared to each other

		• **Note:** comparison group should be on the same insulin regimen as intervention group (e.g., rapid acting, short acting, intermediate, long acting or mixed insulin) as the treatment group.
9.	Types of study to be included	• RCTs • Systematic review of RCTs • If insufficient[1] RCT evidence is identified for individual comparisons, comparative prospective observational studies ○ If no prospective cohort studies are identified, comparative retrospective observational studies will be included. **Note:** Only cohort and other observational studies that attempt to assess and adjust for baseline differences (e.g., through propensity matching) or adjust for confounding (e.g., maternal age, smoking and BMI) in multivariable analysis will be included. [1]: This will be assessed for the review. There is no strict definition, but in discussion with the guideline committee we will consider whether we have a large enough quantity of data to form the basis for a recommendation.

10.	Other exclusion criteria	• Exclude studies <1-week duration
		
		• Studies with mixed adult and children populations will be excluded if:
		
		  ○ data has not been reported for the subgroup of children AND
		
		  ○ ≤50% of people are aged <18 years

		• 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 OR,
		  ○ the population contains ≤70% of type 1 diabetes patients
		• Non-English language studies
		• Conference abstracts
		• Studies which examine retrospective (blinded) glucose monitoring
		• Studies with closed-loop systems.

11.	Context	This review is part of an update of the NICE guideline on Type 1 diabetes in children: diagnosis and management (NG18). https://www.nice.org.uk/guidance/ng17 This update covers continuous glucose monitoring in children and young people with type 1 diabetes. This guideline will also cover all settings where NHS healthcare is provided or commissioned.
12.	Primary outcomes (critical outcomes)	All outcomes will be sorted into up to 3 months, up to 6 months, up to 12 months, >12 months • HbA1c (dichotomous or continuous outcome, depending how it is reported

		• Time spent in target glucose range
		  ○ Time spent above target glucose range
		  ○ Time spent below target glucose range
		• Hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) including:
		  ○ severe hypoglycaemia
		  ○ nocturnal hypoglycaemia
		• Glycaemic variability
		• Mortality
		• Children and young people's and families' satisfaction with intervention (including impact of pain and burden of intervention) – measured by validated tools
		• Diabetic ketoacidosis (DKA)
		• % of data captured

13.	Secondary outcomes (important outcomes)	• Other adverse events (dichotomous) limited to:
		  ○ Diabetes related hospitalisation
		  ○ malfunction of CGM monitor
		  ○ serious adverse events

		• Mental health outcomes:
		  ○ Diabetes distress (including fear of hypoglycaemia and diabetes burnout)
		  ○ Diabetes related depression
		  ○ Body image issues related to device
		• Awareness of hypoglycaemia
		• Adherence (dichotomous)
		• Attendance to care services
		• Educational attainment
		• Quality of life (continuous) – measured by validated tools (e.g., Short Form 12 (SF-12), Glucose Monitoring System Satisfaction Survey (GMSS), BG Monitoring System Rating Questionnaire (BGMSRQ), Hypoglycaemia Fear Survey- II (HFS-II))

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software.

		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Randomised control trials (individuals or cluster) will be assessed using the Cochrane risk of bias tool 2.0. Assessment of observational studies will be dependent on study design. Cohort studies will be assessed using the Cochrane ROBINS-I tool while case-control studies will be assessed using CASP case control checklist.
16.	Strategy for data synthesis	For details please see section 6 of Developing NICE guidelines: the manual Meta-analysis will be conducted where appropriate. Evidence will be grouped into the following categories: • ≤6 months (or the one nearest to 6 months if multiple time-points are given) • >6 months (or the longest one if multiple time-points are given)
17.	Analysis of sub-groups	The following groups will be considered for subgroup analysis if heterogeneity is present: • Children under 5 years old • School age children (6 - 12 years)

		• Adolescents (>12 years) Results will be stratified by the following subgroups where possible: • Type of insulin regimen (e.g., rapid acting, short acting, intermediate, long acting or mixed insulin) • Mode of insulin delivery (e.g., multiple daily injections, continuous subcutaneous insulin infusion or insulin pump) • Length of CGM monitoring • Different testing sites in SMBG The following groups will be considered for subgroup analysis if heterogeneity is present: • People with learning difficulties or autism • People with renal impairment • People who have hypoglycaemic unawareness • People who are unable to self-test • People with distress/depression/co-morbid mental ill-health • frequency of CGM (real time) • frequency of CGM (intermittently scanned) • 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)
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-ng18
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

32.	Keywords	Continuous glucose monitoring, flash glucose monitoring, intermittent capillary blood glucose monitoring, type 1 diabetes, glycaemic control, children, young people
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]
36.	Details of final publication	www.nice.org.uk

Appendix B – Methods

Priority screening

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

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

Evidence of effectiveness of interventions

Quality assessment

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

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

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

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

Methods for combining intervention evidence

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

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences.

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

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

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

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

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

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

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

Minimal clinically important differences (MIDs)

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

In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any

questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 2. For other continuous outcomes not specified in the table below, no MID was defined.

Table 6: 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
PEDS-QL generic youth	4.72 score	Hilliard 2013
PEDS-QL generic parent	4.88 score	Hilliard 2013
PEDS-QL diabetes youth	5.27 score	Hilliard 2013
PEDSQL diabetes parent	4.54 score	Hilliard 2013
*Full reference provided in reference section.		

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For relative risks where no other MID was available, 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 3.

Table 7: Rationale for downgrading quality of evidence for intervention studies

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

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

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

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

Appendix C – Literature search strategies

Clinical 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)

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)

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)

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

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

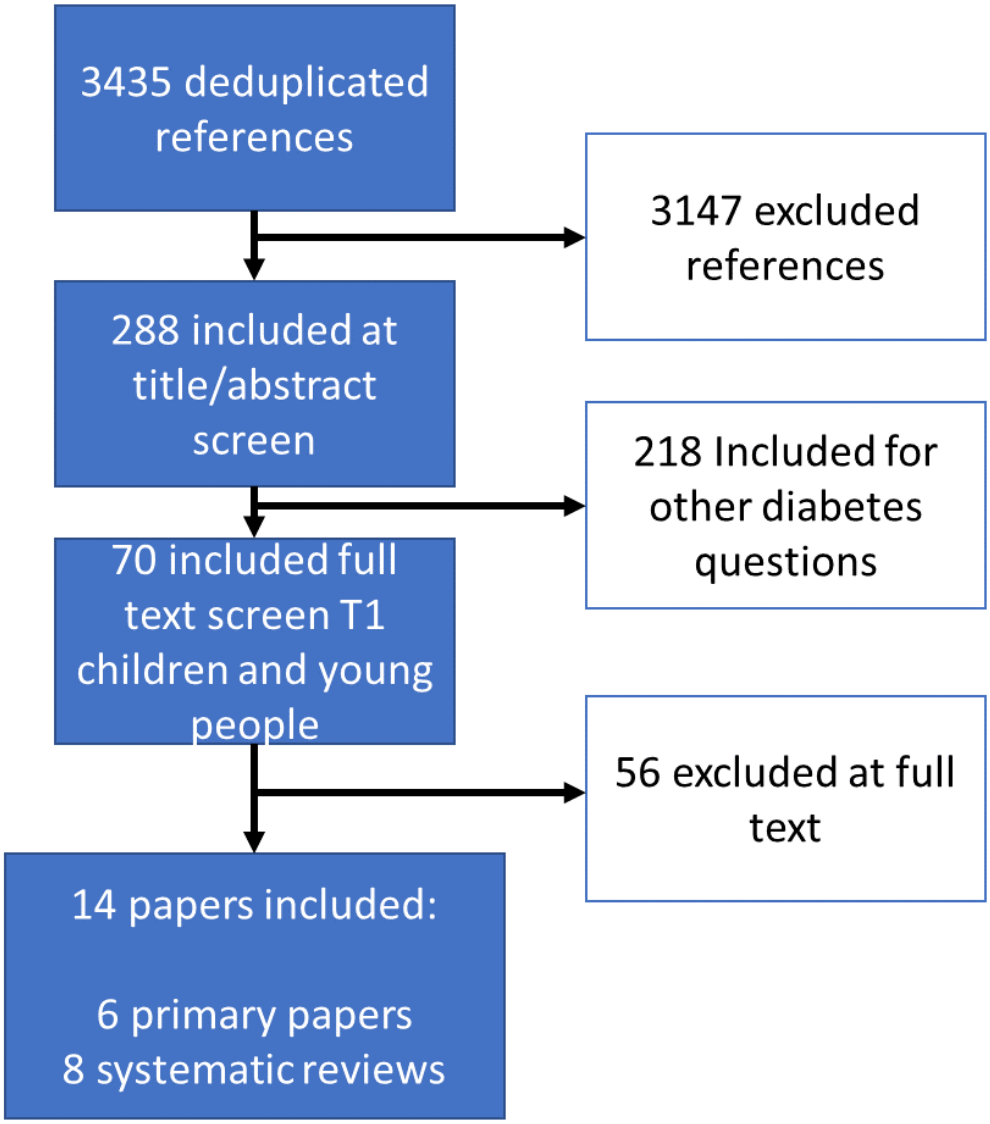
6	(((dm1 or iddm or t1d* or dka)))	53
7	(((dm2 or t2d* or mody or niddm)))	83
8	(((DM near4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II))))	4
9	((DM near4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)))	0
10	(((DM near4 onset* near4 (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

Appendix D – Effectiveness evidence study selection



Appendix E – Evidence tables

Boucher, 2020

Bibliographic Reference	Boucher, Sara E.; Galland, Barbara C.; Tomlinson, Paul A.; Rose, Shelley; Gray, Andrew R.; Wiltshire, Esko J.; de Bock, Martin I.; Mackenzie, Karen E.; Rayns, Jenny A.; Chan, Huan; Wheeler, Benjamin J.; Effect of 6 months of flash glucose monitoring in youth with type 1 diabetes and high-risk glycemic control: A randomized controlled trial; Diabetes Care; 2020; vol. 43 (no. 10); 2388-2395

Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	
Trial registration number and/or trial name	ACTRN12618000320257
Study type	Randomised controlled trial (RCT)
Study location	New Zealand
Study setting	multi-centre
Study dates	April 2018 - May 2019
Inclusion criteria	Age 13-20 years Duration of diabetes

	>= 12 months HbA1c level >=9% 6 months prior to enrolment
Exclusion criteria	Previous CGM use Current or in previous 4 months (not including intermittent hospital or clinic based use) Comorbidity any severe diabetes related complication, other uncontrolled medical comorbidity Pregnancy
Intervention(s)	
Outcome measures	HbA1c (%) + mmol/mol % of CGM data captured Glucose monitor checks / day Adverse events DKA Severe hypoglycemia Hospitalisations QoL (validated tools) PedsQL generic PedsQL Diabetes HFS DTSQ
Number of participants	64
Type of insulin delivery system	MDI 55 (86) CSII 9 (14)
SMBG checks per day	1.9 +/- 2.7
CGM use per day	

Duration of follow-up	3 months 6 months
Loss to follow-up	3 months -1 6 months - 0
Methods of analysis	ITT (subset: pp)

Study arms

isCGM (N = 33)
FreeStyle Libre system; Abbott Diabetes Care - 1 additional visit with sensor education

SMBG (N = 31)
Self-monitored blood glucose concentrations using their usual glucometer.

Characteristics

Arm-level characteristics

Characteristic	isCGM (N = 33)	SMBG (N = 31)
% Female Nominal	16	15
Mean age (SD) Mean (SD)	16.5 (1.9)	16.7 (2.2)
BMI (z score) Mean (SD)	0.67 (1.05)	0.73 (0.96)
Time since diabetes diagnosis (years) Mean (SD)	7 (3.5)	8 (4)

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

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 *(In line with T1 guideline, knowledge of treatment for subjective markers was seen as one intended consequence of intervention and thus study not marked down for this.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(per protocol analysis conducted for HbA1c but not used to replace ITT and not significant)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Inclusion criteria 13-20 years)*

Burckhardt, 2018

Bibliographic Reference	Burckhardt, Marie-Anne; Roberts, Alison; Smith, Grant J; Abraham, Mary B; Davis, Elizabeth A; Jones, Timothy W; The Use of Continuous Glucose Monitoring With Remote Monitoring Improves Psychosocial Measures in Parents of Children With Type 1 Diabetes: A Randomized Crossover Trial.; Diabetes care; 2018; vol. 41 (no. 12); 2641-2643

Study details

Trial registration number and/or trial name	ACTRN12616000463471
Study type	Crossover RCT

Study location	Australia
Study setting	At home with visits to children's hospital
Study dates	
Sources of funding	This work was performed at the Children's Diabetes Centre in Perth, a JDRF/National Health and Medical Research Council–funded Centre of Research Excellence (APP1078190).
Inclusion criteria	People with T1D + 1 parent Age 2 - 12 Duration of diabetes More than 1 year No previous CGM use last 6 months
Outcome measures	QoL (validated tools) PArental HFS PedsQL generic PedsQL diabetes Dass STAI PSQI
Number of participants	49
Type of insulin delivery system	MDI 20 (36%) CSII 29 (64%)
CGM use per day	minimum of 80% over 2 weeks
Duration of follow-up	3 months

Loss to follow-up	0
Methods of analysis	Continuous outcomes were analyzed using linear mixed models. Least squares means (LSM), based on the fixed terms in the model, and differences in LSM along with their 95% CIs were calculated. To analyze the change in frequency of SMBG, a generalized linear mixed model with a negative binomial distribution and log link was used. All data were analyzed on an intent-to-treat basis.P values,0.05 were considered statistically significant.
Additional comments	Most parents chose a low alert between 3.1 and 5.3 mmol/L and a high alert between 8.0 and 20.0 mmol/L

Study arms

rtCGM (N = 49)
Dexcom G5 mobile CGM system

SMBG (N = 49)
conventional blood glucose monitoring

Characteristics

Study-level characteristics

Characteristic	Study (N = 49)
% Female Nominal	31
Mean age (SD) Mean (SD)	9.5 (1.9)
Time since diabetes diagnosis (years) Mean (SD)	3.9 (2.5)
HbA1c (%)	7.7 (0.7)

Characteristic	Study (N = 49)
Mean (SD)	

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

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
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 *(In line with T1 guideline, knowledge of treatment for subjective markers was seen as one intended consequence of ntervention and thus study not marked down for this.)*
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

Deiss, 2006

Bibliographic Reference Deiss, D; Hartmann, R; Schmidt, J; Kordonouri, O; Results of a randomised controlled cross-over trial on the effect of continuous subcutaneous glucose monitoring (CGMS) on glycaemic control in children and adolescents with type 1 diabetes.; Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association; 2006; vol. 114 (no. 2); 63-7

Study details

Secondary publication of another included study- see primary study for details	
Study location	Berlin, Germany
Study setting	Diabetes outpatient clinic
Study dates	July 2002 to April 2003
Sources of funding	research grant from Medtronic MiniMed Inc., Germany
Inclusion criteria	People with T1D Age "children and adolescents"
Outcome measures	HbA1c (%) mean [take post crossover data only!] Hypoglycaemia >180 [10] 3 months not a crossover % of CGM data captured Adverse events mild local side effects
Type of insulin delivery system	MDI 3 or more
SMBG checks per day	Capillary self-monitoring blood glucose was comparable between the arms A and B (median 175 mg/dl [99 – 260] vs. 191 mg/dl [117 – 320], p = 0.384) without any significant change from baseline (p = 0.776 and p = 0.112, respectively)
Additional comments	v poor crossover study have to treat 1st bit as poor RCT

Study arms

rtCGM (N = 15)

A continuous glucose monitoring system (CGMS, Medtronic MiniMed Inc., Northridge, CA, USA)

SMBG (N = 15)
SMBG only

Characteristics

Arm-level characteristics

Characteristic	rtCGM (N = 15)	SMBG (N = 15)
% Female Nominal	5	9
Mean age (SD) Custom value	Median 10.3 range 2-16	Median 12.4 range 3-16
BMI Custom value	Median 17.6 range 14.6 - 21.8	Median 19.7 range 13.6 - 28.3
Time since diabetes diagnosis (years) Custom value	Median 1.7 range 0.4 - 7.1	Median 2.6 range 0.2 - 6.0

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

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(No information 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	High *(Concerns due to timepoints being measured in this crossover*

Section	Question	Answer
		feasibility study. Timepoint only take pre-crossover and no data taken after crossover before both arms put on unblinded treatment.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Data not shown at second timepoint prior to both arms being given unblinded treatment. Could be due to nature of feasibility studies but still presents a risk.)*
Overall bias and Directness	Risk of bias judgement	High *(No randomisation data and concerns about timepoints reported compared to study flow. Cannot be used as crossover study as would introduce unit of analysis errors due to only pre crossover data being reported as if a parallel RCT)*
Overall bias and Directness	Overall Directness	Direct

Hommel 2014

Study details

Trial registration number and/or trial name	SWITCH; NCT00598663
Study type	Cross-over randomised controlled trial
Study location	Europe
Study setting	Four adult sites in Europe with experience in the use of insulin pumps and CGM.
Study dates	January 2008 to July 2010
Sources of funding	The study was funded by Medtronic International Trading Sarl, Tolochenaz, Switzerland.
Inclusion criteria	People with T1D Duration of diabetes >1 year Adults Participants were aged <= 18 years

	Treatment with continuous subcutaneous insulin infusion (CSII) therapy with rapid-acting insulin analogues for more than 6 months HbA1c between 7.5% and 9.5% (58.5 and 80.3 mmol/mol) Naive to CGM Had successfully completed a five-question multiple choice test concerning pump therapy and general understanding of diabetes
Exclusion criteria	Hypoglycaemia unawareness (i.e. hypoglycaemia without symptoms) Concomitant chronic illness known to affect diabetes control and any pharmacological treatment that might modify glycaemic values ≥3 incidents of severe hypoglycaemia in the last 12 months
Intervention(s)	"During a 1-month run-in phase, participants used a glucometer (Bayer Ascensia Contour; Bayer Diabetes Care, Basel, Switzerland) and an insulin pump system (Mini-Med Paradigm REAL-Time System; Medtronic, Tolochenaz, Switzerland) able to integrate CGM in the study phase. All participants received structured training on diabetes management and device use and had their knowledge assessed. Each treatment period was 6 months long, with a 4-month washout phase between the two periods. All participants wore a continuous glucose monitor (Guardian REAL-Time Clinical; Medtronic, Tolochenaz, Switzerland), which they were blinded to (the device screen was turned off), for 2 weeks prior to randomisation and prior to crossover. Participants in the Sensor Off arm wore the device for 2 weeks prior to each study visit. No common treatment protocols or fixed algorithms were provided to the centres, and therapy adjustments were made in consultation with participants at clinic visits. Participants were individually encouraged to make self-adjustments to their treatment using real-time CGM values, hyper- and hypoglycaemic alerts and trends, or to incorporate self-monitoring of blood glucose (SMBG) results into treatment adjustments, with written examples of therapy changes provided in the optional patient diary. Participants completed a ten-question test to demonstrate technical knowledge on the pump (4 weeks before randomisation) and a 12-question test on CGM (at visit 1 of the On/Off sequence or visit 6 of the Off/On sequence)."
Outcome measures	PEDs-QL (children and parents) DTSQ
Number of participants	Continuous glucose monitoring Sensor On/Sensor Off N=72 Continuous glucose monitoring Sensor Off/Sensor On N=72
IGNORE	
Type of insulin delivery system	Continuous subcutaneous insulin infusion Insulin pump

Type of insulin regimen	Rapid acting
Duration of follow-up	6 months
Loss to follow-up	Reported for all participants without separate information for adults.
Additional comments	Sensor data for the secondary endpoints were extracted from CareLink Clinical (CareLink Therapy Management System for Diabetes-Clinical, Medtronic, Tolochenaz, Switzerland) during the 15-day period prior to the end-of period (6-month) visit. For the Sensor On arm, 100% sensor use was calculated as the number of days in the Sensor On period multiplied by 288, the maximum number of sensor readings per day. The study also included children but only data from adults was extracted for this evidence review.

Study arms

Continuous glucose monitoring Sensor Off/Sensor On (N = 72)

Guardian REAL-Time Clinical; Medtronic, Tolochenaz, Switzerland

Continuous glucose monitoring Sensor On/Sensor Off (N = 72)

Guardian REAL-Time Clinical; Medtronic, Tolochenaz, Switzerland

Characteristics

Arm-level characteristics

No specific arm level characteristics for children were given.

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

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

Section	Question	Answer
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low *(4 months long enough to lose CGM learning effect? Committee opinion. Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*
Overall bias and Directness	Overall Directness	Directly applicable *(Only data on children was taken from in this study publication.)*

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, 2010

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

Study details

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

study- see primary study for details	

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, 2008

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

Study details

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

	Duration of diabetes ≥1 year 8 years of age or older Using an insulin pump or receiving at least three daily insulin injections HbA1c level 7.0 to 10.0% Not used continuous glucose monitoring at home in the 6 months leading up to the trial
Intervention(s)	**Continuous glucose monitoring** Each of the devices for CGM consisted of a glucose oxidase–based electrochemical sensor, which was placed subcutaneously and replaced every 3 to 7 days (depending on the type of device), along with a receiver to which interstitial glucose measurements were sent wirelessly and stored. Since the purpose of the study was to evaluate a treatment strategy using the technology of continuous glucose monitoring and not a specific device, a device was assigned to each patient by the clinical centre on the basis of device features and the participants' preferences. Participants were instructed to use the device on a daily basis and to verify the accuracy of the glucose measurement with a home blood glucose meter (provided by the study) before making management decisions, according to the regulatory labelling of the devices. **Intermittent capillary blood glucose monitoring** Participants were given blood glucose meters and test strips and asked to perform home blood glucose monitoring at least four times daily.
Outcome measures	HbA1c Time in range Amount of time per day the glucose level was in the target range (71 to 180 mg per decilitre [3.9 to 10.0 mmol per litre]). Time spent above/below target glucose range Amount of time per day the glucose level was hypoglycaemic (≤70 mg per decilitre or ≤50 mg per decilitre [≤3.9 or ≤2.8 mmol per litre]) or hyperglycaemic (>180 mg per decilitre or >250 mg per decilitre [10.0 or 13.9 mmol per litre]). Hypoglycaemia Severe hypoglycaemia defined as an event that required assistance from another person to administer oral carbohydrate, glucagon, or other resuscitative actions. Glycaemic variability Diabetic ketoacidosis Hyperglycaemia resulting in ketoacidosis. Adverse events Severe hypoglycaemia, ketoacidosis, unexpected study-related or device-related events, and serious adverse events regardless of cause. Quality of life measured by validated tools

	Participants ≥18 years old completed the Hypoglycaemia Fear Survey (HFS) and Social Functioning Health Survey (SF-12) version 2; reported by JDRF (2010). Continuous Glucose Monitoring Satisfaction Scale (CGM-SAT); reported by Tansey (2011).
Number of participants	Continuous glucose monitoring N=52 Intermittent capillary blood glucose monitoring N=46
Type of insulin delivery system	Multiple daily injections (16%) Insulin pump (84%)
Duration of follow-up	26 weeks
Additional comments	Participants completed a run-in phase using a continuous glucose monitor that was modified so that the glucose values were recorded in the receiver but were not visible to the participant; this was referred as a “blinded” continuous glucose monitor. Eligibility required that participants wore a sensor for at least 6 of 7 days before randomisation, with a minimum of 96 hours of glucose values including at least 24 hours overnight, and that home blood glucose monitoring be performed at least three times daily. Data regarding continuous glucose monitoring in both arms after the 26-week visit (blinded monitors in the intermittent capillary blood glucose monitoring arm and unblinded monitors in the continuous glucose monitoring arm) were used to estimate time spent in range, time spent above target glucose range and time spent below target blood glucose range. Type of insulin regimen was not reported.

Study arms

Continuous glucose monitoring (N = 56)

Loss to follow-up	2 participants dropped

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

Intermittent capillary blood glucose monitoring (N = 58)

Loss to follow-up	0

Participants were given blood glucose meters and test strips.

Characteristics

Arm-level characteristics

Characteristic	Continuous glucose monitoring Sensor Off/Sensor On (N = 41)	Continuous glucose monitoring Sensor On/Sensor Off (N = 40)
% Female Nominal	48	50
Mean age (SD) (years) Mean (SD)	11.4 (2)	11.6 (2.1)
Time since diabetes diagnosis (kg/m²) Mean (SD)	6.2 (3.1)	5.3 (2.8)

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

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Committee discretion regarding the risk of bias for subjective outcomes. Impossible to really blind for intervention in this study.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unblinded assignment to intervention judged as impossible to avoid and thus not marked down here.)*
Overall bias and Directness	Overall Directness	Directly applicable *(The JDRF trial included children, young people and adults but data was reported separately for adults ≥25 years old.)*

Laffel, 2020

Bibliographic Reference Laffel, Lori M; Kanapka, Lauren G; Beck, Roy W; Bergamo, Katherine; Clements, Mark A; Criego, Amy; DeSalvo, Daniel J; Goland, Robin; Hood, Korey; Liljenquist, David; Messer, Laurel H; Monzavi, Roshanak; Mouse, Thomas J; Prahalad, Priya; Sherr, Jennifer; Simmons, Jill H; Wadwa, R Paul; Weinstock, Ruth S; Willi, Steven M; Miller, Kellee M; CGM Intervention in Teens and Young Adults with T1D (CITY) Study, Group; CDE10; Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes: A Randomized Clinical Trial.; JAMA; 2020; vol. 323 (no. 23); 2388-2396

Study details

Secondary publication of another included study- see primary study for details	
Trial registration number and/or trial name	NCT03263494
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	14 endocrinology practices
Study dates	January 2018 - May 2019

Sources of funding	This study was funded by a grant provided by the Leona M. and Harry B. Helmsley Charitable Trust given to the Jaeb Center for Health Research. Dexcom Inc provided nonfinancial support by providing continuous glucose monitoring devices and sensors for the study.
Inclusion criteria	People with T1D Age 14 - 24 No previous CGM use for 3 months Insulin regimen total daily insulin of at least 0.4 units/kg/d HbA1c level >7.5% to <11%
Intervention(s)	
Outcome measures	HbA1c (%) Time in range 70 to 180mg/dL Time above/below target glucose range Time in hyper >180 / >250 Time in hypo Glycemic variability CV Diabetic ketoacidosis % of CGM data captured CGM use days/week hours of CGm data Adverse events Severe hypoglycemia DKA SAE QoL (validated tools) PAID-P GMSS

	Hypoglycemia confidence Sleep quality
Number of participants	153
Type of insulin delivery system	MDI 38 (54%) 32 (41%) CSII CGM: 36 (49%) SMBG: 47 (59%)
SMBG checks per day	
CGM use per day	
Duration of follow-up	26 weeks
Loss to follow-up	0
Methods of analysis	All participants were analyzed according to their randomization group and included in the primary analysis. For the primary analysis, the difference in change in HbA1c from baseline to 26 weeks between the 2 treatment groups was assessed in a longitudinal linear regression model including the HbA1c value at baseline, 13 weeks, and 26 weeks and clinical center as a random effect. Missing data were handled by direct likelihood, which maximizes the likelihood function integrated over possible values of the missing data.

Study arms

CGM (N = 74)
Dexcom G5, Dexcom, Inc

SMBG (N = 79)
Continue BGM with a blood glucose meter without CGM

Characteristics

Arm-level characteristics

Characteristic	CGM (N = 74)	SMBG (N = 79)
% Female Nominal	33	43
Mean age (SD) Mean (SD)	17 (3)	18 (3)
14 - <19 Nominal	48	53
19 - <25 Nominal	26	26
Time since diabetes diagnosis Mean (SD)	9 (5)	10 (5)
Past but not current Nominal	24	30
Never Nominal	50	49

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

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

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(In line with T1 guideline, knowledge of treatment for subjective markers was seen as one intended consequence of intervention and thus study not marked down for this.)*
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	Partially applicable *(~34% 19 - <25 years old)*

Xu, 2021

Bibliographic Reference Xu, Yuejie; Xu, Lei; Zhao, Weijing; Li, Qing; Li, Ming; Lu, Wei; Zeng, Hui; Pan, Jiemin; Liu, Fang; Yan, Jinhua; Yang, Daizhi; Weng, Jianping; Wu, Wei; Effectiveness of a wechat combined continuous flash glucose monitoring system on glycemic control in juvenile type 1 diabetes mellitus management: Randomized controlled trial; Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy; 2021; vol. 14; 1085-1094

Study details

Trial registration number and/or trial name	ChiCTR1900025495
Study type	Randomised controlled trial (RCT)
Study location	Shanghai, China
Study setting	department of Endocrinology and Metabolism of Shanghai Jiao Tong University Affiliated Sixth People's Hospital
Study dates	Recruitment January 2019 - June 2019
Sources of funding	supported by grants from the National key Research and development program (2017YFC1309601 for Fang Liu), National Science Foundation Items of China (81770802 for Fang Liu), and Shanghai Municipal Education Commission-Gaofeng Clinical Medicine (20152232 for Fang Liu)

Inclusion criteria	People with T1D WHO 1999 criteria Age 10-19 Duration of diabetes >1 year No previous CGM use 3 months before study Insulin regimen use of multiple daily insulin (MDI) and continuous subcutaneous insulin infusion (CSII) for at least 3 months, stable diabetes medication regimen for 3 months before study entry (change in insulin <= 20%), previous documentation of blood glucose level self-monitoring regularly for 2 months (at least three times per day) and willingness to continue for at least 6 months HbA1c level >7 - <10 % Willingness to wear CGM Language Can speak, read, and write Chinese Ability to use WeChat program
Exclusion criteria	Comorbidity severe diabetic complications such as diabetic retinopathy and diabetic nephropathy, recent severe diseases like myocardial infarction, stroke, psychiatric diseases (historical/recent), malignant tumor, kidney disease (defined as eGFR <45), dermatosis, decided by the investigator any condition that could impact the reliability of the HbA1c measurement (eg, hemoglobinopathy, hemolytic anemia, chronic liver disease), decided by the investigator. abuse of illicit drugs, alcohol or prescription drugs Pregnancy Allergy to CGm device or adhesive
Outcome measures	HbA1c (%) Hypoglycaemia number of episodes <3.9mmol

	QoL (validated tools) DMTSQ DQoL CHFSII
Number of participants	80
Duration of follow-up	6 months
Loss to follow-up	Flash = 5 Flash and we chat = 5 SMBg = 10
Methods of analysis	Data with a normal distribution were presented as mean and standard deviations (SD), and data with a non-normal distribution were presented as median with interquartile ranges (IQR). Analyses of variance (ANOVA) and covariance were used for intergroup comparisons of normally distributed data, whereas nonparametric analysis was used for non-normally distributed data.
Additional comments	Really unclear what n they analysed

Study arms

Flash Glucose monitoring (N = 25)

(Libre 1, Abbott Diabetes Care) - A specialist applied the flash glucose monitor to the back of the upper arm through a simple disposable applicator: a thin wire (flexible probe) was subcutaneously implanted, and the sensor was fixed to the application site with an adhesive film. It recorded the blood glucose value at 15-minute intervals automatically, and the blood glucose value can be determined at any time from the display

Flash glucose monitoring with WeChat (N = 25)

n Group C, patients with the Abbott FreeStyle Libre monitor were asked to subscribe to a WeChat Official Account named “KongTangTianDi,” which disseminates scientific diabetes-related information once a week. Furthermore, the WeChat Official Account platform was also used for real-time patient-doctor interactions. A thirdparty health manager was involved in interactive management with patients through the platform. Further, a nurse who specialized in diabetes helped analyze, evaluate, and review the glycemic monitoring data

SMBG (N = 30)
a conventional home glucometer was used to monitor blood glucose ≥ three times a day, and the blood glucose monitoring values were uploaded to the Wenjuan survey platform.

Characteristics

Arm-level characteristics

Characteristic	Flash Glucose monitoring (N = 25)	Flash glucose monitoring with WeChat (N = 25)	SMBG (N = 30)
% Female Nominal	9	13	7
Mean age (SD) Mean (SD)	12.65 (1.73)	13.6 (1.27)	12.65 (1.73)
BMI Mean (SD)	20.01 (2.42)	20.83 (1.71)	20.25 (2.1)
Time since diabetes diagnosis (years) Mean (SD)	2.42 (1.75)	3.33 (2.46)	2.11 (1.82)

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

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 *(Unclear whether an ITT or PP analysis was performed, discontinuation rates higher in control arm could be due to participants being unhappy with not receiving treatment.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Due to unclear analysis type cannot say for sure whether all HbA1c data or QoL data was included.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(In line with T1 guideline, knowledge of treatment for subjective markers was seen as one intended consequence of itnevrentionintervention and thus study not marked down for this.)*
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 *(No information on whether ITT or PP analysis performed and thus unclear whether analysis is appropriate so high risk.)*
Overall bias and Directness	Overall Directness	Direct *19 year old threshold accepted as acceptable in protocol*

Appendix F – Forest plots

rtCGM vs SMBG

Figure 1: Change in HbA1c (mmol/mol) - 6 months

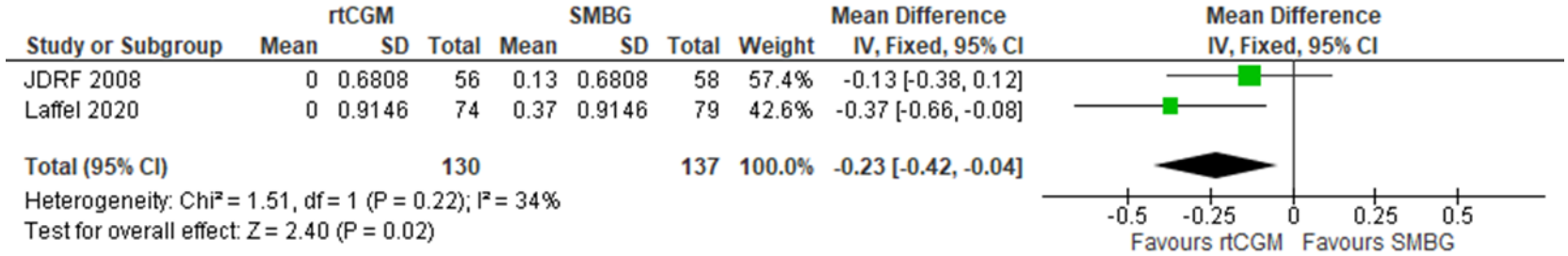


Figure 2: HbA1c relative reduction >10% 6 months

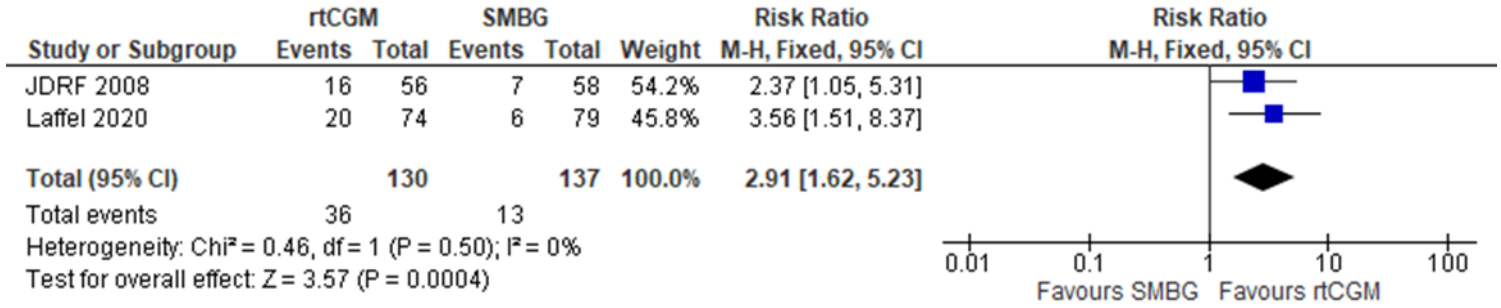


Figure 3: HbA1c achieved target <7.0% 3 months

Figure 4: Severe hypoglycemia (n) <3.9 mmol/l 6 months

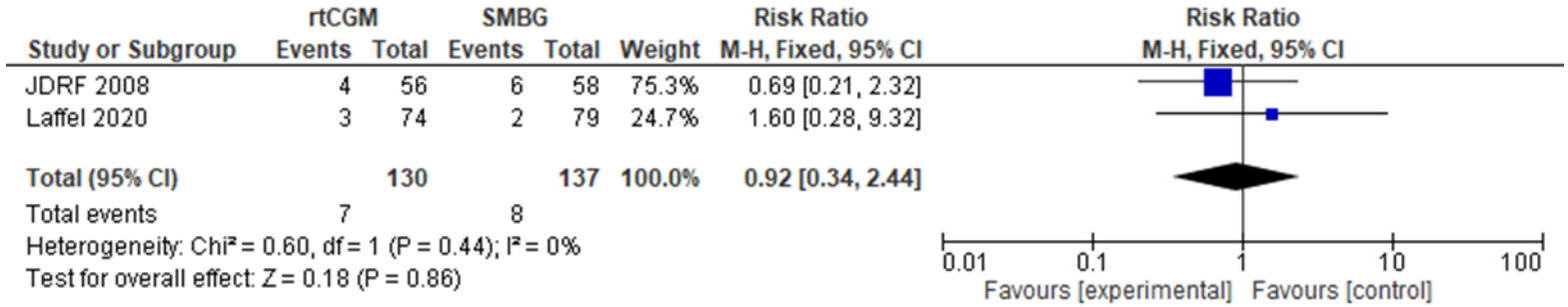


Figure 5: Quality of life (PEDS) - generic - 6 months

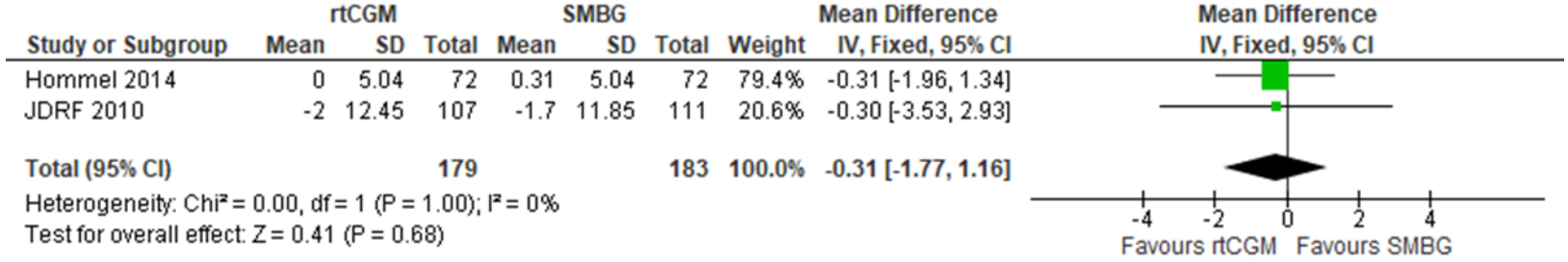


Figure 6: Quality of life (PEDS) - generic - parents 6 months

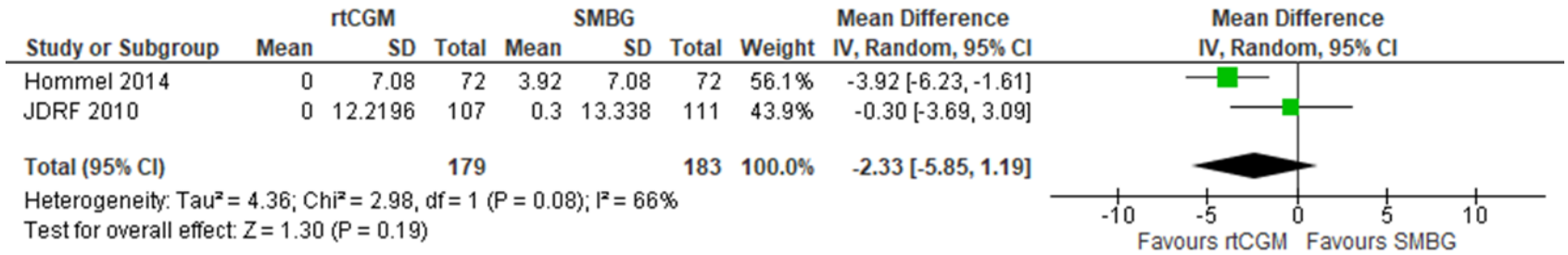
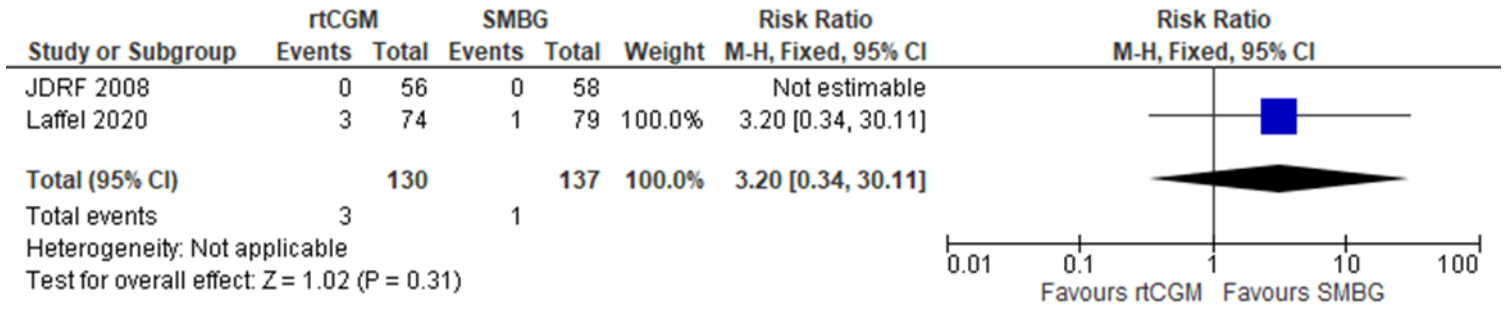
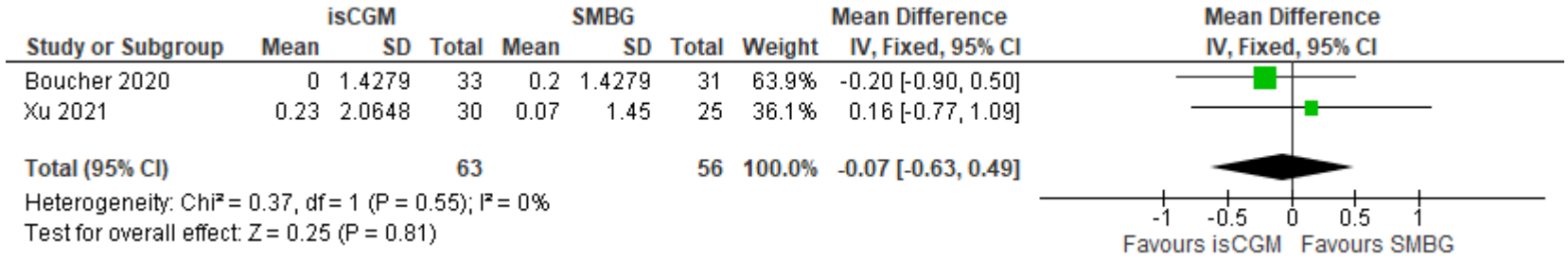


Figure 7: DKA (n) 6 months



isCGM vs SMBG

Figure 8: HbA1c (%) >= 6 months



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 (%) at 3 months (<0 favours intervention)											
1 (Deiss 2006)	Parallel RCT	30	+/- 0.50	MD 0.20 (-0.59, 0.99)	-	-	Very serious1	Not serious	NA4	Very serious7	Very low
HbA1c (mmol/mol) - 6 months (<0 favours intervention)											
2	Parallel RCT	267	+/- 0.50	MD -0.23 (-0.42, -0.04)	-	-	Serious2	Serious3	Serious5	Not serious	Very low
HbA1c relative reduction >10% 6 months (>1 favours intervention)											
2	Parallel RCT	267	0.80 , 1.25	RR 2.91 (1.62, 5.23)	9 per 100	18 more per 100 (6 more to 40 more)	Serious2	Serious3	Not serious	Not serious	Low
HbA1c relative reduction >= 5% 6 months (>1 favours intervention)											
1 (JDRF 2008)	Parallel RCT	114	0.80 , 1.25	RR 1.73 (1.10, 2.72)	31 per 100	23 more per 100 (3 more to 53 more)	Serious2	Not serious	NA4	Serious8	Low
HbA1c achieved target <7.0% 3 months (>1 favours intervention)											
2	Parallel RCT	267	0.80 , 1.25	RR 1.96 (1.10, 3.50)	11 per 100	11 more per 100 (1 more to 27 more)	Serious2	Serious3	Not serious	Serious8	Very low
HbA1c achieved target <7.5% 6 months (>1 favours intervention)											
1 (Laffel 2020)	Parallel RCT	153	0.80 , 1.25	RR 1.37 (0.54, 3.50)	9 per 100	3 more per 100 (4 fewer to 22 more)	Not serious	Serious3	NA4	Very serious7	Very low
Time in range (%) [70 - 180 mg/dL] 6 months (>0 favours intervention)											

1 (Laffel 2020)	Parallel RCT	153	+/- 5.00	MD 6.90 (3.10, 10.70)	-	-	Not serious	Serious3	NA4	Serious8	Low
Time above range (%) >180 mg/dL 6 months (<0 favours intervention)											
1 (Laffel 2020)	Parallel RCT	153	+/- 6.62	MD -5.80 (-10.00, -1.60)	-	-	Not serious	Serious3	NA4	Serious8	Low
Time above range (%) >250 mg/dL 6 months (<0 favours intervention)											
1 (Laffel 2020)	Parallel RCT	153	+/- 6.94	MD -7.90 (-12.30, -3.50)	-	-	Not serious	Serious3	NA4	Serious8	Low
Glycemic variability: coefficient of variation 6 months (<0 favours intervention)											
1 (Laffel 2020)	Parallel RCT	153	+/- 2.68	MD -2.20 (-3.90, -0.50)	-	-	Not serious	Serious3	NA4	Serious8	Low
Severe hypoglycemia (n) <3.9 mmol/l 6 months (<1 favours intervention)											
2	Parallel RCT	267	0.80 , 1.25	RR 0.92 (0.34, 2.44)	6 per 100	0 fewer per 100 (4 fewer to 8 more)	Serious2	Not serious	Not serious	Very serious7	Very low
Hypoglycemia fear survey - total 3 months (<0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 5.30	MD -8.50 (-12.70, -4.30)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
Hypoglycemia fear survey - behaviour 3 months (<0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 2.15	MD -3.30 (-5.00, -1.60)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
Hypoglycemia fear survey - worry 3 months (<0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 3.66	MD -5.20 (-8.10, -2.30)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
Hypoglycemia fear survey - worry 6 months (<0 favours intervention)											
1 (JDRF 2010)	Parallel RCT	218	+/- 7.33	MD 1.60 (-2.36, 5.56)	-	-	Not serious	Not serious	NA4	Not serious	High
Hypoglycemia fear survey - parents 6 months (<0 favours intervention)											

1 (JDRF 2010)	Parallel RCT	218	+/- 9.32	MD 0.30 (-4.22, 4.82)	-	-	Not serious	Not serious	NA4	Not serious	High
Quality of life (PEDS) - generic - 3 months (>0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 4.42	MD 2.60 (-0.90, 6.10)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
Quality of life (PEDS) - generic - 6 months (>0 favours intervention)											
2	Crossover RCT and Parallel RCT	362	+/- 5.92	MD -0.31 (-1.77, 1.16)	-	-	Serious2	Not serious	Not serious	Not serious	Moderate
Quality of life (PEDS) - diabetes - 3 months (>0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 3.54	MD 2.60 (-0.20, 5.40)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
Quality of life (PEDS) - diabetes - 6 months (>0 favours intervention)											
1 (Hommel 2014)	Crossover RCT	218	+/- 6.53	MD 1.50 (-1.90, 4.90)	-	-	Not serious	Not serious	NA4	Not serious	High
Quality of life (PEDS) - family impact - 3 months (>0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 3.54	MD 2.60 (-0.20, 5.40)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
Quality of life (PEDS) - generic - parents 6 months (>0 favours intervention)											
2	Crossover RCT and Parallel RCT	362	+/- 4.88	MD -2.00 (-6.12, 2.12)	-	-	Serious2	Not serious	Very serious6	Serious8	Very low
Quality of life (PEDS) - diabetes - parents 6 months (>0 favours intervention)											
1 (JDRF 2010)	Parallel RCT	218	+/- 4.54	MD -1.60 (-5.19, 1.99)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
DASS - Stress - 3 months (<0 favours intervention)											

1 (Burckhardt 2018)	Crossover RCT	98	+/- 2.02	MD -2.20 (-3.80, -0.60)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
DASS - Anxiety - 3 months (<0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 1.89	MD -1.00 (-2.50, 0.50)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
DASS - Depression - 3 months (<0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 1.64	MD -1.10 (-2.40, 0.20)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
STAI - state - 3 months (<0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 3.54	MD -3.60 (-6.40, -0.80)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
STAI - trait - 3 months (<0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 2.40	MD -3.50 (-5.40, -1.60)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
PSQI - 3 months (<0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	98	+/- 1.26	MD -1.50 (-2.50, -0.50)	-	-	Not serious	Not serious	NA4	Serious8	Moderate
PAID-p 6 months (<0 favours intervention)											
1 (Burckhardt 2018)	Crossover RCT	218	+/- 8.24	MD -0.80 (-4.78, 3.18)	-	-	Not serious	Not serious	NA4	Not serious	High
DKA (n) 6 months (<1 favours intervention)											
2	Parallel RCT	267	0.80 , 1.25	RR 3.20 (0.34, 30.11)	1 per 100	2 more per 100 (0 more to 21 more)	Not serious	Serious3	Not serious	Very serious7	Very low
SAE 6 months (<1 favours intervention)											
1 (Laffel 2020)	Parallel RCT	153	0.80 , 1.25	RR 1.07 (0.15, 7.39)	3 per 100	0 more per 100 (2 fewer to 16 more)	Not serious	Serious3	NA4	Very serious7	Very low

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

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

3. >33.3% of the weight in a meta-analysis came from partially direct or indirect studies

4. Only one study so no inconsistency

5. I2 between 33.3% and 66.7%

6. I2 > 66.7%

7. 95% confidence intervals cross both ends of the defined MIDs

8. 95% confidence intervals cross one end of the defined MIDs

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 (%) - 3 months (<0 favours intervention)											
1 Boucher 2020)	Parallel RCT	64	+/- 0.50	MD -0.70 (-1.51, 0.11)	-	-	Not serious	Serious2	NA3	Serious4	Low
HbA1c (%)6 months (<0 favours intervention)											
2	Parallel RCT	119	+/- 0.50	MD -0.07 (-0.63, 0.49)	-	-	Very serious1	Serious2	Not serious	Serious4	Very low
HbA1c (mmol/mol) 3 months (<0 favours intervention)											
1 Boucher 2020)	Parallel RCT	64	+/- 5.50	MD -6.60 (-15.29, 2.09)	-	-	Not serious	Serious2	NA3	Serious4	Low
HbA1c (mmol/mol) 6 months (<0 favours intervention)											
1 Boucher 2020)	Parallel RCT	64	+/- 5.50	MD -2.10 (-9.60, 5.40)	-	-	Not serious	Serious2	NA3	Serious4	Low
Number of glucose checks 3 months (<0 favours intervention)											

1 Boucher 2020)	Parallel RCT	64	+/- 0.23	MD 3.20 (2.97, 3.43)	-	-	Not serious	Serious2	NA3	Not serious	Moderate
Number of glucose checks 6 months (<0 favours intervention)											
1 Boucher 2020)	Parallel RCT	64	+/- 1.10	MD 2.80 (1.72, 3.88)	-	-	Not serious	Serious2	NA3	Not serious	Moderate
Hypoglycemia episodes per month <3.1 mmol/l 6 months (<0 favours intervention)											
1 (Xu 2021)	Parallel RCT	55	+/- 3.50	MD 1.85 (-1.08, 4.78)	-	-	Very serious1	Not serious	NA3	Serious4	Very low
Quality of life (PEDS) generic - total6 months (>0 favours intervention)											
1 Boucher 2020)	Parallel RCT	64	+/- 5.41	MD -1.20 (-6.50, 4.10)	-	-	Not serious	Serious2	NA3	Serious4	Low
Quality of life (PEDS) diabetes - total 6 months (>0 favours intervention)											
1 Boucher 2020)	Parallel RCT	64	+/- 5.20	MD -1.10 (-6.20, 4.00)	-	-	Not serious	Serious2	NA3	Serious4	Low
Hypoglycemia fear survey - behaviour scale 6 months (<0 favours intervention)											
1 Boucher 2020)	Parallel RCT	64	+/- 0.27	MD 0.18 (-0.08, 0.44)	-	-	Not serious	Serious2	NA3	Serious4	Low
Hypoglycemia fear survey - worry scale 6 months (<0 favours intervention)											
1 Boucher 2020)	Parallel RCT	64	+/- 0.24	MD -0.13 (-0.37, 0.11)	-	-	Not serious	Serious2	NA3	Serious4	Low
DTSQ 6 months (>0 favours intervention)											
1 Boucher 2020)	Parallel RCT	64	+/- 0.48	MD 0.47 (0.00, 0.94)	-	-	Not serious	Serious2	NA3	Serious4	Low
DMTSQ 6 months (>0 favours intervention)											
1 (Xu 2021)	Parallel RCT	55	+/- 5.47	MD -2.80 (-7.87, 2.27)	-	-	Very serious1	Not serious	NA3	Serious4	Very low
DQOL 6 months (>0 favours intervention)											
1 (Xu 2021)	Parallel RCT	55	+/- 11.28	MD 2.55 (-8.20, 13.30)	-	-	Very serious1	Not serious	NA3	Serious4	Very low
Chinese hypoglycemia fear survey 6 months (<0 favours intervention)											

1 (Xu 2021)	Parallel RCT	55	+/- 5.96	MD 1.25 (-6.57, 9.07)	-	-	Very serious1	Not serious	NA3	Very serious5	Very low
DKA (<1 favours intervention)											
1 (Boucher 2020)	Parallel RCT	64	0.80 , 1.25	RR 1.13 (0.38, 3.32)	16 per 100	2 more per 100 (10 fewer to 37 more)	Not serious	Serious2	NA3	Very serious5	Very low

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

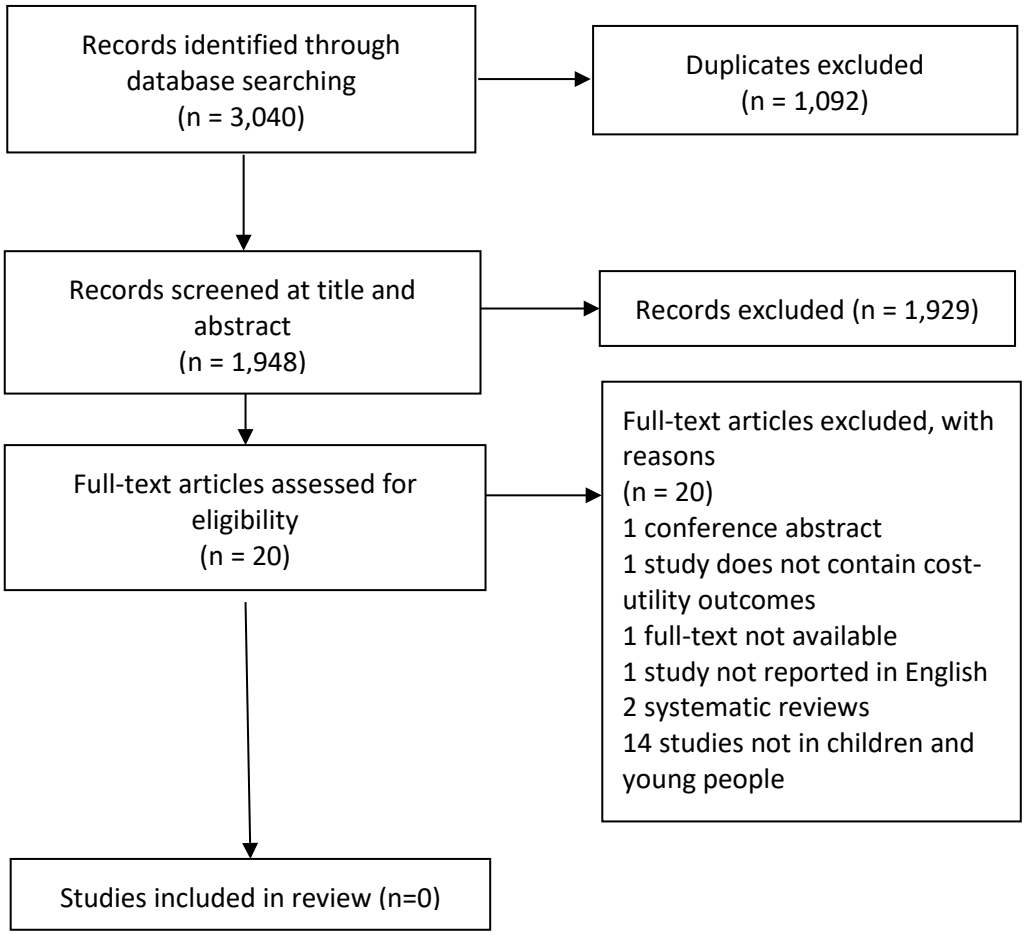
2. >33.3% of the weight in a meta-analysis came from partially direct or indirect studies

3. Only one study so no inconsistency

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

5. 95% confidence intervals cross both ends of the defined MID

Appendix H – Economic evidence study selection



Appendix I – Economic evidence tables

No economic studies were included in this evidence review.

Appendix J – Health economic model

No economic modelling was undertaken for this review question.

Appendix K – Excluded studies

Clinical

Study	Reason
Astley, CM, Garvey, KC, Steil, GM et al. (2019) Analysis of continuous glucose monitoring data reveals vacation-associated deterioration of glycemic control in pediatric type 1 diabetes. Pediatric diabetes 20: 38	- Conference abstract *poster*
Beardsall, K., Thomson, L., Guy, C. et al. (2018) Protocol of a randomised controlled trial of real-time continuous glucose monitoring in neonatal intensive care 'REACT'. BMJ Open 8(6): e020816	- study protocol *Full react study being included at later date*
Beardsall, K, Vanhaesebrouck, S, Ogilvy-Stuart, A L et al. (2013) Validation of the continuous glucose monitoring sensor in preterm infants. Archives of disease in childhood. Fetal and neonatal edition 98(2): f136-40	- No relevant outcomes of interest based on protocol
Beardsall, Kathryn, Thomson, Lynn, Guy, Catherine et al. (2021) Real-time continuous glucose monitoring in preterm infants (REACT): an international, open-label, randomised controlled trial. The Lancet. Child & adolescent health 5(4): 265-273	- Does not contain the correct population *not T1 diabetes*
Boucher, S.E., Aum, S.H., Crocket, H.R. et al. (2019) Exploring parental perspectives after commencement of flash glucose monitoring for type 1 diabetes in adolescents and young adults not meeting glycaemic targets: a qualitative study. Diabetic medicine : a journal of the British Diabetic Association	- Not a relevant study design *qualitative*
Boucher, S, Gray, A, Wiltshire, E et al. (2020) Managing diabetes in a 'flash': effect of 6 months' flash glucose monitoring in adolescents with high-risk glycaemic control-a randomised controlled trial. Diabetes technology & therapeutics 22: A-56	- Conference abstract *poster ATTD*
Boucher, Sara E, Gray, Andrew R, de Bock, Martin et al. (2019) Effect of 6 months' flash glucose monitoring in adolescents and young adults with type 1 diabetes and suboptimal glycaemic control: managing diabetes in a 'flash' randomised controlled trial protocol. BMC endocrine disorders 19(1): 50	- study protocol
Boucher, SE, Gray, AR, Wiltshire, EJ et al. (2020) Effect of 6 Months of Flash Glucose Monitoring in Youth With Type 1 Diabetes and High-Risk Control: a Randomized Controlled Trial. Diabetes care	- Duplicate reference *Duplicate of other Boucher 2020*
Bukara-Radujkovic, Gordana; Zdravkovic, Dragan; Lakic, Sinisa (2011) Short-term use of continuous glucose monitoring system	- Study does not contain a relevant intervention

Study	Reason
adds to glycemic control in young type 1 diabetes mellitus patients in the long run: a clinical trial. Vojnosanitetski pregled 68(8): 650-4	*72 hrs CGM*
Burckhardt, M.-A., Fried, L., Bebbington, K. et al. (2019) Use of remote monitoring with continuous glucose monitoring in young children with Type 1 diabetes: the parents' perspective. Diabetic Medicine 36(11): 1453-1459	- Not a relevant study design *Qualitative*
Chase, H P, Kim, L M, Owen, S L et al. (2001) Continuous subcutaneous glucose monitoring in children with type 1 diabetes. Pediatrics 107(2): 222-6	- Study does not contain a relevant intervention *Length of CGM period not enough to class as CGM*
Chase, H Peter, Beck, Roy W, Xing, Dongyuan et al. (2010) Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. Diabetes technology & therapeutics 12(7): 507-15	- Comparator in study does not match that specified in protocol *Single arm extension of JDRF so non-comparative data as no control arm.*
Deiss, D, Bolinder, J, Riveline, JP et al. (2006) Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes care 29(12): 2730-2732	- Does not contain a population of people with *<= 50% of patients paediatric*
DeSalvo (2018) Continuous glucose monitoring and glycemic control among youth with type 1 diabetes: international comparison from the T1D Exchange and DPV Initiative. Pediatric diabetes	- Not a relevant study design *Looking at clinic registries*
Diabetes Research in Children Network (DirecNet) Study, Group, Buckingham, Bruce, Beck, Roy W et al. (2007) Continuous glucose monitoring in children with type 1 diabetes. The Journal of pediatrics 151(4): 388-2	- Not a relevant study design *single arm*
Dimeglio, L, Kanapka, L, Desalov, D et al. (2019) Strategies to enhance new CGM use in early childhood (SENCE): results from a randomized clinical trial of continuous glucose monitoring (CGM) in young children with type 1 diabetes (T1D). Pediatric diabetes 20: 192-193	- Conference abstract *poster*
Dorando, Elena; Haak, Thomas; Pieper, Dawid (2020) Correction: Continuous Glucose Monitoring for Glycemic Control in Children and Adolescents Diagnosed with Diabetes Type 1: A Systematic Review and Meta-Analysis. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association	- Erratum
Elbalshy, Mona, Boucher, Sara, Galland, Barbara et al. (2020) The MiaoMiao study: can do-it-yourself continuous glucose monitoring technology improve fear of hypoglycaemia in parents of children	- Study does not contain a relevant intervention *DIY CGM - not RtCGM as its an add-on*

Study	Reason
affected by type 1 diabetes? Journal of Diabetes and Metabolic Disorders 19(2): 1647-1658	
Englert, K, Ruedy, K, Coffey, J et al. (2014) Skin and adhesive issues with continuous glucose monitors: a sticky situation. Journal of diabetes science and technology 8(4): 745-751	- Not a relevant study design *narrative summary of direcnet findings*
Faulds, Eileen R., Hoffman, Robert P., Grey, Margaret et al. (2020) Self-management among pre-teen and adolescent diabetes device users. Pediatric Diabetes 21(8): 1525-1536	- Not a relevant study design *prospective cohort*
Forlenza, Gregory P, Pyle, Laura L, Maahs, David M et al. (2017) Ambulatory glucose profile analysis of the juvenile diabetes research foundation continuous glucose monitoring dataset-Applications to the pediatric diabetes population. Pediatric diabetes 18(7): 622-628	- Secondary publication of an included study that does not provide any additional relevant information *Uses JDRF dataset to generate outcome not in protocol*
Ilkowitz, J, Raisingani, M, Wu, F et al. (2020) Short-term continuous glucose monitoring use in adolescents with type 1 diabetes enhances empowerment. Diabetes 69	- Conference abstract *poster*
JDRF CGM Study, Group (2008) JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: research design and methods. Diabetes technology & therapeutics 10(4): 310-21	- study protocol *JDRF protocol*
Klonoff, DC (2009) Continuous glucose monitoring study does not demonstrate benefit in children and adolescents. Journal of pediatrics 154(3): 463-464	- Not a relevant study design *Comment*
Lagarde, William H, Barrows, Frank P, Davenport, Marsha L et al. (2006) Continuous subcutaneous glucose monitoring in children with type 1 diabetes mellitus: a single-blind, randomized, controlled trial. Pediatric diabetes 7(3): 159-64	- Study does not contain a relevant intervention *Not a long enough period of CGM to be recognised*
Lanning, MS, Dimeglio, L, Lange, S et al. (2019) Continuous glucose monitoring interventions in toddlers with type 1 diabetes (T1D). Diabetes 68	- Conference abstract *poster*
Lawson, Margaret L., Richardson, Christine, Cooper, Tammy et al. (2021) Timing of CGM initiation in pediatric diabetes: The CGM TIME Trial. Pediatric Diabetes 22(2): 279-287	- Study does not contain a relevant intervention *Studying LGS + CGM vs CGm alone*
Lawson, Margaret L, Bradley, Brenda, McAssey, Karen et al. (2014) The JDRF CCTN CGM TIME Trial: Timing of Initiation of continuous glucose Monitoring in Established pediatric type 1 diabetes: study protocol, recruitment and baseline characteristics. BMC pediatrics 14: 183	- study protocol *CGM TIME*

Study	Reason
Ludvigsson, Johnny and Hanas, Ragnar (2003) Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. Pediatrics 111(5pt1): 933-8	- Study does not contain a relevant intervention *Committee judged that length of CGM in this study was not adequate enough to be useful. (3 days every 2 weeks)*
Ly, Trang T, Hewitt, Jacqueline, Davey, Raymond J et al. (2011) Improving epinephrine responses in hypoglycemia unawareness with real-time continuous glucose monitoring in adolescents with type 1 diabetes. Diabetes care 34(1): 50-2	- No relevant outcomes of interest based on protocol *Biochemical outcomes not of interest*
Marsters, BL, Boucher, S, Galland, B et al. (2020) Cutaneous adverse events in a randomised control trial of flash glucose monitoring among adolescents with type 1 diabetes. Diabetes technology & therapeutics 22: A-146	- Conference abstract *posters*
Marsters, Brooke L., Boucher, Sara E., Galland, Barbara C. et al. (2020) Cutaneous adverse events in a randomized controlled trial of flash glucose monitoring among youth with type 1 diabetes mellitus. Pediatric Diabetes 21(8): 1516-1524	- No relevant outcomes of interest based on protocol *Presents cutaneous adverse events only, which are not in list of prespecified AEs in review protocol*
Mauras, N., Beck, R., Xing, D. et al. (2013) A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. Diabetes Technology and Therapeutics 15(suppl1): 110-s111	- Study does not contain a relevant intervention *Pools rtCGM and isCGM and does not report by subgroup, meaning unclear what decisions/data can be drawn from results.*
Mauras, N., Beck, R., Xing, D. et al. (2012) A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. Diabetes Care 35(2): 204-210	- Duplicate reference
Mauras, Nelly, Beck, Roy, Xing, Dongyuan et al. (2012) A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. Diabetes care 35(2): 204-10	- Duplicate reference
McEachron, Kendall R., Potlapalli, Neha, Kirchner, Varvara A. et al. (2021) Early use of continuous glucose monitoring in children and adolescents after total pancreatectomy with islet autotransplantation. Pediatric Diabetes 22(3): 434-438	- Does not contain correct population *pancreatectomy not T1D*

Study	Reason
McKinlay, Christopher J D, Chase, J Geoffrey, Dickson, Jennifer et al. (2017) Continuous glucose monitoring in neonates: a review. Maternal health, neonatology and perinatology 3: 18	- Not a relevant study design *Review not SR*
Messer, L, Kanapka, L, Clements, M et al. (2020) Evaluation of CGM use features in adolescents with type 1 diabetes (T1D): a report from the CGM intervention in teens and young adults (CITY) study. Diabetes technology & therapeutics 22: A-22	- Conference abstract *poster*
Miller (2021) A Randomized Clinical Trial Assessing Continuous Glucose Monitoring (CGM) Use With Standardized Education With or Without a Family Behavioral Intervention Compared With Fingerstick Blood Glucose Monitoring in Very Young Children With Type 1 Diabetes. Diabetes care 44(2): 464-472	- Conference abstract *poster*
Miller, K, Kanapka, L, Clements, M et al. (2019) Continuous glucose monitoring in teens and young adults (CITY) improves glycemic control: primary results from a multi-center randomized clinical trial (RCT). Pediatric diabetes 20: 188-189	- Conference abstract *poster*
Moreno-Fernandez, Jesus, Gomez, Francisco Javier, Gazquez, Montserrat et al. (2013) Real-time continuous glucose monitoring or continuous subcutaneous insulin infusion, what goes first?: results of a pilot study. Diabetes technology & therapeutics 15(7): 596-600	- Does not contain correct population *Not a paediatric population*
Olivier, Patricia, Lawson, Margaret L, Huot, Celine et al. (2014) Lessons learned from a pilot RCT of simultaneous versus delayed initiation of continuous glucose monitoring in children and adolescents with type 1 diabetes starting insulin pump therapy. Journal of diabetes science and technology 8(3): 523-8	- No relevant outcomes of interest based on protocol *feasibility study with no statistical power*
Prabhu, Joshi Navis, Mubita, Womba, Azmi, Shazli et al. (2020) Use of factory-calibrated real-time continuous glucose monitoring improves time in target and HbA1c in a multiethnic cohort of adolescents and young adults with type 1 diabetes: The MILLENNIALS study. Diabetes Care 43(10): 2537-2543	- Does not contain correct population *<50% under 18*
Rachmiel, M, Landau, Z, Boaz, M et al. (2015) The use of continuous glucose monitoring systems in a pediatric population with type 1 diabetes mellitus in real-life settings: the AWeSoMe Study Group experience. Acta diabetologica 52(2): 323-329	- Not a relevant study design *Not an RCT*
Raviteja, K.V., Kumar, R., Dayal, D. et al. (2019) Clinical efficacy of Professional Continuous Glucose Monitoring in improving glycemic control among children with Type 1 Diabetes Mellitus: An Open-label Randomized Control Trial. Scientific reports 9(1): 6120	- Study does not contain a relevant intervention *professional CGM not unblinded CGM*
Sanderson, E, Smith, G, Abraham, M et al. (2019) The impact of CGM availability: real world data from a population based clinic. Hormone research in paediatrics 91: 144	- Conference abstract *Posters*

Study	Reason
Shah, Rajesh; McKinlay, Christopher J D; Harding, Jane E (2018) Neonatal hypoglycemia: continuous glucose monitoring. Current opinion in pediatrics 30(2): 204-208	- Not a relevant study design *review not SR*
Sinisterra (2020) Parent characteristics associated with diabetes device use in young children newly diagnosed with type 1 diabetes (T1D). Diabetes 69	- Conference abstract *poster*
Tansey, Michael, Weinzimer, Stuart, Beck, Roy et al. (2013) Extended 6-month follow-up of a randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. Diabetes care 36(5): e63	- Not a relevant study design *letter*
Thabit, H, Prabhu, JN, Mubita, W et al. (2020) Use of Factory-Calibrated Real-time Continuous Glucose Monitoring Improves Time in Target and HbA1c in a Multiethnic Cohort of Adolescents and Young Adults With Type 1 Diabetes: the MILLENNIAL Study. Diabetes care	- Duplicate reference *Prabhu dupe*
Thomas, F., Signal, M., Harris, D.L. et al. (2014) Continuous glucose monitoring in newborn infants: How do errors in calibration measurements affect detected hypoglycemia?. Journal of Diabetes Science and Technology 8(3): 543-550	- Does not contain correct population *Neonatal hypoglycemia not diabetes*
Tiberg (2019) E-health to support adolescents with type 1 diabetes. Pediatric diabetes 20: 201	- Conference abstract *poster*
Tsalikian E, Fox L, Weinzimer S et al. (2012) Feasibility of prolonged continuous glucose monitoring in toddlers with type 1 diabetes. Pediatric diabetes 13(4): 301-307	- Not a relevant study design *Single arm*
Wadwa, RP, Hanes, S, Clay, M et al. (2019) Impact of early initiation of continuous glucose monitoring on glycemic control in pediatric patients with type 1 diabetes. Diabetes technology & therapeutics 21: A98-A99	- Conference abstract *poster*
Wong, J, Hanes, S, Forlenza, G et al. (2020) Early initiation of continuous glucose monitoring among children and adolescents: benefits and timing. Diabetes technology & therapeutics 22: A146-A147	- Conference abstract *poster*
Yates, Kylie, Hasnat Milton, Abul, Dear, Keith et al. (2006) Continuous glucose monitoring-guided insulin adjustment in children and adolescents on near-physiological insulin regimens: a randomized controlled trial. Diabetes care 29(7): 1512-7	- Study does not contain a relevant intervention *Committee judged length of CGM to be too short to be useful for review (3 days every 2 weeks)*

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.	- Not in a population of children and young people
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.	- Not in a population of children and young people
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.	- Not in a population of children and young people
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.	- Not in a population of children and young people
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.	- Not in a population of children and young people
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	- Not in a population of children and young people

Study	Reason for exclusion
diabetes from the Canadian societal perspective." Journal of Medical Economics 20(11): 1128-1135.	
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.	- Not in a population of children and young people
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.	- Not in a population of children and young people
Huang, E. S., et al. (2010). "The cost-effectiveness of continuous glucose monitoring in type 1 diabetes." Diabetes care 33(6): 1269-1274.	- Not in a population of children and young people
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).	- Not in a population of children and young people
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.	- Not in a population of children and young people
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.	- Not in a population of children and young people
Healthcare Improvement Scotland (2018). "What is the clinical and cost effectiveness of Freestyle Libre flash glucose monitoring for patients with diabetes mellitus treated with intensive insulin therapy?" Advice on health technologies Retrieved 11 July, 2021.	- Not in a population of children and young people
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.	- Not in a population of children and young people

Appendix L - Research recommendations

L.1.1 What is the effectiveness and cost effectiveness of CGM devices in children and young people with type 2 diabetes?

L.1.1.1 Why this is important

There is some evidence on the effectiveness and cost-effectiveness of CGM devices to improve glycaemic control in children and young people with type 1 diabetes. However, there is none for people in this age group who have type 2 diabetes. Evidence is therefore needed to see whether children and young people with type 2 diabetes could gain similar benefits from the use of CGM devices as those who have type 1 diabetes. This may make it possible to recommend CGM for use with this group in future.

L.1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	There is an increasing number of children with type 2 diabetes, who need to be catered for with specific guidance.
Relevance to NICE guidance	NICE requires recommendations for type 2 diabetes in children and young people to sit alongside type 1 recommendations. It cannot be assumed that recommendations for children and young people with type 1 diabetes or adults with type 2 diabetes would be relevant.
Relevance to the NHS	If CGM devices are shown to be effective at improving glycaemic control for children and young people with type 2 diabetes then they can be recommended for use with this group. 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 no RCTs for CGM for children and young people with type 2 diabetes
Equality considerations	Type 2 diabetes remains far less common than type 1 diabetes in children and young people in the UK. However, the number of cases continues to rise, with significantly increased incidence among girls and South-Asian children and young people. Female gender, family history, non-white ethnicity and obesity were found to be strongly associated with the condition.

L.1.1.3 Modified PICO table

Population	Children and young people with type 2 diabetes

Intervention	CGM device (real-time continuous glucose monitor, intermittent scanning glucose monitor (Flash), self-monitoring of blood glucose (intermittent capillary blood glucose monitoring)
Comparator	Compared to each other
Outcome	• HbA1c • Time in target glucose range • Time above/below target glucose range • Hypoglycemia (severe/nocturnal) • Glycemic variability • Mortality • Satisfaction with CGM • Diabetic ketoacidosis (DKA) • % of data captured • Other adverse events (diabetes related hospitalisation, serious adverse events, severe monitor malfunction, hypersmolar hyperglycemic state) • Mental health outcomes: Diabetes distress (including fear of hypoglycaemia and diabetes burnout), Diabetes related depression, Body image issues related to device • Awareness of hypoglycemia • Adherence • Attendance to care services • Educational attainment • Quality of life (validated and continuous)
Study design	Randomised controlled trials.
Timeframe	Long term
Additional information	None

L.1.2 What is the effectiveness and cost effectiveness of CGM devices to improve glycaemic control in children and young people using routinely collected real-world data?

L.1.2.1 Why this is important

There is currently no evidence on the effectiveness and cost-effectiveness of CGM devices to improve glycaemic control in children and young people with type 2 diabetes, and only RCT evidence for children and young people with type 1 diabetes. While RCT evidence is useful, it does not necessarily provide the same evaluation of how well these devices work on a daily basis in normal life as real-world data. By using real-world data, it will be possible to identify how effective different CGM devices are to a wide range of children and young people from different backgrounds. This may lead to an increased understanding of CGM devices and make it possible to produce recommendations about their use for children and young people in future.

L.1.2.2 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	If CGM devices are shown to be effective at improving glycaemic control for children and young people, then they can be recommended for use with this group. 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 is currently no evidence for CGM for children and young people with type 2 diabetes and only RCT evidence for children and young people with type 1 diabetes.
Equality considerations	Increased monitoring of routine healthcare data will ensure a broader population is captured, rather than just those eligible for clinical trials.

L.1.2.3 Modified PICO table

Population	Children and young people with type 1 and 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

L.1.3 What is the best CGM sensor adhesive to prevent sensitivities to the device, for example local skin reactions?

L.1.3.1 Why this is important

One of the factors which affects the use of CGM devices in children and young people is sensitivities to the device, such as reactions to the adhesive used for the sensors. More research will help to determine which adhesives are least likely to result in these sensitivities, therefore potentially increasing adherence to the use of CGM devices.

L.1.3.2 Rationale for research recommendation

Importance to 'patients' or the population	One of known factors determining the use of CGM devices amongst children and young people with type 1 diabetes is sensitivities to the device, for example local skin reactions to the adhesive used in the sensor. Further research is needed to investigate strategies to reduce local skin reactions to promote ease of use and adherence of these devices.
Relevance to NICE guidance	This will help improve implementation of the updated recommendations
Relevance to the NHS	It will be possible to recommend the adhesives that produce the fewest sensitivities to children and young people. This may increase uptake and adherence to CGM devices in this group, thereby helping them to control their blood glucose levels more effectively.
National priorities	Low
Current evidence base	There is currently no evidence for CGM for children and young people with type 2 diabetes
Equality considerations	The current updated recommendations extending CGM to all children and young people with type 1 diabetes would help remove the observed discrepancies in clinical practice and address known inequalities in access. For example, those from lower socioeconomic groups or those from black, Asian and minority ethnic minority groups who from their clinical experience have been less likely to be prescribed these devices. A reduction in sensitives to the CGM device will promote adherence to children and young people with type 1 diabetes.

L.1.3.3 Modified PICO table

Population	Children and young people with type 1 diabetes using CGM devices
Intervention	CGM sensor adhesive
Comparator	Compared to each other
Outcome	• CGM adherence • Local skin reactions • Satisfaction with CGM device
Study design	Randomised controlled trial
Timeframe	Long term
Additional information	None