Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Flash glucose monitoring for the management of diabetes (update)

This is an updated version of the original Evidence Appraisal Report published by Health Technology Wales in November 2018.

Executive summary

- This report aims to identify and summarise evidence that addresses the following question: What is the clinical and cost effectiveness of flash glucose monitoring in people with diabetes? This rapid review used evidence from randomised controlled trials (RCTs), existing evidence reviews, and non-randomised trials where limited outcome data from RCTs was available.
- We identified 10 RCTs that followed patients for up to 6 months of FGM use and compared flash glucose monitoring (FGM) to self monitoring of blood glucose (SMBG, 7 trials) or real-time continuous glucose monitoring (rtCGM, 3 trials). We used evidence from 5 observational studies to supply longer term evidence on healthcare utilisation, which was not reported by any RCTs. We also combined two existing pooled analyses of observational studies to provide evidence on longer term changes in HbA1c after FGM initiation.
- Compared to SMBG:
    - There is no evidence of a difference in HbA1c outcomes between people using FGM or SMBG (six RCTs).
    - Two RCTs reported FGM to be beneficial in terms of improved time in target glucose range, but a further 2 RCTs found no statistically significantly difference between the interventions. Similarly, some evidence suggests FGM reduces time below or above target glucose range, but other trials reported uncertainty for these outcomes.
    - Two trials reported improvements in reported quality of life after FGM use, but these did not always differ significantly from quality of life reported by people using SMBG.
    - One RCT found significantly higher numbers of glucose checks by FGM users compared to those using SMBG; this trial was conducted in people aged 13-20 years (no equivalent evidence in other age groups was found).
- Compared to rtCGM:
    - Evidence from one RCT reported higher HbA1c after FGM use (suggesting rtCGM may be more beneficial than FGM for this outcome). All participants in the trial were previous experienced users of FGM, which might limit the generalisability of this finding to FGM-naïve users. A second trial reported no difference between the two interventions for this outcome.
    - Evidence suggests the amount of time spent in target glucose range may be poorer with FGM (two RCTs), or that there is no statistically significant difference between the interventions (one RCT). The trials that found rtCGM to be beneficial were conducted in adults with T1DM who also took part in an exercise programme, or who

were experienced FGM users. Their generalisability to other populations/scenarios is therefore unclear.
    - No evidence was found for frequency of glucose monitoring or quality of life outcomes.
- We also included larger-scale observational studies that reflect use of FGM in broader populations and provide data on outcomes that were not reported by RCTs. Due to the lack of control group and for the specific reasons described below, this evidence is more prone to bias and should be treated as having lower certainty than findings from RCTs.
    - A pooled analysis of observational studies suggests HbA1C levels improve in people using FGM and that this benefit is sustained for at least 9 months after first use. However, statistical analysis indicated high levels of heterogeneity, reducing the certainty of this finding.
    - Five large-scale audits of real-world evidence suggest a reduction in paramedic callouts, hospital admissions, visits to diabetes/endocrine specialists and primary care visits following initiation of FGM over follow up times of 7.5 to 14 months. However, some of these studies had high levels of dropouts, and no analyses to determine the statistical significance for these outcomes were reported.
- Patient and carer evidence came from a patient organisation submission and a review of published evidence. These highlight the pain and burden associated with SMBG for all people with diabetes. Specific challenges related to performing SMBG have been identified for children/adolescents at home and at school, for adults in the workplace and for elderly/older people with memory loss/dementia. FGM is generally considered by patients, their families and carers as a significant improvement to SMBG. FGM can reduce the burden of monitoring responsibility, thereby increasing the rate at which people check their glucose levels. FGM is reported to enable individuals to make more informed choices and encourages healthier behaviour, and reduces barriers to taking part in social and work-related activities. While there were adverse effects to the wearing of FGM sensors reported, from skin conditions to damage/loss of sensors and a potential for sensors to serve as 'constant reminders' of diabetes, the majority of participants reported that these would not put them off using FGM in the future. Compared to rtCGM, use of FGM is viewed by patients, their families and carers as less technically challenging. FGM may be favourable to rtCGM for people who feel overwhelmed by the constant stream of information provided by rtCGM and the negative emotional impacts related, such as increased disease anxiety and constant disease reminders. Conversely, FGM may be considered to be less favourable to rtCGM for older patients where constant glucose readings may better suit patients' needs.
- Economic evidence shows the potential for the higher upfront costs of the FGM system to be offset, at least partially, by reductions in the frequency of SMBG tests and non-severe hypoglycaemic events. Further cost savings and benefits with FGM may be achieved through a reduction in severe hypoglycaemic events or improvements in HbA1c. However, there is uncertainty around these potential effects.
- Evidence from three cost-utility analyses show the potential for FGM to be cost-effective in cost per QALY terms. However, there is uncertainty around key assumptions in the analyses, such as the inclusion of a process-related improvement in quality of life associated with using FGM. This improvement was based on a study, which elicited preferences from the general population rather than people with diabetes.
- A de novo cost-utility analysis developed by HTW aimed to provide a more conservative estimate of the cost-effectiveness of FGM as it was based only on reductions in non-severe hypoglycaemic events and SMBG usage. The results suggest that FGM is cost-effective in people with T1DM and T2DM. Key areas of uncertainty were the quality of life benefits associated with reducing non-severe hypoglycaemic events and baseline SMBG testing frequency.

List of abbreviations

ANCOVA	Analysis of covariance
BGRI	Blood glucose risk index
CGM	Continuous glucose monitoring
CI	Confidence interval
CSII	Continuous subcutaneous insulin infusion
CV	Coefficient of variance
DM	Diabetes mellitus
DTSQ	Diabetes treatment satisfaction questionnaire
EAR	Evidence appraisal report
FGM	Flash glucose monitoring
GRADE	Glycaemic risk assessment diabetes equation
HTA	Health technology assessment
HTW	Health Technology Wales
IQR	Interquartile range
isCGM	Intermittently scanned continuous glucose monitoring
L	Litre
MAGE	Mean amplitude of glycaemic excursion
MDI	Multiple daily injections
MODD	Mean of daily differences
NA	Not applicable
NR	Not reported
PedsQL	Paediatric quality of life inventory
RCT	Randomised controlled trial
rtCGM	Real-time continuous glucose monitoring
SD	Standard deviation
SE	Standard error
SMBG	Self-monitoring of blood glucose
SOC	Standard of care
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAR	Time above range
TBR	Time below range
TIR	Time in range

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question: What is the clinical and cost effectiveness of flash glucose monitoring in people with diabetes?

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

2. Health problem

Diabetes mellitus is a group of metabolic diseases resulting from defects in insulin secretion, insulin action or a combination of both. Two major categories of diabetes exist. Type 1 diabetes mellitus (T1DM) is characterised by an absolute deficiency of insulin secretion. Conversely, type 2 diabetes mellitus (T2DM) is much more prevalent and is characterised by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (American Diabetes Association 2005). The International Diabetes Federation estimates that one in every 11 adults worldwide has diabetes, which equates to approximately 425 million people with the disease (Janapala et al. 2019). The disease has a great impact on the public health systems as it accrues high costs related to the control of the disease and management of complications (da Rocha et al. 2020). According to Diabetes UK, Wales has the highest prevalence of diabetes in the UK. More than 200,000 people in Wales are now living with diabetes (8% of the population aged 17 and over), with the numbers rising every year: in 2020, an additional 10,695 people were diagnosed with diabetes. Approximately 90% of people with diabetes have T2DM. It is estimated that a further 65,501 people in Wales have T2DM but have not been diagnosed yet and approximately 580,000 people in Wales could be at risk of developing T2DM. If the current trends continue, it is estimated that 311,000 people in Wales could have diabetes by 2030 (Diabetes UK 2020).

Glycaemic management aimed at normalising blood glucose concentrations is key for successful diabetes care. T1DM is treated with insulin replacement therapy, which aims to recreate the normal fluctuations in circulating insulin concentrations as well as to improve the control of blood glucose (NICE 2021). T2DM is usually managed through a combination of lifestyle interventions and pharmaceutical treatments; however, some people with T2DM require insulin treatment when these interventions fail to control blood glucose levels (NICE 2020b). Regular glucose measurements are essential for patients with diabetes for monitoring the progress of diabetes therapies and to guide decision making on adjustments of both insulin and non-insulin anti-diabetic drugs or intake of carbohydrates. Achieving metabolic balance through regular monitoring of blood glucose levels and an optimal adherence to glucose-lowering therapies, a healthy diet and physical activity remain the most important factors for the prevention of the both micro- and macro-vascular complications of the disease. Failure to adhere to these interventions leads to hyper- and hypoglycaemic fluctuations that are associated with a lower quality of life and increased risk of mortality (Kebede et al. 2018).

In recent decades, metabolic monitoring has been achieved by self-measuring of capillary blood glucose (SMBG) with appropriate systems (Heinemann et al. 2019). The process involves pricking a fingertip in order to collect a drop of blood on a test strip that is subsequently inserted into an electronic glucose monitor. It is recommended that adults with T1DM should test their blood glucose at least four times per day, including before each meal and before bed (NICE 2021). In children and young people with T1DM who require blood glucose monitoring, testing at least five times per day is recommended (NICE 2020a). More frequent testing is needed in certain

circumstances such as intercurrent illness, participation in sport, pregnancy and for people who undertake high-risk occupations or who drive for long periods of time. Guidance on other groups who may require regular SMBG testing is less well-established. Feedback from stakeholders indicated that people with T2DM require regular SMBG testing if they are treated with insulin or oral glucose-lowering medication that can result in hypoglycaemia. Other groups suggested to benefit are:

- People with T2DM who are undergoing treatment change or planning pregnancy;
- People with newly diagnosed T2DM;
- People with gestational diabetes.

3. Health technology

Many patients experience a multitude of barriers to frequent testing, including pain and discomfort associated with the finger-prick blood samples and accumulated trauma to the fingers (Fokkert et al. 2017). Continuous glucose monitoring (CGM) systems provide an alternative to SMBG. Unlike SMBG, CGM systems display the immediate glucose value within the context of prior glucose data and the direction and velocity of the changing glucose trends. This information helps patients to react immediately to mitigate or prevent acute glycaemic events (Kudva et al. 2018). It can also assist patients and those involved in their care with ongoing management such as to guide meal intake, physical activity, carbohydrate counting and medication adjustment.

Two types of CGM devices are currently available: real-time continuous CGM (rtCGM) and intermittently-scanned CGM (isCGM), more commonly referred to as flash glucose monitoring (FGM). FGM systems monitor glucose via a factory- or home-calibrated, on body sensor that is inserted sub-cutaneously on the back of the arm for up to 14 days, and it continuously monitors interstitial glucose levels. The sensor can be scanned by a reader to provide both a real-time glucose level reading and a graphical trace of glucose values for the past eight hours (Stueve & Schnell 2019).

As of June 2021, FreeStyle Libre (Abbott Diabetes Care) is the only brand of FGM device available in the UK for non-hospital use. The company also manufactures the FreeStyle Libre PRO for professional use; however this device is out of the scope of this appraisal. FreeStyle Libre received regulatory approval in September 2014. Two FGM systems manufactured by Abbott are currently available on the market: FreeStyle Libre and FreeStyle Libre 2. The newer version of the FGM device provides options for hypo- and hyperglycaemia alarms and features a notification system for the user in case of signal loss. Both versions display eight hours of trend data in a graphical manner only when the reader is scanned and do not require calibration via SMBG. However, SMBG confirmation is recommended if the patient experiences symptoms that do not match the sensor glucose reading or suspects that the reading may be inaccurate.

In October 2019, HTW issued Guidance on the use of rtCGM in pregnant women with diabetes; this states that "The case for adopting continuous glucose monitoring in pregnant women with type 1 diabetes is supported by the evidence." NICE Guidelines NG18 (NICE 2020a) and NG17 (NICE 2021) also make recommendations around certain groups of children and adults with diabetes who may benefit from rtCGM/FGM. These are summarised in Table 1.

Table 1. Summary of NICE Guideline recommendations on the use of real-time continuous and flash glucose monitoring

Guideline	Section: Paragraph	Recommendation
NICE Guideline 17: Type 1 diabetes in adults: diagnosis and management (last updated December 2020) (NICE 2021)	Continuous glucose monitoring: 1.6.21	Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes.
	Continuous glucose monitoring: 1.6.22	Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimised use of insulin therapy and conventional blood glucose monitoring: • More than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause. • Complete loss of awareness of hypoglycaemia. • Frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities. • Extreme fear of hypoglycaemia. • Hyperglycaemia (HbA1c level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day (see recommendations 1.6.11 and 1.6.12). Continue real-time continuous glucose monitoring only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of 27 mmol/mol (2.5%) or more.
	Continuous glucose monitoring: 1.6.23	For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy.
	Continuous glucose monitoring: 1.6.24	Real-time continuous glucose monitoring should be provided by a centre with expertise in its use, as part of strategies to optimise a person's HbA1c levels and reduce the frequency of hypoglycaemic episodes.
	Strategies for managing impaired awareness of hypoglycaemia: 1.10.18	Review insulin regimens and doses and prioritise strategies to avoid hypoglycaemia in adults with type 1 diabetes with impaired awareness of hypoglycaemia, including: • reinforcing the principles of structured education • offering continuous subcutaneous insulin infusion (CSII or insulin pump) therapy • offering real-time continuous glucose monitoring.

Guideline	Section: Paragraph	Recommendation
NICE Guideline 18: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (last updated December 2020) (NICE 2020a)	Blood glucose monitoring: 1.2.63	Offer ongoing real-time continuous glucose monitoring with alarms to children and young people with type 1 diabetes who: • have frequent severe hypoglycaemia or • have impaired hypoglycaemia awareness that is associated with adverse consequences (for example, seizures or anxiety) or • cannot recognise or communicate about symptoms of hypoglycaemia (for example, because of cognitive or neurological disabilities).
	Blood glucose monitoring: 1.2.64	Consider ongoing real-time continuous glucose monitoring for: • babies, infants and pre-school children • children and young people with high levels of physical activity (for example national-level sport) • children and young people who have comorbidities (for example anorexia nervosa), or who are having treatments (for example corticosteroids) that can make blood glucose management difficult. [2015]
	Blood glucose monitoring: 1.2.65	Consider intermittent (real-time or retrospective) continuous glucose monitoring to help improve blood glucose management for children and young people who continue to have hyperglycaemia despite insulin adjustment and additional support.

4. Clinical effectiveness

We searched for evidence that could be used to answer the review question: What is the clinical and cost effectiveness of flash glucose monitoring in people with diabetes? The criteria used to select evidence for the appraisal are outlined in Appendix 2. These criteria were developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts.

Three systematic reviews and health technology appraisals were identified and used as either sources of outcome data or sources of primary studies (detail in Appendix 4). As this is an updated appraisal, we also used our previous Evidence Appraisal Report on FGM, published in November 2018, as a source of evidence. We also searched the literature for trials of any design not covered by any of these sources. As this is a rapid review, we have focussed on outcomes from RCTs, whether reported separately or as part of existing reviews; we have only used outcomes from non-randomised trials where limited or no outcome data from RCTs was reported.

Sources of evidence for the outcomes in this section are summarised in Table 2. Details of the included sources of evidence are provided in Appendix 4. Table 3 summarises the direction and certainty of the effect for each outcome. Other supplementary outcomes are reported in Appendix 5.

The randomised trials we identified (either as part of existing reviews or individually) varied in terms of the type of diabetes studied, the follow-up time used, and the control intervention against which FGM was compared. This meant it was not possible to pool results from any randomised trials. In the RCTs identified, patients were followed up for a relatively short period (minimum of four weeks, maximum of six months). To provide information on longer-term outcomes, we pooled outcome data from two systematic reviews that measured HbA1c over longer periods (up to 2 years) in people using FGM as part of longer-term, uncontrolled studies.

The following sections summarise evidence for each outcome of interest. Definitions of diabetes-related outcomes are listed in Appendix 8 Table 1.

Table 2. Summary of key outcomes measured and sources of evidence used

Outcome (report section)	Comparison	Study design(s) and participants	(Characteristics of) participants		Follow-up period	Study references
			Type of diabetes	Background treatment/management		
HbA1c (4.1)	FGM vs SMBG	RCTs, five studies,	T1DM (two studies) T2DM (three studies) Pregestational diabetes (one study)	Insulin (4 studies, Bolinder 2016; Boucher 2020c; Haak 2017; Yaron 2019), non-insulin (1 study, Wada 2020), any DM treatment (1 study, Tumminia 2021) At baseline, mean frequency of SMBG tests varied from 2 to 5 SMBG tests/day, no prior SMBG use in one study (Wada 2020), baseline SMBG use unclear in one study (Tumminia 2021)	Min 10 weeks; max 6 months	Bolinder et al. (2016) Boucher et al. (2020c) Haak et al. (2017) Tumminia 2021 Yaron et al. (2019) Wada et al. (2020)
	FGM vs rtCGM	RCT, two studies	T1DM	Insulin In one trial (Visser 2021), all participants were FGM users for at least 6 months before the study.	8 weeks to 6 months	Reddy et al. (2018b) Visser et al. (2021)
	No control group (before/after FGM use)	Two systematic reviews of single-arm studies.	T1DM (15 studies, n= 3996) T2DM (2 studies, n = 227)	Not reported by SR authors. Inclusion criteria included any T1DM patients in one review, and people with any type of diabetes in the second review.	Up to 24 months	Evans et al. (2020) Gordon et al. (2020)
Time in target glucose range (4.2.1)	FGM vs SMBG	RCTs, four studies	T1DM (two studies) T2DM (two studies) Adults (three studies) Children/adolescents (one study)	Insulin (3 studies, Bolinder 2016; Haak 2017; Piona 2018), non-insulin (1 study, Wada 2020) At baseline, mean frequency of SMBG tests varied from 2 to 5 SMBG tests/day, no prior SMBG use in one study (Wada 2020); SMBG used by both intervention and control group in one study (Piona 2018)	Min 2 weeks; max 26 weeks	Bolinder et al. (2016) Piona et al. (2018) Haak et al. (2017) Wada et al. (2020)
	FGM vs CGM	RCTs, two studies	T1DM (three studies) Adults (three studies) Impaired hypoglycaemia awareness (one study, Reddy 2018b)	Insulin; intensified MDI injection regimen in one trial (Reddy 2018b) One trial (Haskova 2020) included a 4 day exercise program alongside glucose monitoring	Min 32 days, max 6 months	Haskova et al. (2020) Reddy et al. (2018b) Visser et al. (2021)

Outcome (report section)	Comparison	Study design(s) and participants	(Characteristics of) participants		Follow-up period	Study references
			Type of diabetes	Background treatment/management		
				In one trial (Visser 2021), all participants were FGM users for at least 6 months before the study.		
Time above target glucose range (4.2.2)	FGM vs SMBG	RCTs, three studies	T1DM (one study) T2DM (two studies) Adults (three studies)	Insulin (2 studies, Bolinder 2016; Haak 2017), non-insulin (1 study, Wada 2020) At baseline, mean frequency of SMBG tests varied from 2 to 5 SMBG tests/day, no prior SMBG use in one study (Wada 2020)	24 to 26 weeks	Bolinder et al. (2016) Haak et al. (2017) Wada et al. (2020)
	FGM vs CGM	RCTs, two studies	T1DM, adults	Insulin; 4 day exercise program alongside glucose monitoring in one study (Haskova 2020). In one trial (Visser 2021), all participants were FGM users for at least 6 months before the study.	Min 32 days, max 6 months	Haskova et al. (2020) Visser et al. (2021)
Time/frequency below target glucose range (4.2.3)	FGM vs SMBG	RCTs, five studies	T1DM (two studies) T2DM (three studies) Adults (four studies) Children/adolescents (one study)	Insulin (4 studies, Bolinder 2016; Haak 2017; Piona 2018, Yaron 2019), non-insulin (1 study, Wada 2020) At baseline, mean frequency of SMBG tests varied from 2 to 5 SMBG tests/day, no prior SMBG use in one study (Wada 2020); SMBG used by both intervention and control group in one study (Piona 2018) One trial (Yaron 2019) included specialist diabetes management and counselling alongside glucose monitoring	Min 2 weeks; max 26 weeks	Bolinder et al. (2016) Piona et al. (2018) Haak et al. (2017) Wada et al. (2020) Yaron et al. (2019)
	FGM vs CGM	RCTs, three studies	T1DM (three studies) Adults (three studies) Impaired hypoglycaemia awareness (one study, Reddy 2018b)	Insulin; intensified MDI injection regimen in one trial (Reddy 2018b). In one trial (Visser 2021), all participants were FGM users for at least 6 months before the study. One trial (Haskova 2020) included a 4 day exercise program alongside glucose monitoring	Min 32 days, max 6 months	Haskova et al. (2020) Reddy et al. (2018b)

Outcome (report section)	Comparison	Study design(s) and participants	(Characteristics of) participants		Follow-up period	Study references
			Type of diabetes	Background treatment/management		
Frequency of glucose monitoring (4.3)	FGM vs SMBG	RCTs, one study	T1DM, children/adolescents	Insulin, mean 1.9 SMBG checks/day at baseline	26 weeks	Boucher et al. (2020c)
	FGM vs CGM	No evidence found				
Health care utilisation (4.4)	No control group (before/after FGM use)	Observational/real-world evidence, four studies	Any diabetes type (2 studies); T1DM only (1 study); diabetes and hypoglycaemia unawareness, unexplained or high-risk hypoglycaemia, or poor glycaemic control (1 study)	Insulin for majority of participants[1] Mean SMBG checks at baseline varied from 2 to 8/day; in one study 26% of participants were non-compliant with SMBG testing (Roussel, 2021)	Min 7.5 months, max 14 months	Deshmukh et al. (2020) Fokkert et al. (2019) Roussel et al. (2021) Tsur et al. (2021)
Quality of life (4.5)	FGM vs SMBG	RCTs, two studies	T1DM Adults (1 study); children/adolescents (1 study)	Insulin At baseline, mean frequency of SMBG tests varied from 2 to 5 SMBG tests/day	26 weeks	Haak et al. (2017) Boucher et al. (2020c)
	FGM vs CGM	No evidence found				
Device-related adverse events (4.6)	FGM vs SMBG	RCTs, 3 studies	T1DM Adults (2 studies); children/adolescents (1 study)	Insulin At baseline, mean frequency of SMBG tests varied from 2 to 5 SMBG tests/day	26 weeks	Boucher et al. (2020c) Haak et al. (2017) Bolinder et al. (2016)
	FGM vs CGM	No evidence found				

FGM: flash glucose monitoring; rtCGM: real-time continuous glucose monitoring; SMBG: self-monitoring of blood glucose; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus

[1]The nature of the data available and detail reported by each study make the exact number of patients treated with insulin or other therapies difficult to quantify.

Table 3. Evidence map: all outcomes and comparisons

Outcome (report section)	Control = SMBG 7 RCTS, 815 participants, adults and children T1DM (3 studies); T2DM (3 studies); pregestational diabetes (1 study) Treatment with insulin (5 studies); non-insulin treatment (1 study); any treatment (1 study)	Control = rtCGM 3 RCTs, 354 participants, adults T1DM (all studies) MDI or insulin pump (2 studies); any insulin treatment (1 study)	Before/after FGM (no controls) 5 observational studies, 91,699 participants[1]; 2 SRs T1DM (1 study); T2DM (1 study); any diabetes (3 studies) Treatments varied/not specified
HbA1c (4.1)	6 RCTs; T1DM (2 studies); T2DM (3 studies); pregestational diabetes (1 study)	2 RCTs, T1DM	2 SRs; T1DM (15 studies, n= 3996) T2DM (2 studies, n = 227)
Time in target glucose range (4.2.1)	4 RCTs; T1DM (two studies); T2DM (two studies)	3 RCTs, T1DM	Not reported[2]
Time above target glucose range (4.2.2)	3 RCTs; T1DM (one study); T2DM (two studies)	2 RCT; T1DM	Not reported[2]
Time/frequency below target glucose range (4.2.3)	5 RCTs; T1DM (two studies); T2DM (three studies)	3 RCTs; T1DM	Not reported[2]
Frequency of glucose monitoring (4.3)	1 RCT; T1DM (adolescents)	No evidence found	Not reported[2]
Health care utilisation (4.4)	No evidence found	No evidence found	5 observational studies, T1DM and T2DM
Quality of life (4.5)	2 RCTs; T1DM	No evidence found	Not reported[2]
Device-related adverse events (4.6)	3 RCTs; T1DM	No evidence found	Not reported[2]

[1]Number of patients enrolled: outcomes were not reported for all those enrolled in some studies.
[2]We have only used outcomes from non-randomised trials where limited or no outcome data from RCTs was reported

FGM: flash glucose monitoring; RCT; randomised controlled trial; SMBG: self-monitoring of blood glucose; SR: systematic review; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus

Evidence likely favours FGM | Evidence favours FGM but with uncertainty | Limited/indirect evidence favours FGM but with uncertainty | Equivocal/uncertain evidence

Evidence likely favours control | Evidence favours control but with uncertainty | Limited/indirect evidence favours control but with uncertainty | No evidence identified

4.1 Changes in HbA1c

4.1.1 FGM versus SMBG

For this outcome we identified six RCTs comparing FGM to SMBG. One study was conducted in adults with T1DM (Bolinder et al. 2016), and one RCT was conducted in adolescents (aged 13-20 years) with T1DM (Boucher et al. 2020c). Three RCTs were conducted in adults with T2DM (Haak et al. 2017, Wada et al. 2020, Yaron et al. 2019). The remaining study (Tumminia et al. 2021) recruited pregnant women with either T1DM or T2DM. HbA1c outcomes from these studies are reported in Table 4.

In one study of adults with T1DM by Bolinder et al. (2016) no statistically significant reduction was reported in the whole study population (0.0 95% CI -0.12 to 0.12, p=0.9556). The RCT by Boucher et al. (2020c) reports a non-statistically significant difference in adjusted changes in HbA1c at six months in HbA1c in participants aged 13-20 with T1DM using FGM in comparison to SMBG (-0.2% (-2.1 mmol/mol) 95% CI -0.9 to 0.5, p=0.576).

Two studies assessed FGM in people with T2DM managed with insulin treatment. Haak et al. (2017) did not find any statistically significant change in HbA1c between FGM and SMBG. The second study by Yaron et al. (2019) reports a decrease in HbA1c in patients with uncontrolled T2DM on insulin therapy, when comparing FGM to SMBG (-0.82% vs -0.33%, p=0.005). One study compared FGM to SMBG in non-insulin treated T2DM. Wada et al. (2020)) reports no statistically significant between-group difference in the ANCOVA model between FGM and SMBG in patients with T2DM at the end of the 12 week intervention period (-0.13% (-1.4 mmol/mol) 95% CI -0.35 to 0.09, p=0.241). However, a statistically significant between-group difference in the same model was found between FGM and SMBG at 24 weeks, 12 weeks after treatment with FGM ended (-0.29 (-3.2 mmol/mol) 95% CI -0.54 to -0.05, p=0.022). Finally, Tumminia et al. (2021) reported a significant decrease in HbA1c levels with both FGM and SMBG during pregnancy, but the difference between groups was not statistically significant.

4.1.2 FGM versus rtCGM

We identified two RCTs comparing changes in HbA1c in people using FGM or rtCGM (Reddy et al. 2018b, Visser et al. 2021). All participants were adults with T1DM; one trial (Visser et al. 2021) only recruited people who had previous experience using FGM (for at least 6 months prior use). In the trial by Visser et al (2021), people assigned to rtCGM experienced a statistically significant decrease in HbA1c compared to those who used FGM (−0·36 percentage points (95% CI −0·48 to −0·24)); in the latter group mean % HbA1c did not change during the study. In the second study by Reddy et al. (2018b), HbA1c levels decreased in both groups but the difference between FGM and rtCGM was not statistically significant.

4.1.3 Changes in HbA1c from long-term studies

Evans et al. (2020) and Gordon et al. (2020) are two systematic reviews that report pooled longitudinal changes in HbA1c. These analyses did not include a control group but are included here as they provide longer follow-up in a larger population than is available from RCTs. Details regarding the individual studies included, disease type, number of participants and follow-up period can be found in Appendix 6, Tables 3 and 4. We extracted outcome data from both existing analyses and updated this to provide one single set of outcomes, stratified by age of the included population, diabetes type and follow up time. Outcomes across all ages are reported here and summarised in Table 4; outcomes for subgroups of different ages are reported in Appendix 5.

Data on Hba1c was available from 39 studies, reporting follow up over various time periods. For the overall population, all studies included T1DM cases only. Depending on follow up time, between 822 and 3,996 participants where included. At each time point (≤3 months to >9 months

of FGM usage, maximum follow up 24 months) the mean change in HbA1c decreased by a statistically significant amount. However, high levels of heterogeneity at statistically significant levels were also found for all the overall effect meta-analyses, which reduces the certainty of this finding.

Table 4. Changes in HbA1c for FGM compared to SMBG or rtCGM

Outcome	Evidence source(s)	Number of participants	Comparison	Follow up	Absolute effect	Relative effect	Comments
FGM compared to SMBG							
Change in HbA1c, %	Bolinder et al. (2016)	n = 239	SMBG	6 months	Baseline: FGM: 6.79 ± 0.52 SMBG: 6.78 ± 0.64 Study end: FGM: 6.94 ± 0.65 SMBG: 6.95 ± 0.66	Difference in adjusted means in intervention vs control: 0.00 ± 0.059 p = 0.9556 **(favours neither intervention)**	9 patients from the intervention group and 19 patients from the control group either withdrew or were excluded.
Change in HbA1c, %	Haak et al. (2017)	n = 224	SMBG	6 months	Baseline mean (SD) FGM: 8.65 ± 1.01 SMBG: 8.75 ± 0.98 Study end mean (SD) FGM: 8.37 ± 0.83 SMBG: 8.34 ± 1.14	Difference in adjusted means in intervention vs control (SE): 0.03 ± 0.114 p = 0.8222 **(favours neither intervention)**	23 participants in total withdrew from study
Change in HbA1c, %	Yaron et al. (2019)	n = 101	SMBG	10 weeks	Mean ± SD change from baseline to end of follow-up: FGM: -0.82 ± 0.84 SMBG: -0.33 ± 0.78 p = 0.005 (**favours FGM**)	**NR**	Follow-up HbA1c data were missing for seven patients (n = 2 for intervention and n = 5 for control). It is unclear how these patients were accounted for in the results.
Change in HbA1c, %	Wada et al. (2020)	n = 100	SMBG	24 weeks	Baseline FGM: 7.83 ± 0.25 SMBG: 7.84 ± 0.27 Study end (24 weeks): FGM vs SMBG: -0.29 ± NR P = 0.022 **(favours FGM)**	HbA1c was significantly decreased in the FGM group compared with the SMBG group at 24 weeks in the ANCOVA model FGM: -0.46% (-5.0 mmol/mol), 95% CI -0.59 to -0.32, p<0.001; SMBG: -0.17% (-1.8 mmol/mol), 95% CI -0.05 to 0.11, p=0.124 **(favours FGM)**	1 patient from SMBG group lost to follow-up

Outcome	Evidence source(s)	Number of participants	Comparison	Follow up	Absolute effect	Relative effect	Comments
Change in HbA1c, %	Boucher et al. (2020c)	n = 64	SMBG	6 months	Mean ± SD at baseline and end of follow-up: isCGM: Baseline: 10.8 ± 1.7. 6 months: 10.0 ± 1.5 SMBG: Baseline: 11.2 ± 1.6. 6 months: 10.7 ± 1.5	Difference in adjusted changes at 6 months (95% CI): -0.2% (95% CI -0.9 to 0.5) P = 0.576 **(favours neither intervention)**	
Change in HbA1c, %	Tumminia et al. (2021)	n = 40	SMBG	See comments	Mean ± SD change from baseline to end of follow-up: FGM: -0.65 ± 0.7 SMBG: -0.67 ± 0.8 p = 0.89 **(favours neither intervention)**	**NR**	Significant decrease (p<0.01) in HbA1c levels was observed with both groups. Follow-up period was duration pregnancy; it is not clear which study visit this decrease was calculated from.
FGM compared to rtCGM							
Change in HbA1c, %	Visser et al. (2021)	n = 254	rtCGM	6 months	FGM: 0.0 ± NR rtCGM: -0.3 ± NR	-0·36 percentage points (95% CI -0·48 to -0·24)[a] p<0.0001 (**favours rtCGM**)	
Change in HbA1c, %	Reddy et al. (2018b)	n = 39	rtCGM	8 weeks	Median change from baseline to end of follow up (95% CI): FGM: -0.35 % (-0.6 to 0.0) CGM: -0.15 % (-0.8 to - 0.05) **(favours neither intervention)**	NR	P value not reported.
Uncontrolled before-after studies							
Change in HbA1c, %	Evans et al. (2020) and	20 studies (n=1331)	No control group (before-after	≤3 months	-0.50 (-0.57 to -0.43), I^2=94.0%, p=0.000	n/a	

Outcome	Evidence source(s)	Number of participants	Comparison	Follow up	Absolute effect	Relative effect	Comments
	Gordon et al. (2020)		study)				
Change in HbA1c, %	Evans et al. (2020) and Gordon et al. (2020)	11 studies (n=909)	No control group (before-after study)	3 to 6 months	-0.48 (-0.58 to -0.38), I^2=95.8%, p=0.000	n/a	
Change in HbA1c, %	Evans et al. (2020) and Gordon et al. (2020)	4 studies (n=822)	No control group (before-after study)	6 to 9 months	-0.35 (-0.52 to -0.18), I^2=90.5%, p=0.000	n/a	
Change in HbA1c, %	Evans et al. (2020) and Gordon et al. (2020)	15 studies (n=3996)	No control group (before-after study)	>9 months (max follow-up 24 months)	-0.18 (-0.26 to -0.10), I^2=94.2%, p=0.000	n/a	

CI: Confidence interval, CSII: Continuous subcutaneous insulin infusion, FGM: Flash glucose monitoring, rtCGM: real-time continuous glucose monitor, MDI: Multiple daily injections, NR: Not reported, T1/T2DM: Type 1/Type 2 diabetes mellitus, RCT: Randomised controlled trial, SOC: Standard of care, SMBG: Self-monitoring of blood glucose

4.2 Glycaemic control: time in/out of target glucose range

4.2.1 Time in target glucose range

For this outcome, seven RCTs were found to report data. Four of the RCTs evaluated FGM in comparison to SMBG: one in adults with T1DM (Bolinder et al. 2016), one in children and adolescents with T1DM (Piona et al. 2018), and two in adults with T2DM (Haak et al. 2017, Wada et al. 2020). Additionally, three studies investigated FGM in comparison to rtCGM in adults with T1DM (Haskova et al. 2020, Reddy et al. 2018b, Visser et al. 2021).

For T1DM, a statistically significant increase in the time spent in the target glucose range (3.9-10.0 mmol/L) within 24 hours was reported by Bolinder et al. (2016) (mean difference 1.0 hr per day, 95% CI 0.41 to 1.59, p=0.0006). Piona et al. (2018) reported no difference in the proportion of time spent in glycaemic range among children and adolescents with T1DM after two weeks of FGM compared to SMBG (50.9% – 11.3% and 50.8% – 13.8%, p=0.64).

The RCT by Haak et al. (2017) reports a non-statistically significant increase in the adjusted means between FGM and SMBG for the time spent in the same target glucose range for adults with T2DM (0.2, 95% CI -0.94 to 1.4, p=0.7925). Furthermore, the variation remained statistically non-significant when subgroup analysis were conducted in relation to the age of the participants at a cut-off threshold of 65 years of age (Table 6). Additionally, the authors also highlight that there was no change in the time spent in glycaemic range for adult patients with uncontrolled T2DM using insulin for the intervention with FGM versus SMBG. In contrast, Wada et al. (2020) measured the time spent in sensor glucose (70-180 mg/dl – 3.9-10.0 mmol/L) within 24 hours and reports an improvement in the FGM group when compared with SMBG (2.36, 95% CI 1.21 to 3.51, p<0.001).

When FGM is compared to rtCGM, Reddy et al. (2018b) reports that in patients with T1DM and impaired awareness of hypoglycaemia, there was no change in the time spent in glycaemic range. Time spent in glucose range (3.9-10.0 mmol/L for overall, day time (06:00-23:59 h) and night time (00:00-05:59 h) was also reported by the study conducted by Haskova et al. (2020) for the overall post-randomisation phase (exercise plus home phase, total 32 days). A statistically significant increase for the time spent in glucose range for the overall, day and night time was found in the rtCGM group (Table 6). Similarly, Visser et al. (2021) reported a statistically significant improvement in overall time in range after 6 months in people who used rtCGM compared to those who used FGM.

4.2.2 Time above target glucose range

Five RCTs reported data on this outcome. One RCT evaluated FGM in comparison to SMBG in adults with T1DM (Bolinder et al. 2016) and two in adults with T2DM (Haak et al. 2017, Wada et al. 2020). Two additional RCTs conducted in adults with T1DM compared FGM with rtCGM (Haskova et al. 2020, Visser et al. 2021).

For T1DM, Bolinder et al. (2016) reports a statistically significant reduction in the hours above target glucose range (>13.3 mmol/L) within 24 hours in the FGM group when compared to SMBG, with the intervention favouring FGM (-0.37, 95%CI -0.69 to 0.05, p=0.0247). In people with T2DM, Haak et al. (2017) measured hours in hyperglycaemia (>13.3 mmol/L) within 24 hours for T2DM and found no statistically significant difference between FGM and SMBG (0.1, 95% CI -0.80 to 1.00, p=0.8729). No statistically significant reduction was noticed in the subgroup analysis stratified by age at a cut-off point of 65 years of age (Table 6). Wada et al. (2020) measured time in hyperglycaemia within 24 hours at three different thresholds in a cohort of adults aged ≥20 years old with T2DM assigned to FGM or SMBG. The results showed a statistically significant difference at all the thresholds as a result of the FGM intervention, with the highest difference in adjusted means observed at >180 mg/dl (10.0 mmol/L) (hours) (-2.66, 95%CI -3.85 to -1.48, p<0.001), followed

by >240 mg/dl (13.3 mmol/L) (hours) (-1.23, 95% CI -1.73 to -0.73), p<0.001) and lastly >300 mg/dl (16.7 mmol/L) (hours) (-0.39, 95% CI -0.57 to -0.20, p<0.001) (Table 6).

The RCTs by Haskova et al. (2020) and Visser et al. (2021), which compared FGM and rtCGM, report measurements of the overall time above glucose range. A statistically significant reduction was found in the rtCGM group when compared to FGM in both studies. In the study by Haskova et al. (2020), rtCGM was also beneficial compared to FGM when day time (06:00-23:59 h) and night time (00:00-05:59 h) time above glucose range was considered, and for two different glucose thresholds: 10.0 mmol/L and 13.9 mmol/L (Table 6).

4.2.3 Time/frequency below target glucose range

For this outcome, eight RCTs were found to report data. Two RCTs evaluated the effectiveness of FGM in comparison to SMBG in people with T1DM: one in adults Bolinder et al. (2016) and one in children (Piona et al. 2018). Three RCTs studied the same comparison in adults with T2DM (Haak et al. 2017, Wada et al. 2020, Yaron et al. 2019). Additionally, three studies investigated the effectiveness of FGM in comparison to rtCGM in adults with T1DM (Haskova et al. 2020, Reddy et al. 2018b, Visser et al. 2021).

Bolinder et al. (2016) report a statistically significant difference between FGM and SMBG in patients with T1DM for the following measurements: hours in hypoglycaemia (< 3.9 mmol/L) within 24 hours, hours in hypoglycaemia at night (11 pm–6 am) within 7 hours and mean hypoglycaemia events < 3.9 mmol/L (70 mg/dL) within 24 hours. The difference is statistically significant across all the measurements for both studies with p<0.0001 and favours the FGM intervention (Table 6). Bolinder et al. (2016) also highlighted that there is a statistically significant reduction in hypoglycaemia (time and events) in patients with well-controlled T1DM in the comparison between SMBG and FGM when used for 6 months (-1.24h/day, SE=0.239, p<0.0001).

For T2DM, Haak et al. (2017) reports measurements on hours in hypoglycaemia (< 3.9 mmol/L) within 24 hours, hours in hypoglycaemia at night (11 pm–6 am) within 7 hours and mean hypoglycaemia events < 3.9 mmol/L (70 mg/dL) within 24 hours that show a statistically significant difference between FGM and SMBG (Table 6). Furthermore, a sub-group analysis that stratifies participants by age at a threshold of 65 years, indicates that there a statistically significant difference in the hours spent in hypoglycaemia (< 3.9 mmol/L) within 24 hours for both groups, with a higher effect noticed in the ≥65 years of age group as a result of the intervention with FGM. The study showed a reduction in the time spent in hypoglycaemia among patients with uncontrolled T2DM for two different ranges (below 70mg/dL: -0.47– 0.13 h/day, p=0.0006 and below 55mg/dL: -0.22 – 0.07 h/day, p=0.0014) as well as a 54% reduction in nocturnal hypoglycaemic episodes (-0.29 – 0.08 h/7 h, p=0.0001). Additionally, Wada et al. (2020) also reports measurements for the time spent below glucose range within 24 hours for the following thresholds: <70 mg/dL (3.9 mmol/L), <55 mg/dL (3.1 mmol/L) and <45 mg/dL (2.5 mmol/L). However, the variation was statistically non-significant as a result of the intervention with FGM when compared to SMBG in adults with T2DM (Table 6).

Yaron et al. (2019), Piona et al. (2018) and Reddy et al. (2018b) report that FGM did not decrease the time spent in hypoglycaemia in adults with T1DM or T2DM and among adolescents with T1DM. In addition, Reddy et al. (2018b) reports that rtCGM reduced time spent in hypoglycaemia for patients with T1DM in comparison to FGM. Measurements on the time spent below glucose range for the comparison between FGM and rtCGM are also reported by Haskova et al. (2020) and Visser et al. (2021): overall time above glucose range improved for rtCGM compared to FGM in both studies. Haskova et al. (2020) also reported time above range during day time (06:00-23:59 h) and night time (00:00-05:59 h) for two different glucose thresholds: 3.0 mmol/L and 3.9 mmol/L. A statistically significant reduction in the time spent below glucose range for the rtCGM group

was observed for all the time frames and thresholds (Table 6). The greatest reduction was observed in the night time for the 3.9 mmol/L glucose threshold (-5.94, 95% CI -9.0 to -2.9, p=0.001).

Two RCTs were identified that report data on the incidence of hypoglycaemic events; both investigated interventions with FGM in comparison to SMBG and only reported severe incidences of hypoglycaemia, defined as those requiring third-party assistance (Bolinder et al. 2016, Haak et al. 2017). Outcomes are reported in Table 7. The low number of events reported in each trial makes it difficult to draw conclusions with certainty. For T1DM, Bolinder et al. (2016) reports that severe hypoglycaemia was observed in two participants in the FGM group and four in the SMBG group with a risk difference of -0.02 95% CI -0.07 to 0.04). For T2DM, Haak et al. (2017) reported four hypoglycaemic events (three in the FGM group and one in the SMBG) with a risk difference of -0.03 95% CI -0.10 to 0.01 (Table 7).

Table 6. Combined outcome data for time spent in/above/below glucose range

Study	Outcome	Difference in adjusted means between FGM and SMBG (95% CI)	p value
Bolinder et al. (2016) T1DM Adults (n=241) RCT (FGM vs SMBG) Follow-up: 6 months	Hours in target glucose range (3.9–10.0 mmol/L) within 24 hours	1.0 (0.41 to 1.59)	0.0006
	Hours above target glucose range (> 13.3 mmol/L) within 24 hours	-0.37 (-0.69 to -0.05)	0.0247
	Hours in hypoglycaemia (< 3.9 mmol/L) within 24 hours	-1.24 (-1.71 to -0.77)	<0.0001
	Hours in hypoglycaemia at night (11 pm–6 am) within 7 hours	-0.47 (-0.70 to -0.24)	<0.0001
	Mean no. of hypoglycaemia events < 3.9 mmol/L (70 mg/dL) within 24 hours	-0.45 (-0.62 to -0.28)	<0.0001
Haak et al. (2017) T2DM Adults (n=224) RCT (FGM vs SMBG) Follow-up: 6 months	Hours in target glucose range (3.9–10.0 mmol/L) within 24 hours	0.2 (-0.94, 1.34)	0.7925
	Hours above target glucose range (> 13.3 mmol/L) within 24 hours	0.1 (-0.80 to 1.00)	0.8729
	Hours in hypoglycaemia (< 3.9 mmol/L) within 24 hours	-1.24 (-1.71 to -0.77)	<0.0001
	Hours in hypoglycaemia at night (11 pm–6 am) within 7 hours	-0.29 (-0.45, -0.13)	0.0001
	Mean hypoglycaemia events < 3.9 mmol/L (70 mg/dL) within 24 hours	-0.16 (-0.29 to -0.03)	0.0164
	Hours in hyperglycaemia (> 13.3 mmol/L) within 24 hours	0.1 (-0.80, 1.00)	0.8729
	Subgroup analyses of time in target glucose range and hypoglycaemia among people with T2DM		
	Hours in target glucose range (3.9–10.0 mmol/L) within 24 hours, <65 years	0.3 (-1.19 to 1.79)	0.6777
	Hours in target glucose range (3.9–10.0 mmol/L) within 24 hours, ≥65 years	0.3 (-1.44 to 2.04)	0.7476
	Hours in hypoglycaemia (< 3.9 mmol/L) within 24 hours, <65 years	-0.37 (-0.70 to -0.04)	0.0279
	Hours in hypoglycaemia (< 3.9 mmol/L) within 24 hours, ≥65 years	-0.60 (-1.03 to -0.17)	0.0083
	Hours in hyperglycaemia (> 13.3 mmol/L) within 24 hours, <65 years	-0.1 (-1.33 to 1.13)	0.9063
Wada et al. (2020) T2DM Adults ≥20 years and <70 years (n=100) RCT (FGM vs SMBG) Follow-up: 24 weeks	Glucose 70–180 mg/dL (3.9–10.0 mmol/L) within 24 hours period (duration hours)	2.36 (1.21 to 3.51)	<0.001
	Glucose <70 mg/dL (3.9 mmol/L) within 24 hours period (duration hours)	0.13 (-0.19 to 0.45)	0.423
	Glucose <70 mg/dL (3.9 mmol/L) within 24 hours period, AUC (hour×mg/dL)	3.46 (-1.37 to 8.29)	0.163
	Glucose <55 mg/dL (3.1 mmol/L) within 24 hours period (duration hours)	0.13 (-0.03 to 0.28)	0.103
	Glucose <55 mg/dL (3.1 mmol/L) within 24 hours period, AUC (hour×mg/dL)	1.51 (-0.15 to 3.17)	0.077
	Glucose <45 mg/dL (2.5 mmol/L) within 24 hours period (duration hours)	0.10 (-0.00 to 0.20)	0.064
	Glucose <45 mg/dL (2.5 mmol/L) within 24 hours period, AUC (hour×mg/dL)	1.37 (-0.07 to 2.81)	0.065
	Time in hyperglycaemia glucose level within 24 hours period, >180 mg/dL (10.0 mmol/L) (hours)	-2.66 (-3.85 to -1.48)	<0.001
	Time in hyperglycaemia glucose level within 24 hours period, >240 mg/dL (13.3 mmol/L) (hours)	-1.23 (-1.73 to -0.73)	<0.001
	Time in hyperglycaemia glucose level within 24 hours period, >300 mg/dL (16.7 mmol/L) (hours)	-0.39 (-0.57 to -0.20)	<0.001

Study	Measure	Mean difference between FGM and rtCGM (95% CI)	p value
Haskova et al. (2020) T1DM Adults ≥18 years (n=60) RCT (FGM vs rtCGM) Follow-up: 32 days	All TBR (3.9 mmol/L) %	-2.85 (-4.9 to -0.8)	0.0062
	Day (0600–2359 h) TBR (3.9 mmol/L) %	-2.31 (-4.5 to -0.1)	0.0384
	Night (0000–0559 h) TBR (3.9 mmol/L) %	-5.94 (-9.0 to -2.9)	0.0001
	All TBR (3.0 mmol/L) %	-1.18 (-2.1 to -0.3)	0.0107
	Day (0600–2359 h) TBR (3.0 mmol/L) %	-1.00 (-1.9 to -0.1)	0.0277
	Night (0000–0559 h) TBR (3.0 mmol/L) %	-3.47 (-5.3 to -1.6)	0.0002
	All TIR (3.9–10.0 mmol/L) %	8.52 (2.0 to 15.1)	0.0117
	Day (0600–2359 h) TIR (3.9–10.0 mmol/L) %	8.56 (2.0 to 15.1)	0.0111
	Night (0000–0559 h) TIR (3.9–10.0 mmol/L) %	16.27 (8.8 to 23.7)	0.0001
	All TAR (10.0 mmol/L) %	-7.23 (-14.1 to -0.4)	0.0391
	Day (0600–2359 h) TAR (10.0 mmol/L) %	-6.90 (-13.8 to 0.00)	0.0489
	Night (0000–0559 h) TAR (10.0 mmol/L) %	-10.80 (-18.4 to -3.2)	0.0058
	All TAR (13.9 mmol/L) %	-3.19 (-6.3 to 0.00)	0.0465
	Day (0600–2359 h) TAR (13.9 mmol/L) %	-3.47 (-6.8, -0.1)	0.0426
	Night (0000–0559 h) TAR (13.9 mmol/L) %	-5.02 (-8.6 to -1.5)	0.0060
Visser et al. (2021) T1DM Adults (n=254) RCT (FGM vs rtCGM) Follow-up: 6 months	Time in hypoglycaemia (<3.0 mmol/L), %	−0·35 (−0·61 to −0·10)	0.0070
	Time in range (3.9 to 10.0 mmol/L), %	6·85 (4·36 to 9·34)	<0.0001
	Time in hyperglycaemia (>10.0 mmol/L), %	−6·27 (−8·94 to −3·59)	<0·0001

Table 7. Hypoglycaemic events associated with the use of FGM

Study	Outcome	Risk difference (95% CI)	p value
Bolinder et al. (2016) T1DM Adults (n=241) RCT (FGM vs SMBG) Follow up: 6 months	Severe hypoglycaemia - FGM group (n=2), SMBG (n=4)	-0.02 (-0.07 to 0.04)	NA
Haak et al. (2017) T2DM Adults (n=224) RCT (FGM vs SMBG) Follow up: 6 months	Severe hypoglycaemic events – n=4 (3 in studies of FGM and 1 in a study of SMBG)	-0.03 (-0.10 to 0.01)	NA

CI: Confidence interval, FGM: Flash glucose monitoring, IQR: Interquartile range rtCGM: real-time continuous glucose monitor, L: litre, NA: Not applicable, NR: Not reported, T1/T2DM: Type 1/Type 2 diabetes mellitus, SMBG: Self-monitoring of blood glucose

4.3 Frequency of glucose monitoring

Outcomes related to the frequency of glucose monitoring were only reported in comparison to SMBG in the RCT conducted by Boucher et al. (2020c) in a cohort of participants aged 13-20 years old with T1DM. An increase in the group rate of glucose checking as a result of the intervention was noticed at both three and six months (Table 8). The between-group differences for change in glucose checks per day was significant at six months for the comparison between FGM and SMBG (2.6 times the SMBG group, 95% CI 1.56 to 4.26, p<0.001). When the intervention with FGM was considered in addition to SMBG, the rate of glucose checking was 2.8 times the rate of the SMBG group (95% CI 1.72 to 4.65, p<0.001).

Table 8. Glucose monitoring outcomes for FGM compared to SMBG

Study	Measure (mean ± SD)	Baseline Data		3 months		6 months		Difference in adjusted changes at 6 months (95% CI)	p value
		Intervention (n=33)	Control (n=31)	Intervention (n=31)	Control (n=30)	Intervention (n=33)	Control (n=31)		
Boucher et al. (2020c) T1DM 13-20 years (n=64) RCT (FGM vs SMBG)	FGM vs SMBG	1.8 ± 1.6	1.9 ± 3.6	4.1 ± 4.1	1.5 ± 3.5	3.5 ± 3.2	1.4 ± 3.0	2.6 (1.56 – 4.26)	<0.001
	FGM+SMBG vs SMBG	1.8 ± 1.6	1.9 ± 3.6	4.5 ± 4.3	1.5 ± 3.5	3.8 ± 3.1	1.4 ± 3.0	2.8 (1.72 – 4.65)	<0.001

CI: Confidence interval, FGM: Flash glucose monitoring, T1/T2DM: Type 1/Type 2 diabetes mellitus, SD: Standard deviation, SMBG: Self-monitoring of blood glucose

4.4 Healthcare utilisation

We identified five observational studies that reported healthcare utilisation outcomes (Bergenstal et al. 2021, Deshmukh et al. 2020, Fokkert et al. 2019, Roussel et al. 2021, Tsur et al. 2021); no RCTs were identified that reported on these outcomes. Reported outcomes varied between studies, as did follow-up periods. None of the studies compared utilisation outcomes between FGM and SMBG; instead, all four studies measure outcomes before and after FGM use.

All healthcare utilisation outcomes are detailed in Table 9. Overall, the studies showed a reduction in paramedic callouts, hospital admissions, visits to diabetes/endocrine specialists and primary care visits. However, analyses to determine the statistical significance for these outcomes are not reported, and it is unclear whether these reductions are significantly or clinically meaningful.

Deshmukh et al. (2020) reported on paramedic callouts and hospital admissions, due to hypoglycaemia or hyperglycaemia, from a prospective audit of 102 centres in the UK. During a median follow-up of 7.5 months using FGM, the total number of paramedic callouts decreased from 275 to 38. Total number of hospital admissions due to hyperglycaemia/DKA reduced from 269 to 86, and total number of hospital admissions due to hypoglycaemia reduced from 120 to 45. It should be noted that these analyses included a shorter intervention follow-up period compared to the time without intervention (pre-FGM, 12 months), which impacts the ability to make a true before/after comparison for FGM use.

When restricting the analyses to a smaller cohort of patients with 12 months of follow-up, Deshmukh et al. (2020) reported a reduction with FGM use from 83 to 4 total number of paramedic callouts, 38 to 30 hospital admissions due to hyperglycaemia/DKA and 27 to 2 hospital admissions due to hypoglycaemia. Two other studies also reported on hospital admissions at 12-month follow-up: Fokkert et al. (2019) reported a reduction in hospital admissions from 13.7% to 4.7% per year, and Roussel et al. (2021) reported a decrease in the number of patients hospitalised for at least one acute event (from 4.3% to 2.6% per year).

Deshmukh et al. (2020) also analysed change in events per month; again, following use of FGM there was a reduction in the number of paramedic callouts (from 22 to 5 per month), hospital admissions due to hyperglycaemia/DKA (22 to 11 per month) and admissions due to hypoglycaemia (86 to 31 per month). Similarly, Tsur et al. (2021) and Bergenstal et al. (2021) reported a reduction between pre- and post-FGM use for hospital admissions (reducing from 19.0 per 100 patient years to 15.8 per 100 patient years and 0.420 per patient years to 0.283 per patient years, respectively). Tsur et al. (2021) also reported change in visits to specialists and primary care. Visits to diabetes/endocrine specialists decreased from 117.4 to 83.3 per 100 patient years. Similarly, number of primary care visits reduce from 1033.4 to 829.1 per 100 patient years following use of FGM. Finally, Bergenstal et al. (2021) also reported change in number of acute diabetes-related events before and after FGM use (those which required inpatient or emergency outpatient care): rates of these events decreased from 0.180 per patient year to 0.072 per patient year.

Table 9. Healthcare utilisation outcomes with flash glucose monitoring

Outcome	Evidence source(s)	Number of participants (where data for this outcome was available)	Age of population	Comparison	Follow-up period, months	Absolute effect	Comments
Events with <12 months follow-up							
Total number of paramedic callouts	Deshmukh et al. (2020)	n = 1,940	All	None (outcomes were measure before/after FGM use)	7.5 (IQR 3.4-7.8)	Total in 12 months pre-FGM use: 275 Total in follow up period: 38	"[These] analyses were restricted to those who had both baseline and follow-up events recorded" Follow up period for the intervention is shorter than without intervention, hindering direct comparison of before/after intervention.
Total number of hospital admissions (due to hyperglycaemia/DKA)	Deshmukh et al. (2020)	n = 1,978	All	None (outcomes were measure before/after FGM use)	7.5 (IQR 3.4-7.8)	Total in 12 months pre-FGM use: 269 Total in follow up period: 86	
Total number of hospital admissions (due to hypoglycaemia)	Deshmukh et al. (2020)	n = 1,952	All	None (outcomes were measure before/after FGM use)	7.5 (IQR 3.4-7.8)	Total in 12 months pre-FGM use: 120 Total in follow up period: 45	
Incidence of acute diabetes-related events (in inpatient or emergency outpatient care), number of events per patient-year	Bergenstal et al. (2021)	n = 2,463	Adults	None (outcomes were measured before/after FGM use)	6	Pre-FGM: 0.180 Post-FGM: 0.072	
Incidence of all-cause hospitalisation, number of events per patient-year	Bergenstal et al. (2021)	n = 2,463	Adults	None (outcomes were measured before/after FGM use)	6	Pre-FGM: 0.420 Post-FGM: 0.283	
Events with ≥12 months follow up							
Total number of paramedic callouts	Deshmukh et al. (2020)	n = 409	All	None (outcomes were measure before/after FGM use)	Minimum 12	Total in 12 months pre-FGM use: 83 Total in follow up period: 4	Based on a "sensitivity analysis restricted to those with 12

Outcome	Evidence source(s)	Number of participants (where data for this outcome was available)	Age of population	Comparison	Follow-up period, months	Absolute effect	Comments
Total number of hospital admissions (due to hyperglycemia/DKA)	Deshmukh et al. (2020)	n = 409	All	None (outcomes were measure before/after FGM use)	Minimum 12	Total in 12 months pre-FGM use: 38 Total in follow up period: 30	months' follow-up".
Total number of hospital admissions (due to hypoglycemia)	Deshmukh et al. (2020)	n = 409	All	None (outcomes were measure before/after FGM use)	Minimum 12	Total in 12 months pre-FGM use: 27 Total in follow up period: 2	
Patients admitted to hospital in past 12 months, n (%)	Fokkert et al. (2019)	n = 681	Adults	None (outcomes were measure before/after FGM use)	12	Pre FGM: 187 per year (13.7%) Post FGM: 32 per year (4.7%)	Data 12 months after FGM initiation only available for 681 out of 1365 patient who had data collected at baseline.
Number of patients hospitalised for at least one acute event, per year	Roussel et al. (2021)	n = 74,011	All	None (before/after measurements of outcomes)	12	Pre FGM: 3,204 per year (4.3%) Post FGM: 1,740 per year (2.6%)	Reported as "statistically significant" but no statistics reported.
Events per month							
Paramedic callouts per month	Deshmukh et al. (2020)	n = 1,940.	All	None (outcomes were measure before/after FGM use)	7.5 (IQR 3.4-7.8)	Pre FGM: 22 per month Post FGM: 5 per month	Pro-rated by time/number of patients in the analysis. Exact method of calculation unclear
Hospital admissions (due to hyperglycaemia/DKA) per month	Deshmukh et al. (2020)	n = 1,978	All	None (outcomes were measure before/after FGM use)	7.5 (IQR 3.4-7.8)	Pre FGM: 22 per month Post FGM: 11 per month	

Outcome	Evidence source(s)	Number of participants (where data for this outcome was available)	Age of population	Comparison	Follow-up period, months	Absolute effect	Comments
Hospital admissions (due to hypoglycaemia) per month	Deshmukh et al. (2020)	n = 1,952.	All	None (outcomes were measure before/after FGM use)	7.5 (IQR 3.4-7.8)	Pre FGM: 86 per month Post FGM: 31 per month	
Events per 100 patient years							
Hospital admission to internal medicine ward, number of events per 100 patient years	Tsur et al. (2021)	n = 3,490	Adults	None (before/after measurements of outcomes)	Median 14 (IQR 11-15 months)	Pre FGM: 19.0 per 100 patient years Post FGM: 15.8 per 100 patient years	
Visits to diabetes/endocrine specialist, number of events per 100 patient years	Tsur et al. (2021)	n = 3,490	Adults	None (before/after measurements of outcomes)	Median 14 (IQR 11-15 months)	Pre FGM: 117.4 per 100 patient years Post FGM: 83.3 per 100 patient years	
Primary care visits, number of events per 100 patient years	Tsur et al. (2021)	n = 3,490	Adults	None (before/after measurements of outcomes)	Median 14 (IQR 11-15 months)	Pre FGM: 1033.4 per 100 patient years Post FGM: 829.1 per 100 patient years	

DKA: diabetic ketoacidosis; FGM: flash glucose monitoring; IQR: interquartile range; n: number.

4.5 Quality of life

Two RCTs report data for this outcome. All studies evaluated the effects of the intervention with FGM in comparison to SMBG. One study was conducted in adult populations with T2DM (Haak et al. 2017) while the other one in a cohort of participants aged 13-20 years old with T2DM (Boucher et al. 2020c).

Haak et al. (2017) reports a statistically non-significant increase in the quality of life for people with T2DM using FGM in comparison to SMBG. The RCT by Boucher et al. (2020c) also measured and reported psychosocial outcomes in patients with T1DM, aged 13-20 years of age through the PedsQL Generic and PedsQL Diabetes tools for an intervention with FGM in addition to usual care in comparison to usual care alone. The difference in change at six months is reported for the total score in the PedsQL and for the following categories in PedsQL Diabetes: diabetes subscale, treatment I subscale, treatment II subscale, worry subscale, communication subscale and total score. The only statistically significant difference was found in the diabetes subscale with a difference in change at six months of -9.2, 95% CI -15.2 to -3.3, p=0.002. The authors also report measurements on fear of hypoglycaemia (behaviour and worry subscale). No statistically significant difference was found in either of the subscales as a result of the intervention (Table 10).

Table 10. Quality of life outcomes associated with the use of FGM

Study	Outcome		Description	Comments
Haak et al. (2017) T2DM Adults (n=224) RCT (FGM vs SMBG) Follow up: 6 months	Diabetes Quality of Life questionnaire, total score, change from baseline to end of follow-up		No statistically significant change in quality of life for people using flash glucose monitoring versus SMBG	Exact figures for total score not reported by the authors
	Outcome	**Measure**	**Difference in change at 6 months (95% CI)**	**p value**
Boucher et al. (2020c) T1DM 13-20 years (n=64) RCT (FGM vs SMBG) Follow up: 6 months	PedsQL Generic	Total score	-1.2 (-6.5 to 4.1)	0.661
	PedsQL Diabetes	Diabetes subscale	-9.2 (-15.2 to -3.3)	0.002
		Treatment I subscale	8.1 (-0.1 to 16.4)	0.053
		Treatment II subscale	4.8 (-2.6 to 12.3)	0.204
		Worry subscale	7.7 (-2.3 to 17.8)	0.130
		Communication subscale	-5.2 (-16.7 to 6.2)	0.370
		Total score	-1.1 (-6.2 to 4.1)	0.688
	Fear of hypoglycaemia	Behaviour subscale	0.18 (-0.08 to 0.44)	0.182
		Worry subscale	-0.13 (-0.37 to 0.11)	0.302

CI: Confidence interval, HFS: Fear of hypoglycaemia, PedsQL: Paediatric quality of life inventory, T1/T2DM: Type 1/Type 2 diabetes mellitus, SMBG: Self-monitoring of blood glucose

4.6 Device-related adverse events and complications

For this outcome, four articles reporting data from three RCTs were found. Two RCTs were conducted in adult populations with T1DM (Bolinder et al. 2016) or T2DM (Haak et al. 2017). The other two studies are different reports of the same RCT (Boucher et al. 2020c, Marsters et al. 2020) conducted in participants aged 13-20 years with T1DM.

For T1DM, Bolinder et al. (2016) reported 13 device-related adverse events (including allergy, itching, rash, insertion-site symptoms and oedema) in a total of 121 participants who used FGM; however, none contributed to severe hypoglycaemia or hospitalisation. No adverse events were reported in the control group who used SMGB alone, Haak et al. (2017) reported a total of nine device-related adverse events experienced by six patients (out of 149 who used FGM); there were no device-related adverse events reported in the SMBG group.

The RCT by Boucher et al. (2020c) reports adverse events in participants with T1DM aged 13-20 years of age in the comparison between FGM in addition to SMBG. The authors report six participants (18%) in the intervention group and five participants (16%) in the control group that experienced at least one episode of diabetic ketoacidosis with no significant difference between the groups. The report by Marsters et al. (2020) describes cutaneous adverse events that occurred in the same trial. In the FGM group, 11% of safety questionnaires reported at least one FGM-associated cutaneous adverse event. The FGM group had a cutaneous adverse event rate of 1 event for every 18.1 weeks of use while the SMBG group had a rate of 1 event for every 18.3 weeks of use ($p = 0.96$). However, the proportion of participants reporting at least one adverse event was greater for FGM compared to SMBG: (19 participants (58%) experienced FGM –associated cutaneous adverse events in comparison to seven (23%) participants in the control group ($p=0.004$).

For full details of the nature of adverse events reported in each study, refer to appendix 5.

4.7 Certainty of the evidence

This section highlights any gaps, uncertainties, or issues with the reliability and/or generalisability of the evidence.

- The RCTs identified included between 40 and 240 participants. The majority of trials included 100 or fewer participants and may not have been adequately powered to detect true differences between the interventions.
- The majority of RCTs included people with diabetes that is already well controlled and/or who are already using glucose monitoring. Experts highlighted that this only represents a subset of people who could potentially use flash glucose monitoring in clinical practice, particularly groups who currently cannot or do not routinely use self-monitoring of blood glucose, but may be willing/able to use flash glucose monitoring. It was also highlighted that there may be groups of people with diabetes who are not willing or able to routinely test and monitor their blood glucose using SMBG (or rtCGM) but who could benefit from FGM. Comparison to SMBG (or rtCGM) may not therefore always be appropriate, as FGM would be addition to care for these groups and not a replacement.
- Comparative evidence was weighted heavily towards the effectiveness of FGM vs SMBG, with more limited evidence vs rtCGM. Comparisons to rtCGM tended to be in smaller populations, meaning there is less certainty associated with their findings, and it is unclear whether the populations studied and their management is generalisable. The larger of the trials, by Visser et al (2021), recruited participants who had at least 6 months experience of using FGM. This reduces the generalisability of the findings to this appraisal, as people being considered for FGM in NHS Wales are likely to have minimal or no experience using the technology. Studies of FGM in comparison to rtCGM also had

shorter follow-up times than in trials comparing FGM to SMBG, and reported fewer outcomes of interest to this review. Overall, the certainty of the evidence comparing FGM to rtCGM should be considered lower than the evidence comparing FGM to SMBG.

- We also included some long-term uncontrolled studies to address critical evidence gaps (where outcome data was not provided by RCTs). Due to the lack of a control group, this evidence is in general more prone to bias. Furthermore, effect estimates for long-term changes in HbA1c were associated with high levels of statistical heterogeneity. In the real-world evidence on healthcare utilisation, many of the effects observed were large (in terms of changes to healthcare utilisation before/after FGM use), but the studies did not include sufficient analyses to determine the statistical significance for these outcomes to be reported. The way patients were selected or their data reported also introduces bias in some of these studies: in some cases follow-up data was only available for <50% of the patients whose outcomes were reported at baseline, and therefore the outcomes reported may not be representative of the whole study population. Because of these factors, evidence from these observational studies should be considered to have lower certainty than evidence from RCTs. However, this evidence does provide data on longer-term outcomes (up to 14 months median follow up), and included broad diabetes populations that may be more representative than the populations included within RCTs.

5. Economic evaluation

5.1 Original health economic evidence review

Three economic studies were included in the original evidence review for this topic (Hellmund et al. 2018a, Hellmund et al. 2018b, SHTG 2018). All three studies were deemed directly applicable as they considered the perspective of the UK NHS. The two studies by Hellmund et al. estimated the cost associated with FGM, using the Freestyle Libre device, as a replacement for routine SMBG. One of the studies considered people with T1DM (Hellmund et al. 2018b) while the other considered T2DM (Hellmund et al. 2018a). The Scottish Health Technologies Group (SHTG) reported the results of an economic analysis they developed as part of an assessment of FGM in 2018. The SHTG developed a cost-utility analysis comparing FGM to conventional SMBG in a T1DM and T2DM population (SHTG 2018).

The cost analysis by Hellmund et al. (2018b) estimated costs for FGM and SMBG in the T1DM population based on data from the IMPACT trial. In the base case scenario, 10 tests per day was assumed based on the maximum frequency of glucose monitoring recommended in the NICE guideline on T1DM (NICE NG17, 2015). It was estimated that the annual cost per patient with FGM was £234 lower than SMBG. However, in an alternative scenario, where SMBG use was based on the testing frequency observed in the IMPACT trial (5.6 SMBG tests per day), the cost of FGM was estimated to be £296 higher per patient than SMBG. This decreased to £88 more per patient compared to SMBG when the costs associated with hypoglycaemic events were taken into account. A further scenario assumed SMBG frequency would be equivalent to the frequency of FGM observed in a real-world analysis (16 tests per day). In this scenario, the annual cost of FGM was estimated to be £970 lower per patient than SMBG.

The cost analysis by Hellmund et al. (2018a) estimated costs for FGM and SMBG in the T2DM population based on data from the REPLACE trial. In a scenario using a daily frequency of three SMBG tests (as observed in the REPLACE trial), it was estimated that FGM would result in an additional annual cost of £585 per patient. In a further scenario where reduced healthcare resource use with FGM was taken into account (as observed in the REPLACE trial), it was estimated that FGM would result in an annual cost saving of £191 per patient. However, it should be noted the reductions in resource use is based on a low number of events. Without including

the cost of healthcare resource use, the use of flash glucose monitoring will become cost-saving compared to SMBG for patients who test more than 8.3 times a day.

The cost-utility analysis by SHTG used data from the IMPACT trial for the T1DM analysis and data from the REPLACE trial for the T2DM analysis. The incidence of hypoglycaemic events applied in the model was based on published data from the Diabetes Audit and Research in Tayside, Scotland (DARTS) and Medicines Monitoring Unit (MEMO) Collaboration resource (Donnelly et al. 2005). Blood glucose monitoring costs were based on Scottish procurement data. The cost associated with managing hypoglycaemic events was included based on estimated values from the published literature. QALYs were estimated using quality of life data from numerous sources. A key assumption was that there is a direct quality of life benefit associated with the use of the FGM device (0.03 per annum). This assumption was based on values reported in a time-trade-off study in the general population.

The results of the SHTG analysis show FGM to be more effective but more costly than SMBG in both the T1DM and T2DM population. Resulting ICERs of £2,459 and £4,498 for T1DM and T2DM, respectively indicated that FGM is cost-effective at a threshold of £20,000 per QALY. In a scenario where no impact on hypoglycaemic events was assumed, the ICERs increased to £12,340 and £18,125 for T1DM and T2DM, respectively but were still below £20,000 per QALY, indicating that FGM is cost-effective.

The ICER values remained below the threshold of £20,000 per QALY in all sensitivity analyses except for a scenario where FGM was assumed to result in a low reduction of SMBG tests. In probabilistic sensitivity analysis, FGM was found to have a 99% probability of being cost-effective in both the T1DM and T2DM populations. When it was assumed that FGM would have no impact on hypoglycaemic events, FGM was found to have a 99.1% probability of being cost-effective in T1DM and 72.3% probability of being cost-effective in T2DM.

5.2 Updated health economic evidence review

An updated health economic evidence review was conducted for the update of this guidance. The titles and abstracts of records identified in the search were screened and five health economic studies were deemed potentially relevant. The full texts of these studies were reviewed against the inclusion/exclusion criteria. Following consideration of the full texts, three studies were excluded because they were not cost-utility analyses and did not consider the UK context (Gil-Ibanez & Aispuru 2020, Oyaguez et al. 2020, Shi & Hellmund 2020). The remaining two studies were included in the review (Bilir et al. 2018a, Bilir et al. 2018b). Both studies considered the healthcare system in Sweden and adopted a societal perspective, meaning that indirect costs (such as lost productivity) were considered as well as direct costs. Therefore, the studies were deemed only partially applicable to the perspective of the UK NHS.

The cost-utility analyses are summarised in Table 11. Both analyses assessed the cost-utility of FGM, using the Freestyle Libre device, as a replacement for routine SMBG. One of the studies considered people with T1DM while the other considered T2DM. The study considering the T1DM population was based on data from the IMPACT trial (Bilir et al. 2018a) while the study considering the T2DM population was based on data from the REPLACE trial (Bilir et al. 2018b). Both analyses found FGM to be more effective but more costly than SMBG. An incremental cost-effectiveness ratio (ICER) of SEK291,130 per QALY was estimated for the type 1 diabetes population while an ICER of SEK306,082 per QALY was estimated for the type 2 diabetes population. Sweden does not have an explicit cost-effectiveness threshold but the authors report that interventions have been accepted with an approximate ICER of SEK400,000 per QALY and thus conclude that FGM is cost-effective for both T1DM and T2DM.

Alternative scenarios explored in sensitivity analysis showed that cost-effectiveness improved when assuming there were additional intervention effects with FGM, such as reducing severe

hypoglycaemia or improving HbA1c. Conversely, the cost-effectiveness of FGM was found to worsen when reducing the size of the utility benefit due to FGM use. Probabilistic sensitivity analysis was not conducted and thus the full uncertainty around results cannot be assessed.

Table 11. Summary of included health economic studies: Bilir et al. (2018a), Bilir et al. (2018b)

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Bilir et al. (2018a) **Country:** Sweden **Type of economic analysis:** Cost-utility analysis **Perspective:** Societal perspective **Currency:** Swedish Krona (SEK) **Price year:** 2016 **Time horizon:** 50 years (intended to cover lifetime) **Discounting:** Costs and benefits were discounted at 3% per year. **Potential conflict of interest:** One of the authors is a full-time employee of Abbott Diabetes Care and is a stock holder. All other authors	**Population** The modelled cohort was based on the study population in the IMPACT trial, a six-month, multicentre RCT which compared FGM to SMBG in adults with well controlled Type 1 diabetes (HbA1c ≤7.5% mmol/mol]). The population was described as 'intensively insulin-treated' as they used multiple daily insulin injections or continuous subcutaneous insulin infusion and tested glucose levels at least 10 times per week. The starting age of the modelled population was assumed to be 43.7 years old and 56.9% were assumed to be male. **Interventions** FGM using Freestyle Libre **Comparator** SMBG **Study design**	**Source of baseline and effectiveness data:** Baseline estimates of risk factors used in the economic model were sourced from published studies. The majority of risk factors were sourced from a study of patients with type 2 diabetes, based on the UKPDS outcomes model. Treatment effects associated with SMBG and FGM were sourced from the IMPACT trial. There were no significant differences in the evolution of HbA1c between the FGM and SMBG treatment arms of the IMPACT trial. Therefore, a HbA1c increase of 0.12%; 1.32 mmol/mol compared to baseline was modelled in both the SMBG and FGM treatment arms. . The rates of non-severe hypoglycaemic events for people using SMBG or FGM were sourced from the IMPACT trial. The event rate for people using SMBG was based on symptomatic hypoglycaemia event data as a proxy for events below 70 mg/dL. The event rate for FGM was estimated by reducing the baseline rate by the percentage reductions observed over the study period (25.5% decrease in daytime events and 33.2% decrease in nocturnal events). The rates of severe hypoglycaemic events were not based on the IMPACT trial, as the study was not designed to assess severe events. These events rates were instead based on values from the UK Hypoglycaemia Study Group. Severe hypoglycaemic event rates were assumed to be equivalent in people using SMBG and FGM. **Source of resource use and cost data:** Data on resource use associated with SMBG and FGM was based on reported values from the IMPACT trial.	**Base case results** **Costs** FGM: SEK1,222,333 SMBG: SEK989,051 Incremental: SEK233,283 **QALYs** FGM: 13.26 SMBG: 12.46 Incremental: 0.801 **ICER (cost per QALY)** SEK291,130 per QALY **Sensitivity analysis** A series of sensitivity analyses were conducted to assess the impact of making different assumptions or changing key input values. The results showed that cost-effectiveness improved when assuming there was additional intervention effects with FGM, such as reducing severe hypoglycaemia or improving HbA1c. Conversely, the cost-effectiveness of FGM was found to worsen when reducing the size of the utility benefit due to FGM use.	**Applicability** The analysis was deemed only partially applicable to the UK NHS because it considered the Swedish healthcare system. The analysis also considered a societal perspective rather than the healthcare perspective that would normally be preferred for interventions of this type. **Limitations** Some potentially serious limitations were identified: • Probabilistic sensitivity analysis was not conducted, meaning that uncertainty has not been fully explored • Uncertainty was also not fully explored in deterministic sensitivity analysis because of the limited number of scenarios considered • Methodology used to estimate key input values is not fully reported • Some input values were based on studies of people with type 2

Study details	Study population and design	Data sources	Results	Quality assessment
were employed by IQVIA, Inc., which received payment from Abbott Diabetes Care to provide health economic consulting services.	Cost-utility analysis using the IQVIA Core Diabetes Model. The model uses changes in physiological parameters (e.g. HbA1c, blood pressure, weight, lipid parameters) as an input to risk equations which are then used to estimate long-term microvascular and macrovascular complications. Estimated outcomes are then used to estimate life expectancy, QALYs and costs.	Patients using SMBG used 1,971 test strips per year, 657.6 lancets per year and 38.4 units of insulin per day. Patients using FGM required 182.5 test strips per year, 267.4 lancets per year and 45.8 units of insulin per day. It was also assumed that FGM patients required 26 sensors per year and an extra physician visit in the first year. Unit costs for the senor, reader and test strips used with the FGM system were sourced Abbot Diabetes Care. Units costs for SMBG test strips, lancets and insulin were based on the lowest-cost items available from Tandvårds-Läkemedelförmånsverket (TLV). Physician visit costs were estimated using regional reference cost data. The cost of severe hypoglycaemic events requiring third-party medical assistance was estimated using data from three published sources. The methodology used to derive the figure is not reported but it appears to include indirect costs (relating to lost productivity) as well as direct costs. Severe hypoglycaemic events requiring third-party non-medical assistance and non-severe hypoglycaemic events were assumed to incur no costs. **Source of quality of life data:** Utilities and disutilities were estimated using values from the published literature. The baseline utility value for people with type 1 diabetes was sourced from a study, which reported EQ-5D values for patients with type 2 diabetes (UKPDS 62). Complication-related utility values were also obtained from populations with type 2 diabetes.	Sweden does not have an explicit cost-effectiveness threshold but interventions have been accepted with an average ICER of €36,000 per QALY, which is approximately SEK400,000 per QALY. ICERs remained under this threshold in all modelled scenarios. Probabilistic sensitivity analysis was not conducted.	diabetes rather than the population of interest (type 1 diabetes) • The main source of clinical data is a trial of patients with well-controlled type 1 diabetes. This may not represent the patient population using flash monitoring in the real world. • Uncertainty around the applicability of the quality of life gain associated with using the FGM device. The quality of life value was based on a survey of the general population rather than people with type 1 diabetes.

Study details	Study population and design	Data sources	Results	Quality assessment
		Disutilities for severe hypoglycaemic events requiring third-party medical assistance and third-party non-medical assistance were estimated from two published quality of life studies. Disutilities associated with non-severe hypoglycaemic events were estimated using the automated approach within the IQVIA Core Diabetes Model. This approach is based on a published study showing the diminishing marginal disutility of hypoglycaemic events. It was assumed that patients receiving FGM would have a utility benefit associated with using the device. Based on a time trade-off study in the general population, a treatment-related utility benefit of 0.03 was applied for people using FGM.		
Author and year: Bilir et al. (2018b) **Country:** Sweden **Type of economic analysis:** Cost-utility analysis **Perspective:** Societal perspective **Currency:** Swedish Krona (SEK) **Price year:** 2016 **Time horizon:**	**Population** The modelled cohort was based on the population in the REPLACE trial, a six-month, multicentre, RCT comparing FGM and SMBG in adults with type 2 diabetes. Patients in trial had HbA1c between 7.5–12% (58–108 mmol/mol), and were using multiple daily injections or continuous subcutaneous insulin infusion for at least six months. **Interventions** FGM using Freestyle Libre	**Source of baseline and effectiveness data:** Baseline estimates of risk factors used in the economic model were sourced from published studies. The majority of risk factors were sourced from a study of patients with type 2 diabetes, based on the UKPDS outcomes model and an open-label RCT assessing FGM as a replacement for SMBG. Other risk factors (including proportion of smokers and alcohol consumption) were based on data on file from Abbot Diabetes Care. Although there was no significant difference in HbA1c effect in the REPLACE trial, the model used HbA1c reductions observed in the REPLACE trial (0.29% in the FGM arm and 0.31% in the SMBG arm). Hypoglycaemic event rates were sourced from the published literature. The rate for major hypoglycaemic events was sourced from a meta-analysis of population based studies. The same rate	**Base case results** **Costs** FGM: SEK1,630,586 SMBG: SEK1,459,394 Incremental: SEK171,192 **QALYs** FGM: 6.21 SMBG: 5.65 Incremental: 0.560 **ICER (cost per QALY)** SEK306,082 per QALY **Sensitivity analysis** A series of sensitivity analyses were conducted to assess the impact of making different	**Applicability** The analysis was deemed only partially applicable to the UK NHS because it considered the Swedish healthcare system. The analysis also considered a societal perspective rather than the healthcare perspective that would normally be preferred for interventions of this type. **Limitations** Some potentially serious limitations were identified: • Probabilistic sensitivity analysis was not

Study details	Study population and design	Data sources	Results	Quality assessment
40 years (intended to cover lifetime) **Discounting:** Costs and benefits were discounted at 3% per year. **Potential conflict of interest:** One of the authors is a full-time employee of Abbott Diabetes Care and is a stock holder. All other authors were employed by IQVIA, Inc., which received payment from Abbott Diabetes Care to provide health economic consulting services.	**Comparator** SMBG **Study design** Cost-utility analysis using the IQVIA CORE Diabetes model. The model uses intervention effects on diabetes-related adverse events, as well as HbA1c levels and other physiological parameters to estimate major diabetes complications. Estimated outcomes are then used to estimate life expectancy, QALYs and costs. HbA1c progression reflects the Swedish National Diabetes Registry, while HbA1c-dependent adjustments reflect the UKPDS risk engine.	was used for both the FGM and SMBG arms. The minor hypoglycaemia rate with SMBG was sourced from the same meta-analysis as the major hypoglycaemic events. The relative reduction on non-severe hypoglycaemia due to FGM observed in the REPLACE trial was applied to this rate to estimate the minor hypoglycaemia rate with FGM. **Source of resource use and cost data:** Data on resource use associated with SMBG and FGM was based on reported values from the REPLACE trial. Patients using SMBG used 1,095 test strips per year, 459.9 lancets per year and 87.8 units of insulin per day. Patients using FGM required 109.5 test strips per year, 251.85 lancets per year and 85.2 units of insulin per day. It was also assumed that FGM patients required 26 sensors per year and an extra physician visit in the first year. All patients received 1,500 mg of metformin daily. Unit costs for the senor, reader and test strips used with the FGM system were sourced Abbot Diabetes Care. Units costs for SMBG test strips, lancets, insulin and metformin were based on the lowest-cost items available from Tandvårds-Läkemedelförmånsverket (TLV). Physician visit costs were estimated using regional reference cost data. The cost of hypoglycaemic events were estimated for two types. Major events were assumed to require and therefore incur costs while minor events were assumed to require no outside care and therefore no costs. Data from three published sources was used to generate the estimated cost for major hypoglycaemic events. The methodology used to derive the figure is not reported but it appears to include indirect costs (relating to lost productivity)	assumptions or changing key input values. The results showed that FGM became dominant (less costly and more effective) when assuming there was a 0.94% reduction in HbA1c with FGM (based on real-world data). Conversely, the cost-effectiveness of FGM was found to worsen when reducing the size of the utility benefit due to FGM use. Sweden does not have an explicit cost-effectiveness threshold but interventions have been accepted with an average ICER of €36,000 per QALY, which is approximately SEK400,000 per QALY. ICERs remained under this threshold in all modelled scenarios. Probabilistic sensitivity analysis was not conducted.	conducted, meaning that uncertainty has not been fully explored • Uncertainty was also not fully explored in deterministic sensitivity analysis because of the limited number of scenarios considered • Methodology used to estimate key input values is not fully reported • Uncertainty around the applicability of the quality of life gain associated with using the FGM device. The quality of life value was based on a survey of the general population rather than people with type 2 diabetes.

Study details	Study population and design	Data sources	Results	Quality assessment
		as well as direct costs. Minor hypoglycaemic events were assumed to incur no costs. **Source of quality of life data:** Utilities and disutilities were estimated using values from the published literature. The baseline utility value for people with type 2 diabetes was sourced from a study, which reported EQ-5D values for patients with type 2 diabetes (UKPDS 62). The disutility value for major hypoglycaemic events was sourced from a study which used multivariate models of health-related utility and fear of hypoglycaemia in people with diabetes. Disutilities associated with minor hypoglycaemic events were estimated separately for the FGM and SMBG arms using a diminishing disutility approach. This approach is based on a published study showing the diminishing marginal disutility of hypoglycaemic events. Therefore, the average disutility per event is contingent on the total rate of minor hypoglycaemic events. It was assumed that patients receiving FGM would have a utility benefit associated with using the device. Based on a time trade-off study in the general population, a treatment-related utility benefit of 0.03 was applied for people using FGM.		
Abbreviations QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; EQ-5D: EuroQol five-dimensions questionnaire; FGM: flash glucose monitoring; SMBG: self-monitoring blood glucose; UKPDS: United Kingdom Prospective Diabetes Study; RCT: randomised controlled trial				

5.3 De novo economic analysis

A de novo economic model was developed to estimate the cost-effectiveness of introducing FGM, using the Freestyle Libre device, for people with T1DM and T2DM who require daily injections of insulin (MDI). The analysis considered a UK NHS and personal social services (PSS) perspective and future costs and benefits were discounted at 3.5% per year.

Following a similar approach to that adopted in the SHTG economic analysis, the model focused on the impact of FGM on the cost of glucose monitoring, managing hypoglycaemia and the associated impact on quality of life. The model does not consider the potential impact of FGM on HbA1c or other outcomes linked to diabetes control or management.

5.3.1 Clinical data

Baseline characteristics of people with T1DM and T2DM were based on those reported in the IMPACT and REPLACE trials, respectively (Bolinder et al. 2016, Haak et al. 2017). Age and sex estimates were used in combination with UK life tables to estimate all-cause mortality for the general population. To reflect the higher risk of mortality in people with diabetes, these general mortality estimates were adjusted upwards using published multipliers. The analysis considered a time horizon of 50 years, which was designed to cover the expected lifetime of people with T1DM and T2DM.

Baseline estimates of non-severe hypoglycaemic events were based on those used in the SHTG analysis (42.89 and 23.31 per patient year for T1DM and T2DM, respectively). Reductions in non-severe hypoglycaemic events were based on those reported in the IMPACT and REPLACE trials, which reported a reduction of 25.8% and 27.7%, respectively (Bolinder et al. 2016, Haak et al. 2017). Severe hypoglycaemic events were not considered in the analysis as the IMPACT and REPLACE trials were not designed to assess severe events.

5.3.2 Costs

Costs for the FreeStyle Libre device (£35 per sensor), as well as costs per lancet (£0.04) and test strip (£0.29) were based on values from the NHS Drug Tariff. It was assumed that 26 sensors would be required per year, reflecting the expected sensor lifetime of 14 days. Following the approach adopted in previous analyses (including the SHTG analysis) and reflecting arrangements with the manufacturers, the scanners involved in both types of monitoring were assumed to be offered at no cost by the manufacturers.

In people receiving standard care, SMBG test frequency per day was assumed to be 5.6 and 3.8 in people with T1DM and T2DM, respectively. In people receiving FGM, SMBG test usage per day was assumed to reduce to 0.5 and 0.4 in people with T1DM and T2DM, respectively. This matches usage observed in the IMPACT and REPLACE trials.

Based on these values, the total cost per year for people receiving standard care was estimated to be £675 and £458 for T1DM and T2DM, respectively. The total cost per year for people receiving FGM was estimated to be £971 and £958 for T1DM and T2DM, respectively.

Following the approach adopted in previous economic analyses, it was assumed that there would be no cost associated with the management of non-severe hypoglycaemic events.

5.3.3 Quality of life estimates

Quality of life estimates were sourced from a published study, which investigated the impact of daytime and nocturnal hypoglycaemia on quality of life (Evans et al. 2013). The study used a time trade-off survey in five different countries (including the UK) and presented baseline values for the population as well as disutilities incurred for hypoglycaemic events. UK values were used in the analysis. A baseline value of 0.70 was applied for people with T1DM and T2DM while a non-

severe hypoglycaemic event was assumed to have an associated disutility of 0.005 and 0.007 for daytime and nocturnal events, respectively.

Hypoglycaemia disutility in the model was assumed to be constant and additive. This approach may lead to an overestimation of the impact of hypoglycaemia on quality of life as it doesn't account for the potential for diminishing marginal disutility as the baseline number of events increases. For example, if an individual is experiencing 40 non-severe hypoglycaemic events per year, then a change to 41 events per year may not alter their health in the same way that a change from one event to two events would.

Previous economic analyses on FGM have incorporated a process-related improvement in quality of life associated with using the FGM system (utility gain of 0.03 per year). This improvement has not been considered in the base case analysis because of applicability concerns. The value was based on a study, which elicited preferences from the general population rather than people with diabetes. This does not match the generally preferred approach of using values from the indicated population.

5.3.4 Results

The results of the analysis are presented in Table 12 and Table 13 for T1DM and T2DM, respectively. In both populations, the results show FGM to be more effective and more costly than standard monitoring. The resulting ICERs of £4,706 per QALY for T1DM and £13,137 per QALY for T2DM are below the commonly applied threshold of £20,000 per QALY, indicating that FGM is cost effective.

Note that the better cost-effectiveness result in people with T1DM reflects the higher baseline rate of non-severe hypoglycaemic events in this population as well as the higher SMBG test frequency in people receiving standard care.

Table 12. Base case results for the T1DM population

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Standard monitoring	£11,329	-	7.65	-	-
Flash glucose monitoring	£16,314	£4,985	8.71	1.06	£4,706
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year					

Table 13. Base case results for the T2DM population

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Standard monitoring	£6,256	-	7.69	-	-
Flash glucose monitoring	£13,097	£6,841	8.21	0.52	£13,137
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year					

5.3.5 Deterministic sensitivity analysis results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the deterministic sensitivity analyses are presented in Table 14.

In most modelled scenarios the conclusion of the analysis remained unchanged from the base case with FGM found to be cost-effective in comparison to standard care. The notable exceptions were two analyses in which the quality of life benefits associated with reducing non-severe hypoglycaemic events was assumed to be lower. In one scenario the disutility was assumed to be 50% lower and in another it was lower as a result of accounting for the potential for diminishing marginal utility benefit (based on Lauridsen et al. 2014). In both scenarios, FGM remained more costly and more effective than standard care but the incremental effectiveness gain was smaller as a result of the lower disutility values. This resulted in ICER values above £20,000 per QALY in people with T1DM and T2DM in the scenario based on Lauridsen et al. (2014). In the scenario where the disutility from reducing non-severe hypoglycaemic events was assumed to be 50% lower, the ICER value was found to be above £20,000 per QALY in people with T2DM but still below £20,000 per QALY in people with T1DM.

The analysis was also found to be sensitive to changes in baseline SMBG testing frequency. Increasing baseline SMBG testing frequency improved the cost-effectiveness of FGM. Indeed FGM was even found to be dominant (less costly and more effective) in T1DM when assuming a 50% increase in SMBG usage per day. Decreasing SMBG testing frequency by 50% worsened the cost-effectiveness of FGM but it was still found to be cost-effective as the ICER did not exceed the threshold of £20,000 per QALY.

The inclusion of reductions in severe hypoglycaemic events based on the SHTG analysis was found to further improve the cost-effectiveness of FGM in people with T1DM and T2DM. Similarly the inclusion of reductions in severe hypoglycaemic events, hyperglycaemic events and paramedic callouts based on audit data from Deshmukh et al. (2020) was found to improve the cost-effectiveness of FGM in people with T1DM (changes were not applied to the T2DM population as the audit primarily included people with T1DM).

Table 14. Deterministic sensitivity analysis results

Model scenario	ICER (cost per QALY)	
	T1DM	T2DM
Base case	£4,706	£13,137
Reduction in severe hypos with FGM - SHTG	£2,192	£5,725
Reduction in severe hypos - audit	£4,191	-
Reduction in other events - audit	£2,151	-
NSHE disutility reduced by 25%	£6,274	£17,516
NSHE disutility reduced by 50%	£9,411	£26,274
QoL gain from hypo reductions – Lauridsen et al. (2014)	£36,130	£68,182
Process QoL gain with FGM included	£3,189	£7,350
SMBG usage per day – 50% higher	Dominant	£7,762
SMBG usage per day – 50% lower	£9,567	£18,512

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; FGM: flash glucose monitoring; SMBG: self-monitoring OF blood glucose; NSHE: non-severe hypoglycaemic event; SHTG: Scottish Health Technologies Group; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; QoL: quality of life

5.3.6 Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case

were replaced with values drawn from distributions around the mean values. This process was repeated for 10,000 PSA runs and the overall probability of each strategy being cost-effective was assessed. At a threshold of £20,000 per QALY, FGM was found to have a 99% and 71% probability of being cost effective in people with T1DM and T2DM, respectively.

6. Organisational Issues

No issues specifically relating to procurement for NHS Wales were identified. The FreeStyle Libre reader and first sensor as well as training are provided free of charge by the manufacturer. No capacity or availability issues are anticipated.

Abbott Diabetes Care offers training (e-learning) about their glucose monitors for healthcare professionals. The manufacturer noted that FreeStyle Libre is associated with a digital ecosystem that can connect patients, caregivers and health care professionals, so that patient information can be accessed remotely for assessment and discussion. Stakeholders in Wales report that remote assessment and monitoring of glucose levels has become much more prevalent since the beginning of the COVID-19 pandemic. FGM has the potential to be initiated in either primary or secondary care, and stakeholders also noted that initiation of the intervention in primary care is becoming increasingly common. This could be particularly advantageous to people with diabetes who are not accessing secondary/specialist care services. However, it is unclear what barriers, if any, exist to initiating FGM in primary care independently of specialist diabetes care.

7. Patient issues

7.1 Patient and Carer Submission from Diabetes UK Cymru

HTW consulted with Diabetes UK Cymru on a patient submission for the use of flash glucose monitoring (FGM) in adults and children with type 1 and type 2 diabetes. The full patient submission can be found in Appendix 1.

Diabetes UK Cymru raise the following points for consideration in their submission:

On the burden of living with diabetes and diabetes management;

- Diabetes is a relentless, complicated, and often underestimated condition.
- On average, people with diabetes make 180 additional high-risk decisions every day and 73% of people feel overwhelmed by the management of their condition.
- Administering the correct amounts of insulin can be a demanding task, and getting dosages wrong can have serious consequences. Having an accurate, efficient reliable system to regularly measure blood glucose levels can make a big improvement to the quality of life for those reliant on insulin.
- The long-term consequences of poor glycaemic control can lead to traumatic, acute, irreversible and costly complications such as sight loss and amputation.
- The costs of diabetes, and the costs associated with the complications of diabetes, which are largely preventable, make up around 10% of NHS Wales expenditure.
- The risk of complications can be a constant concern for people with diabetes, one that increases rates of anxiety and depression compared with those who do not have diabetes and as a result of poor glycaemic control, people with diabetes are also at increased risk of heart disease, cancer and stroke.

On current treatment practices;

- Diabetes is a complicated condition, which people experience differently.
- The type of support people receive differs depending on if they have type 1, type 2 or gestational diabetes, and as such awareness of access to appropriate technology differs both by patients and by health care professionals.
- Many cases of type 1 diabetes go initially undiagnosed until the patient is critically ill. From then on patients are generally cared for in secondary care, taught how to manage their insulin medications, how to inject and to read their blood glucose levels. Many report this experience as overwhelming.
- People with type 2 diabetes can begin with oral medications such as metformin which acts as an insulin sensitizer – tackling insulin resistance and making the body more susceptible to the insulin the pancreas is still able to produce. Those with type 2 diabetes are also recommended to make lifestyle changes including diet and exercise, to help control their condition.
- As type 2 diabetes progresses oral medications can become less effective, and some will then require multiple daily injections of insulin similar to those with type 1 diabetes. There is a lot of stigma attached to type 2 diabetes and many people struggle with their diagnosis.

On flash glucose monitoring technology:

- Benefits include improved blood glucose levels, fewer hypoglycaemic incidents, improvements in emotional wellbeing or mental health, more confidence in managing conditions, better quality of life, fewer hospital visits, fewer GP visits, fewer hyperglycaemic incidents and fewer episodes of DKA (diabetic ketoacidosis)
- 62% of people in Wales have tried to access some sort of technology to help manage their diabetes, and 44% have used the Freestyle Libre *(brand of)* flash glucose monitoring. Both of these figures are the lowest of any nation in the UK, between 4-6% behind the national average.
- Most people have found that diabetes technology in general has been successful in helping them manage their blood glucose (63%), achieve fewer incidents of hypoglycaemia (51%), improve their confidence (64%) and improve their quality of life (50%).
- Diabetes is a condition that is managed by the patient, so giving them the tools to not only manage but better understand how their blood glucose behaves is important to improving outcomes. Flash monitoring and continuous glucose monitoring do this much better than traditional finger prick methods allow. This is because for optimum management more than 10 checks are needed every day, with technology it is easy for patients to do 30 or more checks with ease.
- Data suggests that Wales is behind other nations on the adoption of diabetes technology across the board, with significantly lower uptake of the Freestyle Libre and of insulin pumps.
- The positive applications of the Freestyle Libre are endless, particularly for vulnerable groups. This technology can also be crucial for those caring for people living with diabetes, both in managing the condition in older people who may be in care, but also children with type 1.

Other considerations raised by Diabetes UK Cymru:

- As technology in this area moves towards closed loop systems (pumps that talk to sensors that are able to operate automatically and therefore act as an artificial pancreas) we have fewer people accessing technology, and fewer patients and clinicians comfortable with using, supporting and prescribing technology. This is despite better

outcomes and significant cost savings for those that do. As a result, Wales risks being left behind.

- Effect on those who have been trying to access diabetes technology and failed include; 36% told us their mental health had worsened, 49% told us their blood glucose management had worsened, 47% told us they feel less confident, 33% told us feel less motivated to manage their diabetes, 26% told us they have tried to self-fund the technology but struggled financially as a result and 14% told us their quality of life has worsened.
- Diabetes UK Cymru would urge Health Technology Wales to undertake a wider review of diabetes technology and make recommendations on increasing access to diabetes technology by making more technology available on the NHS and through supporting more clinicians to advocate for and help patients who would benefit from technology to access it.

7.2 Patient Evidence Literature Review

A patient experience literature review was undertaken, based on a dedicated search which aimed to identify and summarise any additional reports of experiences, perspectives and opinions of patients, to supplement the Patient Submission document supplied by Diabetes Cymru in section 9.2. 55 studies focusing on patient reported outcomes on the use of flash glucose monitoring (FGM) and continuous glucose monitoring (CGM) and/or self-monitoring (SMBG) were found for the following sub-categories; adults with type 1 and 2 diabetes, elderly/older people with type 1 and 2 diabetes, paediatric and adolescences with type 1 and 2 diabetes and parent/carer perspectives for people with diabetes.

7.2.1 Flash Glucose Monitoring

7.2.1.1 In older people

One study considering the use of FGM in older populations was identified (Mattishent et al. 2019). The study focused on older people with diabetes type 1 and 2 and memory loss/dementia. Participants were selected according to age (≥65) and abbreviated mental test score (≤8) or a known dementia. Participants and their carers took part in qualitative interviews at the close of the two week study period.

The barriers and challenges associated with SMBG for older people were described in this study to include; limited recall of the dangers of hypoglycaemia and what remedial action to take; increased risk of hypoglycaemia due to medication use and subsequent cognitive complications; failure of SMBG to capture nocturnal or atypical hypoglycaemia and reliance of SMBG on the patient/carer memory. The findings of a systematic review of studies using CGM in older people were also referenced in this study to define the needs of older people with diabetes, specifically noting that hypoglycaemic episodes occurred in 28%–65% of participants with most episodes (80%) being asymptomatic with some participants spending up to 2 hours per day in the hypoglycaemic range.

Four categories of participant's experiences were gathered in this study; Accessibility, Expectations, Effectiveness and Consequences. 'Expectations' has been excluded from this summary as it concerned participant's expectations of taking part in the study itself.

For Accessibility, all participants and/or their carers reported that the device was acceptable to wear, that they were not conscious of wearing the device during the two week period, that it did not impede their ability to complete daily activities and that they were not aware of it while sleeping. For Effectiveness, participants/carers found using the device effective, some preferring it over SMBG; carers spoke favourably about the simplicity of the device, being 'handy at night-times' for checking glucose levels without disturbing the participant and noting that it did not

limit the number of times they could check a participants glucose levels as it was less invasive than SMBG and caused less distress. For Consequences, no participants reported any anxiety or stress concerned with wearing the device while one remarked that it made them feel more confident. Carers reported that the device made them feel reassured and they felt it was safer and more reliant compared to SMBG, particularly for those patients who may not always understand the need for SMBG due to their underlying dementia. No carers reported any anxiety or stress in using the device. Most participants considered the chief benefit to be the elimination of finger-prick testing, eliminating pain/soreness from their fingers. All participants responded positively about recommending the device to others. There was some concern reported when readings from the device differed from those gathered by SMBG and one participant reported that they would consider the results of the SMBG test to be 'more accurate'.

The study notes that data capture varied depending on how many times the reader was used to scan the sensor during the study period and proposes that a continuous monitoring device may be of more use to this particular patient population; nevertheless, the study concludes that "carers found it to be a useful and reassuring tool in managing this complex group of patients without having to resort to finger prick testing in a person who may not be able to understand the reasons for it."

7.2.1.2 In adults

Two studies on the use of FGM in adult patients were found (Overend et al. 2019, White & Knezevich 2020). Participants across these studies were aged between 18 years and 65 years old/retirement age and took part in questionnaires across study periods between 2 weeks to 1 year with one 18 month follow-up.

Barriers to SMBG for adult populations across both studies were identified as; fear of needles and self-testing; pain/ low pain thresholds; inconvenience; psychological burdens due to unexpected fluctuations in blood glucose levels; poor mental wellbeing and stigma.

In their article, White & Knezevich (2020) consider the impact of FGM on diabetes self-care and report such outcomes as; increases in glucose monitoring and subsequent improvements in glycaemic control as a result of "less pain and scarring, less concern about using and depleting testing supplies, and less environmental barriers to testing (do not have to wash hands, can test while exercising/working)"; increased engagement in self-management and a greater sense of control; a greater understanding of how insulin, food, and physical activity affect blood glucose levels; increased empowerment to make healthy choices and less worry or uncertainty undertaking physical activity.

In their study, Overend et al. (2019) considered the impacts of FGM on patient quality of life and explored themes through follow-up visits consisting of semi-structured interviews supported by the ABCD FreeStyle Libre Follow-Up Visit Data Collection form, conducted at a 6 month interval. Within this study, two participants were recognised to have cognitive impairment or learning disability and were dependent on additional care.

Benefits highlighted included; reduction in pain associated with SMBG, including "no longer having sore fingers" and a reduction in scarring with particular reference to one participant with learning disabilities who "no longer needed to pick at scabs to obtain blood for glucose monitoring" and impacts on work-related outcomes, such as using hands at work; exclusion of "excessive consumption of blood glucose testing equipment"; convenient, quick and easy to use, supporting frequent testing; greater opportunity to identify and intervene earlier during hypoglycaemia, reducing episodes and improving quality of life, reduced fear of episodes in public; improved self-care and independence; improved confidence and an increased ability to take part in social activities.

7.2.1.3 In children/adolescents

8 studies on the use of FGM for children and young people with type 1 diabetes were found (Al Hayek et al. 2020, Boucher et al. 2020a, Boucher et al. 2020b, Deja et al. 2018, Hannon et al. 2018, Lim et al. 2020, Massa et al. 2018, Pintus & Ng 2019). Young people/adolescent participants were aged between 13 to 19 years old and children participants ranged from 6 months to 12 years old. Study durations ranged from 7 days to 1 year and participants were assessed using interviews and questionnaires.

The specific considerations for children and adolescents with type 1 diabetes in relation to maintaining their own glycaemic control were identified across the studies as including; neglect and/or rejection of using finger-prick testing (SMBG) due to fear of needles, physical cognitive and hormonal developmental changes, increasing independence with regard to eating behaviours and physical activity, increasing risk-taking behaviour, social anxiety, physical pain, strain/burden of SMBG responsibility, lifestyle changes (time spent asleep etc.), invasiveness, lack of discretion and subsequent embarrassment leading to reduced adherence to diabetes self-management and deterioration in glycaemic control in addition to a poorer quality of life.

The experiences of using FGM devices as an alternative to SMBG were classified across the studies in the following categories; accessibility/usability, benefits/improvements and adverse effects.

For accessibility/usability, most study participants (91-95%) reported the FGM device to be less painful than SMBG, easy to use and discreet enough to use in a variety of settings including at school (where their use did not draw attention); that readers were less bulky and therefore easier to carry than blood glucose meter kits and that scanning devices was quicker than preforming SMBG. Most studies reported an increase in the number of daily scans performed by participants when compared to the number of finger-prick tests previously being taken during SMBG. There was a high level of agreement between studies that the FGM devices did not interfere with daily activities, increased user's confidence, did not cause stress or anxiety and alleviated the burdens concerned with SMBG (visibility, pain, responsibility, embarrassment etc.) as well as being faster and simpler to use.

Adverse effects and challenges to using FGM reported across the studies included; skin conditions, such as local itching and skin discolouration as the most common to scarring, local erythema, bruising, local bleeding and local pain for the minority of participants (from 5 %); loss of sensors as a result of falling off when getting caught on objects, becoming damp, during play/activities and adhesive detachment (up to 29%), forgetting to scan or failing to scan due to poor mood causing indifference and/or forgetting the scanner/reader; technical issues, such as error messages and cold weather effects on readers and allergic reaction from one participant.

Only one study (Lim et al. 2020) reported less overall favourable attitudes towards FGM, citing "improved self-efficacy with regard to diabetes self-care did not equate to greater frequency of engagement in self-care tasks to reduce hypoglycaemic events due to busy school schedules and a lack of motivation or commitment to using FGM" and proposed that 'diabetes burnout', which is described by Lim et al as "generally long duration of diabetes (mean 7.0 ± 5 years) in combination with pre-existing stress related to interference with self-care tasks" may have had an impact on adherence rates.

Other benefits of FGM reported across studies included; increased compatibility with lifestyles, excitement to share with others their experiences, increased scanning habits where participants developed the habit of scanning when feeling unwell as well as out of curiosity, improvements in diabetes self-management, improvements in disease knowledge and understanding, improvements in food selection, increased participation in exercise, increased social acceptance (including showing off devices to friends and asking friends to take scans etc.), improvements

in attitudes and confidence, improvements in 'mood' due to reduction in hassle/burden/embarrassment etc., improved concentration in school due to lack of worry, improved socialisation due to being able to take preventative measures against hypoglycaemia and improved sleep.

7.2.1.4 Perspectives of parents/carers of people with diabetes

One study that considered the use of FGM devices for children with congenital hyperinsulinism (CHI) was identified (Alsaffar et al. 2018). In this study, parents of children aged 6 months to 5 years with a CHI episode history of no less than 6 months were asked to complete questionnaires after using FGM for 14 days.

CHI occurs mainly in infancy. Hyperinsulinism inhibits ketogenesis, where the brain is deprived of glucose as well as ketone bodies, thereby increasing the risk of neurological damage. It is therefore important to maintain glucose levels in order to avoid neurodevelopmental issues.

All parents who responded to the questionnaire agreed that the FGM device was easy to understand and the measuring of glucose was excellent. The majority of parents reported that it had made a positive impact on the quality of life of their child and some parents reported an improvement to their own quality of life. Some parents felt that the FGM sensor insertion was extremely painful and 77% of the parents felt that FGM is not always reliable. Despite this, 56% of parents advised that they would continue using FGM. Despite the ease of using the FGM system, concerns related to accuracy, especially at low glucose values do remain although parents find the glucose trend to be very useful.

7.2.2 Continuous Glucose Monitoring

7.2.2.1 In older people

Four studies on the use of CGM for elderly people were identified (Chiu et al. 2019, Palmer 2020, Rasche et al. 2018, Volcansek et al. 2019). One study considered elderly people with unspecified diabetes (Rasche et al. 2018) and one considered elderly people with diabetes type 2 (Chiu et al. 2019). Participants across all studies took part in interviews at the close of the study period.

Across the studies, the benefits of using CGM were reported to include; ease of use of devices, automated documentation of their blood glucose levels, improved therapy adherence and diabetic control, increased disease understanding (i.e. relationship between food intake and glucose levels, due to the visualization of the effects) and increased confidence and self-efficacy and improvements in health behaviour (i.e. changing food intake, snacking less due to feeling 'supervised')

Barriers included; personal preference to the 'paper system' where users were less technologically experienced, certain sub-groups of patients being less able to use devices (i.e. limited visibility due to retinopathy), personal familiarity with smart tech (i.e. mobile devices to download apps), concerns around control/use of medical data (mostly concerning the use of data by medical insurers, which is not applicable to a Welsh setting), preference for the continued involvement of healthcare professionals and obstructions to some daily activities (concerns around damaging the device during activity and not being able to bath).

7.2.2.2 In adults

21 papers on the use of CGM for adults with type 1 and type 2 diabetes were identified (Akturk & Garg 2019, Al-Tamimi et al. 2019, Asarani et al. 2020, Ashrafzadeh & Hamdy 2019, Barnard et al. 2018, Chen et al. 2018, Divan et al. 2020, Dowling et al. 2020, Down 2019, Ehrhardt & Al Zaghal 2019, Engler et al. 2018, Farrant & Friend 2020, Gilbert et al. 2021, May et al. 2021, Meetoo et al. 2018, Messer et al. 2018, Polonsky & Fortmann 2021, Ritholz et al. 2019, Scharf et al. 2019, Sorgard

et al. 2019, Tanaka et al. 2018). Of these, 3 considered implications of using technologies to monitor glucose levels in general, 2 were systematic reviews and 1 was a literature review. Participants of the studies took part in questionnaires, surveys and interviews over the phone or face-to-face.

There were no additional barriers/challenges to SMBG reported in these studies to those already listed above.

Similar benefits reported by patients to those identified in FGM include; increased frequency of checking glucose levels; increased confidence with diabetes control; increased optimism; feeling safer when sleeping; increased confidence about avoiding severe hypoglycaemia; increased motivated to keep up with diabetes management; ease of use; convenience and comfort; improved mood and mental wellbeing; improved health behaviours and health knowledge; increased sense of security due to alarms and alerts, particularly at night leading to improved sleep; positive outcomes for relationships due to the ability to share information and responsibilities, increasing the sense of partnership.

Challenges and burdens to using CGM reported by participants across studies included; questions of accuracy of devices when compared with SMBG; instruction in using devices; being overwhelmed by the volume of information provided causing feelings of stress and the potential for over-treatment; sensor size and views that it was 'unattractive' causing heightened concern about 'other people knowing I have diabetes'; sensor presence being a 'constant reminder' of diabetes; technical difficulties, particularly repeated calibration failure, leading to a decrease in confidence; alarms being 'embarrassing' and causing disruption during work and/or sleep; reluctance and/or refusal to use all data provided, such as graphs and a preference not to use sensors for certain social situations, such as parties, holidays, Christmas etc. and some negative impacts on relationships such as sleep disruption due to alarms.

In their study, (Scharf et al. 2019) found that for adults in the workplace, CGM improved user experiences in the following ways; not needing to interrupt current tasks, positively affecting functioning at work; more time spent on work tasks; reductions of interruptions and absences; reduction in unwanted attention, feeling uncomfortable and shame; improved concentration; eliminating the need for SMBG tools/kits/needles and an increased adherence to checking glucose levels due to the easy and socially covert CGM method in stressful situations or when being around colleagues and supervisors. Challenges included; obtrusiveness (i.e., skin-attached components, pain, discomfort, and skin irritation) and impact on body image due to sensor size and cost.

7.2.2.3 In children/adolescents

13 studies on the use of CGM in children and adolescents were identified (Barnes et al. 2018, Berget & Wykoff 2020, Boyce 2020, Bukhsh et al. 2020, Burckhardt et al. 2019a, Burckhardt et al. 2019b, Erie et al. 2018, Hannon et al. 2018, Hilliard et al. 2019, Messer et al. 2019, Miller et al. 2021, Sinisterra et al. 2020, Vesco et al. 2018). Participants were aged between 1 year old and 18 years old and undertook questionnaires and semi-structured interviews.

Benefits of CGM reported across the studies include; increased confidence about health and safety due to immediate access to glucose level readings; relief regarding not having to test glucose levels constantly; improved sleep due to less worry over missing hypo- and hyperglycaemia events; easier to identify hypo- and hyperglycaemia events, with particular emphasis on parents of children who could not report feeling unwell or recognize or communicate symptoms.

Barriers to the use of CGM reported across studies include; painful insertions of the sensor, skin reactions and irritation from the adhesive; the continuous data stream creating a constant need

for diabetes related attention, preventing focus on other issues and cognitive breaks from diabetes; feeling overwhelmed by the frequency and detail of the data which can be difficult to interpret; technical challenges, such as interruption of sensor connection.

7.2.2.4 Perspectives of parents/carers of people with diabetes

Five studies considering the perspectives of parents and/or carers of children, adolescences and adults with type 1 diabetes were identified (Burckhardt et al. 2018, Burckhardt et al. 2019a, Burckhardt et al. 2019b, Elbalshy et al. 2020, Lawton et al. 2018). Parents/caregivers of people who were diagnosed for > 1year with type one diabetes or had HbA1c levels ≥7.5% (58.5 mmol/mol) and ≤10% (86 mmol/mol) and a diabetes duration of at least 6 months were selected to take part in questionnaires/interviews.

For parents/care givers of children aged 2–12 years, benefits of CGM identified include; impact on sleep quality for the parents, peace of mind, reduction of anxiety, freedom and confidence for the parents and children, and impact on relationships. Many parents who were used to waking several times a night to preform finger-prick tests on their children reported "*they were sleeping through the night with the reassurance of alarms or waking only momentarily to check the CGM on their phone. Some parents felt they were able to return to work because of the improved sleep*" This reassurance provided parents with peace of mind during the day also, particularly if their child was in school. Some parents reported feeling some anxiety and feeling overwhelmed when using a CGM because of the quantity of information they received, whereas others felt it caused them to worry less. Parents felt that CGM allowed a greater freedom for themselves and their child, feeling able to leave home during the day with less risk of having to pick their children up from school prematurely due to hypoglycaemic events as they had the ability to remotely monitor developing lows and highs and help either their children or other carers respond sooner. Parents reported some improvements to spousal relationships where a more equal sharing of the child's care resulted, although some advised that data sharing between people involved in the child's care could also lead to conflict. The study concludes that "*parents developed a greater understanding of their child's diabetes with continuous data compared with snapshots provided by finger pricks. Furthermore, participants commented on the positive effect that using the CGM had on their child's participation in physical activity and their capacity to learn about the effects of various foods on blood glucose levels*"

For parents/care givers of adolescence aged 12 to 15 years, impacts were considered on the usability of devices and improvements to diabetes management considering the parent/carer as a sharer of the responsibility and no different outcomes were reported in addition to those already covered above (Lawton et al. 2018).

For partners of adults with type 1 diabetes, emerging themes included enhanced hypoglycaemic control, overall well-being and sleep quality with the same considerations as those already covered above (Polonsky & Fortmann 2021).

8. Contributors

The HTW staff involved in writing this report were:

- A Evans – patient and public involvement coordination and research
- D Jarrom – clinical effectiveness research and quality assurance
- K McDermott – project management and coordination of expert review
- A Mironas – clinical effectiveness research
- M Prettyjohns – health economics research and analysis
- J Washington – systematic literature searching and information management support

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

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

Experts who contributed to this appraisal:

- Alan Clatworthy, Clinical Effectiveness and NICE lead for Medicines Management, Swansea Bay University Health Board
- Stephen Charles Bain, Professor of Medicine (Diabetes) and Honorary Consultant Physician, Swansea Bay University Health Board/Diabetes Research Unit, Swansea University/Wales National Services Advisory Group (NSAG) for Diabetes
- Julie Anne Lewis, Nurse Consultant. Primary Care Diabetes, Betsi Cadwaladr University Health Board/Welsh Academy for Nurses in Diabetes (WAND),
- Julia Platts, Consultant in Diabetes and Medicine, Cardiff and Vale University Health Board/National Clinical Lead for Diabetes in Wales
- Richard Chudleigh, Consultant in Medicine and Diabetes, Swansea Bay, University Health Board
- Samantha Howard, Market Access Director, Abbott Diabetes Care

9. References

Abdalaziz A, Lan K, Bilous M, et al. (2018). P422 Flash glucose monitoring (FGM) in people with type 1 diabetes: single-centre real-world experience. Diabetic Medicine. 35(supplement 1): S168. doi: https://dx.doi.org/10.1111/dme.48_13571

Ajjan RA, Jackson N, Thomson SA. (2019). Reduction in HbA1c using professional flash glucose monitoring in insulin-treated type 2 diabetes patients managed in primary and secondary care settings: a pilot, multicentre, randomised controlled trial. Diabetes and Vascular Disease Research. 16(4): 385-95. doi: https://doi.org/10.1177/1479164119827456

Akturk HK, Garg S. (2019). Technological advances shaping diabetes care. Current Opinion in Endocrinology, Diabetes & Obesity. 26(2): 84-9. doi: https://dx.doi.org/10.1097/MED.0000000000000467

Al-Tamimi N, Slater N, Kayyali R, et al. (2019). Perceptions by adult patients with type 1 and 2 diabetes of current and advanced technologies of blood glucose monitoring: a prospective study. Canadian Journal of Diabetes. 43(1): 27-33. doi: https://dx.doi.org/10.1016/j.jcjd.2018.02.005

Al Hayek AA, Robert AA, Al Dawish MA. (2017). Evaluation of FreeStyle Libre flash glucose monitoring system on glycemic control, health-related quality of life, and fear of hypoglycemia in patients with type 1 diabetes. Clinical Medicine Insights: Endocrinology and Diabetes. 10: 1179551417746957. doi: https://doi.org/10.1177/1179551417746957

Al Hayek AA, Robert AA, Al Dawish MA. (2020). Acceptability of the FreeStyle Libre flash glucose monitoring system: the experience of young patients with type 1 diabetes. Clinical Medicine Insights: Endocrinology and Diabetes. 13: 1179551420910122. doi: https://dx.doi.org/10.1177/1179551420910122

Alsaffar H, Turner L, Yung Z, et al. (2018). Continuous flash glucose monitoring in children with congenital hyperinsulinism: first report on accuracy and patient experience. International Journal of Pediatric Endocrinology. 2018: 3. doi: https://dx.doi.org/10.1186/s13633-018-0057-2

American Diabetes Association. (2005). Standards of medical care in diabetes. Diabetes Care. 28(supplement 1): S4-36. doi: https://doi.org/10.2337/diacare.28.suppl_1.S4

Asarani NAM, Reynolds AN, Boucher SE, et al. (2020). Cutaneous complications with continuous or flash glucose monitoring use: systematic review of trials and observational studies. Journal of Diabetes Science and Technology. 14(2): 328-37. doi: https://dx.doi.org/10.1177/1932296819870849

Ashrafzadeh S, Hamdy O. (2019). Patient-driven diabetes care of the future in the technology era. Cell Metabolism. 29(3): 564-75. doi: https://dx.doi.org/10.1016/j.cmet.2018.09.005

Avari P, Moscardo V, Jugnee N, et al. (2020). Glycemic variability and hypoglycemic excursions with continuous glucose monitoring compared to intermittently scanned continuous glucose monitoring in adults with highest risk type 1 diabetes. Journal of Diabetes Science and Technology. 14(3): 567-74. doi: https://doi.org/10.1177/1932296819867688

Bacon S, O'Dwyer B, Chambers C, et al. (2017). The performance & technical usability of a flash glucometer monitoring system. Irish Journal of Medical Science. 186(9 supplement 1): S357. doi: https://dx.doi.org/10.1007/s11845-017-1670-4

Barnard KD, Kropff J, Choudhary P, et al. (2018). Acceptability of implantable continuous glucose monitoring sensor. Journal of Diabetes Science and Technology. 12(3): 634-8. doi: https://dx.doi.org/10.1177/1932296817735123

Barnes TL, Lee S, Thompson N, et al. (2018). Barriers to Glucose Testing and Attitudes Toward Mobile App and Device Use in a Large Cohort of T1D Pediatric Patients: Implications for Diabetes Management. Journal of Diabetes Science and Technology. 12(6): 1246-7. doi: https://dx.doi.org/10.1177/1932296818794706

Bergenstal RM, Kerr MSD, Roberts GJ, et al. (2021). Flash CGM Is associated with reduced diabetes events and hospitalizations in insulin-treated type 2 diabetes. Journal of the Endocrine Society. 5(4): bvab013. doi: https://dx.doi.org/10.1210/jendso/bvab013

Berget C, Wykoff L. (2020). Use of Technology in Managing Diabetes in Youth, Part 1: Continuous Glucose Monitoring: Information and Tips for the School Nurse. NASN School Nurse. 35(2): 63-9. doi: https://dx.doi.org/10.1177/1942602X19899143

Bilir SP, Hellmund R, Wehler B, et al. (2018a). 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): 73-9. doi: https://dx.doi.org/10.17925/EE.2018.14.2.73

Bilir SP, Hellmund R, Wehler E, et al. (2018b). 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): 80-5. doi: https://dx.doi.org/10.17925/EE.2018.14.2.80

Bolinder J, Antuna R, Geelhoed-Duijvestijn P, et al. (2016). Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet. 388(10057): 2254-63. doi: https://doi.org/10.1016/S0140-6736(16)31535-5

Boucher S, Blackwell M, Galland B, et al. (2020a). Initial experiences of adolescents and young adults with type 1 diabetes and high-risk glycemic control after starting flash glucose monitoring - a qualitative study. Journal of Diabetes & Metabolic Disorders. 19(1): 37-46. doi: https://dx.doi.org/10.1007/s40200-019-00472-5

Boucher SE, Aum SH, Crocket HR, et al. (2020b). 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. 37(4): 657-64. doi: https://dx.doi.org/10.1111/dme.14188

Boucher SE, Gray AR, Wiltshire EJ, et al. (2020c). 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): 2388-95. doi: https://dx.doi.org/10.2337/dc20-0613

Boyce E. (2020). Knowledge is power? How continuous blood glucose monitoring systems are changing the management of type 1 diabetes mellitus. Pediatric Nursing. 46(4): 179-83.

Bukhsh A, Goh BH, Zimbudzi E, et al. (2020). Type 2 diabetes patients' perspectives, experiences, and barriers toward diabetes-related self-care: a qualitative study from Pakistan. Frontiers in Endocrinology. 11: 534873. doi: https://dx.doi.org/10.3389/fendo.2020.534873

Burckhardt MA, Abraham MB, Mountain J, et al. (2019a). Improvement in psychosocial outcomes in children with type 1 diabetes and their parents following subsidy for continuous glucose monitoring. Diabetes Technology & Therapeutics. 21(10): 575-80. doi: https://dx.doi.org/10.1089/dia.2019.0149

Burckhardt MA, Fried L, Bebbington K, et al. (2019b). Use of remote monitoring with continuous glucose monitoring in young children with type 1 diabetes: the parents' perspective. Diabetic Medicine. 36(11): 1453-9. doi: https://dx.doi.org/10.1111/dme.14061

Burckhardt MA, Roberts A, Smith GJ, 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): 2641-3. doi: https://dx.doi.org/10.2337/dc18-0938

Campbell FM, Murphy NP, Stewart C, et al. (2018). Outcomes of using flash glucose monitoring technology by children and young people with type 1 diabetes in a single arm study. Pediatric Diabetes. 19(7): 1294-301. doi: https://doi.org/10.1111/pedi.12735

Charleer S, De Block C, Van Huffel L, et al. (2020). Quality of life and glucose control after 1 year of nationwide reimbursement of intermittently scanned continuous glucose monitoring in adults living with type 1 diabetes (FUTURE): a prospective observational real-world cohort study. Diabetes Care. 43(2): 389-97. doi: https://doi.org/10.2337/dc19-1610

Chen CM, Hung LC, Chen YL, et al. (2018). Perspectives of patients with non-insulin-treated type 2 diabetes on self-monitoring of blood glucose: a qualitative study. Journal of Clinical Nursing. 27(7-8): 1673-83. doi: https://dx.doi.org/10.1111/jocn.14227

Chiu CJ, Chou YH, Chen YJ, et al. (2019). Impact of new technologies for middle-aged and older patients: in-depth interviews with type 2 diabetes patients using continuous glucose monitoring. JMIR Diabetes. 4(1): e10992. doi: https://dx.doi.org/10.2196/10992

Costigan C, Norris M, McNerney O, et al. (2019). P233 One year post-introduction of centrally-funded flash glucose monitoring in paediatric type 1 diabetes: a regional centre's experience. Archives of Disease in Childhood. 104(supplement 3): A249. doi: https://doi.org/10.1136/archdischild-2019-epa.583

Cowart K, Updike W, Bullers K. (2020). Systematic review of randomized controlled trials evaluating glycemic efficacy and patient satisfaction of intermittent-scanned continuous glucose monitoring in patients with diabetes. Diabetes Technology & Therapeutics. 22(5): 337-45. doi: https://dx.doi.org/10.1089/dia.2019.0345

da Rocha RB, Silva CS, Cardoso VS. (2020). Self-care in adults with type 2 diabetes mellitus: a systematic review. Current Diabetes Reviews. 16(6): 598-607. doi: https://doi.org/10.2174/1573399815666190702161849

De Oliveira MCS, Nascimento GA, Andrade TK, et al. (2019). P103 Evaluation of glycemic control in patients with type 1 diabetes with flash continuous glucose monitoring. Diabetology & Metabolic Syndrome. 11(supplement 1): S82. doi: http://dx.doi.org/10.1186/s13098-019-0473-3

Deja G, Kleczek M, Chumiecki M, et al. (2018). The usefulness of the FlashStyle Libre system in glycemic control in children with type 1 diabetes during summer camp. Pediatric Endocrinology, Diabetes, and Metabolism. 24(1): 11-9. doi: https://dx.doi.org/10.18544/PEDM-24.01.0098

Deshmukh H, Wilmot EG, Gregory R, et al. (2020). Effect of flash glucose monitoring on glycemic control, hypoglycemia, diabetes-related distress, and resource utilization in the Association of British Clinical Diabetologists (ABCD) nationwide audit. Diabetes Care. 43(9): 2153-60. doi: https://dx.doi.org/10.2337/dc20-0738

Diabetes UK. (2020). Diabetes in Wales. Diabetes UK. Available at: https://www.diabetes.org.uk/in_your_area/wales/diabetes-in-wales [Accessed 9 Apr 2021].

Divan V, Greenfield M, Morley CP, et al. (2020). Perceived burdens and benefits associated with continuous glucose monitor use in type 1 diabetes across the lifespan. Journal of Diabetes Science and Technology. 1932296820978769. doi: https://dx.doi.org/10.1177/1932296820978769

Donnelly LA, Morris AD, Frier BM, et al. (2005). Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. Diabetic Medicine. 22(6): 749-55. doi: https://doi.org/10.1111/j.1464-5491.2005.01501.x

Dorflinger GH, Ostergaard JA, Fisker S, et al. (2018). 942-P The effect of flash glucose monitoring on glycemic control in patients with type 1 diabetes. Diabetes. 67(supplement 1): A244-5.

Dover AR, Stimson RH, Zammitt NN, et al. (2017). Flash glucose monitoring improves outcomes in a type 1 diabetes clinic. Journal of Diabetes Science and Technology. 11(2): 442-3. doi: https://doi.org/10.1177/1932296816661560

Dowling L, Wilmot EG, Choudhary P. (2020). Do-it-yourself closed-loop systems for people living with type 1 diabetes. Diabetic Medicine. 37(12): 1977-80. doi: https://doi.org/10.1111/dme.14321

Down S. (2019). Glucose monitoring technology: do you and your patients have the skills and knowledge to use it effectively? Journal of Diabetes Nursing. 23(4): 73.

Ehrhardt N, Al Zaghal E. (2019). Behavior modification in prediabetes and diabetes: potential use of real-time continuous glucose monitoring. Journal of Diabetes Science and Technology. 13(2): 271-5. doi: https://dx.doi.org/10.1177/1932296818790994

Elbalshy M, Boucher S, Galland B, et al. (2020). The MiaoMiao study: can do-it-yourself continuous glucose monitoring technology improve fear of hypoglycaemia in parents of children affected by type 1 diabetes? Journal of Diabetes & Metabolic Disorders. 19(2): 1647-58. doi: https://dx.doi.org/10.1007/s40200-020-00671-5

Engler R, Routh TL, Lucisano JY. (2018). Adoption barriers for continuous glucose monitoring and their potential reduction with a fully implanted system: results from patient preference surveys. Clinical Diabetes. 36(1): 50-8. doi: https://dx.doi.org/10.2337/cd17-0053

Erie C, Van Name MA, Weyman K, et al. (2018). Schooling diabetes: use of continuous glucose monitoring and remote monitors in the home and school settings. Pediatric Diabetes. 19(1): 92-7. doi: https://dx.doi.org/10.1111/pedi.12518

Evans M, Khunti K, Mamdani M, et al. (2013). Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. Health & Quality of Life Outcomes. 11: 90. doi: https://dx.doi.org/10.1186/1477-7525-11-90

Evans M, Welsh Z, Ells S, et al. (2020). The impact of flash glucose monitoring on glycaemic control as measured by HbA1c: a meta-analysis of clinical trials and real-world observational studies. Diabetes Therapy. 11(1): 83-95. doi: https://dx.doi.org/10.1007/s13300-019-00720-0

Farrant M, Friend AJ. (2020). Continuous glucose monitoring improves patient satisfaction and frequency of glucose monitoring but does not lead to better glycaemic control in youth with type 1 diabetes. Archives of Disease in Childhood: Education and Practice Edition. edpract-2020-320967. doi: https://dx.doi.org/10.1136/archdischild-2020-320967

Ferreira LV, Souza ALV, De Oliveira RF, et al. (2018). A174 Flash glucose monitoring system use on type 1 diabetes patients attending a public health system diabetes reference center at Belo Horizonte, Minas Gerais. Diabetology & Metabolic Syndrome. 10(supplement 1): S80. doi: http://dx.doi.org/10.1186/s13098-018-0315-8

Fokkert M, van Dijk P, Edens M, et al. (2017). Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1 and 2 diabetes mellitus. BMJ Open Diabetes Research & Care. 5(1): e000320. doi: https://doi.org/10.1136/bmjdrc-2016-000320

Fokkert M, van Dijk P, Edens M, et al. (2019). Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). BMJ Open Diabetes Research & Care. 7(1): e000809. doi: https://doi.org/10.1136/bmjdrc-2019-000809

Gibb F, Stimson R, Zammitt N, et al. (2018). 797 Flash glucose monitoring is associated with improved glycaemic control and quality of life in people with type 1 diabetes: a large 'real-world' assessment. Diabetologia. 61(supplement 1): S391. doi: https://dx.doi.org/10.1007/s00125-018-4693-0

Gil-Ibanez MT, Aispuru GR. (2020). 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. 30(2): 82-8. doi: https://dx.doi.org/10.1016/j.enfcli.2019.07.011

Gilbert TR, Noar A, Blalock O, et al. (2021). Change in hemoglobin A1c and quality of life with real-time continuous glucose monitoring use by people with insulin-treated diabetes in the Landmark study. Diabetes Technology & Therapeutics. 23(supplement 1): S35-9. doi: https://dx.doi.org/10.1089/dia.2020.0666

Gordon I, Rutherford C, Makarounas-Kirchmann K, et al. (2020). Meta-analysis of average change in laboratory-measured HbA1c among people with type 1 diabetes mellitus using the 14 day Flash Glucose Monitoring System. Diabetes Research and Clinical Practice. 164: 108158. doi: https://dx.doi.org/10.1016/j.diabres.2020.108158

Haak T, Hanaire H, Ajjan R, et al. (2017). Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. Diabetes Therapy. 8(1): 55-73. doi: https://doi.org/10.1007/s13300-016-0223-6

Haak T, Hanaire H, Ajjan R, et al. (2016a). 181 The impact on quality of life, glucose monitoring frequency and safety of novel glucose-sensing technology used by individuals with type 2 diabetes on intensive-insulin therapy. Diabetes Technology & Therapeutics. 18(1): A73. doi: http://dx.doi.org/10.1089/dia.2016.2525

Haak T, Hanaire H, Ajjan RA, et al. (2016b). 074 Use of novel flash glucose-sensing technology to optimise glucose control in individuals with type 2 diabetes on intensive insulin therapy. Diabetes Technology & Therapeutics. 18(supplement 1): A28-9. doi: http://dx.doi.org/10.1089/dia.2016.2525

Halbron M, Bourron O, Andreelli F, et al. (2019). Insulin pump combined with flash glucose monitoring: a therapeutic option to improve glycemic control in severely nonadherent patients with type 1 diabetes. Diabetes Technology & Therapeutics. 21(7): 409-12. doi: https://doi.org/10.1089/dia.2019.0041

Hannon TS, Yazel-Smith LG, Hatton AS, et al. (2018). Advancing diabetes management in adolescents: comparative effectiveness of mobile self-monitoring blood glucose technology and family-centered goal setting. Pediatric Diabetes. 19(4): 776-81. doi: https://dx.doi.org/10.1111/pedi.12648

Haskova A, Radovnicka L, Petruzelkova L, et al. (2020). Real-time CGM is superior to flash glucose monitoring for glucose control in type 1 diabetes: the CORRIDA randomized controlled trial. Diabetes Care. 43(11): 2744-50. doi: https://dx.doi.org/10.2337/dc20-0112

Heald AH, Yadegarfar G, Anderson SG, et al. (2019). The FreeStyle Libre flash glucose monitoring system: How it has improved glycaemic control for people with type 1 diabetes in Eastern Cheshire, UK. Journal of Diabetes Nursing. 23(3): JDN072.

Heinemann L, Deiss D, Siegmund T, et al. (2019). Glucose measurement and control in patients with type 1 or type 2 diabetes. Experimental and Clinical Endocrinology and Diabetes. 127(supplement 1): S8-26. doi: https://dx.doi.org/10.1055/a-1018-9090

Hellmund R, Weitgasser R, Blissett D. (2018a). Cost calculation for a flash glucose monitoring system for adults with type 2 diabetes mellitus using intensive insulin - a UK perspective. European Endocrinology. 14(2): 86-92. doi: https://dx.doi.org/10.17925/EE.2018.14.2.86

Hellmund R, Weitgasser R, Blissett D. (2018b). Cost calculation for a flash glucose monitoring system for UK adults with type 1 diabetes mellitus receiving intensive insulin treatment. Diabetes Research and Clinical Practice. 138: 193-200. doi: https://dx.doi.org/10.1016/j.diabres.2018.01.028

Helm N, De Mendonca Lindstrom T, Forsman S, et al. (2016). P210 Flash glucose monitoring improves perception and frequency of glucose monitoring leading to improved glucose control. Pediatric Diabetes. 17(supplement 24): S115. doi: http://dx.doi.org/10.1111/pedi.12451

Hermanns N, Ehrmann D, Schipfer M, et al. (2019). The impact of a structured education and treatment programme (FLASH) for people with diabetes using a flash sensor-based glucose monitoring system: results of a randomized controlled trial. Diabetes Research and Clinical Practice. 150: 111-21. doi: https://doi.org/10.1016/j.diabres.2019.03.003

Hey C, Alkharaiji M, Anyanwagu U, et al. (2018). P508 Impact of FreeStyle Libre on glycaemic control, frequency of glucose monitoring and treatment satisfaction. Diabetic Medicine. 35(supplement 1): S195. doi: https://dx.doi.org/10.1111/dme.57_13571

Hilliard ME, Levy W, Anderson BJ, et al. (2019). Benefits and barriers of continuous glucose monitoring in young children with type 1 diabetes. Diabetes Technology & Therapeutics. 21(9): 493-8. doi: https://dx.doi.org/10.1089/dia.2019.0142

Holcombe A, Karunakaran V, Streeting J, et al. (2017). P418 Trial of FreeStyle Libre in a local service: impact on diabetes outcomes. Diabetic Medicine. 34(supplement 1): S160. doi: https://doi.org/10.1111/dme.37_13304

Ish-Shalom M, Wainstein J, Raz I, et al. (2016). Improvement in glucose control in difficult-to-control patients with diabetes using a novel flash glucose monitoring device. Journal of Diabetes Science and Technology. 10(6): 1412-3. doi: https://doi.org/10.1177/1932296816653412

Janapala RN, Jayaraj JS, Fathima N, et al. (2019). Continuous glucose monitoring versus self-monitoring of blood glucose in type 2 diabetes mellitus: a systematic review with meta-analysis. Cureus. 11(9): e5634. doi: https://dx.doi.org/10.7759/cureus.5634

Karlsson E. (2016). [The effect on HbA1c following a year of using FGM in patients with type 1-diabetes]. Thesis. University of Orebero, Sweden. Available at: http://urn.kb.se/resolve?urn=urn:nbn:se:oru:diva-55052 [Accessed 15 March 2021].

Kebede MM, Zeeb H, Peters M, et al. (2018). Effectiveness of digital interventions for improving glycemic control in persons with poorly controlled type 2 diabetes: a systematic review, meta-analysis, and meta-regression analysis. Diabetes Technology & Therapeutics. 20(11): 767-82. doi: https://dx.doi.org/10.1089/dia.2018.0216

Kramer G, Michalak L, Müller UA, et al. (2019). Association between flash glucose monitoring and metabolic control as well as treatment satisfaction in outpatients with diabetes type 1. Experimental and Clinical Endocrinology and Diabetes. doi: https://doi.org/10.1055/a-0875-3988

Kudva YC, Ahmann AJ, Bergenstal RM, et al. (2018). Approach to using trend arrows in the FreeStyle Libre flash glucose monitoring systems in adults. Journal of the Endocrine Society. 2(12): 1320-37. doi: https://doi.org/10.1210/js.2018-00294

Landau Z, Abiri S, Gruber N, et al. (2018). Use of flash glucose-sensing technology (FreeStyle Libre) in youth with type 1 diabetes: AWeSoMe study group real-life observational experience. Acta Diabetologica. 55(12): 1303-10. doi: https://doi.org/10.1007/s00592-018-1218-8

Lauridsen JT, Lonborg J, Gundgaard J, et al. (2014). Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries. Quality of Life Research. 23(9): 2645-50. doi: https://dx.doi.org/10.1007/s11136-014-0712-x

Lawton J, Blackburn M, Allen J, et al. (2018). Patients' and caregivers' experiences of using continuous glucose monitoring to support diabetes self-management: qualitative study. BMC Endocrine Disorders. 18: 12. doi: https://dx.doi.org/10.1186/s12902-018-0239-1

Leiva-Gea I, Vázquez JG, Jurado FRL, et al. (2019). LB-20 Introduction of flash glucose monitoring in children with type 1 diabetes: experience of a single-centre in Spain. Hormone Research in Paediatrics. 91(supplement 1): S355. doi: https://dx.doi.org/10.1159/000501868

Lim STJ, Huang F, Lek N, et al. (2020). Flash continuous home glucose monitoring to improve adherence to self-monitoring of blood glucose and self-efficacy in adolescents with type 1 diabetes. Clinical Diabetes. 38(2): 152-8. doi: https://doi.org/10.2337/cd19-0051

Londahl M, Fagher K, Katzman P, et al. (2018). 958-P Beneficial effect of flash glucose monitoring persists in a two-year perspective: a clinical follow-up study of 334 individuals with type 1 diabetes. Diabetes. 67(supplement 1): A249.

Londahl M, Filipsson K, Lindholm E, et al. (2017). Effect of flash glucose monitoring on metabolic control and self esteemed treatment satisfaction in people with type 1 diabetes. Diabetes Technology & Therapeutics. 19(supplement 1): A81. doi: http://dx.doi.org/10.1089/dia.2017.2525.abstracts

Marsters BL, Boucher SE, Galland BC, 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): 1516-24. doi: https://dx.doi.org/10.1111/pedi.13121

Massa GG, Gys I, Op 't Eyndt A, et al. (2018). Evaluation of the FreeStyle® Libre flash glucose monitoring system in children and adolescents with type 1 diabetes. Hormone Research in Paediatrics. 89(3): 189-99. doi: https://dx.doi.org/10.1159/000487361

Mattishent K, Lane K, Salter C, et al. (2019). Continuous glucose monitoring in older people with diabetes and memory problems: a mixed-methods feasibility study in the UK. BMJ Open. 9(11): e032037. doi: https://dx.doi.org/10.1136/bmjopen-2019-032037

May SG, Huber C, Roach M, et al. (2021). Adoption of digital health technologies in the practice of behavioral health: qualitative case study of glucose monitoring technology. Journal of Medical Internet Research. 23(2): e18119. doi: https://dx.doi.org/10.2196/18119

McKnight J, Gibb F. (2017). Flash glucose monitoring is associated with improved glycaemic control but use is largely limited to more affluent people in a UK diabetes centre. Diabetic Medicine. 34(5): 732. doi: https://doi.org/10.1111/dme.13315

Meetoo D, Wong L, Fatani T. (2018). 'Knowing where I am': self-monitoring of blood glucose in diabetes. British Journal of Nursing. 27(10): 537-41. doi: https://doi.org/10.12968/bjon.2018.27.10.537

Messaaoui A, Tenoutasse S, Crenier L. (2018). 946-P Flash glucose monitoring in children: one-year experience. Diabetes. 67(supplement 1): A245-6.

Messer LH, Cook PF, Tanenbaum ML, et al. (2019). CGM benefits and burdens: two brief measures of continuous glucose monitoring. Journal of Diabetes Science and Technology. 13(6): 1135-41. doi: https://dx.doi.org/10.1177/1932296819832909

Messer LH, Johnson R, Driscoll KA, et al. (2018). Best friend or spy: a qualitative meta-synthesis on the impact of continuous glucose monitoring on life with type 1 diabetes. Diabetic Medicine. 35(4): 409-18. doi: https://dx.doi.org/10.1111/dme.13568

Miller V, Xiao R, Willi S. (2021). Correlates of continuous glucose monitoring use trajectories in children and adolescents with type 1 diabetes. Diabetes Technology & Therapeutics. 23(8): 590-4. doi: https://dx.doi.org/10.1089/dia.2020.0668

Mitchell K, McDougall C. (2018). P398 Trial of FreeStyle Libre flash glucose monitoring (FGM) in patients with poorly controlled type 1 diabetes. Diabetic Medicine. 35(supplement 1): S160. doi: https://dx.doi.org/10.1111/dme.45_13571

Mitsuishi S, Nishimura R, Harashima SI, et al. (2018). The effect of novel glucose monitoring system (flash glucose monitoring) on mental well-being and treatment satisfaction in Japanese people with diabetes. Advances in Therapy. 35(1): 72-80. doi: https://dx.doi.org/10.1007/s12325-017-0649-x

Moreno-Fernandez J, Pazos-Couselo M, González-Rodriguez M, et al. (2018). Clinical value of flash glucose monitoring in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion. Endocrinología, Diabetes y Nutrición. 65(10): 556-63. doi: https://doi.org/10.1016/j.endinu.2018.04.003

Nana M, Moore SL, Ang E, et al. (2019). Flash glucose monitoring: impact on markers of glycaemic control and patient-reported outcomes in individuals with type 1 diabetes mellitus in the real-world setting. Diabetes Research and Clinical Practice. 157: 107893. doi: https://dx.doi.org/10.1016/j.diabres.2019.107893

NICE. (2020a). Diabetes (type 1 and type 2) in children and young people: diagnosis and management [NG18]. NICE guideline NG18. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng18/ [Accessed 25 Feb 2021].

NICE. (2020b). Type 2 diabetes in adults: management. NICE guideline NG28. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng28/ [Accessed 25 Feb 2021].

NICE. (2021). Type 1 diabetes in adults: diagnosis and management. NICE guideline NG17. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng17/ [Accessed 8 Sep 2021].

Ohsugi K, Nishiyama K, Ebina K, et al. (2018). P196 Comparison of freestyle libre and freestyle libre pro on glycemic control and glycemic variability in youth with type 1 diabetes mellitus. Pediatric Diabetes. 19(supplement 26): S116. doi: http://dx.doi.org/10.1111/pedi.12746

Ontario Health. (2019). Flash glucose monitoring system for people with type 1 or type 2 diabetes: a health technology assessment. Ontario Health Technology Assessment Series. 19(8). Available at: https://www.hqontario.ca/Portals/0/documents/evidence/reports/hta-flash-glucose-monitoring-system.pdf [Accessed 23 Mar 2021].

Oskarsson P, Antuna R, Geelhoed-Duijvestijn P, et al. (2018). Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy:

a pre-specified subgroup analysis of the IMPACT randomised controlled trial. Diabetologia. 61(3): 539-50. doi: https://doi.org/10.1007/s00125-017-4527-5

Overend L, Simpson E, Grimwood T. (2019). Qualitative analysis of patient responses to the ABCD FreeStyle Libre audit questionnaire. Practical Diabetes. 36(2): 45-50. doi: https://doi.org/10.1002/pdi.2213

Oyaguez I, Merino-Torres JF, Brito M, et al. (2020). Cost analysis of the flash monitoring system (FreeStyle Libre 2) in adults with type 1 diabetes mellitus. BMJ Open Diabetes Research & Care. 8(1): e001330. doi: https://doi.org/10.1136/bmjdrc-2020-001330

Palmer SJ. (2020). Tackling diabetes management in patients with dementia: the use of continuous glucose monitoring. Nursing & Residential Care. 22(1): 38-42. doi: https://doi.org/10.12968/nrec.2020.22.1.38

Paris I, Henry C, Pirard F, et al. (2018). The new FreeStyle libre flash glucose monitoring system improves the glycaemic control in a cohort of people with type 1 diabetes followed in real-life conditions over a period of one year. Endocrinology, Diabetes & Metabolism. 1(3): e00023. doi: https://doi.org/10.1002/edm2.23

Pintus D, Ng S. (2017). eP004 FreeStyle Libre Flash glucose monitoring (Flash GM) system improves glycaemic control and patient quality of life measures in children with type 1 diabetes with appropriate provision of Flash GM education and support by healthcare professionals. Pediatric Diabetes. 18(supplement 25): S48. doi: https://dx.doi.org/10.1111/pedi.12589

Pintus D, Ng SM. (2019). Freestyle libre flash glucose monitoring improves patient quality of life measures in children with type 1 diabetes mellitus (T1DM) with appropriate provision of education and support by healthcare professionals. Diabetes & Metabolic Syndrome. 13(5): 2923-6. doi: https://dx.doi.org/10.1016/j.dsx.2019.07.054

Piona C, Dovc K, Mutlu GY, et al. (2018). Non-adjunctive flash glucose monitoring system use during summer-camp in children with type 1 diabetes: the free-summer study. Pediatric Diabetes. 19(7): 1285-93. doi: https://doi.org/10.1111/pedi.12729

Polonsky WH, Fortmann AL. (2021). Impact of real-time continuous glucose monitoring data sharing on quality of life and health outcomes in adults with type 1 diabetes. Diabetes Technology & Therapeutics. 23(3): 195-202. doi: https://dx.doi.org/10.1089/dia.2020.0466

Rasche P, Mertens A, Miron-Shatz T, et al. (2018). Seamless recording of glucometer measurements among older experienced diabetic patients - a study of perception and usability. PloS One. 13(5): e0197455. doi: https://dx.doi.org/10.1371/journal.pone.0197455

Reddy M, Jugnee N, Anantharaja S, et al. (2018a). Switching from flash glucose monitoring to continuous glucose monitoring on hypoglycemia in adults with type 1 diabetes at high hypoglycemia risk: the extension phase of the I HART CGM study. Diabetes Technology & Therapeutics. 20(11): 751-7. doi: https://doi.org/10.1089/dia.2018.0252

Reddy M, Jugnee N, El Laboudi A, et al. (2018b). A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with type 1 diabetes and impaired awareness of hypoglycaemia. Diabetic Medicine. 35(4): 483-90. doi: https://doi.org/10.1111/dme.13561

Ritholz MD, Henn O, Atakov Castillo A, et al. (2019). Experiences of adults with type 1 diabetes using glucose sensor-based mobile technology for glycemic variability: qualitative study. JMIR Diabetes. 4(3): e14032. doi: https://dx.doi.org/10.2196/14032

Rodia C, Bianchi C, Bertolotto A, et al. (2019). 920-P Flash Glucose Monitoring (FGM) in real-life: 18-month clinical experience. Diabetes. 68(supplement 1). doi: https://doi.org/10.2337/db19-920-P

Rouhard S, Buysschaert M, Alexopoulou O, et al. (2020). Impact of flash glucose monitoring on glycaemic control and quality of life in patients with type 1 diabetes: a 18-month follow-up in real life. Diabetes & Metabolic Syndrome. 14(2): 65-9. doi: https://dx.doi.org/10.1016/j.dsx.2019.12.007

Roussel R, Riveline J-P, Vicaut E, et al. (2021). Important drop in rate of acute diabetes complications in people with type 1 or type 2 diabetes after initiation of flash glucose monitoring in France: the RELIEF study. Diabetes Care. 44(6): 1368-76. doi: https://doi.org/10.2337/dc20-1690

Scharf J, Nguyen XQ, Vu-Eickmann P, et al. (2019). Perceived usefulness of continuous glucose monitoring devices at the workplace: secondary analysis of data from a qualitative study. Journal of Diabetes Science and Technology. 13(2): 242-7. doi: https://dx.doi.org/10.1177/1932296818789143

Shi L, Hellmund R. (2020). Cost comparison of flash continuous glucose monitoring with self-monitoring of blood glucose in adults with type 1 or type 2 diabetes using intensive insulin- from a US private payer perspective. US Endocrinology. 16(1): 24-30. doi: http://dx.doi.org/10.17925/use.2020.16.1.24

SHTG. (2018). Freestyle Libre® flash glucose monitoring. Evidence note 81. Scottish Health Technologies Group. Available at: https://shtg.scot/our-advice/freestyle-libre-flash-glucose-monitoring/ [Accessed 6 Sep 2021].

Sinisterra M, Hamburger S, Tully C, et al. (2020). Young children with type 1 diabetes: sleep, health-related quality of life, and continuous glucose monitor use. Diabetes Technology & Therapeutics. 22(8): 639-42. doi: https://dx.doi.org/10.1089/dia.2019.0437

Sorgard B, Iversen MM, Martensson J. (2019). Continuous glucose monitoring in adults with type 1 diabetes: a balance between benefits and barriers: a critical incident study. Journal of Clinical Nursing. 28(17-18): 3318-29. doi: https://dx.doi.org/10.1111/jocn.14911

Stueve M, Schnell O. (2019). Health technology assessments for flash glucose monitoring and how to use them in everyday clinical practice. Journal of Diabetes Science and Technology. 13(3): 584-91. doi: https://dx.doi.org/10.1177/1932296818794668

Tanaka N, Yabe D, Murotani K, et al. (2018). Mental distress and health-related quality of life among type 1 and type 2 diabetes patients using self-monitoring of blood glucose: a cross-sectional questionnaire study in Japan. Journal of Diabetes Investigation. 9(5): 1203-11. doi: https://dx.doi.org/10.1111/jdi.12827

Tirelli E, Frontino G, Favalli V, et al. (2017). Flash glucose monitoring in noncompliant children and adolescents with type 1 diabetes. Diabetes Technology & Therapeutics. 19(supplement 1): A83. doi: https://dx.doi.org/10.1089/dia.2017.2525.abstracts

Tsur A, Cahn A, Israel M, et al. (2021). Impact of flash glucose monitoring on glucose control and hospitalization in type 1 diabetes: a nationwide cohort study. Diabetes/Metabolism Research and Reviews. 31(1): e3355. doi: https://dx.doi.org/10.1002/dmrr.3355

Tumminia A, Milluzzo A, Festa C, et al. (2021). Efficacy of flash glucose monitoring in pregnant women with poorly controlled pregestational diabetes (FlashMom): a randomized pilot study. Nutrition, Metabolism, and Cardiovascular Diseases. 31(6): 1851-9. doi: https://dx.doi.org/10.1016/j.numecd.2021.03.013

Tyndall V, Stimson RH, Zammitt NN, et al. (2019). Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. Diabetologia. 62(8): 1349-56. doi: https://doi.org/10.1007/s00125-019-4894-1

Vesco AT, Jedraszko AM, Garza KP, et al. (2018). Continuous glucose monitoring associated with less diabetes-specific emotional distress and lower a1c among adolescents with type 1 diabetes. Journal of Diabetes Science and Technology. 12(4): 792-9. doi: https://dx.doi.org/10.1177/1932296818766381

Visser MM, Charleer S, Fieuws S, et al. (2021). Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial. Lancet. 397(10291): 2275-83. doi: https://dx.doi.org/10.1016/S0140-6736(21)00789-3

Volcansek S, Lunder M, Janez A. (2019). Acceptability of continuous glucose monitoring in elderly diabetes patients using multiple daily insulin injections. Diabetes Technology & Therapeutics. 21(10): 566-74. doi: https://dx.doi.org/10.1089/dia.2019.0131

Wada E, Onoue T, Kobayashi T, et al. (2020). Flash glucose monitoring helps achieve better glycemic control than conventional self-monitoring of blood glucose in non-insulin-treated type 2 diabetes: a randomized controlled trial. BMJ Open Diabetes Research & Care. 8(1): e001115. doi: https://dx.doi.org/10.1136/bmjdrc-2019-001115

Walton-Betancourth S, Amin R. (2017). eP003 A clinic-based study of the impact of flash glucose sensing technology on glycaemic control and self-monitoring of blood glucose in children and young people with type 1 diabetes. Pediatric Diabetes. 18(supplement 25): S47-8. doi: https://dx.doi.org/10.1111/pedi.12589

Weiss J, Cohen N, Zajac JD, et al. (2018). Flash glucose monitoring: using technology to improve outcomes for patients with diabetes. Australian Journal of Rural Health. 26(6): 453-4. doi: https://doi.org/10.1111/ajr.12440

White ND, Knezevich E. (2020). Flash glucose monitoring technology impact on diabetes self-care behavior. American Journal of Lifestyle Medicine. 14(2): 130-2. doi: https://dx.doi.org/10.1177/1559827619890955

Wijnands A, Gys I, Bevilacqua E, et al. (2017). O46 The FreeStyle flash glucose monitoring system has limited effect on the metabolic control of children and adolescents with type 1 diabetes mellitus. Pediatric Diabetes. 18(supplement 25): S38. doi: https://dx.doi.org/10.1111/pedi.12587

Xatzipsalti M, Mentesidou L, Kourti A, et al. (2017). eP083 Flash glucose monitoring system improves glycemic control. Pediatric Diabetes. 18(supplement 25): S78. doi: https://doi.org/10.1111/pedi.12589

Yaron M, Roitman E, Aharon-Hananel G, et al. (2018). 908-P Intervention of the flash glucose sensing technology on glycemic control and treatment satisfaction in patients with type 2 diabetes treated intensively by insulin: a randomized controlled trial. Diabetes. 67(supplement 1): A236.

Yaron M, Roitman E, Aharon-Hananel G, et al. (2019). Effect of flash glucose monitoring technology on glycemic control and treatment satisfaction in patients with type 2 diabetes. Diabetes Care. 42(7): 1178-84. doi: https://doi.org/10.2337/dc18-0166

10. Evidence review methods

This review used rapid review methods to search for, appraise and summarise evidence according to the inclusion/exclusion criteria detailed in Appendix 2. Search details can be found in Appendix 9; the search was last updated on 9 July 2021.

We prioritised the following study types, in the order listed:

- Well-conducted sources of secondary evidence, including studies of any comparative design
- Randomised controlled trials
- Non-randomised, observational studies that included a relevant control group
- Uncontrolled studies that used a before/after or longitudinal design

We prioritised the above separately for each outcome if required; i.e. outcomes were included from 'lower priority' study designs where no higher priority sources reported these outcomes, or to fill other evidence gaps such as to provide information on long-term follow up.

Where relevant and well-conducted systematic reviews existed we used these by:

- Reporting or adapting their reported outcome measures where these are fully relevant to the scope of our review, and appropriate synthesis methods have been used
- Using these reviews as a source of potentially relevant studies where the review cannot be used as a source of outcome data

We prioritised systematic reviews in terms of the sources of evidence they include, using the order described above, and also in terms of their certainty (in terms of methodological conduct and relevance to the research questions of interest).

We synthesised outcomes narratively with the exception of long-term data on HbA1c outcomes. For this outcome, we combined and updated pooled analyses carried out in two systematic reviews (Evans et al. 2020, Gordon et al. 2020). The data tables used for the meta-analyses can be found in Appendix 6. Data stratification for the meta-analyses was attempted in relation to the usage of the device. A number of observations were excluded in order to either avoid data duplication or because insufficient information was provided in order to classify the observation under the appropriate stratification class. Only a limited number of studies covered either mixed populations (T1DM and T2DM combined) and those observations were also excluded in order to avoid introducing heterogeneity. A full list of the excluded observations can be found in Appendix 6. The meta-analyses and associated forest plots were computed in Stata v.16 using the "metan" module. The forest plots can be found in Appendix 7.

For key outcomes, we 'mapped' the direction and certainty of the evidence as shown in Table 2. We determined these outcomes to be of greatest importance for decision making based on formal stakeholder feedback during external review of the EAR and discussion with HTW's Assessment Group. For each outcome and comparison, the certainty of the evidence was rated based on the amount of evidence available, the likelihood of bias in the evidence, and the precision of the measured treatment effects.

Appendix 1. Patient Submission from Diabetes UK Cymru

Patient/Carer Group Submission Form

Health conditions and technology

1. Describe any sources you used to gather information for this submission

This information comes from stakeholder engagement with those who use diabetes technology regularly as volunteers, campaigners and ambassadors of Diabetes UK Cymru. As an organization we are in constant contact with a cross-section of the diabetes community.

This submission will also reference survey data Diabetes UK Cymru collected in Spring 2020 on experiences accessing technology. It will also reference data and statistics collected in 2017 for Diabetes UK's *Future of Diabetes* report and the *Too often Missing* report on mental health from 2018.

Diabetes UK Cymru also contributes to the work of the Welsh Endocrine Diabetes Society, the National Service Advisory group for Diabetes, the all-Wales Diabetes Implementation Group and Welsh Academy for Nursing in Diabetes. These may also be referenced in this submission.

2. What is the health condition and how does it affect the day-to-day lives of patients and their carers?

Diabetes is a relentless, complicated, and often underestimated condition, and it is important to differentiate between type 1 diabetes, type 2 diabetes and other types of diabetes like gestational diabetes. However, beyond clinical differences, there is a great deal of shared experience by those who live with diabetes.

On average people with diabetes make 180 additional high-risk decisions every day. This is particularly the case for those with type 1 diabetes, and those with type 2 who are insulin dependent. In Diabetes UK's *Future of Diabetes* report (2019), 73% of people felt overwhelmed by the management of their condition.

People with type 1 diabetes and those on type 2 who are insulin dependent have to either inject themselves multiple times a day, or administer the insulin using a pump. Administering the correct amounts of insulin can be a demanding task, and getting dosages wrong can have serious consequences. Having an accurate, efficient reliable system to regularly measure blood glucose levels can make a big improvement to the quality of life for those reliant on insulin.

Poor management of diabetes is manifested in blood glucose levels (or glycaemic control), poor management of this leads to poor physical and mental health. The long-term consequences of poor glycaemic control can lead to traumatic, acute, irreversible and costly complications such as sight loss and amputation. The costs of diabetes, and the costs associated with the complications of diabetes (which are largely preventable, estimates are placed at around 85% or £1bn) make up around 10% of NHS Wales expenditure. Most importantly, the risk of complications can be a constant concern for people with diabetes, one that increases rates of anxiety and depression compared with those who do not have diabetes.

As a result of poor glycaemic control, people with diabetes are also at increased risk of heart disease, cancer and stroke.

3. How is the health condition currently diagnosed and/or treated?

Diabetes is a complicated condition, which people experience differently. Technology which measures blood glucose levels such as the Freestyle Libre and continuous glucose monitoring is used by both those with type 1, type 2 who are on multiple daily insulin injections (MDI) and gestational diabetes. Patient journeys for each of these groups will differ substantially.

Those with type 2 will be diagnosed and receive the majority of their care in primary care. Those with type 1 diabetes and those with gestational diabetes will mostly be seen in secondary care by specialists. These means that the type of support the receive differs, and as such awareness of access to appropriate technology differs both by patients and by health care professionals.

Those with type 1 diabetes need urgent medical care upon presentation. Sadly, many cases (c. 23%) of type 1 diabetes go initially undiagnosed until the patient is critically ill. From then on patients are generally cared for in secondary care, taught how to manage their insulin medications, how to inject and to read their blood glucose levels. Many report this experience as overwhelming.

Treatment for those with type 2 diabetes can begin with oral medications such as metformin which acts as an insulin sensitizer – tackling insulin resistance and making the body more susceptible to the insulin the pancreas is still able to produce. Those with type 2 are also recommended to make lifestyle changes including diet and exercise, to help control their condition. In some newly diagnosed cases, with extreme lifestyle change it is possible to put diabetes into remission. This is not possible for everyone. As type 2 diabetes progresses oral medications can become less effective, and some will then require multiple daily injections of insulin similar to those with type 1 diabetes. There is a lot of stigma attached to type 2 diabetes and many people struggle with their diagnosis.

4. What do patients and carers expect from the health technology?

Overall, people have many differing expectations about what technology can do for them. These are often personal goals, such as competing in sport, or succeed academically due to easier to manage blood glucose levels and the physiological and psychological benefits that come with this.

Specific reasons given as part of our research include:

- Improved blood glucose levels
- Fewer hypoglycaemic incidents
- Improvements in emotional wellbeing or mental health
- More confidence in managing my condition
- Better quality of life
- Fewer hospital visits
- Fewer GP visits

- Fewer hyperglycaemic incidents
- Fewer episodes of DKA (diabetic ketoacidosis)

5. What difference did the health technology make to the lives of patients that have had it?

In the last 10 years, 62% of people in Wales have tried to access some sort of technology to help manage their diabetes, and 44% have used the Freestyle Libre Flash Glucose Monitoring. Both of these figures are the lowest of any nation in the UK, between 4-6% behind the national average.

Most people have found that diabetes technology in general has been successful in helping them manage their blood glucose (63%), achieve fewer incidents of hypoglycaemia (51%), improve their confidence (64%) and improve their quality of life (50%)

It is worth noting at this stage that the physiological and psychological impact of living with diabetes can be huge and for many people with diabetes, and that many people expect that diabetes technology can help to reduce some of this impact.

Technology in general can offer patients peace of mind. Diabetes is a condition that is managed by the patient, so giving them the tools to not only manage but better understand how their blood glucose behaves is important to improving outcomes. Flash monitoring and continuous glucose monitoring do this much better than traditional finger prick methods allow. This is because for optimum management more than 10 checks are needed every day, with technology it is easy for patients to do 30 or more checks with ease.

6. Additional information you believe would be helpful for HTW to consider.

Flash monitoring is an important tool to support people with type 1, type 2 on MDI and those with gestational diabetes control their condition. As it is now readily available on the NHS in Wales many people have started using diabetes technology with the Freestyle Libre. In fact by far the most common response to why have you stopped using Freestyle Libre was because they have moved on to other more advanced technology (60%), responses indicating it wasn't for them or it didn't work as they hoped were extremely low (median figure for these responses was 5.6%)

Other interesting responses were that amongst those using Freestyle Libre Flash monitoring, 96% are now accessing it through the NHS, however when they first accessed the technology only 48% were getting it through the NHS, 58% were self-funding the technology through manufacturers or pharmacy. This fits with what we hear anecdotally – that Wales is slow to make available diabetes technology through the NHS. This is concerning due to the effects on health inequalities and outcomes.

Our data suggests that Wales is behind other nations on the adoption of diabetes technology across the board, with significantly lower uptake of the Freestyle Libre and of insulin pumps. Insulin pump use in Wales is at 35% compared to 40% in England and 41% in Scotland.

Of those not currently using the Freestyle Libre, 63% said it is because they have not been offered it by their healthcare professional, and 25% said because they do not currently know enough about it. This suggests that those who aren't utilising Freestyle Libre are doing so

because despite being in theory available on the NHS in Wales for some years, the opportunities aren't there for all patients to learn about and to try this technology.

Furthermore, 77% of our respondents would try to, or continue to access this technology through the NHS.

This is worth noting because as technology in this area moves towards closed loop systems (pumps that talk to sensors that are able to operate automatically and therefore act as an artificial pancreas) we have fewer people accessing technology, and fewer patients and clinicians comfortable with using, supporting and prescribing technology. This is despite better outcomes and significant cost savings for those that do. As a result, Wales risks being left behind.

Perhaps most concerning is the effect on those who have been trying to access diabetes technology and failed:

- 36% told us their mental health had worsened
- 49% told us their blood glucose management had worsened
- 47% told us they feel less confident
- 33% told us feel less motivated to manage their diabetes
- 26% told us they have tried to self-fund the technology but struggled financially as a result
- 14% told us their quality of life has worsened.

It is clear that failure to better adopt diabetes technology in Wales is extremely costly. Both in terms of the cost to our NHS in dealing with complications that could have been avoided, and in the cost to individuals who struggle both physiologically and psychologically as a result of the lack of support technology can offer.

We would urge Health Technology Wales to undertake a wider review of diabetes technology and make recommendations on increasing access to diabetes technology by making more technology available on the NHS and through supporting more clinicians to advocate for and help patients who would benefit from technology to access it.

7. Summarise the key points of your submission in up to 5 statements.

Wales is significantly behind in the adoption of technology to support patients in Wales. With roughly £800 million in costs to our NHS from preventable costs and complications of diabetes, not adopting technologies leads to a huge drain on NHS resources and a large negative impact on patient outcomes and patient experience. Current attitudes and policies fail to enact Welsh Government and NHS Wales principles of prudent and value based healthcare.

There are many diabetes technologies which can greatly improve the patient's understanding of their blood glucose levels and therefore manage their condition more effectively. This leads to better quality of life in many aspects. The Freestyle Libre Flash monitoring is one such technology.

The positive effects of people using the Freestyle Libre Flash monitoring system are not just physiological, with around 73% of people with diabetes reporting feeling overwhelmed in the management of their condition, this technology can also improve patient's mental health.

The long term outcomes delivered by tech in keeping blood glucose levels in range which the evidence is now showing will have tremendous benefits in reducing the costly complications

of diabetes which the evidence shows are a clear consequence of suboptimal management of the condition.

The positive applications of the Freestyle Libre are endless, particularly for vulnerable groups. This technology can also be crucial for those caring for people living with diabetes, both in managing the condition in older people who may be in care, but also children with type 1.

8. Please give us details of anyone outside your group that had a role in preparing your submission.

The evidence submitted is based on a combination of anecdotal evidence from our patient ambassadors including our Council of People with Diabetes and the NHS all-Wales Patient Reference Group on Diabetes, as well as expert advice from clinicians we work with and specialist clinicians working at Diabetes UK Cymru, and from data we have collected from surveys carried out in Wales in the last 12 months.

9. Have you completed the Declaration of Interest form?

I state that I have no interests or income in or from any external companies or organisations linked to diabetes.

D J Williams

J James

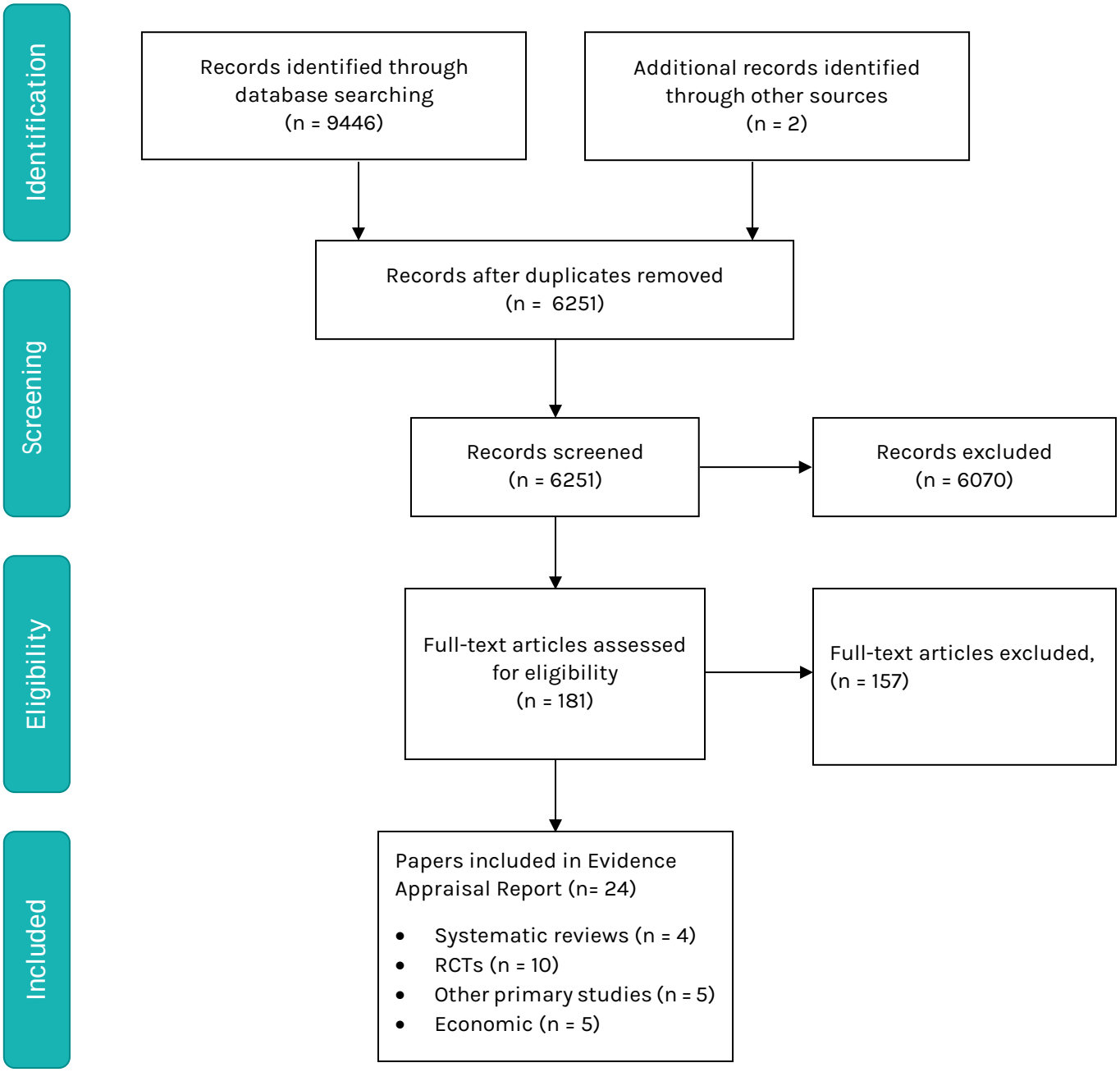
Appendix 2. Inclusion and exclusion criteria for evidence included in the review

Research Question	What is the clinical and cost effectiveness of flash glucose monitoring in people with diabetes?

	Inclusion criteria	Exclusion criteria
Population	People with Type 1, Type 2 or gestational diabetes mellitus We will report data on the following subgroups, if available: • Type 1 diabetes • Type 2 diabetes • Gestational diabetes • People with learning disabilities who have diabetes • People who test their blood glucose at different frequencies • People with conditions such as dementia who require residential or community care	
Intervention	Flash glucose monitoring/intermittently-scanned continuous glucose monitoring. Included, but not limited to: • FreeStyle Libre • FreeStyle Libre 2	We will exclude 'professional' monitoring systems, ie those that only make data available to healthcare professionals and not to system users (eg FreeStyle Libre Pro)
Comparison/ Comparators	• Self-monitoring of blood glucose (SMBG) • Continuous glucose monitoring (CGM) Flash glucose monitoring may either replace, or be used in addition to, these interventions.	We will not include studies that only compare between-device accuracy/precision without reporting any other outcomes of interest.

Outcome measures	HbA1c Glucose levels Hypoglycaemia – frequency; duration Hyperglycaemia/diabetic ketoacidosis – frequency; duration Fear of hypoglycaemia (worry) Health-related quality of life Diabetes distress Patient satisfaction Adverse events from testing or treatment Frequency of glucose monitoring (SMBG of flash glucose monitoring) Health care utilization (including hospital admissions) (Patient-reported) usability Cost-effectiveness
Study design	We will include the following clinical evidence in order of priority: • Systematic reviews. • Randomised trials. • Non-randomised trials. We will only include evidence for "lower priority" evidence where outcomes are not reported by a "higher priority" source. We will also search for economic evaluations or original research that can form the basis of an economic assessment.
Search limits	We will search for evidence from 2018 onwards. We will use our original EAR, and other previously published technology appraisals, as sources of evidence prior to this date.

Appendix 3. Flow diagram outlining selection of relevant evidence sources



Appendix 4. Included evidence sources for clinical effectiveness

Table 1. Included systematic reviews: design and characteristics

Study reference	Design, search period	Eligibility criteria	Trial/patient characteristics	Outcomes measured
Cowart et al. (2020)	Up to November 2019	RCTs reporting glycaemic outcomes and/or patient satisfaction with the use FGM	Children, adolescents or adults with T1DM or T2DM as well as pregnant women or those with gestational diabetes	• Change in HbA1c • Time spent in hypoglycaemia • Time spent in glycaemic range • Satisfaction with treatment • Patient satisfaction • Diabetes distress
Evans et al. (2020)	NR	RCTs and observational studies reporting changes in HbA1c before and after FGM use	Participants with T1DM or T2DM (adults, children and adolescents) using FreeStyle Libre over periods from 1 to 24 months	• Change in HbA1c
Gordon et al. (2020)	Search carried out in February 2020	Publications of any study design reporting use of FGM for a minimum of 8 weeks to a maximum of 2 years	Studies conducted with 5 or more people with T1DM that included outcome 'change from baseline in HbA1c' or presented sufficient data to allow its calculation	• Change in HbA1c
Ontario Health (2019)	HTA including studies published between 1st of January 2014 and 6th of April 2018	Randomised controlled trial or observational cohort study design (before-after or parallel groups)	Studies that recruited people of any age diagnosed with T1DM or T2DM that evaluated FGM devices designed for use by patients compared with SMBG	• Glycaemic variability • Time spent in glucose range • Time spent in hypoglycaemia or hyperglycaemia • Behaviour • Worry (fear of hypoglycaemia) • Quality of life • Severe hypoglycaemic events • Glycated haemoglobin levels • Device-related adverse events

Table 2. Cowart et al. (2020) included studies characteristics and eligibility criteria

Cowart et al. (2020) – Systematic review
Included studies
Ajjan et al. (2019) – Adults (T2DM, 7 months, n=148)
Bolinder et al. (2016) – Adults (T1DM, 6 months, n=241)
Haak et al. (2017) – Adults (T2DM, 6 months, n=224)
Hermanns et al. (2019) – Adults and Adolescents (Mixed, 6 weeks, n=216)
Ohsugi et al. (2018) – Adults and Children (T1DM, 14 days, n=9)
Piona et al. (2018) – Children and Adolescents (T1DM, 14 days, n=45)
Reddy et al. (2018a) – Adults (T1DM, 8 weeks, n=40)
Reddy et al. (2018b) – Adults (T1DM, 8 weeks, n=40)
Yaron et al. (2019) – Adults (T2DM, 10 weeks, n=101)
Eligibility criteria
• Patient population: children, adolescents or adults with T1DM or T2DM as well as pregnant women or those with gestational diabetes • RCTs reporting glycaemic outcomes and/or patient satisfaction with the use of intermittent-scanned continuous glucose monitoring (isCGM)

Table 3. Evans et al. (2020) included studies characteristics and eligibility criteria

Evans et al. (2020) – Systematic review
Included studies
Abdalaziz et al. (2018) – Adults (T1DM, 6 months (n=40) and 12 months (n=40))
Al Hayek et al. (2017) – Children, (T1DM, 3 months, n=47)
Bacon et al. (2017) – Adults (T1DM, 3 months, n=58)
Bolinder et al. (2016) – Adults (T1DM, 3 months (n=119) and 6 months (n=119))
Campbell et al. (2018) – Children (T1DM, 2 months, n=75)
Dorflinger et al. (2018) – Adults (T1DM, 3 months (n=209), 6 months (n=146), 9 months (n=75) and 12 months (n=25))
Dover et al. (2017) – Adults (T1DM, 4 months, n=25)

Gibb et al. (2018) – Adults (T1DM, 10 months, n=204)

Haak et al. (2017) – Adults (T2DM, 3 months (n=149) and 6 months (n=149))

Helm et al. (2016) – Children (T1DM, 2 months, n=31)

Hey et al. (2018) – Adults (T1DM, 1 month, n=29)

Holcombe et al. (2017) – Adults (T1DM, 2 months, n=13)

Ish-Shalom et al. (2016) – Adults (Mixed T1DM (n=6) and T2DM (n=25), 1 month (n=31), 2 months (n=31), 3 months (n=31) and 6 months (n=31))

Karlsson (2016) – Adults (T1DM, 12 months, n=164)

Landau et al. (2018) – Children (T1DM, 3 months, n=59)

Londahl et al. (2017) – Adults (T1DM, 3 months (n=226) and 12 months (n=226)

McKnight & Gibb (2017) – Adults (T1DM, n=169)

Messaaoui et al. (2018) – Children (T1DM, 12 months, n=278)

Mitchell & McDougall (2018) – Adults (T1DM, 3 months, n=13)

Moreno-Fernandez et al. (2018) – Adults (T1DM, 6 months, n=18)

Paris et al. (2018) – Adults (T1DM, 3 months (n=107), 6 months (n=109), 9 months (n=104) and 12 months (n=102))

Pintus & Ng (2017) – Children (T1DM, 3 months, n=52)

Reddy et al. (2018b) – Adults (T1DM, 2 months, n=20)

Tirelli et al. (2017) – Children (T1DM, 3 months, n=13)

Walton-Betancourth & Amin (2017) – Children (T1DM, 3 months, n=47)

Weiss et al. (2018) – Adults (Mixed T1DM and T2DM, n=22)

Wijnands et al. (2017) – Children (T1DM, 3 months, n=72)

Xatzipsalti et al. (2017) – Children (T1DM, 3 months, n=51)

Yaron et al. (2018) – Adults (T2DM, 2 months, n=53)

Eligibility criteria

- Studies that reported longitudinal HbA1C data in participants with T1DM or T2DM (adults, children and adolescents) using FreeStyle Libra system over periods from 1 to 24 months
- Included RCTs and observational studies reported an absolute change from baseline to ensure a consistent approach and reflect the real-world patient-centred outcome

Table 4. Gordon et al. (2020) included studies characteristics and eligibility criteria

Gordon et al. (2020) – Systematic review
Included studies
Abdalaziz et al. (2018) – Adults (T1DM, 12 months, n=40)
Al Hayek et al. (2017) – Children (T1DM, 3 months, n=47)
Bacon et al. (2017) – Adults (T1DM, 3 months, n=58)
Bolinder et al. (2016) – Adults (T1DM, 6 months, n=119)
Campbell et al. (2018) – Children (T1DM, 2 months, n=76)
Charleer et al. (2020) – Adults (T1DM, 12 months, n=1711)
Costigan et al. (2019) – Children (T1DM, 6 months, n=108)
De Oliveira et al. (2019) – Adults (T1DM, 3 months, n=35)
Dorflinger et al. (2018) – Adults (T1DM, 3 months, n=209)
Dover et al. (2017) – Adults (T1DM, 4 months, n=25)
Ferreira et al. (2018) – Adults (T1DM, 3 months, n=15)
Fokkert et al. (2019) – Adults (T1DM, 12 months, n=543)
Gibb et al. (2018) – Adults (T1DM, 10 months, n=204)
Halbron et al. (2019) – Adults (T1DM, 6 months, n=17)
Heald et al. (2019) – Adults (T1DM, 6 months, n=92)
Holcombe et al. (2017) – Adults (T1DM, 8 weeks, n=15)
Karlsson (2016) – Adults (T1DM, 12 months, n=164)
Kramer et al. (2019) – Adults (T1DM, 12 months, n=40)
Landau et al. (2018) – Children (T1DM, 12 months, n=59)
Leiva-Gea et al. (2019) – Children (T1DM, 6 months, n=145)
Londahl et al. (2018) – Adults (T1DM, 2 years, n=269)
Messaaoui et al. (2018) – Children (T1DM, 12.7 months, n= 278)
Mitchell & McDougall (2018) – Adults (T1DM, 3 months, n=16)
Moreno-Fernandez et al. (2018) – Adults (T1DM, 6 months, n=18)

Nana et al. (2019) – Adults (T1DM, 6 months, n=90)
Paris et al. (2018) – Adults (T1DM, 12 months, n=117)
Pintus & Ng (2017) – Children (T1DM, 3 months, n=52)
Reddy et al. (2018b) – Adults (T1DM, 8 weeks, n=20)
Rodia et al. (2019) – Adults (T1DM, 18 months, n=35)
Rouhard et al. (2020) – Adults (T1DM, 18 months, n=248)
Tirelli et al. (2017) – Children (T1DM, 3 months, n=13)
Tyndall et al. (2019) – Adults (T1DM, 8.2 months, n=565)
Walton-Betancourth & Amin (2017) – Children (T1DM, 12 months, n=52)
Wijnands et al. (2017) – Children (T1DM, 8 months, n=78)
Xatzipsalti et al. (2017) – Children (T1DM, 12 months, n=51)
Eligibility criteria
• Publications with study designs reporting use of FGM for a minimum of 8 weeks to a maximum of 2 years by 5 or more people with T1DM that included outcome 'change from baseline in HbA1c' or presented sufficient data to allow its calculation

Table 5. Ontario Health (2019) included studies characteristics and eligibility criteria

Ontario Health (2019) - HTA
Included studies
Bolinder et al. (2016) – Adults (T1DM, 6 months, n=241)
Haak et al. (2016a) & Haak et al. (2016b)– Adults (T2DM, 6 months, n=224)
Mitsuishi et al. (2018) – Adults (Mixed, n=160)
Oskarsson et al. (2018) – Adults (T1DM, 6 months, n=163)
Al Hayek et al. (2017) – Children (T1DM, 3 months, n=94)
Moreno-Fernandez et al. (2018) – Adults (T1DM, 6 months, n=36)
Eligibility criteria

- HTA including studies published between 1st of January 2014 and 6th of April 2018 of randomised controlled trial or observational cohort study design (before-after or parallel groups)
- Studies that recruited people of any age diagnosed with T1 or T2DM that evaluated flash glucose monitoring devices designed for use by patients compared with SMBG

Table 6. Included randomised trials: design and characteristics

Study reference	Setting and Design	Participants	Interventions	Outcomes	Follow-up period	Comments
Bolinder et al. (2016)	Randomised controlled trial, multicentre (23 centres, Sweden, Austria, Germany, Spain, Netherlands).	• Intervention (Men, 77; Women, 42) • Control group (Men, 59; Women, 61). • Inclusion criteria: people aged 18 years or older who had been diagnosed with type 1 diabetes for 5 years or longer, had been on their current insulin regimen for at least 3 months before study entry, had a screening HbA1c concentration of 58 mmol/mol (7·5%) or lower, reported self-monitoring of blood glucose levels on a regular basis (equivalent to ≥3 times a day) for 2 months or more before study entry.	• FGM (n = 120) or SMBG (n = 121) • After two weeks of all participants wearing a blinded sensor, those with readings for at least 50% of the period were randomised.	• Time in hypoglycaemia • Duration of hypoglycaemic episodes	6 months	Emergency room visits or admissions and non-protocol related additional clinic time were listed as outcomes in the study methods but no results were reported by the authors for these outcomes. No adjustment was made for multiple testing of secondary endpoints. The study was not powered to detect any statistically significant differences in the incidence of adverse events associated with hypoglycaemia.
Boucher et al. (2020c)	New Zealand, Randomised controlled trial, multicentre (3 centres)	n= 64 (33 male, 31 female) Mean age 16.6 (SD 2.1) years Inclusion criteria: • People aged 13-20 with T1DM for ≥12 months.	• FGM (FreeStyle Libre) (n=33) or SMBG (n=31)	• Changes in HbA1c • Changes in number of glucose measurements	6 months	HbA1c data were available for 61 out of 64 participants at 3 months and all participants at 6 months.

Study reference	Setting and Design	Participants	Interventions	Outcomes	Follow-up period	Comments
		• HbA1c 9% or less (75mmol/mol) within 6 months of enrolment.		• Psychosocial outcomes		
Haak et al. (2017)	Randomised controlled trial (26 European diabetes centres).	• 224 participants in total. • Inclusion criteria: participants aged 18 years or older with type 2 diabetes treated with insulin for at least six months and on their current regimen (prandial only or prandial and basal intensive insulin therapy or CSII therapy) for 3 months or more, an HbA1c level 58–108 mmol/mol (7.5–12.0%), self-reported regular blood glucose testing (more than 10/week for at least 2 months prior to studyentry),	• FGM (n = 149) or SMBG (n = 75). Randomisation was done following 2 weeks of blinded sensor wear.	• Change in HbA1c levels • Time in hypoglycemia • Patient satisfaction	6 months	The following outcomes of interest were detailed in the methods but no results were reported by the authors: • Emergency room visits • Hospital admissions • Additional clinic time • Lancet use No adjustments were made for multiple testing by subgroup.
Haskova et al. (2020)	Randomised controlled trial. Czech Republic, number of centres not reported.	• 60 participants (mean age 38 ± 13 years; A1C 62 ± 12 mmol/mol [7.8 ± 1.1%]) • Inclusion criteria: adults with type 1 diabetes aged 18 years or older, more than 2 years' duration of diabetes; Gold score 4 or less; no history of severe hypoglycemia within last 6 months prior to the study initiation; and no previous experience with rtCGM and/or FGM.	• rtCGM (n=30) or FGM (n=30) • Participants were scheduled for a total of three clinic visits and a four-day exercise phase. • The FGM group wore an additional masked Enlite sensor (iPro2) for 6 days to check for bias between the different sensors used by the rtCGM and isCGM systems.	• Time in hypoglycaemia • Time in range • Quality of life	4 weeks (originally planned for 6 months)	A limitation of the study was use of WHOQOL-BREF to assess changes in quality of life, as it is not specific to diabetes and thus does not cover elements such as diabetes distress and hypoglycemia confidence. Study had a shorter-than-planned duration due to FGM sensors available only on prescription and not on the open market at the time.

Study reference	Setting and Design	Participants	Interventions	Outcomes	Follow-up period	Comments
Piona et al. (2018)	Slovenia, Randomised controlled trial, single centre	n=46 (21 males, 25 females) Mean age 11.1 (SD 2.6) years Inclusion criteria: • Children with T1DM for at least 6 months • Children with ≥ 3 months of current use of an insulin pump • HbA1c between 6.3% (45 mmol/mol) and 10% (86 mmol/mol)	• FGM (n=26) or SMBG (n=25) • In the SMBG group, participants wore an FGM sensor but results were masked to them and their caregivers. In the FGM group, participants performed SMBG measurements at least six times per day but results were masked to them and their caregivers.	• Time in glucose target range	2 weeks	
Reddy et al. (2018b)	UK, Randomised controlled trial, single centre	n=40 (26 male, 16 female) Mean age 49.5 Inclusion criteria: • Adults with T1DM for ≥3 years and an impaired awareness of hypoglycaemia. • All participants had been using intensified multiple-dose insulin injection regimen for over 6 months. • All participants had received T1DM education. • Additional inclusion criteria were a hypoglycaemic event in the past 12 months (≥Gold Score 4).	• rtCGM (Dexcom G5) (n=20) or FGM (n=20) • Before randomisation participants underwent a blinded 2-week run-in phase using the Dexcom G5 device to calculate baseline glucose metrics. • All participants also received standardised CGM or FGM education.	• Change in time spent in hypoglycaemia from baseline. • Time spent in hypoglycaemia • Time in euglycaemia • Time spent in hyperglycaemia • Change in HbA1c	8 weeks	The baseline estimate of glucose data was derived from blinded CGM in both groups, but the final glucose data was derived from either CGM or flash glucose monitoring. Study funded by Dexcom.
Tumminia et al. (2021)	Italy, Randomised controlled trial, multicentre (5	• n=40 • Pregnant women with poorly controlled (peri-conception HbA1c >6.5%,	• Participants were randomised 1:1 to either FGM or SMBG (at least 6 times daily).	• Change in HbA1c levels	Duration of pregnancy	Sensor-derived average glucose, the risk of hypo- and hyperglycemia and several glucose variability indices were

Study reference	Setting and Design	Participants	Interventions	Outcomes	Follow-up period	Comments
	centres)	48mmol/mol) pre-gestational T1DM or T2DM. • All patients were naïve to FGM at enrolment • Both groups were trained to the proper use of FGM	• To verify the accuracy of the sensor and allow ketone sensing, participants were advised to perform fingerprick tests every time they were in the hypoglycaemic (<63 mg/dl) or hyperglycaemic (>180 mg/dl) range for FGM, and at least 6 times daily for SMBG. • All participants also received structured diabetes education.			assessed at the subsequent study visits. At baseline, 10 patients (25%) were on insulin pump while the remaining 20 (75%) were on multiple daily injections. Reported time-in-range (or above/below range) was reported in this study but not clearly defined/reported and these outcomes were therefore excluded from this review.
Visser et al. (2021)	Belgium, Randomised controlled trial, multicentre (6 centres).	• n=254 (157 male, 97 female) • People with T1DM diagnosed at least 6 months before inclusion. • Additional inclusion criteria were treatment with multiple daily injections or insulin pump, HbA1c 10% or less (86 mmol/mol) and exclusive FGM (FreeStyle Libre) use for at least 6 months beforehand.	• Participants randomised 1:1 to rtCGM (Dexcom G6; 10-day wear) or FGM (FreeStyle Libre; 14-day wear).	• Time in target glucose range • Change in HbA1c levels • Time in hypoglycaemia • Time in hyperglycaemia	6 months	Comparisons of the secondary outcomes were done on an intent-to-treat basis. Authors performed statistical adjustments (ANCOVA) using constrained longitudinal data analysis to address missing data (e.g., patients with missing values after baseline).
Wada et al. (2020)	Randomised controlled trial Japan, multicentre	• Patients were eligible for inclusion if they (1) had type 2 diabetes, (2) had HbA1c =7.5% (59 mmol/mol) and <8.5% (69 mmol/mol) and (3) were aged =20 years and <70 years.	• FGM (n=49) or SMBG (n=51) • All participants wore a sensor for a baseline period of >7 days; the sensor glucose measurements obtained during this period were	• Change in HbA1c levels • Quality of life (DTSQ score) • Glucose variability measures (time in/out of target glucose range)	24 weeks	Outcomes were measured at 12 weeks (when the intervention period ended and patients assigned to FGM stopped using it) and at 24 weeks. The care participants received during the period from 12 to 24 weeks

Study reference	Setting and Design	Participants	Interventions	Outcomes	Follow-up period	Comments
			blinded to the participants and investigators. • Participants in each group were instructed on how to use each device and how to adjust their diet and lifestyle based on the blood glucose levels. • The devices were provided for 12 weeks. Participants in the SMBG group wore a blinded sensor again for the last two weeks of the 12-week period.			is not clearly described by the study authors
Yaron et al. (2019)	Israel, Randomised controlled trial, multicentre (2 centres)	n=101 Mean age 65.9 (SD 8.4) years Inclusion criteria: • People with T2DM on ≥ 2 daily insulin injections for at least 1 year • HbA1c of 7.5–10.0% (58–86 mmol/mol).	• Participants were randomised to FGM (n = 53) (FreeStyle Libre) or SMBG (n = 48) • All participants received diabetic counselling and diabetic management instructions.	• Change in HbA1c • Changes in frequency of hypoglycaemic events • Changes in QoL	10 weeks	Funded by Abbott.

Table7. Included non-randomised trials: design and characteristics

Study reference	Setting and Design	Participants	Intervention	Outcomes	Follow-up period	Comments
Bergenstal et al. (2021)	United States, Retrospective database study	• n=2,463 (1,304 male and 1,159 female). • Patients with T2DM treated with short- or rapid-acting insulin therapy, aged ≥18 years	• FGM (FreeStyle Libre) • Outcomes were measured for the 6 months before and after the intervention (no control group)	• Incidence of acute diabetes-related events (in inpatient or emergency outpatient care). • Incidence of all-cause hospitalisations.	6 months	Diabetes related events were identified as either inpatient events with the associated ICD-10 code as the primary diagnosis code, or as emergency outpatient events. Incidence of all-cause hospitalisations were calculated as number of observed events divided by the total observation time. 10-day FGM sensors were an earlier version of FreeStyle Libre, available between 2017 and 2019.
Deshmukh et al. (2020)	UK, nationwide audit.	• Data were available for 10,370 FSL users (97% with type 1 diabetes), age 38.0 (618.8) years, 51% female, diabetes duration 16.0 (649.9) years, and BMI of 25.2 (616.5) kg/m2 (mean [6SD]).	• Clinicians from 102 NHS hospitals in the UK submitted FSL user data, collected during routine clinical care, to a secure web-based tool held within the NHS N3 network. • Data were collected at baseline and follow-up during routine clinical care.	• Change in HbA1c levels • Time in hypoglycaemia • Time in hyperglycaemia • Paramedic callouts	7.5 months	
Fokkert et al. (2019)	Netherlands, Prospective Observational study	n=1365 (744 male, 621 female) Mean age 46.1 (SD 16.1) years Inclusion criteria: • People aged ≥18 years with DM using insulin.	• FGM (FreeStyle Libre)	• Change in HbA1c. • Change in hypoglycaemic events. • Health related quality of life.	12 months	Prospective intervention study without a control group. Data for disease burden was incomplete due to user dropout as completion was voluntary.

Study reference	Setting and Design	Participants	Intervention	Outcomes	Follow-up period	Comments
				• Disease burden. • Incidence of hospital admissions related to DM.		Approximately 50% of users completed the questionnaires at 12 months. Unvalidated questionnaires were used.
Roussel et al. (2021)	France, Longitudinal Retrospective cohort study	• A total of 74,011 patients with type 1 diabetes or type 2 diabetes who initiated the FreeStyle Libre system were identified from the French national claims database with use of ICD-10 codes, from hospitalisations with diabetes as a contributing diagnosis, or the prescription of insulin.	• Patients were subclassified based on self-monitoring of blood glucose (SMBG) strip acquisition prior to starting FreeStyle Libre. • Hospitalizations for DKA severe hypoglycemia, diabetes-related coma, and hyperglycemia were recorded for the 12 months before and after initiation.	• Hospitalisations for acute diabetes complications • Time in hypoglycaemia • Time in hyperglycaemia	12 months	
Tsur et al. (2021)	Israel, Retrospective cohort study	n=3490 (1908 male, 1582 female) Mean age 46.6 (SD 17.1) years Inclusion criteria: • People with T1DM aged ≥18 years.	• FGM (FreeStyle Libre)	• Change in HbA1c. • Change in rate of hospital admissions. • Change in rate of primary care visits.	Median 14 months	2682 participants were included in change in HbA1c analysis.

Appendix 5. Supplementary outcome data

Supplementary data on changes in HbA1c over time

The pooled estimates of the mean changes in HbA1c and associated statistics can be found in Table 1. The largest mean difference in the adult population can be observed in the 3 to 6 months FGM usage group for T1DM (-0.64 95% CI -0.76 to -0.52, I^2=97.4%, p=0.000) while the lowest mean change appears to be present in the >9 months FGM usage group (-0.19 95% CI -0.28 to -0.11, I^2=94.6%, p=0.000). In the absence of available data, a pooled estimate for the mean change in HbA1c in adults with T2DM could only be derived for the ≤3 months timepoint (-0.54 95% CI -0.67 to -0.41, I2=86.1%, p=0.007). Regardless of the FGM usage period, all the computed meta-analyses indicate that the interventions favours the use of FGM for a reduction in HbA1c. A high degree of heterogeneity at statistically significant levels was found in four out of the five meta-analyses. No heterogeneity was found in the meta-analysis for the 6-9 months FGM usage group.

In children, the largest mean difference in HbA1c was found in the group with ≤3 months of FGM usage (-0.54 95% CI -0.67 to -0.41, I2=94.1%, p=0.000). A marginal reduction in the mean change in HbA1c was observed in the 3 to 6 months of FGM usage as computed with data from two studies, while an increase in HbA1c was observed with 6 to 9 months of FGM usage in children as reported by one study. Given the low number of studies, a pooled estimate was derived for the 3 to 9 months of FGM usage. No reduction was observed in the mean change of HbA1c for this timepoint (0.00 95% CI -0.14 to 0.14, I2=79.4%, p=0.008). Similarly, only a marginal reduction was observed in the >9 months of FGM group (-0.08 95% CI -0.20 to 0.05, I2=88.2%, p=0.000). Statistically significant levels of heterogeneity were found in all the computed meta-analyses.

Table 1. Mean change in HbA1c from meta-analyses of longitudinal data: outcomes for adults, children and all age groups combined.

Population	Usage	Disease Type	Number of studies (n)	Mean change % (95% CI)	Statistics
Adults	≤3 months	T1DM	11 studies (n=884)	-0.48 (-0.56 to -0.41)	I^2=93.8%, p=0.000
	≤3 months	T2DM	2 studies (n=202)	-0.54 (-0.67 to -0.41)	I^2=86.1%, p=0.007
	3 to 6 months	T1DM	9 studies (n=656)	-0.64 (-0.76 to -0.52)	I^2=97.4%, p=0.000
	6 to 9 months	T1DM	3 studies (n=744)	-0.41 (-0.59 to -0.22)	I^2=0.0%, p=0.786
	>9 months (max follow-up 24 months)	T1DM	12 studies (n=3607)	-0.19 (-0.28 to -0.11)	I^2=94.6%, p=0.000
Children	≤3 months	T1DM	9 studies (n=447)	-0.54 (-0.67 to -0.41)	I^2=94.1%, p=0.000
	3 to 6 months	T1DM	2 studies (n=253)	-0.06 (-0.24 to 0.12)	I^2=80.6%, p=0.023
	6 to 9 months	T1DM	1 study (n=78)	0.20 (0.00 to 0.40)	NA
	3 to 9 months	T1DM	3 studies (n=331)	0.00 (-0.14 to 0.14)	I^2=79.4%, p=0.008
	>9 months (max follow-up 12 months)	T1DM	3 studies (n=389)	-0.08 (-0.20 to 0.05)	I^2=88.2%, p=0.000
Overall effect (adults + children)	≤3 months	T1DM	20 studies (n=1331)	-0.50 (-0.57 to -0.43)	I^2=94.0%, p=0.000
	3 to 6 months	T1DM	11 studies (n=909)	-0.48 (-0.58 to -0.38)	I^2=95.8%, p=0.000

	6 to 9 months	T1DM	4 studies (n=822)	-0.35 (-0.52 to -0.18)	I^2=90.5%, p=0.000
	>9 months (max follow-up 24 months)	T1DM	15 studies (n=3996)	-0.18 (-0.26 to -0.10)	I^2=94.2%, p=0.000
CI: Confidence interval, NA: Not applicable, T1/T2DM: Type 1/Type 2 diabetes mellitus					

Glycaemic outcomes

Glycaemic variability

For this outcome, five articles that report data from four RCTs were identified. Accordingly, three RCTs investigated the effect of the intervention with FGM in comparison to SMBG in adult populations (one RCT and one subgroup analysis in T1DM (Bolinder et al. 2016, and subgroup analysis by Oskarsson et al. 2018) and two RCTs in T2DM (Haak et al. 2017, Wada et al. 2020). One other RCT compared the effectiveness of FGM in comparison to rtCGM in adults with T1DM.

Bolinder et al. (2016) and the subgroup analysis by Oskarsson et al. (2018) in a subpopulation treated with multiple daily insulin injections, report measurements on mean amplitude of glucose excursion, coefficient of variation in glucose, standard deviation of glucose (mmol/L) and the continuous overlapping net glycaemic action at two and six hours. The study by Bolinder et al. (2016) reports a statistically significant difference favouring the intervention with FGM on all the aforementioned scales of variability. In the subgroup analysis by Oskarsson et al. (2018), the variation was deemed statistically significant only for the coefficient of variation in glucose, standard deviation of glucose and in the continuous overlapping net glycaemic action at two hours.

For T2DM, the same scales of variability were assessed by Haak et al. (2017). A statistically significant variation as a result of the intervention was found for the coefficient of variation in glucose and continuous overall net glycaemic action at two and four hours. Nevertheless, the authors of Ontario Health (2019) indicate that inconsistencies in the results are present across the scales of glucose variability and in the absence of a gold standard it was impossible to evaluate if in this scenario FGM is more effective than SMBG. The differences in adjusted means for the scales of glucose variability can be found in Table 2 A. The RCT by Wada et al. (2020) reports outcomes related to glycaemic variability in adults aged ≥20 years old with T2DM. With the exception of glucose covariance, the measurements performed on the other six scales show a statistically significant variation. Therefore, the mean glucose levels, standard deviation of glucose, mean amplitude of glycaemic excursions, the continuous overlapping net glycaemic action at 2 hours and the mean of daily difference significantly improved after the intervention with FGM when compared to SMBG (Table 2 A).

The RCT by Avari et al. (2020) report glycaemic variability outcomes for measurements performed on different scales in adults with T1DM for greater than three years using an intensified multiple daily insulin injections regimen. The study compares FGM with rtCGM when used over a period of eight weeks. The glycaemic variability scales employed for the measurements were the following: standard deviation, lability index, mean absolute glucose change per unit, mean of daily differences, mean amplitude of glycaemic excursions, coefficient of variation, continuous overall net glycaemic action at one and two hours and the glycaemic variability percentage. The analysis of between-group differences from baseline to eight weeks demonstrated a statistically significant reduction in five of the glycaemic variability scales. A greater reduction was observed in the rtCGM group for the standard deviation, mean amplitude of glycaemic excursions and coefficient of variation when compared to FGM. However, the reduction of mean absolute glucose change per unit and glycaemic variability percentage were greater in the FGM group (Table 2 B).

Table 2. Glycaemic variability outcomes for flash glucose monitoring compared to (A) SMBG; (B) rtCGM

(A)

Study	Outcome	Difference in adjusted means between FGM and SMBG (95% CI)	p value
Bolinder et al. (2016) T1DM Adults (n=241) RCT (FGM vs SMBG) Follow up: 6 months	Mean amplitude of glucose excursion	-8.0 (-13.88 to -2.12)	0.0004
	Coefficient of variation in glucose (%)	-4.4 (-5.62 to -3.18)	<0.0001
	Standard deviation of glucose, mg/dL	-5.0 (-7.27 to -2.73)	<0.0001
	Continuous overlapping net glycaemic action, 2 hours, mg/dL	-9 (-11.55 to -6.45)	<0.0001
	Continuous overlapping net glycemic action, 6 hours, mg/dL	-12 (-18.66 to -5.34)	0.0004
Haak et al. (2017) T2DM Adults (n=224) RCT (FGM vs SMBG) Follow up: 6 months	Mean amplitude of glucose excursion	-4.0 (-10.47 to -2.47)	0.1909
	Coefficient of variation in glucose (%)	-2.26 (-3.65 to -0.868)	0.0017
	Standard deviation of glucose, mg/dL	-1.67 (-4.51 to -1.17)	0.2538
	Continuous overall net glycaemic action, 2 hours, mg/dL	-3.0 (-5.55 to -0.45)	0.0385
	Continuous overall net glycaemic action, 4 hours, mg/dL	-5.0 (-9.31 to -0.69)	0.0133
	Continuous overall net glycaemic action, 6 hours, mg/dL	-8.0 (-13.88 to -2.12)	0.0046
Wada et al. (2020) T2DM Adults ≥20 years and <70 years (n=100) RCT (FGM vs SMBG) Follow up: 24 weeks	Mean glucose, mg/dL	-15 (-22 to -8)	<0.001
	Standard deviation of glucose, mg/dL	-5 (-8 to -2)	<0.001
	Coefficient of variation in glucose (%)	0.2 (-1.2 to 1.7)	0.762
	Mean amplitude of glycaemic excursion, mg/dL	-17 (-24 to -9)	<0.001
	Continuous overall net glycaemic action, 2 hours, mg/dL	-12 (-18 to -6)	<0.001
	Mean of daily differences, mg/dL	-5 (-8 to -1)	0.006

(B)

Study	Outcome	Baseline Data	Median change from baseline to endpoint (IQR) rtCGM (n=19)	Median change from baseline to endpoint (IQR) FGM (n=20)	p value
Avari et al. (2020) T1DM Adults (n=40) RCT (FGM vs rtCGM) Follow up: 8 weeks	Standard deviation	4.0 (3.3-4.8)	-0.8 (-1.2 to -0.4)	-0.4 (-0.7 to 0.0)	0.028
	Lability index	6.4 (4.8-7.9)	-0.1 (-2.4 to 0.6)	0.3 (-0.3 to 0.8)	0.169
	Mean absolute glucose change per unit	2.6 (2.3-2.9)	0.0 (-0.2 to 0.2)	-0.2 (-0.4 to 0.0)	0.025
	Mean of daily differences	4.2 (3.4-4.7)	-0.7 (-1.1 to -0.2)	-0.5 (-0.8 to 0.2)	0.144
	Mean amplitude of glycaemic excursions	7.8 (6.5-8.9)	-1.5 (-2.9 to -0.5)	-0.4 (-1.6 to 0.1)	0.050
	Coefficient of variation	0.5 (0.4-0.5)	-0.1 (-0.1 to 0.0)	0.0 (-0.1 to 0.0)	0.008
	Continuous overall net glycaemic action, 1 hour	3.1 (2.7-3.5)	-0.1 (-0.5 to 0.2)	0.1 (-0.1 to 0.2)	0.177
	Continuous overall net glycaemic action, 2 hours	4.8 (3.9-5.4)	-0.3 (-1.1 to 0.2)	0.1 (-0.3 to 0.4)	0.097
	Glycaemic variability percentage	38.0 (32.1-43.9)	-0.7 (-5.2 to 4.5)	-5.3 (-8.5 to -1.0)	0.031

CI: Confidence interval, CV: Coefficient of variation, FGM: Flash glucose monitoring, IQR: Interquartile range rtCGM: real-time continuous glucose monitor, L: litre MAGE: Mean amplitude of glycaemic excursion, MODD: Mean of daily differences, MDI: Multiple daily injections, NA: Not applicable, T1/T2DM: Type 1/Type 2 diabetes mellitus, SD: Standard deviation, SMBG: Self-monitoring of blood glucose

Quality of glycaemic control

Outcomes related to the quality of glycaemic control were only reported in the RCT by Avari et al. (2020), which compares the effect of FGM against rtCGM in adults with T1DM. Measurements were performed on the following scales: M-value, glycaemic risk assessment diabetes equation (GRADE), GRADE% hypoglycaemia, GRADE% euglycaemia, GRADE% hyperglycaemia, J-index, personal glycaemic status and index of glycaemic control. In the baseline to eight weeks phase, a statistically significant difference was observed in six of the aforementioned scales, with the exception of J-index and personal glycaemic status. A predominant reduction in those scales was observed in the rtCGM group when compared to FGM. However, the FGM group showed a greater reduction in GRADE% hyperglycaemia when compared to rtCGM (Table3).

Table 3. Quality of glycaemic control outcome for FGM compared to rtCGM

Study	Measure	Baseline Data	Median change from baseline to endpoint (IQR) rtCGM (n=19)	Median change from baseline to endpoint (IQR) FGM (n=20)	p value
Avari et al. (2020) T1DM Adults (n=40) RCT (FGM vs rtCGM) Follow up: 8 weeks	M-value	20.0 (13.9-25.3)	-8.6 (-11.8 to -3.3)	-1.8 (-4.1 to 0.9)	0.008
	GRADE	10.5 (8.1-13.7)	-2.4 (-4.2 to -1.8)	-0.8 (-2.2 to 0.5)	0.033
	GRADE%hypoglycaemia	13.7 (10.2-23.2)	-3.1 (-11.5 to 1.1)	8.6 (-5.2 to 16.1)	0.006
	GRADE%euglycaemia	6.9 (4.3-10.5)	3.4 (1.0 to 6.7)	1.5 (-0.5 to 3.1)	0.046
	GRADE%hyperglycaemia	75.2 (64.7-84.3)	-1.0 (-5.3 to 8.3)	-8.0 (-18.5 to 5.2)	0.035
	J-index	50.6 (39.9-68.0)	-13.2 (-18.5 to 1.8)	-9.7 (-18.2 to 0.2)	0.613
	Personal glycaemic status	21.8 (17.5-24.8)	-2.6 (-5.3 to -0.6)	-1.3 (-3.3 to 0.6)	0.187
	Index of glycaemic control	5.0 (3.9-6.8)	-2.0 (-3.0 to -0.7)	0.2 (-1.1 to 2.0)	<0.001

FGM: Flash glucose monitoring, GRADE: Glycaemic Risk Assessment Diabetes Equation, IQR: Interquartile range rtCGM: real-time continuous glucose monitor, T1/T2DM: Type 1/Type 2 diabetes mellitus,

Glycaemic risk

For this outcome, four RCTs that report data were identified. Three RCTs investigated the effect of FGM in comparison to SMBG in adult populations (one RCT in T1DM (Bolinder et al. 2016) and two RCTs in T2DM (Haak et al. 2017, Wada et al. 2020). An additional RCT compared the effects of the intervention with FGM in comparison to rtCGM in adults with T1DM (Avari et al. 2020).

The blood glucose risk index and low blood glucose risk index for T1DM was reported by two studies (reporting the same trial). A statistically significant variation in the both measurements were reported by Bolinder et al. (2016) and the subgroup analysis by Oskarsson et al. (2018) as a result of the intervention with FGM. For T2DM, Haak et al. (2017) reports a statistically significant variation only for the low blood glucose risk index scale. Wada et al. (2020) also shows a statistically significant improvement in the blood glucose risk index as a result of the intervention with FGM in T2DM (-1.7, 95% CI -2.8 to -0.5, p=0.005).

Glycaemic risk measured on four different scales (average daily risk range, low blood glucose index, high blood glucose index and risk index) were reported in the RCT by Avari et al. (2020) for the intervention with FGM in comparison to rtCGM at eight weeks. A statistically significant reduction was observed in the rtCGM group when compared to FGM for the average daily risk range, low blood glucose index and the overall risk index (Table 4).

Table 4. Glycaemic risk outcomes for FGM compared to SMBG and rtCGM

Study	Outcome	Difference in adjusted means between FGM and SMBG (95% CI)	p value
Oskarsson et al. (2018) (Subgroup analysis of Bolinder et al. 2016) T1DM Adults (n=163) RCT (FGM vs SMBG) Follow up: 6 months	Blood glucose risk index	-0.8 (-1.4 to -0.1)	0.017
	Low blood glucose risk index	-1.07 (-1.42 to -0.72)	<0.0001
Bolinder et al. (2016) T1DM Adults (n=241) RCT (FGM vs SMBG) Follow up: 6 months	Blood glucose risk index	-0.90 (-1.41 to -0.39)	0.0004
	Low blood glucose risk index	-0.8 (-1.11 to -0.49)	<0.0001
Haak et al. (2017) T2DM Adults (n=224) RCT (FGM vs SMBG) Follow up: 6 months	Blood glucose risk index	0.0 (-1.37 to 1.37)	0.9431
	Low blood glucose risk index	-0.30 (-0.52 to -0.08)	0.0029
Wada et al. (2020) T2DM Adults ≥20 years and <70 years (n=100) RCT (FGM vs SMBG) Follow up: 24 weeks	Blood glucose risk index	-1.7 (-2.8 to -0.5)	0.005

Study	Measure	Baseline Data	Median change from baseline to endpoint (IQR) rtCGM (n=19)	Median change from baseline to endpoint (IQR) FGM (n=20)	p value
Avari et al. (2020) T1DM Adults (n=40) RCT (FGM vs rtCGM) Follow up: 8 weeks	Average daily risk range	55.1 (46.8-65.1)	-12.8 (-17.1 to -6.1)	-0.3 (-4.9 to 4.7)	<0.001
	Low blood glucose index	2.5 (1.9-3.5)	-0.8 (-1.7 to -0.1)	1.2 (-0.6 to 1.9)	0.002
	High blood glucose index	7.5 (5.1-11.4)	-3.0 (-4.4 to 0.4)	-2.1 (-3.8 to 0.1)	0.757
	Risk index	11.31 (8.3-15.0)	-3.84 (-5.3 to -2.1)	-1.11 (-2.3 to 0.1)	0.026

BGRI: Blood glucose risk index, CI: Confidence interval, FGM: Flash glucose monitoring, IQR: Interquartile range rtCGM: real-time continuous glucose monitor, NA: Not applicable, T1/T2DM: Type 1/Type 2 diabetes mellitus, SD: Standard deviation, SMBG: Self-monitoring of blood glucose

Table 5. Device-related adverse events and complications associated with the use of FGM

Study	Outcome	Description
Bolinder et al. (2016) T1DM Adults (n=241) RCT (FGM vs SMBG) Follow up: 6 months	Number of device-related adverse events: 13 in FGM group, 0 in SMGB group.	Allergy, itching, rash, insertion-site symptoms and oedema. None contributed to severe hypoglycaemia or hospitalisation.
Haak et al. (2017) T2DM Adults (n=224) RCT (FGM vs SMBG) Follow up: 6 months	Device-related adverse events – n=6	Related to flash glucose monitoring and primarily treated with topical preparations.
Boucher et al. (2020c) T1DM 13-20 years (n=64) RCT (FGM vs SMBG) Follow up: 6 months	Adverse events – n=6 (18%) in the intervention group and n=5 (16%) in the control group	Experienced at least one episode of diabetic ketoacidosis with no significant difference between the groups.

Study	Outcome	Description	p value
Marsters et al. (2020) (Different report describing AE of the RCT by Boucher et al. (2020c)) T1DM 13-20 years (n=64) RCT (FGM vs SMBG) Follow up: 6 months	Cutaneous adverse events	For the FGM group, 40/362 (11%) of safety questionnaires reported at least 1 FGM-associated cutaneous adverse events compared to the control group where 40/366 (11%) reported at least 1 SMBG associated adverse event	0.96
	Cutaneous adverse events rate	FGM group has a cutaneous adverse event rate of 1 event for every 18.1 weeks of use while the control group had a rate of 1 event for every 18.3 weeks of use	-
	Cutaneous adverse events	FGM-associated cutaneous adverse events involved 19/33 (58%) of participants whereas SMBG-associated cutaneous adverse events involved 7/31 (23%) of participants	0.004
	Cutaneous adverse events (FGM)	In the FGM group 11 (33%) of participants reported 1 cutaneous adverse event; 5 (15%) reported 2 to 4 events; 3 (9%) reported 5 or more events. One participants reported 8 separate events and ceased using FGM	-
	Cutaneous adverse events (SMBG)	In the control group, 1 (3%) of participants reported 1 cutaneous adverse event; 3 (10%) reported 2 to 4 events; 3 (10%) reported 5 or more events	-

	Cutaneous adverse events symptoms (average control 2.3 symptoms compared to average FGM 2.1 symptoms, p=0.69)				
	Symptom type	**FGM – n (%)**		**Control (SMBG) – n (%)**	
		Adverse event with reported symptom (n=40)	**Participants that reported symptom (n=33)**	**Adverse event with reported symptom (n=40)**	**Participants that reported symptom (n=31)**
	Abrasion	1 (3)	1 (3)	0 (0)	0 (0)
	Bleeding	5 (13)	4 (12)	1 (3)	1 (3)
	Bruising	8 (20)	4 (12)	3 (8)	2 (6)
	Dent	0 (0)	0 (0)	11 (28)	2 (6)
	Erythema	20 (50)	11 (33)	4 (10)	2 (6)
	Infection	2 (5)	2 (6)	0 (0)	0 (0)
	Lump	3 (8)	3 (9)	8 (20)	1 (3)
	Pain	10 (25)	7 (21)	10 (25)	1 (3)
	Pruritus	17 (43)	8 (24)	11 (28)	3 (10)
	Rash	7 (18)	6 (18)	3 (8)	1 (3)
	Scarring	4 (10)	3 (9)	18 (45)	3 (10)
	Skin hardening	1 (3)	1 (3)	24 (60)	5 (16)
	Swelling	5 (13)	5 (15)	0 (0)	0 (0)
	Severity of cutaneous adverse events (no significant difference between groups, p=1.00)				
	Symptom severity	**FGM – n (%)**		**Control (SMBG)– n (%)**	
		Adverse event with reported symptom (n=40)	**Participants that reported symptom (n=33)**	**Adverse event with reported symptom (n=40)**	**Participants that reported symptom (n=31)**
	Mild	32 (80.0)	20 (60.6)	33 (82.5)	8 (25.8)
	Moderate	7 (17.5)	4 (12.1)	7 (17.5)	7 (22.6)
	Severe	1 (2.5)	1 (3.0)	0 (0)	0 (0)

AE: adverse events, FGM: Flash glucose monitoring, rtCGM: real-time continuous glucose monitor, T1/T2DM: Type 1/Type 2 diabetes mellitus, SMBG: Self-monitoring of blood glucose

Patient satisfaction

For this outcome, three studies reporting data from two RCTs were found. One RCT compares the effect of interventions with FGM in adults with T2DM (Haak et al. 2017) while the other two are different reports of the same study conducted in participants with T1DM aged 13-20 years. Both RCTs have SMBG as a comparator.

Improved patient satisfaction as reflected in the diabetes treatment questionnaire was reported by one study (Haak et al. 2017) (Table 6) for T2DM. Boucher et al. (2020c) reports outcomes related to the acceptance of FGM. Accordingly, all (n=33) participants in the FGM group would recommend the device to a friend and 32 planned to continue using the system. Furthermore, 97% participants reported that FGM was less painful and 100% of the participants reported that it was quicker and easier in comparison to SMBG (Table 6). Lastly, the report by Marsters et al. (2020) describing only the adverse events from Boucher et al. (2020c), reports outcomes related to premature sensor loss. Their study showed that 82% of the participants experienced at least one premature sensor loss during the six months of the study. From the completed safety questionnaires in the FGM group, 87 (24%) detailed reports of premature sensor loss available for analysis, with some reporting multiple causes for premature loss. The most common reasons for premature sensor loss (n = 87) were loss of adhesion 64 (74%), sensor malfunction or damage ten (12%) and accidental removal four (5%) and a further seven (8%) were unspecified. Moreover, the authors highlighted that cutaneous adverse events accounted for a minority of three (3%) premature sensor losses (Table 6).

Table 6. Patient satisfaction outcomes associated with the use of FGM

Study	Outcome
Boucher et al. (2020c) T1DM 13-20 years (n=64) RCT (FGM vs SMBG) Follow up: 6 months	All 33 participants in the FGM group would recommend the device to a friend and 32 planned to continue using the system
	97% participants reported FGM was less painful and 100% of the participants reported that FGM was quicker and easier in comparison to SMBG
Haak et al. (2017) T2DM Adults (n=224) RCT (FGM vs SMBG) Follow up: 6 months	Improved satisfaction as reflected in diabetes treatment questionnaire scores
Marsters et al. (2020) T1DM 13-20 years (n=64) RCT (FGM vs SMBG) Follow up: 6 months	82% of the participants experienced at least 1 premature sensor loss during the 6 month study
	Of the total completed safety questionnaires from the FGM group, 87 (24%) detailed reports of premature sensor loss available for analysis, with some reporting multiple causes for premature loss
	Cutaneous adverse events accounted for a minority 3 (3%) of premature sensor loss
	The most common reasons for premature sensor loss (n = 87) were loss of adhesion 64 (74%), sensor malfunction or damage 10 (12%) and accidental removal 4 (5%) and a further 7 (8%) were unspecified.
FGM: Flash glucose monitoring, T1/T2DM: Type 1/Type 2 diabetes mellitus	

Satisfaction with treatment and diabetes distress

A total of three RCTs were identified that report data for this outcome. All studies evaluated the effects of the intervention with FGM in comparison to SMBG. Two RCTs were conducted on adults with T2DM (Haak et al. 2017, Wada et al. 2020) while the other in a cohort of patients aged 13-20 years with T1DM.

In participant cohort aged 13-20 years old but with T1DM, Boucher et al. (2020c) also reports a statistically significant difference in the treatment satisfaction mean item score in the DTSQ (0.47, 95% CI 0.00 to 0.93, p=0.048).

For T2DM, Haak et al. (2017) reports improved satisfaction as reflected in the diabetes quality of life questionnaire. Additionally, the RCT by Wada et al. (2020) reported results on eight different question in the diabetes treatment satisfaction questionnaire (DTSQ) among participants with T2DM, including current treatment, frequency of hyperglycaemia/hypoglycaemia, convenience, flexibility, understanding, recommend, continue as well as the total score. A statistically significant difference favouring the intervention with FGM was noticed for the following categories: total score (3.4, 95% CI 1.9 to 5.0, p<0.001), frequency of hyperglycaemia (0.4, 95% CI 0.00 to 0.9, p=0.047), convenience (0.9, 95% CI 0.6 to 1.3, p<0.001), flexibility (0.6, 95% CI 0.3 to 1.0, p<0.001), recommend (0.7, 95% CI 0.4 to 1.1, p<0.001) and continue (0.3, 95% CI 0.0 to 0.6, p=0.040).

Table 7. Satisfaction with treatment and diabetes distress for FGM compared to SMBG

Study	Outcome	Description	
Haak et al. (2017) T2DM Adults (n=224) RCT (FGM vs SMBG) Follow up: 6 months	Satisfaction with treatment	Improved satisfaction as reflected in the diabetes quality-of-life questionnaire	
Study	**DTSQ Score**	**Difference in adjusted means in FGM vs SMBE (96% CI)**	**p-value**
Wada et al. (2020) T2DM Adults ≥20 years and <70 years (n=100) RCT (FGM vs SMBG) Follow up: 24 weeks	Total score	3.4 (1.9 to 5.0)	<0.001
	Q1 current treatment	0.3 (-0.0 to 0.5)	0.070
	Q2 frequency of hyperglycaemia	0.4 (0.0 to 0.9)	0.047
	Q3 frequency of hypoglycaemia	-0.0 (-0.4 to 0.5)	0.938
	Q4 convenience	0.9 (0.6 to 1.3)	<0.001
	Q5 flexibility	0.6 (0.3 to 1.0)	<0.001
	Q6 understanding	0.2 (-0.1 to 0.5)	0.120
	Q7 recommend	0.7 (0.4 to 1.1)	<0.001
	Q8 continue	0.3 (0.0 to 0.6)	0.040
Boucher et al. (2020c) T1DM 13-20 years (n=64) RCT (FGM vs SMBG) Follow up: 6 months	Treatment satisfaction mean item score	Difference in change at 6 months: 0.47 (0.00 to 0.93)	0.048

CI: Confidence interval, DTSQ: Diabetes treatment satisfaction questionnaire, FGM: Flash glucose monitoring T1/T2DM: Type 1/Type 2 diabetes mellitus, SD: Standard deviation, SMBG: Self-monitoring of blood glucose

Appendix 6. Data tables for meta-analyses

Table 1. : Data table for the computed meta-analyses

Study reference	Population	Number	Disease type	Baseline HbA1c	Final outcome timepoint	Mean difference (95% CI)
Abdalaziz et al. (2018)	Adults	40	T1DM	8.56	12 months	-0.64 (-0.972 to -0.308)
Abdalaziz et al. (2018)	Adults	40	T1DM	8.56	6 months	-0.55 (-0.898 to -0.202)
Al Hayek et al. (2017)	Children	47	T1DM	8.5	3 months	-0.66 (-1.14 to -0.18)
Bacon et al. (2017)	Adults	58	T1DM	8.1	3 months	-0.55 (-1.01 to -0.09)
Bolinder et al. (2016)	Adults	119	T1DM	6.79	3 months	0.06 (-0.03 to 0.15)
Bolinder et al. (2016)	Adults	119	T1DM	6.79	6 months	0.16 (0.066 to 0.254)
Campbell et al. (2018)	Children	75	T1DM	7.9	2 months	-0.4 (-0.54 to 0.26)
Charleer et al. (2020)	Adults	1711	T1DM	7.8	12 months	0.091 (-0.076 to 0.258)
Costigan et al. (2019)	Children	108	T1DM	8	6 months	-0.3 (-0.568 to -0.032)
De Oliveira et al. (2019)	Adults	35	T1DM	8.6	3 months	-0.7 (-1.081 to -0.319)
Dorflinger et al. (2018)	Adults	25	T1DM	8.1	12 months	-1.01 (-1.62 to -0.4)
Dorflinger et al. (2018)	Adults	209	T1DM	8.1	3 months	-0.46 (-0.65 to -0.26)
Dorflinger et al. (2018)	Adults	146	T1DM	8.1	6 months	-0.64 (-1.02 to -0.26)
Dorflinger et al. (2018)	Adults	75	T1DM	8.1	9 months	-0.37 (-0.584 to -0.156)
Dover et al. (2017)	Adults	25	T1DM	8	4 months	-0.48 (-0.74 to -0.22)
Ferreira et al. (2018)	Adults	15	T1DM	8.4	3 months	-0.38 (-1.115 to 0.355)
Fokkert et al. (2019)	Adults	543	T1DM	7.8	12 months	-0.302 (-0.448 to -0.156)
Gibb et al. (2018)	Adults	204	T1DM	NR	10 months	-0.27 (-0.434 to -0.106)
Haak et al. (2017)	Adults	149	T2DM	8.65	3 months	-0.44 (-0.6 to -0.28)
Haak et al. (2017)	Adults	149	T2DM	8.65	6 months	-0.27 (-0.436 to -0.104)
Halbron et al. (2019)	Adults	17	T1DM	10.8	6 months	-2 (-2.976 to -1.024)
Heald et al. (2019)	Adults	92	T1DM	9.7	6 months	-1.473 (-1.936 to -1.01)
Helm et al. (2016)	Children	31	T1DM	7.42	2 months	-0.22 (-0.45 to 0.01)
Hey et al. (2018)	Adults	29	T1DM	9.9	1 month	-0.34 (-0.782 to 0.102)
Holcombe et al. (2017)	Adults	13	T1DM	9.01	2 months	-0.74 (-1.67 to 0.19)
Karlsson (2016)	Adults	164	T1DM	8.45	12 months	-0.49 (-0.738 to -0.242)
Kramer et al. (2019)	Adults	40	T1DM	7.4	12 months	-0.046 (-0.267 to 0.176)
Landau et al. (2018)	Children	59	T1DM	8.2	12 months	-0.8 (-1.388 to -0.212)
Landau et al. (2018)	Children	59	T1DM	8.86	3 months	-0.81 (-0.87 to -0.75)
Leiva-Gea et al. (2019)	Children	145	T1DM	NR	6 months	0.116 (-0.124 to 0.355)
Londahl et al. (2017)	Adults	226	T1DM	8.72	12 months	-0.74 (-0.866 to -0.614)
Londahl et al. (2017)	Adults	226	T1DM	8.72	3 months	-0.65 (-0.75 to -0.55)
Londahl et al. (2018)	Adults	269	T1DM	8.7	24 months	-0.823 (-0.952 to -0.694)

Study reference	Population	Number	Disease type	Baseline HbA1c	Final outcome timepoint	Mean difference (95% CI)
Messaaoui et al. (2018)	Children	278	T1DM	7.6	12 months	0.1 (-0.008 to 0.208)
Mitchell & McDougall (2018)	Adults	13	T1DM	10.28	3 months	-0.88 (-1.22 to -0.54)
Moreno-Fernandez et al. (2018)	Adults	18	T1DM	7.4	6 months	-0.4 (-0.64 to -0.16)
Nana et al. (2019)	Adults	90	T1DM	8.7	6 months	-0.667 (-0.879 to -0.455)
Paris et al. (2018)	Adults	102	T1DM	8.51	12 months	-0.46 (-0.706 to -0.214)
Paris et al. (2018)	Adults	107	T1DM	8.51	3 months	-0.67 (-0.89 to -0.45)
Paris et al. (2018)	Adults	109	T1DM	8.51	6 months	-0.68 (-0.914 to -0.446)
Paris et al. (2018)	Adults	104	T1DM	8.51	9 months	-0.48 (-0.716 to -0.244)
Pintus & Ng (2017)	Children	52	T1DM	8.23	3 months	-0.73 (-1.27 to -0.19)
Reddy et al. (2018b)	Adults	20	T1DM	7.2	2 months	-0.35 (-0.65 to -0.05)
Rodia et al. (2019)	Adults	35	T1DM	8.5	18 months	-0.274 (-0.512 to -0.037)
Rouhard et al. (2020)	Adults	248	T1DM	8.1	18 months	-0.2 (-0.38 to -0.02)
Tirelli et al. (2017)	Children	13	T1DM	9.56	3 months	-1.37 (-2.13 to -0.62)
Tyndall et al. (2019)	Adults	565	T1DM	7.7	8.2 months	-0.4 (-0.637 to -0.163)
Walton-Betancourth & Amin (2017)	Children	52	T1DM	7.9	12 months	-0.19 (-0.41 to 0.03)
Walton-Betancourth & Amin (2017)	Children	47	T1DM	7.93	3 months	-0.09 (-0.25 to 0.07)
Wijnands et al. (2017)	Children	72	T1DM	7.7	3 months	-0.2 (-0.4 to 0)
Wijnands et al. (2017)	Children	78	T1DM	7.7	8 months	0.2 (0.004 to 0.396)
Xatzipsalti et al. (2017)	Children	51	T1DM	7.06	3 months	-1 (-1.54 to -0.46)
Yaron et al. (2018)	Adults	53	T2DM	8.68	3 months	-0.82 (-1.05 to -0.59)

Table 2. : Observations excluded from the meta-analyses

Excluded observations	Population	Number	Disease type	Baseline HbA1c	Final outcome timepoint	Mean difference (95% CI)
Abdalaziz et al. (2018)	Adults	40	T1DM	8.5	12 months	-0.641 (-0.965 to -0.316)
Al Hayek et al. (2017)	Children	47	T1DM	8.5	3 months	-0.66 (-1.13 to -0.19)
Bacon et al. (2017)	Adults	58	T1DM	8.1	3 months	-0.549 (-0.999 to -0.099)
Bolinder et al. (2016)	Adults	119	T1DM	6.8	6 months	0.12 (0.032 to 0.208)
Campbell et al. (2018)	Children	76	T1DM	7.9	2 months	-0.4 (-0.535 to -0.265)
Dorflinger et al. (2018)	Adults	209	T1DM	8.1	3 months	-0.457 (-0.682 to -0.232)
Gibb et al. (2018)	Adults	204	T1DM	NR	10 months	-0.274 (-0.436 to -0.113)
Holcombe et al. (2017)	Adults	15	T1DM	9	2 months	-0.961 (-2.019 to 0.097)
Ish-Shalom et al. (2016)	Adults	31	Mixed	8.9	1 month	-0.8 (-1.156 to -0.444)
Ish-Shalom et al. (2016)	Adults	31	Mixed	8.9	2 months	-1.33 (-1.91 to -0.75)
Ish-Shalom et al. (2016)	Adults	31	Mixed	8.9	3 months	-1.2 (-1.75 to -0.65)
Ish-Shalom et al. (2016)	Adults	31	Mixed	8.9	6 months	-1.21 (-2.05 to -0.37)
Karlsson (2016)	Adults	164	T1DM	8.5	12 months	-0.494 (-0.736 to -0.252)
McKnight & Gibb (2017)	Adults	169	T1DM	7.73	NR	-0.23 (-0.342 to -0.118)
Messaaoui et al. (2018)	Children	278	T1DM	7.5	12.7 months	0 (-0.154 to 0.154)
Mitchell & McDougall (2018)	Adults	16	T1DM	10.3	3 months	-0.88 (-1.214 to -0.546)
Moreno-Fernandez et al. (2018)	Adults	18	T1DM	7.8	6 months	-0.4 (-0.586 to -0.214)
Paris et al. (2018)	Adults	117	T1DM	8.5	12 months	-0.59 (-0.989 to -0.191)
Pintus & Ng (2017)	Children	52	T1DM	8.2	3 months	-0.729 (-1.255 to -0.204)
Reddy et al. (2018b)	Adults	20	T1DM	7.2	2 months	-0.35 (-0.63 to -0.07)
Tirelli et al. (2017)	Children	13	T1DM	9.6	3 months	-1.373 (-2.052 to -0.693)
Weiss et al. (2018)	Adults	22	Mixed	8.7	NR	-1 (-1.524 to -0.476)
Xatzipsalti et al. (2017)	Children	51	T1DM	NR	12 months	NR

Appendix 7. Forest plots

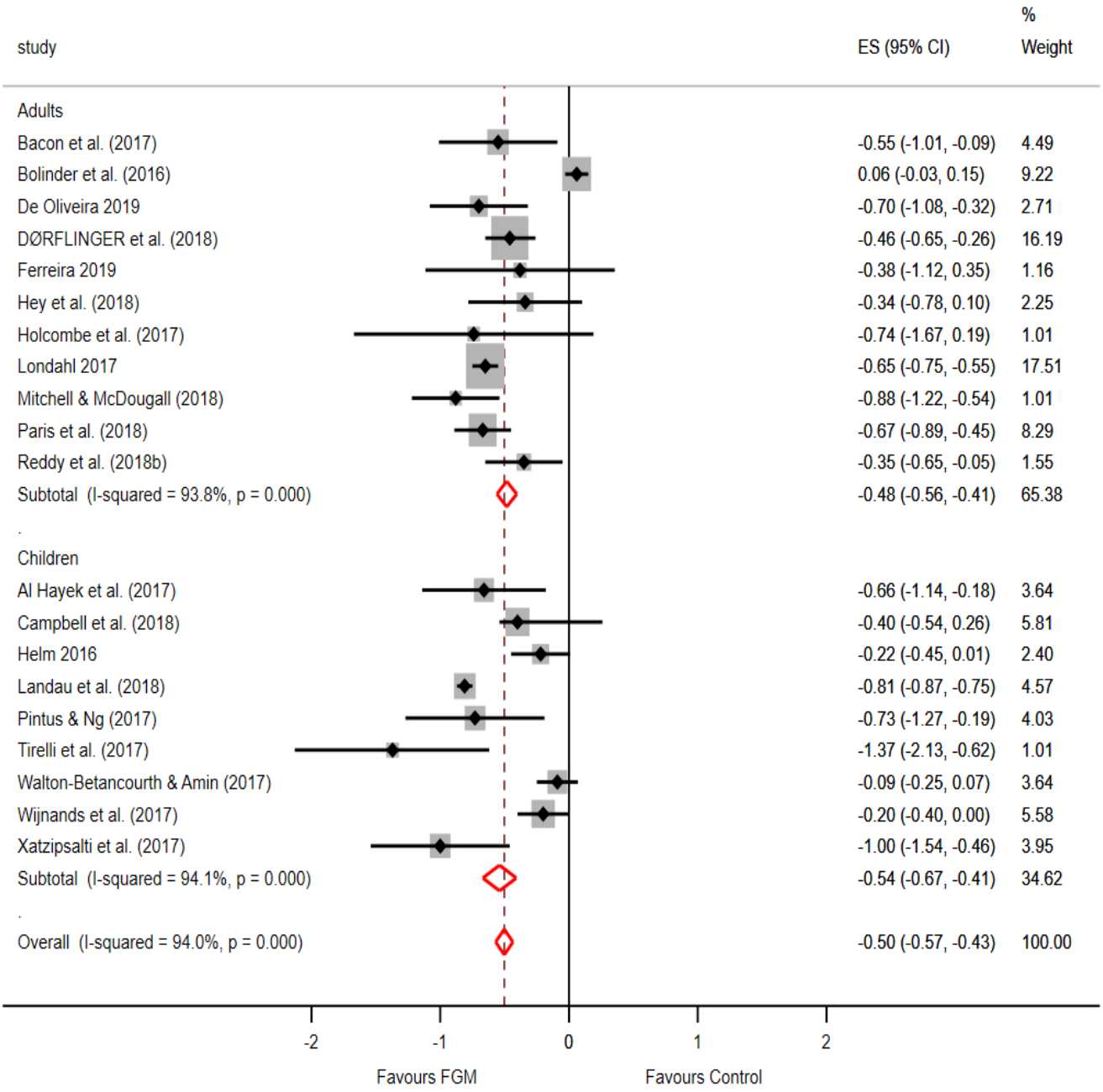


Figure 1. Forest plot for the change in HbA1c for up to 3 months of FGM usage in adults and children with T1DM

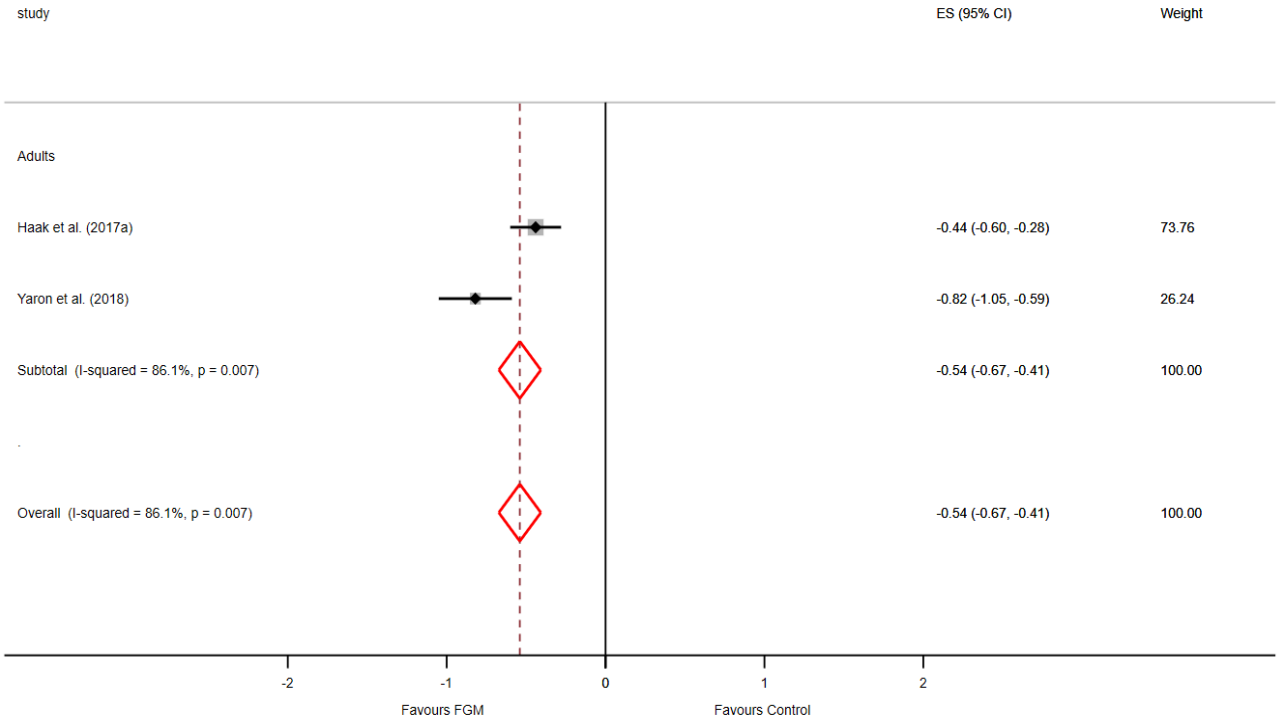


Figure 2. Forest plot for the change in HbA1c for up to 3 months of FGM usage in adults with T2DM

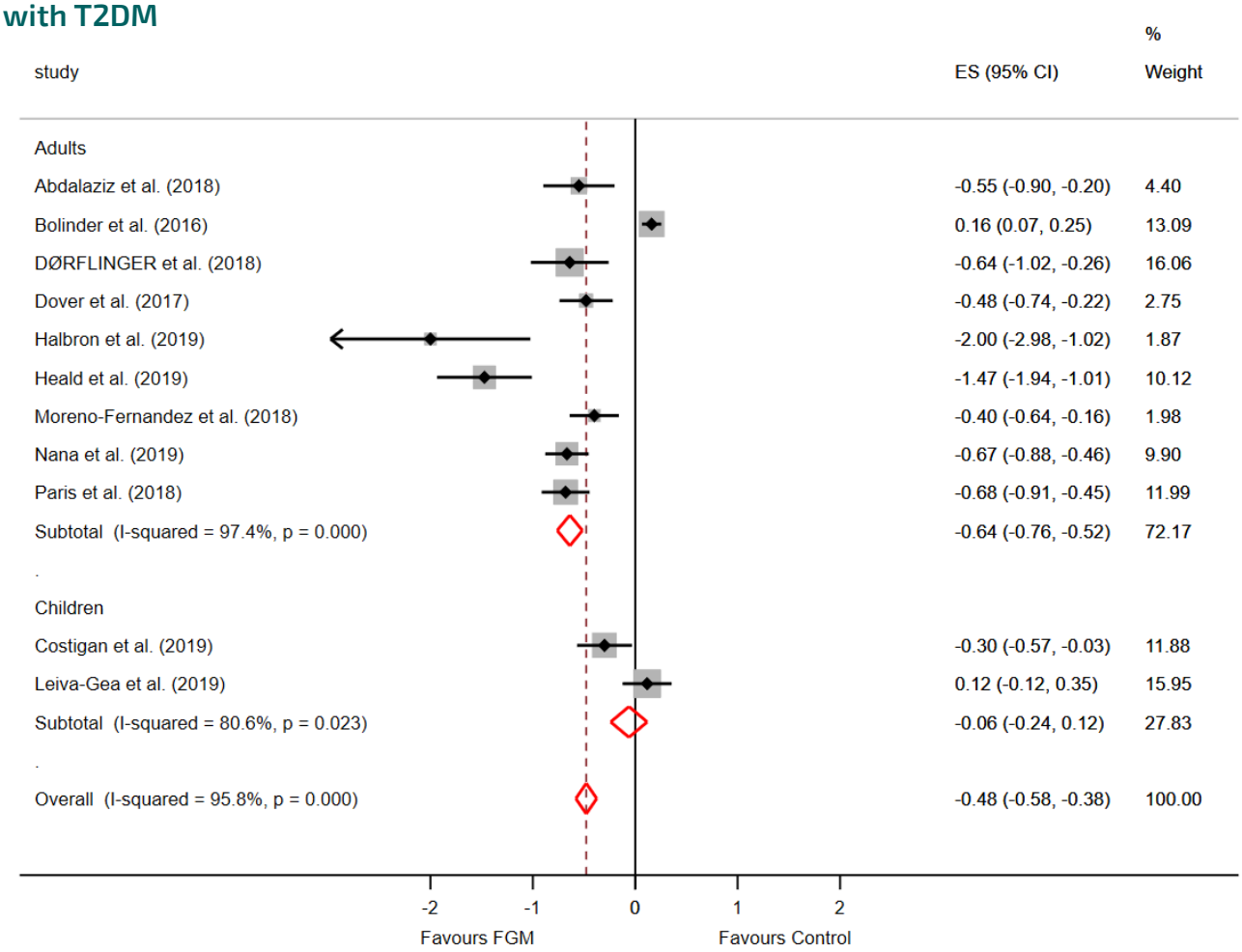


Figure 3. Forest plot for the change in HbA1c for 3 to 6 months of FGM usage in adults and children with T1DM

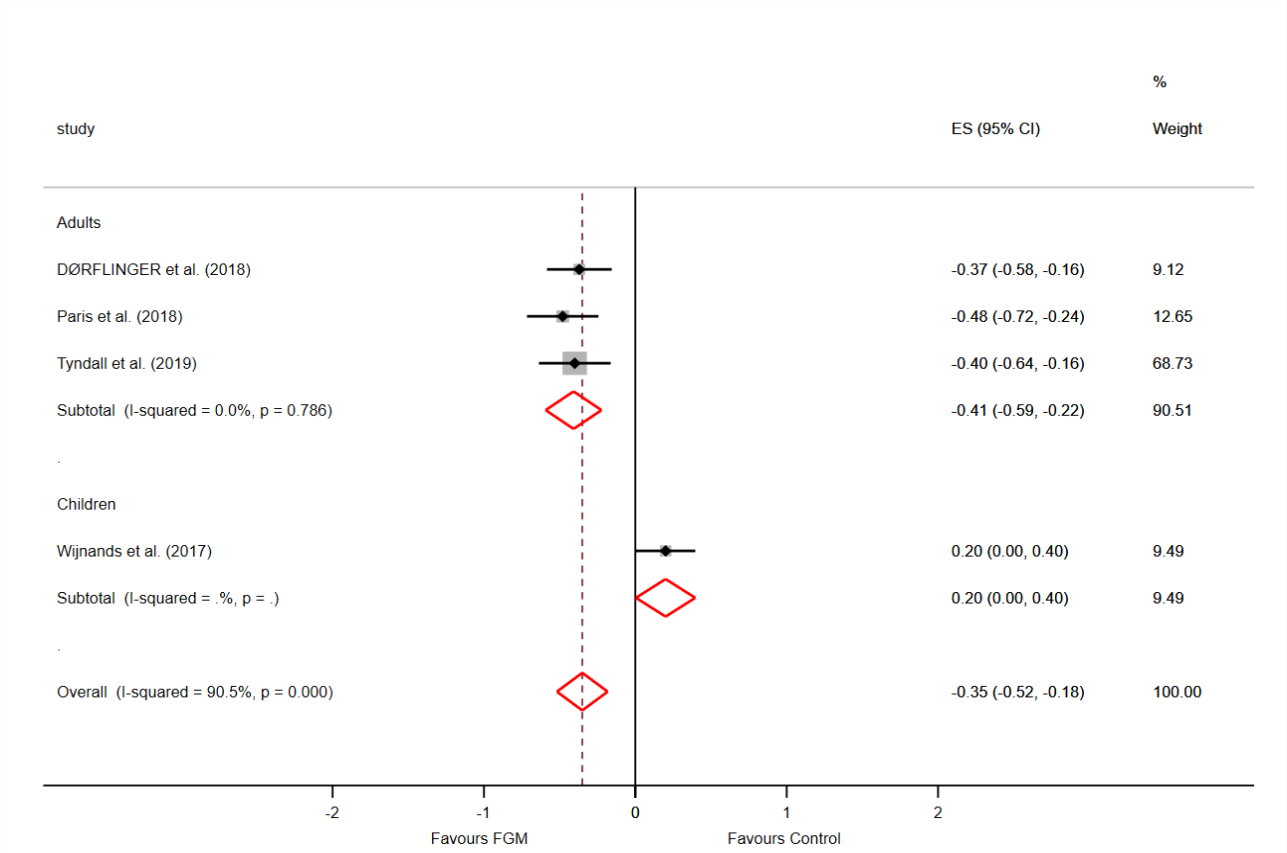


Figure 4. Forest plot for the change in HbA1c for 6 to 9 months of FGM usage in adults and children with T1DM

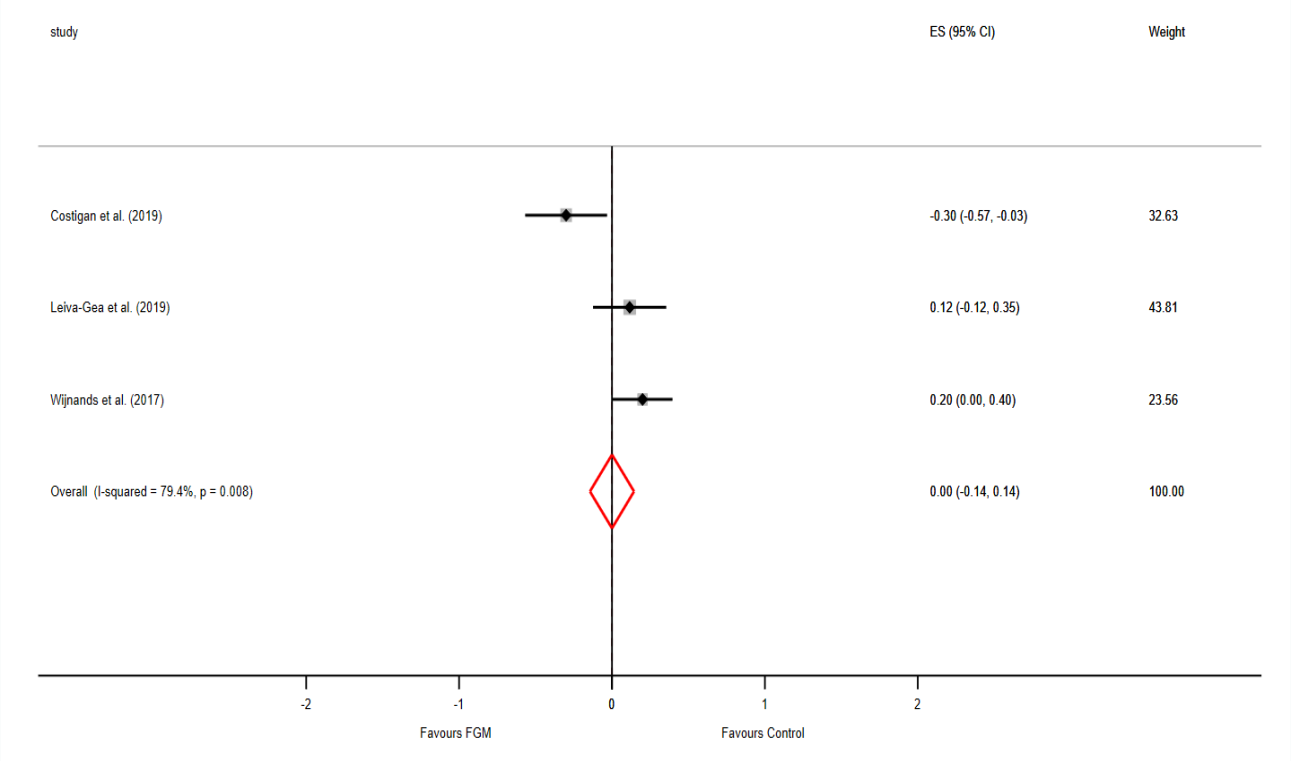


Figure 5. Forest plot for the change in HbA1c for 3 to 9 months of FGM usage in children with T1DM

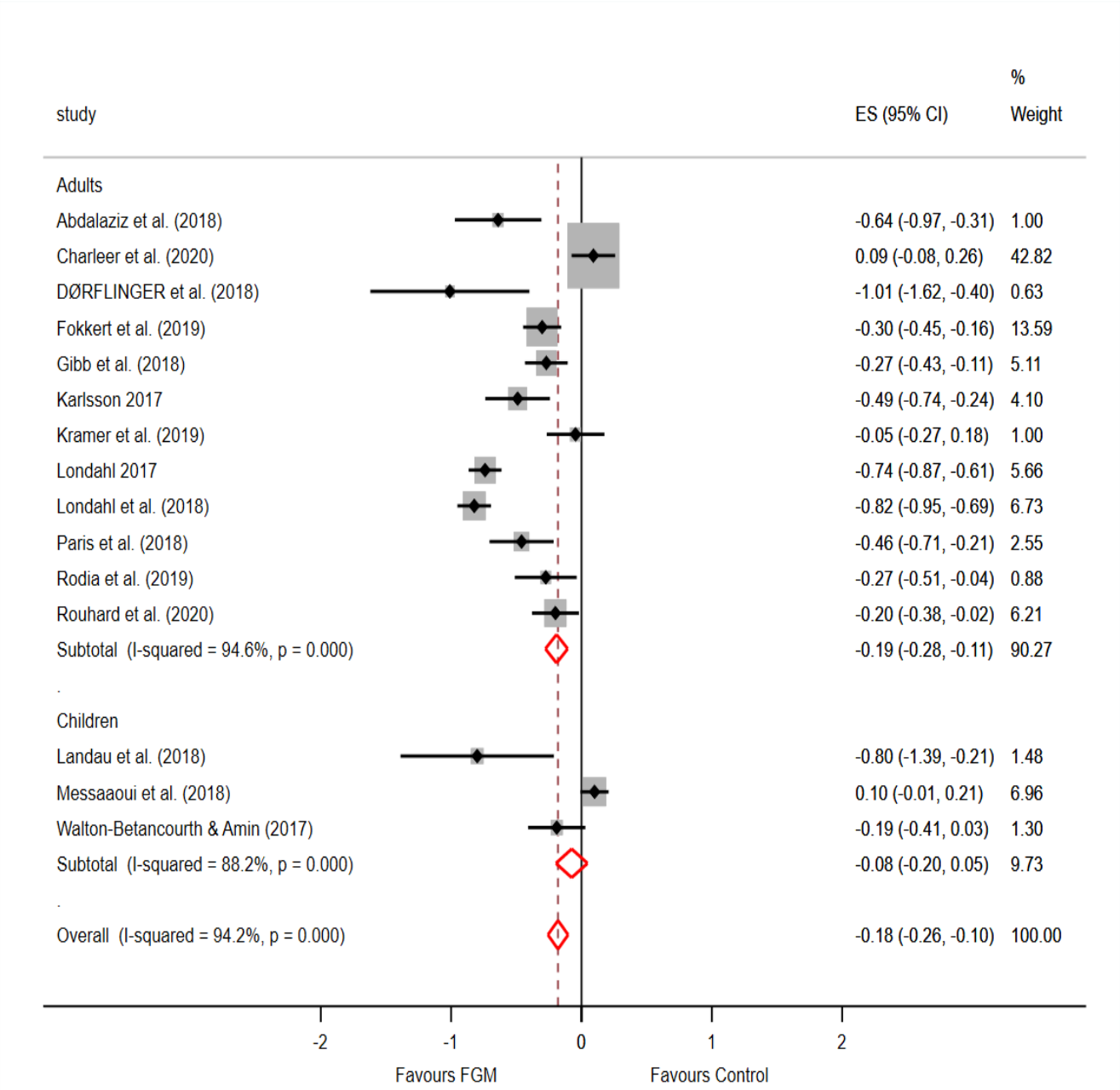


Figure 6. Forest plot for the change in HbA1c for more than 9 months of FGM usage in adults and children with T1DM

Appendix 8. Glossary of definitions

Table 1. : Outcome measures definitions

Average daily risk range	Variability metric based on the risk values obtained from glucose levels that are mathematically transformed to give equal weight to hypo- and hyperglycaemic excursions
Continuous overlapping net glycaemic action	Standard deviation of summated difference between current observation and previous observation
Glycaemic risk assessment diabetes equation	Summarizes the degree of risk associated with a glucose profile. For the determination of GRADE, glucose values are transformed to yield a continuous curvilinear response with a nadir of 90 mg/dL and high adverse weighting to hyperglycaemia and hypoglycaemia
Glycaemic variability percentage	Metric assessing glycaemic variability by analysing the length of the CGM temporal trace normalised to the duration under evaluation
HbA1c	Glycated haemoglobin
J-index	Measurement of both the mean level and variability of glycaemia
Low/High blood glucose index	Metrics used to quantify the risk of hypo- and hyperglycaemia from sparse SMBG. They summarise the number and extent of extreme blood glucose fluctuations into single numbers accounting for hypo- and hyperglycaemic episodes.
Mean absolute glucose change per unit	Summed difference between sequential seven point self measured blood glucose profiles per 24 hours divided by the time in hours between the first and last blood glucose measurement
Mean amplitude of glycaemic excursion	Mean of blood glucose values exceeding one standard deviation from the 24 hour mean blood glucose
Mean of daily differences	Average of the difference between blood glucose values measured at the same time on consecutive days
M-value	Mean of the logarithmic transformation of the deviation from a reference value of six blood sugar measurements taken over a 24 hour period plus an amplitude correction factor
Personal glycaemic status	Composite index that assesses four domains of glycaemic control: mean glucose, glycaemic variability, time in range and frequency and severity of hypoglycaemia

Appendix 9. Systematic search strategy

The systematic search followed HTW's standard rapid review methodology. As this is appraisal is an update to a previous evidence appraisal report (EAR004) the searches were restricted to 2018-2021.

A search was undertaken of Medline, Embase, Cochrane Library, International Network of Agencies for Health Technology Assessment (INAHTA) HTA database & Epistemonikos. Additionally, searches were conducted of key websites and clinical trials registries.

The searches were conducted in December 2020 & January 2021, with an update search of Medline, Embase, Cochrane Library, and INAHTA HTA database run on 9 July 2021.

The Medline strategy is included below. Full search strategy details are available on request.

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily	
Diabetes	
1	exp *Diabetes Mellitus/
2	diabet*.tw.
3	(t1dm or t2dm).tw.
4	or/1-3
FGM & CGM	
5	(flash adj2 (glucose monitor* or sugar monitor*)).tw.
6	(flash adj2 (glucose measur* or sugar measur*)).tw.
7	(continuous adj2 (glucose monitor* or sugar monitor*)).tw.
8	(continuous adj2 (glucose measur* or sugar measur*)).tw.
9	(fgm or cgm).tw.
10	Blood Glucose Self-Monitoring/
11	(blood glucose self monitor* or blood glucose monitor*).tw.
12	(blood sugar self monitor* or blood sugar monitor*).tw.
13	(blood glucose self measur* or blood glucose measur*).tw.
14	(blood sugar self measur* or blood sugar measur*).tw.
15	(glucose monitor* adj4 self).tw.
16	(glucose measur* adj4 self).tw.
17	freestyle libre.tw.
18	or/5-17
Set Combination	
19	4 and 18
20	limit 19 to english language
21	limit 20 to yr="2018 -Current"
22	exp animals/ not exp humans/
23	21 not 22