EVIDENCE APPRAISAL
REPORT

Technoleg Iechyd Cymru
Health Technology Wales

Clinical and cost effectiveness of FreeStyle Libre flash glucose monitoring for the management of type 1 or type 2 diabetes

EAR Number: 004 (November 2018)	**FIELD:** Diabetes
	TYPE: Diagnostic

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Evidence Appraisal Report[1]

Review of systematic reviews and additional primary studies

Clinical and cost effectiveness of FreeStyle Libre flash glucose monitoring for the management of type 1 or type 2 diabetes

Figure 1. Image of FreeStyle Libre sensor and reader (provided by Abbott Diabetes Care)

1. Health problem

Type 1 diabetes, an autoimmune condition that results in destruction of insulin-secreting cells and subsequent loss of control of blood glucose levels, is treated with insulin replacement therapy. In healthy individuals, insulin levels fluctuate, and insulin replacement therapy aims to replicate these normal fluctuations in insulin levels and improve control of blood glucose levels (NICE 2015a). Type 2 diabetes is usually managed through a combination of lifestyle interventions and (non-insulin) pharmaceutical treatments, but some people with type 2 diabetes require insulin treatment when these other interventions have failed to control blood glucose levels or are not suitable for them (NICE 2015b).

People with diabetes who require insulin to control their blood glucose levels are advised to monitor their blood glucose levels. This is most commonly achieved using finger-prick blood glucose testing. It is recommended that adults with type 1 diabetes test their blood glucose at least four times per day, including before each meal and before bed (NICE 2015a). In children with diabetes aged four years or older who require blood glucose monitoring, testing at least five times per day is recommended (NICE 2015c). More frequent testing (up to ten times per day) is needed in certain circumstances such as illness, participation in sport, or pregnancy. Testing more frequently may be needed in, for example, people who undertake high-risk occupations or who drive for long periods of time.

[1] Rapid systematic literature search of published evidence and websites to identify the best clinical and economic evidence. This is critically evaluated by researchers and the draft Evidence Appraisal Report is issued to experts for review and discussed by Health Technology Wales multidisciplinary advisory groups.

Hypoglycaemia is a common complication of type 1 diabetes, with potentially very serious consequences (Östenson et al. 2014). The International Hypoglycaemia Study Group (2017) defined hypoglycaemia as a blood glucose value lower than 3.0 mmol/L, although other thresholds may be used as reference values in practice. In addition to contributing to development of other comorbidities, experiencing recurrent hypoglycaemia can reduce an individual's awareness of future hypoglycaemia (Frier 2014); impaired awareness of hypoglycaemia is estimated to affect 25% of people with type 1 diabetes (Geddes et al. 2008).

In the 2016-17 National Diabetes Audit for England and Wales, the glucose control target (HbA1c) was ≤ 58 mmol/mol in adults with type 1 diabetes (National Clinical Audit Patient Outcomes Programme 2018). For patients with type 2 diabetes who are on a drug which is associated with hypoglycaemia, a target HbA1c level of 53 mmol/mol (7.0%) is recommended (NICE 2015b).

2. Health technology

FreeStyle Libre (Abbott Diabetes Care) measures interstitial fluid glucose levels using a disposable sensor applied to the skin (Figure 1). The sensor is designed to be worn on the upper arm and lasts for up to 14 days, after which replacement is required. A fibre of 0.4 mm thickness within the sensor is inserted into the skin to a depth of 5 mm and draws interstitial fluid into the sensor. Glucose levels are automatically measured every minute, and are accessed by scanning the sensor using either a dedicated reader or via a mobile phone app. Each scan displays current glucose levels, levels over the previous eight hours, and whether glucose levels are trending up or down. This can produce a near-continuous record of measurements, which can be accessed on demand. It can also indicate glucose level trends over time (Abbott Diabetes Care – direct communication; NICE 2017).

FreeStyle Libre is the only flash glucose monitoring (FGM) system currently available in the UK. It is intended as an alternative to finger-prick blood glucose testing – known as self-monitoring of blood glucose (SMBG). SMBG would still be required in some circumstances, such as when FreeStyle Libre indicates impending hyper- or hypoglycaemia, symptoms do not match the system readings, or when glucose levels are changing rapidly and interstitial fluid glucose levels may not accurately reflect blood glucose levels (NICE 2017). FGM could be considered as an "intermittently-viewed" form of Continuous Glucose Monitoring (CGM) (EUnetHTA, 2018), although it lacks the option of displaying a continuous real-time graph, does not provide alerts and cannot be remotely accessed (SHTG, 2018). Whilst other 'real-time' CGM systems exist, they would not be considered standard care in NHS Wales, therefore the main comparator of interest is SMBG.

FreeStyle Libre received regulatory approval in September 2014 (SHTG, 2018), and disposable sensors were placed on the NHS drug tariff on 1 November 2017. The reader cannot be prescribed on the NHS but is supplied free of charge by the manufacturer along with the first sensor. At the time of addition to the drug tariff, Health Technology Wales (2017) published a statement presenting a brief summary of the most relevant evidence-based guidance that applied to NHS Wales. This current appraisal is a more robust, though still relatively rapid, assessment of the clinical and cost effectiveness of FreeStyle Libre.

3. Evidence search methods

The Population-Intervention-Comparator-Outcomes framework for the evidence appraisal (Appendix 1) was developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts.

A systematic literature search to study clinical effectiveness was undertaken on 14 May 2018. This aimed to identify the following types of evidence:

(i) systematic reviews of randomised controlled trials (RCTs) and cost effectiveness studies published within five years of the date of the search. This cut-off date was chosen to reflect the fact that FreeStyle Libre is a new technology and relevant evidence is highly unlikely to have been published before this time.
(ii) RCTs published after May 2013.
(iii) ongoing clinical trials.

Background studies and other papers identified at the scoping stage were also assessed for relevance. Appendix 2 summarises the process of selecting articles for inclusion in the review. Further evidence was published subsequent to the HTW literature review and considered in the context of this review, but none were considered likely to impact significantly on the conclusions of the current HTW appraisal (see Appendix 5). The Scottish Health Technologies Group kindly permitted HTW to adapt their recent review of FreeStyle Libre, and shared details of their economic model (SHTG 2018).

Patient safety and organisational issues were identified from the papers included in the clinical effectiveness section and expert advice, as well as a patient organisation submission. The Diabetes Scotland submission was informed by the Diabetes UK Survey 2017; the Future of Diabetes Report (Scotland) 2017; focus groups, online fora, helpline calls and patient stories provided by Diabetes UK; and NHS Grampian and NHS Lothian patient input. A patient booklet giving real life examples of how flash glucose monitoring has affected the lives of patients was provided.

4. Clinical effectiveness

4.1. Systematic review

Two systematic reviews included meta-analyses of pooled data; these were produced by the Norwegian Institute of Public Health (Bidonde et al. 2017) and EUnetHTA (2018). The two included RCTs applied to different populations – the IMPACT trial (Bolinder et al. 2016) included patients with well-controlled type 1 diabetes, whereas the REPLACE trial (Haak et al. 2017a) was carried out on a population of people with poorly-controlled type 2 diabetes. The pooled results exhibited significant heterogeneity for most of the outcome measures. Due to the differences in the populations for IMPACT and REPLACE, HTW opted to review these two trials separately, alongside other relevant primary studies which were published at a later date.

Several other summary reports were identified (Palylyk-Colwell and Ford 2017; ECRI Institute 2016; HTAG 2017; NICE 2017; SHTG 2018). The review by the Canadian Agency for Drugs and Technologies in Health (Palylyk-Colwell and Ford 2017) was based on FreeStyle Libre Pro, and was excluded as this device is intended for professional use only. Other reviews were based upon the same two RCTs (Bolinder et al. 2016; Haak et al. 2017a), although a NICE Medtech Innovation Briefing (2017) referred also to some lower-quality (intra-patient comparator) evidence.

4.2. Additional studies

The three papers selected for the appraisal of clinical effectiveness were:

- the two original RCTs – IMPACT (Bolinder et al. 2016) and REPLACE (Haak et al. 2017a)
- a subgroup analysis of data from the IMPACT trial (Oskarsson et al. 2018).

The study design and results for the primary outcome measure(s) reported in each paper are summarised in alphabetical order in Tables 1 to 3. Safety outcomes are presented in Table 4. Patient-reported outcomes are summarised in Table 5; other glycaemic outcomes are reported in Appendix 4. No studies

were identified investigating devices with CE mark authorisation indicated for gestational diabetes (EUnetHTA 2018).

The EUnetHTA (2018) report summarised the quality of the body of evidence (including both FGM and CGM studies), using the Cochrane Risk of Bias Tool and GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methods. The authors concluded that all of the trials had risk of bias (particularly with relation to the lack of blinding of outcome assessment). Certainty of evidence was low to very low for the outcomes: time spent in normo- and hypoglycaemia, and severe hypoglycaemia events, quality of life and user satisfaction. For the outcome change in HbA1c (between baseline and study end) evidence certainty was moderate.

4.3. Summary of clinical effectiveness evidence

4.3.1. Flash glucose monitoring in type 1 diabetes

The primary outcome measure for the IMPACT trial in patients with type 1 diabetes was the change in time spent in hypoglycaemia between baseline and six-month follow-up (Bolinder et al. 2016). The authors used a surrogate measure of sensor glucose values <3.9 mmol/L per 24 hour period. Time in hypoglycaemia in hours was 38% less in the FGM group than in the group of patients who relied on SMBG alone, according to a baseline-adjusted difference of -1.24 hours/day (standard error 0.24 hours/day; $p < 0.0001$). FGM patients experienced significantly fewer hypoglycaemic events (at glucose levels < 2.2 mmol/L), with event rates over 24 hours being 55% lower than in the SMBG group ($p < 0.0005$). Patients in the intervention group were able to reduce their number of finger-prick tests per day from a mean (standard deviation) of 5.5 (2.0 SD) at baseline to 0.5 (0.7 SD) during active use of FGM. Differences between groups were greater in the subgroup of patients who relied upon multiple daily injections of insulin (Oskarsson et al. 2018, Table 3).

4.3.2. Flash glucose monitoring in type 2 diabetes

The REPLACE trial (Haak et al. 2017a) sought to compare changes in glucose control (measured using HbA1c) in adults with poorly-controlled type 2 diabetes. The change in HbA1c levels between FGM and SMBG groups after six months was not significantly different (baseline adjusted mean difference 0.3, standard error 1.25; $p = 0.82$). Time in hypoglycaemia <3.1 mmol/L reduced by 0.22 (SE 0.07) hours/day, representing a reduction in time of 53% in the FGM group compared with SMBG ($p = 0.0014$). The rate of hypoglycaemic events < 3.1 mmol/L per 24 hours reduced by 44% for intervention participants compared with controls (adjusted mean difference -0.12, SE 0.037; $p = 0.0017$). Patients using FGM conducted fewer finger-prick tests per day from baseline (mean 3.8; SD 1.4) to six month follow-up (mean 0.3; SD 0.7), whereas there was no significant change in testing frequency in the control group.

Table 1. Bolinder (2016)

<table>
<tr><th>Descriptive Details</th><th>PICO</th><th>Quality of Study</th><th>Observations/notes</th></tr>
<tr>
<td>IMPACT European multi-centre study (23 centres): Austria (6), the Netherlands (6), Germany (5), Sweden (3), Spain (3).

n = 239 (119 intervention, 120 control)
Intervention: 77 male (65%)
Control: 59 male (49%)

Median age (range):
Intervention: 42 (33-51) years
Control: 45 (33-57) years

Recruitment period: September 2014 to February 2015

Length of follow up: Six months</td>
<td>Population: Adults (18+ years) with well-controlled type 1 diabetes (HbA1c ≤ 58 mmol/mol)

Intervention: FreeStyle Libre FGM + SMBG

Comparator: SMBG only

Primary outcome measure: Change in time in hypoglycaemia (<3.9 mmol/L) between baseline and six months</td>
<td>Study design: RCT (unblinded)

Risk of bias:
Selection bias: low risk

Performance bias: participants, investigators, and study staff were not masked to group allocation.

Detection bias: no blinding of outcome assessment.

Attrition bias: low risk

Reporting bias: low risk</td>
<td>• Study sponsored and funded by manufacturer (Abbott Diabetes Care).
• Patients diagnosed with hypoglycaemia unawareness were excluded.
• A two-week run-in period provided baseline data; glucose levels were monitored but not seen by patients during this period.
• 161/239 (67%) patients received multiple daily injections of insulin; the remainder used a continuous subcutaneous insulin infusion.</td>
</tr>
<tr><th colspan="3">Results</th><th>Authors' observations</th></tr>
<tr>
<td colspan="3">Time in hypoglycaemia (mean hours per day, SD)
<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>Adjusted group mean difference (SE)</th><th>p-value</th></tr>
<tr><td>Baseline</td><td>3.38 (2.31)</td><td>3.44 (2.62)</td><td rowspan="2">-1.24 (0.24)</td><td rowspan="2"><0.0001</td></tr>
<tr><td>Study end</td><td>2.03 (1.93)</td><td>3.27 (2.58)</td></tr>
</table>
</td>
<td>• Time in hypoglycaemia was 38% lower in the intervention group compared with the control group.
• Significantly fewer hypoglycaemic events were reported in the intervention group than the control group (26% difference).
• The mean (SD) number of SMBG tests performed per day reduced from 5.5 (2.0) at baseline, to 0.5 (0.7) during FGM; the control group reported 5.8 (1.7) at baseline and 5.6 (2.2) at six months.</td>
</tr>
<tr><td colspan="4">FGM = Flash Glucose Monitoring; SMBG = Self-Monitoring of Blood Glucose</td></tr>
</table>

Table 2. Haak (2017a)

<table>
<tr><th>Descriptive Details</th><th>PICO</th><th>Quality of Study</th><th>Observations/notes</th></tr>
<tr>
<td>REPLACE European multi-centre study (26 centres): Germany (10), France (8), UK (8)

n = 224 (149 intervention, 75 control)
Intervention: 94 male (63%)
Control: 56 male (75%)

Mean age (SD, range):
Intervention: 59.0 (9.9, 33-81) years
Control: 59.5 (11.0, 22-80) years

Recruitment period: March 2014 to October 2014

Length of follow up: Six months</td>
<td>Population: Adults (18+ years) with type 2 diabetes on intensive insulin therapy (and HbA1c 58-108 mmol/mol)

Intervention: FreeStyle Libre + SMBG

Comparator: SMBG

Primary outcome measure: Difference in HbA1c at six months</td>
<td>Study design: RCT (unblinded)

Risk of bias:
Selection bias: low risk.

Performance bias: participants, investigators, and study staff were not masked to group allocation.

Detection bias: no blinding of outcome assessment.

Attrition bias: low risk

Reporting bias: low risk</td>
<td>• Study sponsored and funded by manufacturer (Abbott Diabetes Care).
• A two-week run-in period provided baseline data; glucose levels were monitored but not seen by patients during this period.
• Longer-term (12 month) data are reported separately (Haak 2017b), but were only collected for the intervention arm.</td>
</tr>
<tr><th colspan="3">Results</th><th>Authors' observations</th></tr>
<tr>
<td colspan="3">Mean (SD) HbA1c (mmol/mol)
<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>Adjusted group mean difference (SE)</th><th>p-value</th></tr>
<tr><td>Baseline</td><td>71.0 (11.1)</td><td>72.1 (10.7)</td><td rowspan="2">0.3 (1.25)</td><td rowspan="2">0.83</td></tr>
<tr><td>Study end</td><td>68.0 (9.0)</td><td>67.7 (12.4)</td></tr>
</table>
</td>
<td>• At six months, there was no difference in the change in HbA1c between intervention and control groups.
• The mean (SD) number of SMBG tests performed per day reduced from 3.8 (1.4) at baseline, to 0.3 (0.7) during FGM; the control group reported 3.9 (1.5) at baseline and 3.8 (1.9) at 6 months.</td>
</tr>
<tr><td colspan="4">SMBG = Self-Monitoring of Blood Glucose</td></tr>
</table>

Table 3. Oskarsson (2018)

<table>
<tr><th>Descriptive Details</th><th>PICO</th><th>Quality of Study</th><th>Observations/notes</th></tr>
<tr>
<td>IMPACT European multi-centre study (23 centres): Austria (6), the Netherlands (6), Germany (5), Sweden (3), Spain (3).

n = 161 (81 intervention, 80 control)
Intervention: 56 male (69%)
Control: 47 male (59%)

Median age (range):
Intervention: 42 (32-53) years
Control: 44 (34-53) years

Recruitment period: September 2014 to February 2015

Length of follow up: Six months</td>
<td>Population: Adults (18+ years) with well-controlled type 1 diabetes (HbA1c ≤ 58 mmol/mol), using multiple daily injections of insulin (MDI)

Intervention: FreeStyle Libre + SMBG

Comparator: SMBG only

Primary outcome measure: Change in time in hypoglycaemia (<3.9 mmol/L) between baseline and six months</td>
<td>Study design: Subgroup analysis of the IMPACT trial (Bolinder et al. 2016), focusing on patients receiving MDI (and excluding those on insulin pumps).

Risk of bias:
Selection bias: low risk

Performance bias: participants, investigators, and study staff were not masked to group allocation.

Detection bias: no blinding of outcome assessment.

Attrition bias: low risk

Reporting bias: low risk</td>
<td>• This subgroup analysis had been pre-specified in the study protocol.
• Study sponsored and managed by manufacturer (Abbott Diabetes Care).
• Patients diagnosed with hypoglycaemia unawareness were excluded.
• A two-week run-in period provided baseline data; glucose levels were monitored but not seen by patients during this period.</td>
</tr>
<tr><th colspan="3">Results</th><th>Authors' observations</th></tr>
<tr>
<td colspan="3">Time in hypoglycaemia (mean hours per day, SD)
<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>Adjusted group mean difference (SE)</th><th>p-value</th></tr>
<tr><td>Baseline</td><td>3.44 (2.10)</td><td>3.73 (2.72)</td><td rowspan="2">-1.65 (-2.21, -1.09)</td><td rowspan="2"><0.0001</td></tr>
<tr><td>Study end</td><td>1.86 (1.36)</td><td>3.66 (2.79)</td></tr>
</table>
</td>
<td>• Time in hypoglycaemia was 46% lower in the intervention group compared with the control group.
• Significantly fewer hypoglycaemic events were reported in the intervention group than the control group (33% difference).
• The mean (SD) number of SMBG tests performed per day reduced from 5.5 (2.0) at baseline, to 0.5 (1.0) during FGM; the control group reported 5.6 (1.9) at baseline and 5.5 (2.6) at six months.</td>
</tr>
<tr><td colspan="4">SMBG = Self-Monitoring of Blood Glucose</td></tr>
</table>

4.4. Ongoing trials

Five relevant ongoing RCTs were identified. Each compares flash glucose monitoring to alternatives, with most designs focusing on SMBG as the comparator. Three trials appear to prioritise metabolic outcome measures, whereas two focus primarily on patient perceptions and treatment satisfaction. Details of each trial are summarised in Appendix 3.

5. Safety

A summary of safety data has been taken from the EUnetHTA report (2018), which refers to the same primary studies as were identified by the HTW literature search (Table 4).

The most commonly-reported device-related symptoms related to skin reactions to the sensor adhesive. Some of the adverse events reported by Bolinder et al. (2016) would also have been included in the report of Oskarsson et al. (2018). None of the reported hypoglycaemic events were considered to be device-related. There were no reported incidents of diabetic ketoacidosis or hyperosmolar hyperglycaemic state.

Table 4. Frequency and severity of local adverse events, as reported by EUnetHTA (2018).

Study	Device (or procedure) related local adverse events
Bolinder et al. (2016)	13 adverse events were reported by ten participants related to the sensor – four allergy events (one severe, three moderate); one itching (mild); one rash (mild); four insertion-site symptom (severe); two erythema (one severe, one mild); and one oedema (moderate); all were resolved. There were 248 sensor insertion-site signs and symptoms experienced by 65 participants across both groups. Signs are subdivided into those expected due to sensor insertion: pain (38), bleeding (25), oedema (eight), induration (five), and bruising (five), and those associated with sensor wear: erythema (85), itching (51), and rash (31). Seven participants withdrew from the study due to device-related adverse events or repetitive occurrences of sensor insertion-related symptoms.
Haak et al. (2017)	Six intervention participants (4%) reported nine adverse events for sensor-wear reactions (two severe, six moderate, one mild). These were sensor-adhesive reactions, primarily treated with topical preparations. All were resolved at study exit. Anticipated symptoms refer to those typically expected using a sensor device and equate to symptoms normally experienced with blood glucose finger-stick testing, e.g., pain, bleeding, bruising. There were 158 anticipated sensor insertion site symptoms observed for 41 (27.5%) intervention and 9 (12.0%) control participants. These symptoms were primarily (63%) due to the sensor adhesive (erythema, itching, and rash) and resolved without medical intervention.
Oskarsson et al. (2018)	Eight adverse events for six (7%) intervention participants were related to wearing the study device. Four participants withdrew because of these adverse events. There were 144 sensor insertion-site symptoms experienced by 34 participants. The numbers of participants affected by expected signs or symptoms due to sensor insertion were: pain, n = 14; bleeding, n = 9; oedema, n = 3; and induration, n = 3. The symptoms associated with sensor wear were erythema, n = 23; itching, n = 14; and rash n = 8.

6. Economic evaluation

6.1. Published economic evidence

The HTW literature search identified 20 potentially relevant publications of economic evidence. Of these, 14 were excluded as they did not report relevant health economic or cost evidence or did not focus on the technology of interest. Six articles were reviewed in full: two of which reported costs or cost effectiveness for FreeStyle Libre (Hellmund et al. 2018a; Li et al. 2014). The remainder reported costs or cost-effectiveness of other forms of CGM. Whilst this appraisal was in progress, a further economic paper was published (Hellmund et al. 2018b).

6.2. Cost-effectiveness evidence

6.2.1. Flash glucose monitoring in type 1 diabetes

The only study specifically comparing the cost of FreeStyle Libre to SMBG in type 1 diabetes used data from the IMPACT trial (Hellmund et al. 2018a). This study looked at the costs associated with FGM as a replacement for routine SMBG in people with type 1 diabetes using intensive insulin who need to test their glucose levels frequently. They estimated that the annual cost of FreeStyle Libre was £234 lower per patient than SMBG if ten prick tests a day were assumed in the base case. However, the annual cost of FreeStyle Libre was £296 higher per patient than SMBG if 5.6 prick tests a day were assumed according to the mean IMPACT trial results. This decreased to £88 more per patient compared to SMBG when hypoglycaemic events were taken into account. Annual cost of FreeStyle Libre was £970 lower per patient than SMBG if 16 tests a day were assumed in line with the mean FreeStyle Libre scanning frequency as observed in the IMPACT trial. While the costs used in this study are relevant to the NHS context, the IMPACT trial was conducted in Austria, Spain, Sweden Germany and the Netherlands and did not include UK participants; it only included patients whose type 1 diabetes was well controlled.

6.2.2. Flash glucose monitoring in type 2 diabetes

A UK cost-utility analysis (Li et al. 2014) compared FGM with SMBG using the IMS Core Diabetes model and found Incremental Cost Effectiveness Ratios (ICERs) between £10,034 and £29,068 per QALY (Quality Adjusted Life Year) gained. However, this study is only available as an abstract with very limited information on the Flash glucose monitoring system, methods, data sources used and analyses undertaken.

A recent cost analysis estimated the cost implications of FGM compared to SMBG taking into account cost of monitoring and general healthcare resource use, based on data from the REPLACE trial (Hellmund et al. 2018b). Only considering monitoring costs with a daily frequency of three SMBG tests (as observed in the REPLACE trial), use of flash glucose monitoring would result in additional annual costs of £585 per patient. Taking into account reduced healthcare resource use as observed in the REPLACE trial for patients using FGM, results in an annual cost saving of £191 per patient. However, this 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.

6.3. Evidence submitted by the company

The company submitted two poster presentations that reported cost-utility analyses of FreeStyle Libre compared to SMBG in the UK (Bilir et al. 2016; Wehler et al. 2018). Both analyses used the IMS Core Diabetes model. The type 1 diabetes analysis (Bilir et al. 2016) used clinical outcomes from the IMPACT study and estimated an ICER of £25,045 (between £7,643 and £30,811 in scenario analyses). The type 2

diabetes analysis (Wehler et al. 2018) using clinical data from the REPLACE study (Haak et al. 2017a) found an ICER of £23,842 per QALY gained (with scenario analyses results between £6,555 and £29,517). The limitations of the IMPACT and REPLACE studies apply to the economic analyses.

6.4. Health economic modelling

The Scottish Health Technologies Group developed a Markov model with two health states (alive and dead), and two submodels (type 1 and type 2 diabetes) comparing FreeStyle Libre to conventional SMBG (SHTG, 2018). The model adopts a lifetime horizon from a NHS perspective and costs and benefits are discounted at 3.5%. Cohort characteristics and testing frequency are taken from the IMPACT and REPLACE trials. Incidence of hypoglycaemic events 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 (based on Scottish procurement data) and costs of hypoglycaemic events that require medical intervention (derived from published literature) are included in the model. Baseline health utilities are applied and adjusted to account for the benefits of use of FreeStyle Libre and the effect of hypoglycaemic events on patient quality of life based on a time trade-off study undertaken in five countries including the UK (Evans et al. 2013). General population mortality is adjusted to reflect the increased risk of death in the diabetes population.

The model results show ICERs of £2,459 and £4,498 for type 1 and type 2 diabetes, respectively if an impact of FreeStyle Libre on the frequency of hypoglycaemic events is assumed. If no impact on hypoglycaemic events is assumed, ICERs increase to £12,340 and £18,125. ICERs remained within the acceptable willingness-to-pay threshold of £20,000 in all sensitivity analyses except when FreeStyle Libre was assumed to result in a low reduction of SMBG tests. Probability of FreeStyle Libre being the most cost-effective alternative was above 99% when hypoglycaemic events were included for both types of diabetes and 99.1% for type 1 diabetes and 72.3% for type 2 diabetes if no impact on hypoglycaemic events were assumed.

The feasibility of adjusting the model to reflect a Welsh context was considered, but was not possible due to the lack of relevant Wales-specific data. However, it can be assumed that, while limitations apply, the model will reflect the population of Wales appropriately.

6.5. Budget impact

A budget impact model was developed to estimate the NHS net budgetary impact of the introduction of the FreeStyle Libre flash glucose monitoring system for people with Type 1 and Type 2 diabetes who require multiple daily injections of insulin (MDI). Using Welsh population data and UK diabetes prevalence, the model takes into account population growth over five years, diabetes adjusted mortality, and discontinuation. Costs for FreeStyle Libre and SMBG were taken from literature (Hellmund et al. 2018a) and verified with the manufacturer. The base case analysis assumes a frequency of SMBG finger prick tests of 5.6 tests per day as observed in the IMPACT trial (Bolinder et al. 2016). Sensitivity analysis was conducted to explore the effect of uncertainty surrounding key parameters on the results. Table 5 summarises the results of the budget impact analysis.

The total budget impact of the FreeStyle Libre flash glucose monitoring system over a five-year period is estimated to be £11,847,390 if 5.6 finger prick tests are assumed for SMBG patients. This equates to a net expenditure of £1,463.7 per patient using the FreeStyle Libre system or £559.5 per MDI diabetes patient.

Budget impact increases to £19,085,423 over five years (£2,428.0 per FreeStyle Libre patient, £926.0 per MDI diabetes patient) if only four daily finger prick tests are assumed. Increasing the number of finger prick tests to 10 a day results in a cost saving of £9,485,828 (£1,188.0 per patient using FreeStyle Libre or £448.1 per MDI diabetes patient). Threshold analysis shows that FreeStyle Libre can be expected to be cost saving for patients who undertake eight or more SMBG tests a day, with the point of zero investment at 8.0435 finger prick tests per day.

Table 5. NHS Wales budget impact estimates for the FreeStyle Libre flash glucose monitoring system

Parameter	2018	2019	2020	2021	2022
Number of people with T1DM/T2DM in Wales	195,433	196,028	196,612	197,195	197,790
Number of T1DM MDI patients	15,635	15,682	15,729	15,776	15,823
Number of T2DM MDI patients	5,394	5,410	5,426	5,443	5,459
Total number of people using MDI insulin	21,029	21,093	21,155	21,218	21,282
FreeStyle Libre uptake rate	30%	35%	40%	45%	50%
Discontinuation rate	5%	5%	5%	5%	5%
Number of patients using FreeStyle Libre (discontinuation adjusted)	5,993	7,013	8,039	9,071	10,109
Number of patients using SMBG	15,035	14,079	13,116	12,147	11,173
Estimated cost with FreeStyle Libre (including SMBG when required)	£15,780,572	£16,339,321	£16,689,157	£17,040,732	£17,395,197
Estimated cost without FreeStyle Libre (100% SMBG)	£14,193,942	£14,237,152	£14,279,527	£14,321,861	£14,365,107
Net budget impact of FreeStyle Libre	**£1,586,630**	**£2,102,169**	**£2,409,630**	**£2,718,871**	**£3,030,089**

T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; MDI: multiple daily insulin injections; SMBG: self-monitoring of blood glucose

7. 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. However, pathway efficiencies cannot be realised until this technology is integrated into daily practice.

Data about the frequency of blood glucose monitoring (determined by use of SMBG test strips) and the cost of strips is available for some local Health Boards. Regional variation in the cost of these comparator products could influence cost-effectiveness calculations (Expert reviewer).

8. Patient issues

Some patient-reported outcomes and experiences were reported in the included studies (Table 6). Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Diabetes Quality of Life (DQoL) questionnaire scores measured treatment satisfaction, perceived frequency of hyper- and hypoglycaemia, 'social worry', 'diabetes worry' and impact of treatment.

New users of FreeStyle Libre would need support and training in how to use FreeStyle Libre and interpret readings. When used by a child aged four to 12 years, a caregiver at least 18 years old must supervise, manage and help the child in using the system and interpreting its readings. Online tutorials and videos are available on the company website, which are intended to support patients whilst they are learning to use the system.

As flash glucose testing is not currently accepted by the Driver and Vehicle Licensing Agency (DVLA), it would not be an appropriate choice for those with high frequency testing as a result of their requirement to assess fitness to drive (HTW FreeStyle Libre Statement 2017). It is understood that DVLA is considering revising this requirement, but the outcome is not yet known.

The manufacturer commented that there is a social stigma associated with finger prick testing (the frequency of which is reduced with the use of FreeStyle Libre). Similarly, finger prick testing may be considered an inconvenience. These and similar issues were also highlighted recently in a Diabetes Scotland patient organisation submission to the Scottish Health Technologies Group (SHTG 2018). The equivalent organisation in Wales, Diabetes UK Cymru, was invited to comment on this HTW evidence appraisal report.

Table 6. Patient-reported measures in included studies

Study	Measure(s)	Findings
Bolinder et al. (2016)	DDS, DQoL, DTSQ, HFS & a questionnaire about baseline perception of hypoglycaemia.	Significantly better results were found for FreeStyle Libre (+ SMBG) compared with SMBG alone, in the following measures: • Patient satisfaction with treatment • Total treatment satisfaction • Perceived frequency of hypoglycaemia • Diabetes quality of life (per protocol subgroup only) No between-group differences were found for: • Diabetes distress • Hypoglycaemia fear behaviour • Worry scores
Haak et al. (2017a)	DQoL, DTSQ	Significantly better results were found for FreeStyle Libre (+ SMBG) compared with SMBG alone, in the following measures: • Patient satisfaction with treatment (DQoL) • Overall treatment satisfaction (DTSQ) • Perception of hypoglycaemia • Perception of hyperglycaemia Similar improvements were reported in the subgroup of patients studied by Oskarsson (2018).
DDS = Diabetes Distress Scale; DQoL = Diabetes Quality of Life questionnaire; DTSQ = Diabetes Treatment Satisfaction Questionnaire.		

Diabetes Scotland advised that diabetes can change day-to-day life in a number of ways. This can be from a change in family dynamics to impacting on work. People dependent on insulin are required to undertake self-monitoring of blood glucose, testing up to 6–10 times a day, and self-manage their condition 24 hours a day, 365 days a year. Frequent testing can be painful, inconvenient and difficult to achieve due to the person's daily routine.

One of the most challenging aspects of living with diabetes is the prevention and management of hypoglycaemia, especially at night. Hypoglycaemic events are distressing not only for the person living with the condition but also for parents, spouses and family members. Hypoglycaemia can be difficult and distressing to manage; the person may become aggressive, irritable, uncooperative, unsteady and confused.

Diabetes Scotland advised that people living with diabetes want access to technology that will:

- give them the information, tools and support to live safe and well with their diabetes.
- reduce the need for painful and inconvenient finger prick glucose monitoring.
- reduce stress and anxiety for them and their families.
- reduce the risk of developing devastating complications such as sight loss, amputation, renal failure, stroke, and depression.

Diabetes Scotland reported that from feedback they gathered the use of Freestyle Libre is life-changing, as it allows people the confidence and freedom to manage their condition and get on with daily life. It allows children to experience a 'normal childhood' and gives parents peace of mind. People with

experience of using Freestyle Libre have reported enormous benefits and improved quality of life. Using Freestyle Libre may particularly benefit people in jobs where finger-prick testing is not always practical and they struggle to test regularly.

However not everyone living with diabetes is the same and therefore Freestyle Libre may not suit everyone; many may feel uncomfortable having sensors attached 24 hours, or may not have the inclination to change from their present treatment regime. Diabetes Scotland believe that flash glucose monitoring with Freestyle Libre can support more effective self-management of diabetes, reducing the risk of serious and costly complications including blindness, kidney disease, lower limb amputation, mental illness, stroke, cardiovascular disease and premature death.

9. Conclusions

Evidence from two European multicentre randomised controlled trials suggests that FreeStyle Libre is able to detect and guide the correction of biochemical hypoglycaemia in patients with Type 1 and Type II diabetes mellitus who require multiple daily dosing of subcutaneous insulin. FreeStyle Libre can reduce frequency and duration of hypoglycaemia and the need for finger-stick blood glucose monitoring in people with diabetes. Patients in both trials also reported greater treatment satisfaction with FreeStyle Libre than those treated with SMBG. The available evidence focused on adults with poorly-controlled type 2 diabetes (requiring multiple daily injections of insulin), or well-controlled type 1 diabetes. There is uncertainty about whether the surrogate measures of low sensor glucose levels are an accurate reflection of clinically relevant hypoglycaemic events.

Published cost effectiveness evidence suggests that FreeStyle Libre is likely to be more effective and more costly than SMBG, with mean ICERs within normally-accepted willingness-to-pay thresholds. Budget impact modelling suggests that FreeStyle Libre would result in increased costs. Results are highly sensitive to the number of finger-prick tests replaced by flash glucose monitoring, and suggest that FreeStyle Libre is likely to be cost-saving compared to SMBG in patients who currently conduct a high number of finger-prick tests (8 or more per day).

10. Further Research

The evidence from the randomised trials focused on specific populations and may not accurately reflect the target population of interest. Further robust research is recommended into the effectiveness and cost-effectiveness of FreeStyle Libre as an adjunct to SMBG in adults with diabetes who have poorly-controlled glucose levels, or in children or adolescents with any type of diabetes.

Additional information about the incidence and resource impact of hypoglycaemic and hyperglycaemic events in Wales would also be of value. Resource implications of long-term consequences of poor glucose control are of particular interest.

11. Contributors

The HTW staff and contract researchers involved in writing this report were:

- Poole RL – main author
- Jarrom D – co-author, literature selection and quality assurance
- Washington J – quality assurance
- Cleves A and Coles B – retrieval of literature
- Sewell B – economic evaluation
- Myles S – project oversight.

The HTW Assessment Group advised on methodology throughout the 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:

- Stephen Bain, Professor of Medicine (Diabetes) and Director of Diabetes Research Unit Cymru
- Alan Clatworthy, Clinical Effectiveness Pharmacist, Abertawe Bro Morgannwg University Health Board
- Sam Rice, Consultant Physician, Hywel Dda UHB
- Jonathan Simms, Clinical Director of Pharmacy, Aneurin Bevan University Health Board
- Dai Williams, Diabetes UK Cymru.

A representative of the manufacturer also provided information and comments:

- Samantha Howard, Head of Market Access, Abbott Diabetes Care

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Review period

Two years after the date of publication, a high-level literature search will be undertaken to determine if there is new evidence that could alter the conclusions of this report. If so, the appraisal will be updated.

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Appendix 1. Study selection criteria

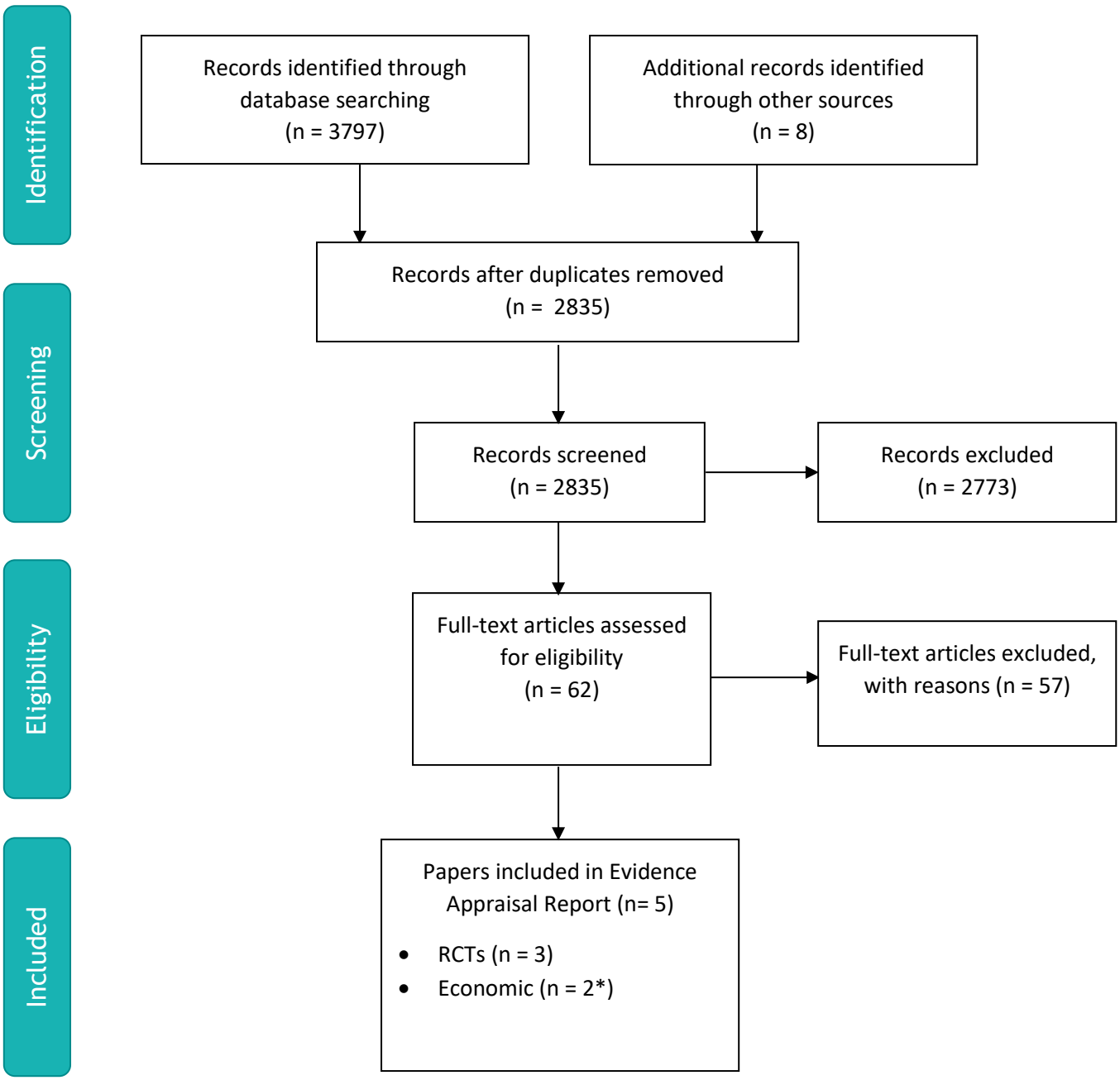
Population	People with Type 1, Type 2 or gestational diabetes mellitus (including children)
Intervention	Flash glucose monitoring (FreeStyle Libre)
Comparators	Self-monitoring of blood glucose (SMBG) Continuous glucose monitoring (CGM)*
Outcome measures	HbA1c Glucose levels Hypoglycaemia – frequency; duration Hyperglycaemia/diabetic ketoacidosis – frequency; duration Fear of hypoglycaemia (worry) Behaviour Diabetes self-care Diabetes-related quality of life (QOL) Diabetes distress Depressive symptoms Patient satisfaction Adverse events from testing or treatment Health care utilization (Patient-reported) usability Cost-effectiveness

*CGM was later removed as a comparator as it is not currently a standard care option (routinely available) in NHS Wales.

Other criteria:

- Language(s): English
- Dates of publication: past 5 years
- Limit study designs to systematic reviews & randomised controlled trial studies
- Exclude studies which only report sensor performance/accuracy outcomes

Appendix 2 - PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness



*One further economic publication (Hellmund 2018b) was incorporated into the report at a later date.

Appendix 3 – Summary of ongoing randomised controlled trials

Study information	Status	Research question & outcome measures
Registration: UMIN000026452: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000030387 **Country:** Japan **Target recruitment:** 100 participants **Follow-up:** not reported	Recruiting **Last updated:** 06/09/2017	Study of the impact of flash glucose monitoring on glycometabolism of type 2 diabetic patients. Randomised, unblinded trial. **Population:** adults (aged 20 to 70 years) with type 2 diabetes, HbA1c ≥7.5% and <8.5%. **Intervention:** flash glucose monitoring in conjunction with lifestyle interventions **Comparator**: self-monitoring of blood glucose in conjunction with lifestyle interventions **Primary Outcome Measure:** not reported **Secondary Outcome Measure:** not reported
Registration: UMIN000026295: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000030129 **Country:** Japan **Target recruitment:** 10 participants **Follow-up:** two weeks	Recruitment completed **Last updated:** 28/08/2017	Investigation of diabetes management with flash glucose monitoring. Randomised, unblinded trial. **Population:** adults (aged 18 to 75 years) with diabetes on insulin treatment **Intervention:** flash glucose monitoring **Comparator:** existing glucose monitoring devices **Primary Outcome Measure:** patient satisfaction, measured with WHO-5 and Diabetes Treatment Satisfaction questionnaires **Secondary Outcome Measure:** not reported
Registration: CTRI/2017/05/008628: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=17551 **Country:** India **Target recruitment:** 30 participants **Follow-up:** 6 months	Recruitment completed **Last updated:** 16/05/2017	A randomised controlled study comparing flash glucose monitoring + self-monitoring of blood glucose (SMBG) versus SMBG alone for glycaemic control in adolescents of 12-18 years of age with Type 1 diabetes mellitus. **Population:** adolescents aged 12-18 years with type 1 diabetes for at least 1 year; on basal bolus insulin regimen insulin (3-4 injections per day) and performing SMBG at least 3-4 times per day; Hba1c >8% and <14%. **Intervention:** Flash glucose monitoring along with SMBG **Comparator:** SMBG alone **Outcome Measures:** change in HbA1c; identification of hyper- and hypoglycaemic episodes; total insulin requirement; feasibility and acceptability of flash glucose monitoring.

Registration: NCT02776007: https://clinicaltrials.gov/ct2/show/NCT02776007 **Country:** Israel **Target recruitment:** 60 participants **Follow-up:** 12 weeks	Active, not recruiting. Estimated completion March 2019. **Last updated:** 15/05/2018	Patients' perceptions of using the "Libre" system compared with conventional self-monitoring of blood glucose in adolescents with type 1 diabetes: The Libre Sat Trial. Randomised unblinded study. **Population:** adolescents (aged 12 to 17 years) with type 1 diabetes for at least one year; used continuous glucose monitoring until 3 months or more before the study start; HbA1c value > 7.5% at time of screening visit. **Intervention:** Flash glucose monitoring (FreeStyle Libre) **Comparator:** Self-measurement of blood glucose (personal glucose meter) **Primary Outcome Measure:** Diabetes treatment satisfaction questionnaire; Libre-user evaluation questionnaire.
Registration: NCT03522870 https://clinicaltrials.gov/ct2/show/study/NCT03522870 **Country:** China **Target recruitment:** 76 participants **Follow-up:** 26 weeks	Recruiting. Estimated completion December 2019. **Last updated:** 11/05/2018	Effect of novel flash glucose monitoring system on glycaemic control in adult patients with type 1 diabetes mellitus **Population:** Adults with type 1 diabetes mellitus **Intervention:** Flash glucose monitoring **Comparator:** Self-monitoring of blood glucose **Primary Outcome Measure:** Change in HbA1c

Appendix 4. All glycaemic outcomes: randomised trials

Table 7. FreeStyle Libre vs self-monitoring of blood glucose; type 1 diabetes (Bolinder 2016)

Outcome	Baseline		Study end		Difference in adjusted means, intervention vs control (SE)	Difference in intervention vs control, %
	Intervention (SD)	Control (SD)	Intervention (SD)	Control (SD)		
HbA1c, mmol/mol	50·7 (5·7)	50·6 (7·0)	52·4 (7·2)	52·4 (7·2)	0·0 (0·65)	NA
HbA1c (%)	6·79 (0·52)	6·78 (0·64)	6·94 (0·65)	6·95 (0·66)	0·00 (0·059)	
Time with glucose 3·9-10·0 mmol/L (70-180 mg/dL) in hours	15·0 (2·5)	14·8 (2·8)	15·8 (2·9)	14·6 (2·9)	1·0 (0·30)	
Glucose <3·9 mmol/L (70 mg/dL) within 24 h						
Events	1·81 (0·90)	1·67 (0·80)	1·32 (0·81)	1·69 (0·83)	−0·45 (0·089)	−25·8%
Time in hours	3·38 (2·31)	3·44 (2·62)	2·03 (1·93)	3·27 (2·58)	−1·24 (0·239)	−38·0%
Glucose <3·1 mmol/L (55 mg/dL) within 24 h						
Events	0·96 (0·65)	0·92 (0·73)	0·56 (0·55)	0·92 (0·74)	−0·38 (0·074)	−41·3%
Time in hours	1·59 (1·42)	1·77 (1·86)	0·80 (0·96)	1·65 (1·97)	−0·82 (0·175)	−50·3%
Glucose <2·5 mmol/L (45 mg/dL) within 24 h						
Events	0·56 (0·52)	0·59 (0·60)	0·29 (0·36)	0·56 (0·59)	−0·26 (0·06)	−48·5%
Time in hours	0·85 (1·03)	1·04 (1·36)	0·38 (0·58)	0·96 (1·57)	−0·55 (0·14)	−59·5%
Glucose <2·2 mmol/L (40 mg/dL) within 24 h						
Events	0·39 (0·43)	0·44 (0·51)	0·19 (0·29)	0·43 (0·55)	−0·22 (0·050)	−55·0%
Time in hours	0·59 (0·85)	0·75 (1·11)	0·26 (0·47)	0·73 (1·41)	−0·46 (0·122)	−65·3%
Glucose >13·3 mmol/L (240 mg/dL) within 24 h						
Time in hours	1·85 (1·44)	1·91 (1·70)	1·67 (1·36)	2·06 (1·61)	−0·37 (0·163)	−19·1%

Intervention group: FreeStyle Libre in addition to self-monitoring of blood glucose. Control group: self-monitoring of blood glucose alone.
SD: standard deviation; SE: standard error.

Table 8. FreeStyle Libre vs self-monitoring of blood glucose; type 2 diabetes (Haak 2017a)

Outcome	Baseline		Study end		Difference in adjusted means, intervention vs control (SE)	Difference in intervention vs control, %
	Intervention (SD)	Control (SD)	Intervention (SD)	Control (SD)		
HbA1c, mmol/mol	71.0 (11.1)	72.1 (10.7)	68.0 (9.0)	67.7 (12.4)	0.3 (1.25)	N/A
HbA1c (%)	8.65 (1.01)	8.75 (0.98)	8.37 (0.83)	8.34 (1.14)	0.03 (0.114)	N/A
Time with glucose 3·9-10·0 mmol/L (70-180 mg/dL) in hours	13.9 (4.5)	13.5 (5.2)	13.6 (4.6)	13.2 (4.9)	0.2 (0.58)	1.1
Glucose <3·9 mmol/L (70 mg/dL) within 24 h						
Events	0.64 (0.63)	0.63 (0.66)	0.38 (0.45)	0.53 (0.59)	-0.16 (0.065)	-27.7
Time in hours	1.30 (1.78)	1.08 (1.58)	0.59 (0.82)	0.99 (1.29)	-0.47 (0.134)	-43.1
Glucose <3·1 mmol/L (55 mg/dL) within 24 h						
Events	0.34 (0.50)	0.27 (0.44)	0.14 (0.24)	0.24 (0.36)	-0.12 (0.037)	-44.3
Time in hours	0.59 (1.13)	0.38 (0.83)	0.19 (0.37)	0.37 (0.69)	-0.22 (0.068)	-53.1
Glucose <2·5 mmol/L (45 mg/dL) within 24 h						
Events	0.19 (0.37)	0.13 (0.34)	0.06 (0.13)	0.11 (0.25)	-0.06 (0.02)	-48.8
Time in hours	0.32 (0.74)	0.17 (0.54)	0.08 (0.21)	0.19 (0.45)	-0.14 (0.04)	-64.1
Glucose <2·2 mmol/L (40 mg/dL) within 24 h						
Events	0.13 (0.30)	0.10 (0.30)	0.05 (0.13)	0.09 (0.22)	-0.05 (0.02)	-52.6
Time in hours	0.22 (0.57)	0.12 (0.43)	0.05 (0.17)	0.14 (0.34)	-0.10 (0.03)	-66.7
Time with glucose >10.0 mmol/L (180 mg/dL) (h)	8.8 (5.0)	9.4 (5.8)	9.8 (4.8)	9.8 (5.4)	0.3 (0.63)	3.5
Time with glucose >13.3 mmol/L (240 mg/dL) (h)	3.1 (3.3)	3.9 (4.5)	3.5 (3.7)	3.9 (4.2)	0.1 (0.46)	2.1

Intervention group: FreeStyle Libre in addition to self-monitoring of blood glucose. Control group: self-monitoring of blood glucose alone.
SD: standard deviation; SE: standard error.

Appendix 5. Additional evidence identified subsequent to original literature searches

Reference	HTW comment
Campbell F, Murphy N, 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. 1-8. Available at: https://doi.org/10.1111/pedi.12735	Observational evidence is not eligible for inclusion in this rapid review as higher level evidence is available.
Yaron M, Roitman E, Aharon-Hananel G, et al. (2018). Intervention of the flash glucose sensing technology on glycaemic control and treatment satisfaction in patients with type 2 diabetes treated intensively by insulin – a randomised controlled trial. American Diabetes Association 78th Scientific Sessions, June 2018, Orlando, USA. Available at https://ada.scientificposters.com/epsAbstractADA.cfm?id=1	Conference abstract. This RCT appears to add potentially useful evidence, but insufficient detail is reported to enable adequate appraisal. HTW will consider the full report (if available) when reviewing its advice in future.
Seibold A, Welsh Z, Ells S et al. (2018). A meta-analysis of real-world observational studies on the impact of flash glucose monitoring on glycaemic control as measured by HbA1c. American Diabetes Association 78th Scientific Sessions, June 2018, Orlando, USA. Available at: https://ada.scientificposters.com/epsAbstractADA.cfm?id=1	Conference abstract. Meta-analysis showed substantial heterogeneity between trials (I^2 = 92.6%).
Hellmund R, Weitgasser R, Blissett D. (2018). 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. Available at: http://www.touchendocrinology.com/articles/cost-calculation-flash-glucose-monitoring-system-adults-type-2-diabetes-mellitus-using	Has been incorporated into the main text.
Bilir S, Hellmund R, Wehler B, et al. (2018). Cost-effectiveness analysis of a flash glucose monitoring system for patients with type 1 diabetes receiving intensive insulin treatment in Sweden. European Endocrinology. 14(2): 73-9. Available at: www.touchendocrinology.com/articles/cost-effectiveness-analysis-flash-glucose-monitoring-system-patients-type-1-diabetes	These two cost-effectiveness analyses were based on Swedish unit costs using Swedish registry data and the REPLACE and IMPACT trials. As Swedish healthcare costs are generally higher the results are unlikely to be generalisable to the UK setting.
Bilir S, Hellmund R, Wehler E, et al. (2018). The cost-effectiveness of a flash glucose monitoring system for management of patients with type 2 diabetes receiving intensive insulin treatment in Sweden. European Endocrinology. 14(2): 80-5. Available at: www.touchendocrinology.com/articles/cost-effectiveness-flash-glucose-monitoring-system-management-patients-type-2-diabetes	