Healthcare Improvement Scotland | SHTG Advice on health technologies

Evidence Note
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In response to an enquiry from the Scottish Diabetes Group (SDG)

What is the clinical and cost effectiveness of Freestyle Libre® flash glucose monitoring for patients with diabetes mellitus treated with intensive insulin therapy?

What is an evidence note?

Evidence notes are rapid reviews of the evidence surrounding health technologies that are under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify, retrieve and develop within the time available. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

The background, technology description, clinical effectiveness and safety sections of this extended evidence note are adapted from a review of continuous glucose monitoring and flash glucose monitoring as personal, standalone systems in patients with diabetes mellitus treated with insulin. This review was developed using the HTA Core Model® for Rapid Relative Effectiveness Assessment as part of the European Network for Health Technology Assessment (EUnetHTA) WP4 Joint Action 3 programme. Healthcare Improvement Scotland was a dedicated reviewer for the project[1], and peer review was conducted as part of the EUnetHTA review. This extended evidence note builds upon the EUnetHTA assessment and incorporates a range of additional evidence sources including:

- A Healthcare Improvement Scotland economic evaluation
- A patient group submission from Diabetes Scotland
- NHS Scotland clinical expert input.

Each of these evidence sources is described in more detail within the relevant section of the extended evidence note, where reference is made to relevant appendices as appropriate.

Key points

- The main evidence for effectiveness of Freestyle Libre® is from two randomised controlled trials (RCTs). Methodological weaknesses mean that the risk of bias should be considered.
- Use of Freestyle Libre® by adults with well controlled type 1 diabetes mellitus (T1 DM) (n=241) or poorly controlled type 2 diabetes mellitus (T2 DM) (n=224) reduces both time in hypoglycaemia and rate of hypoglycaemic events at six months, as measured by a surrogate outcome of sensor glucose values <3.9mmol/L (70mg/dL), when compared with standard self-monitoring of blood glucose (SMBG).
- For people with well-controlled T1 DM, glycaemic control as measured by HbA1c was not statistically significantly different with Freestyle Libre® compared with SMBG.
- For people with poorly-controlled T2 DM aged under 65 years, Freestyle Libre® use led to a statistically significant reduction in HbA1c compared with SMBG. The effect was absent when data from study participants of all ages were considered.
- When compared with SMBG, Freestyle Libre® improved treatment satisfaction. There were no statistically significant differences in RCT participants' Diabetes Distress Scale (DDS), or overall Diabetes Quality of Life (DQoL) scores at six months follow-up.
- The proportion of RCT participants experiencing serious adverse events was similar between the SMBG and Freestyle Libre® groups. Sensor site symptoms, such as itching or erythema, were commonly reported by Freestyle Libre® users.
- Feedback from patients with experience of using Freestyle Libre® highlights substantial benefits and improved quality of life.
- Initial findings from a de novo cost effectiveness analysis illustrate that Freestyle Libre® is cost-effective for people with T1 DM and for people with T2 DM who are intensive insulin users and self-monitor their blood glucose levels.
- The incremental cost-effectiveness ratio (ICER) for Freestyle Libre® compared with SMBG ranged from £2,459 to £12,340 per quality-adjusted life year (QALY) in T1 DM and from £4,498 to £18,125 in T2 DM, depending on the modelling approach considered.
- One-way sensitivity analyses indicated Freestyle Libre® was still likely to be cost-effective under a wide range of scenarios and cost saving against SMBG when a mean number of eight blood glucose tests per day was considered. The probabilistic sensitivity analysis also indicated that Freestyle Libre® is likely to be cost-effective.
- Assuming an uptake rate of 30% in year 1 rising to 50% by year 5, the budget impact for NHSScotland of Freestyle Libre® was estimated to be £3.3m in year 1 rising to

£6.8m by year 5 in the T1 DM population and £5.5m rising to £11.4m in the T2 DM population. This is based on an estimated incremental cost of monitoring of £370 per T1 DM patient and £544 per T2 DM patient.

Literature search

EUnetHTA conducted a systematic search of the published literature during March 2018 using databases including Medline, PubMed, Embase and the Cochrane Library. A search of reference lists from relevant studies was also carried out.

Healthcare Improvement Scotland conducted an additional search focusing on the cost-effectiveness literature during March 2018. The search focused on the use of flash glucose monitoring (Freestyle Libre®) in people with diabetes treated with insulin. Multiple databases were searched (CRD database, Cochrane Library, Medline, Embase, and more) using various search strategies and MeSH terms which are available on request. In addition to searching for existing economic studies, the purpose of this literature search was to inform the economic model structure and identify potential data sources for resource utilisation, costs, utilities, or other key variables used in the analysis.

Introduction

Diabetes mellitus is a major cause of morbidity and mortality in Scotland with around 300,000 people diagnosed with the condition[2].

Self-monitoring of blood glucose is essential for people with type 1 (T1) diabetes mellitus (DM) and is used by roughly one in 10 people with type 2 (T2) DM to manage glycaemic control and adjust insulin or other medications (SCI-Diabetes database). Currently, finger-prick self-monitoring of blood glucose (SMBG) using test strips and blood glucose meters is the most frequently used monitoring method. The National Institute for Health and Care Excellence (NICE) guideline number 17 (NG17) on the management of T1 DM recommends testing blood glucose levels at least four times a day and up to 10 or more in certain situations (e.g. desired target of blood glucose control not met, frequency of hypoglycaemia increases, legal requirement for driving, during periods of illness, during sports, when planning pregnancy, lifestyle considerations, etc.).

EUnetHTA conducted a rapid assessment which encompassed evaluation of the relative effectiveness and safety of flash glucose monitoring as a personal standalone system in

patients with diabetes treated with insulin, either through insulin pump therapy or multiple daily injections. The comparator was self-monitoring of blood glucose[1].

Freestyle Libre® received regulatory approval in September 2014 and was initially available for use in seven European countries including for private purchase in the UK. Freestyle Libre® was added to the Scottish Drug Tariff on 1st November 2017. This assessment of Freestyle Libre® is intended to provide information to support decision makers within NHSScotland. This assessment will build upon the EUnetHTA clinical effectiveness and safety review, by incorporating economic modelling, patient and public involvement, and clinical expert input specific to the Scottish clinical context.

Health technology description

Freestyle Libre® (Abbott Diabetes Care Inc.) is a flash glucose monitoring system. This differs from a continuous glucose monitoring system in that it forfeits the facilities to display a continuous real-time graph of changing glucose values, to provide alarms or remote monitoring and suitability for closed-loop systems. Glucose values are reported only when the user scans the Freestyle Libre® sensor by passing a reader or mobile phone close to the sensor.

The Freestyle Libre® system has two main parts: a handheld reader and a disposable sensor which patients wear on their body. Patients use the reader to wirelessly scan the sensor and obtain their glucose readings.

The disposable sensor has a thin, sterile filament (0.4 mm wide, inserted approximately 5 mm under the skin) attached to a small disc (30 mm × 5 mm); medical grade adhesive is used to keep the sensor in place on top of the skin once applied. The sensor is water-resistant up to 1m for up to 30 minutes and can therefore be worn while bathing, swimming and exercising. The Freestyle Libre® sensor is applied by the patient to the back of the upper arm and continuously measures glucose levels in interstitial fluid for up to 14 days. The filament draws interstitial fluid from the muscle into the sensor, where glucose levels are automatically measured every minute and stored at 15-minute intervals for 8 hours. Glucose levels can be seen at any time by scanning the reader over the sensor. The sensor is factory calibrated, which means it does not require any additional finger prick calibration during the 14 days wearing time.

The reader is handheld, lightweight, has a backlit colour touchscreen, is reusable and has a rechargeable battery that must be charged every seven days. It also has built-in blood glucose and blood ketone meters, which can be used to test finger-prick blood samples. To scan the sensor, the reader is held 1cm to 4cm above the sensor for one second. Readings can be taken through clothing. At each scan, the reader displays current glucose levels, levels over the previous 8 hours, and whether glucose levels are trending upwards or

downwards (and how fast). For a full 24 hours of data, users must scan the sensor at least once every 8 hours.

Three digital products have been created to enhance the value of the Freestyle Libre® platform including two mobile medical apps (Freestyle LibreLink® and LibreLinkUp®) and a cloud-based diabetes management system (LibreView®). As an alternative to using the reader, the sensor can be scanned with a mobile device capable of near-field communication (NFC) and on which the LibreLink® companion app has been installed. It is an optional alternative to the Freestyle Libre® reader, but the two can be used interchangeably. The LibreLink® app can be used on smartphone (Android mobile devices and iPhone) and has similar features to the reader. LibreView® is a free and secure cloud-based diabetes management system which enables patients and health care professionals (HCPs) to generate a series of reports, which reveal trends and patterns in glucose levels that can be used to make faster, more informed treatment decisions. LibreView® can also share data in near real-time with the LibreLinkUp® app, which enables authorised caregivers to remotely monitor the scan activity of their charges.

Freestyle Libre® has a CE mark for the indications below:

- Measuring interstitial fluid glucose levels in people (age 4 and older) with diabetes mellitus, including pregnant women.
- The indication for children (age 4–12) is limited to those who are supervised by a caregiver who is at least 18 years of age. The caregiver is responsible for managing or assisting the child to manage the Freestyle Libre® flash glucose monitoring system and also for interpreting or assisting the child to interpret Freestyle Libre® readings.

It is designed to replace blood glucose testing in the self-management of diabetes with the following exceptions:

- During times of rapidly changing glucose levels, interstitial glucose levels as measured by the Sensor and reported as current may not accurately reflect blood glucose levels. When glucose levels are falling rapidly, glucose readings from the sensor may be higher than blood glucose levels. Conversely when glucose levels are rising rapidly, glucose readings from the sensor may be lower than blood glucose levels.

Under the following circumstances, a blood glucose meter should be used to check the current glucose readings from the Freestyle Libre® flash glucose monitoring system sensor:

- In order to confirm hypoglycaemia or impending hypoglycaemia as reported by the sensor.
- If symptoms do not match the Freestyle Libre® flash glucose monitoring system reading.

Currently, in the UK, finger-prick blood glucose testing is needed to fulfil Driving and Vehicle Licensing Authority (DVLA) requirements to assess fitness to drive.

Epidemiology

In Scotland, at the end of 2016, the crude prevalence of diabetes was 5.4% (n=291,981) according to the Scottish Diabetes Survey[2]. Of these, 10.6% had T1 DM, 88.3% had T2 DM and the remaining <2% had other forms of diabetes. Around 56% of people with diabetes in Scotland are male.

There were 943 new cases of T1 DM in 2016 (crude incidence rate 18 cases per 100,000 population per year). For T2 DM, the number of new cases was 16, 973 (crude incidence rate 316 cases per 100,000 population per year).

In Scotland during 2017 there were approximately 60,000 patients using intensive insulin therapy that were assumed to self-monitor their blood glucose levels (excluding those using continuous glucose monitoring or sensor-augmented insulin pumps) who may meet the criteria for Freestyle Libre®. Of these, 28,531 had T1 DM and 32,342 had T2 DM (C Flach, Business Analyst, SCI-Diabetes. Personal Communication, 8 Jun 2018). A little over 1,000 patients with other types of diabetes may also qualify.

Clinical effectiveness

One European multicentre randomised controlled trial (IMPACT) examined the effects of Freestyle Libre® flash glucose-monitoring compared with SMBG, over a six month period in adults (mean age 43.7 years) with well-controlled T1 DM[3]. Participants had T1 DM for at least five years, an HbA1c concentration of ≤7.5% and reported that they self-monitored blood glucose levels three or more times each day for at least two months prior to study enrollment and were judged capable of using Freestyle Libre® by the study investigators. Although it is not possible to blind participants, a lack of blinding of investigators means that the study is at risk of bias. Another potential source of bias is that participants in the Freestyle Libre® arm had three additional telephone consultations compared with those in the SMBG arm.

At randomisation there were 241 participants. For the 121 participants randomised to the SMBG group, one woman was excluded due to pregnancy and one participant had no baseline sensor data, so the full analysis set for the SMBG group comprised 119 subjects. For the 120 participants randomised to the Freestyle Libre® group, one woman was excluded due to pregnancy. Data were therefore analysed for 119 subjects in the Freestyle Libre® group. Last observation carried forward methods were used to impute missing data for participants who withdrew or were excluded during the trial.

All participants wore the Freestyle Libre® glucose sensor in masked mode to capture 14 days of baseline data, after which the intervention group participants continued to use the device. The device was again worn in masked mode by the SMBG group participants for 14 days prior to the three and six month time points for data collection. Key outcomes from the IMPACT study are reported in Table 1.

For the Freestyle Libre® group, the mean number of SMBG tests reduced from 5.5 (standard deviation (SD) 2.0) tests per day to 0.5 (SD 0.7) during the treatment phase. The mean number of sensor scans per day was 15.1 (SD 6.9). There were no differences in total daily doses of insulin between study groups.

The primary outcome was time (hours) spent in hypoglycaemia using the surrogate outcome of sensor glucose values <3.9mmol/L (70 mg/dL) per 24 hour period calculated for the 14 days preceding the end of the six month study period. The amount of time per day spent in this range reduced for both study groups but the extent of reduction was greater for the Freestyle Libre® group, representing a statistically significant ($p<0.0001$) 38% reduction in the time participants spent in this hypoglycaemic range compared with the SMBG group. When the seven hour night-time period was considered (23.00 to 06.00) the corresponding reduction was 39.8% (statistically significant, $p<0.0001$).

A large number of related secondary outcomes were derived from sensor glucose values. No adjustment was made for multiple testing. The rate of hypoglycaemic events <3.1mmol/L (55 mg/dL) in the Freestyle Libre® group was reduced by 41.3% over 24 hours and by 34.9% at night–time compared with the SMBG group. For events <2.5mmol/L (45 mg/dL) the reduction was 48.5% over 24 hours and 44.9% at night, whilst for events <2.2mmol/L (40 mg/dL) there was a statistically significant reduction in event rates over 24 hours of 55% in the Freestyle Libre® group compared with the SMBG group. All differences were statistically significant at $p<0.0005$.

There was no statistically significant difference between groups in time in hyperglycaemia >10mmol/L (180 mg/dL). Hours per day spent in hyperglycaemia >13.3mmol/L (240 mg/dL) was statistically significantly reduced by 19.1% in the Freestyle Libre® group compared with the SMBG group ($p=0.0247$). For time in range 3.9–10mmol/L (70-180 mg/dL) a statistically significant between-group difference of one hour favoured the Freestyle Libre® group. HBA1c concentrations remained unchanged across the study period for both the Freestyle Libre® and SMBG groups.

Four patient-reported outcome measures were also reported. There were no statistically significant differences between study groups in the Diabetes Distress Scale (DDS), Hypoglycaemia Fear Survey (HFS) or overall Diabetes Quality of Life (DQoL) scores at six months when adjusted for baseline values, study centre and insulin administration method. Patient satisfaction with treatment as measured by the total treatment satisfaction aspect of the Diabetes Treatment (change) Satisfaction Questionnaire (DTSQc) was improved for

the Freestyle Libre® group compared with the SMBG group (mean difference 6.1, standard error (SE) 0.84, p<0.0001).

Table 1: key outcomes from the IMPACT randomised controlled trial (RCT)[3]

	Baseline: Freestyle Libre® n=119 Mean (SD)	Baseline: SMBG n=119 Mean (SD)	6 months: Freestyle Libre® n=119 Mean (SD)	6 months: SMBG n=119 Mean (SD)	Difference in adjusted means (SE)
Hypoglycaemia					
Time (hours) in glucose <3.9mmol/L (70mg/dL) per 24 hours	3.38 (2.31)	3.44 (2.62)	2.03 (1.93)	3.27 (2.58)	-1.24 (0.239) (-38.0%) p<0.0001
Time (hours) in glucose <3.9mmol/L (70mg/dL) per 7 hours (23.00-06.00)	1.32 (1.07)	1.48 (1.29)	0.68 (0.97)	1.23 (1.10)	-0.47 (0.118) (-39.8%) p<0.0001
Number of hypoglycaemic events <3.9mmol/L (70mgldL) per 24 hours	1.81 (0.90)	1.67 (0.80)	1.32 (0.81)	1.69 (0.83)	-0.45 (0.089) (-25.8%) p<0.0001
Number of hypoglycaemic events <3.9mmol/L (70mgldL) per 7 hours (23.00-06.00)	0.47 (0.32)	0.46 (0.29)	0.27 (0.23)	0.40 (0.29)	-0.14 (0.029) (-33.2%) p<0.0001
Hyperglycaemia					
Time (hours) in glucose >13.3mmol/L (240mg/dL) per 24 hours	1.85 (1.44)	1.91 (1.70)	1.67 (1.36)	2.06 (1.61)	-0.37 (0.163) (-19.1%) p=0.0247
Time in range					
Time (hours) glucose 3.9–10mmol/L (240mg/dL) per 24 hours	15.0 (2.5)	14.8 (2.8)	15.8 (2.9)	14.6 (2.9)	1.0 (0.30) p=0.0006
HbA1c					
HbA1c (%)	6.79 (0.52)	6.78 (0.64)	6.94 (0.65)	6.95 (0.66)	0.00 (0.059) p=0.9556
HbA1c (mmol/mol)	50.7 (5.7)	50.6 (7.0)	52.4 (7.2)	52.4 (7.2)	0.0 (0.65) p=0.9543

A prespecified subgroup analysis excluding IMPACT trial participants using continuous subcutaneous insulin infusion (CSII) and focusing on participants using multiple daily insulin injections (MDII, n=161) was reported separately[4]. Findings were in line with the initial IMPACT trial. People using Freestyle Libre® had a 46% reduction in time in hypoglycaemia <3.9mmol/L (70mg/dL) per day calculated for the 14 days preceding the end of the six month study period when compared with the SMBG group (p<0.0001).

A second European multicentre randomised controlled trial (REPLACE) examined the effects of Freestyle Libre® compared with SMBG over a six month period in adults (mean age 59.2 years) with T2 DM who had been on insulin treatment for at least six months[5]. Participants had an HbA1c concentration of between 7.5% and 12% (baseline mean 8.79%), representing a patient group with poor glycaemic control. One of the reported criteria for exclusion was 'considered by investigator to be unsuitable to participate' which may indicate selection bias. A lack of investigator blinding, and the Freestyle Libre® group having had an additional two visits and two telephone calls compared with the SMBG group, means that the study is at risk of bias.

There were 224 participants randomised in a 2:1 ratio; 149 were randomised to the Freestyle Libre® arm and 75 to the SMBG arm. In the intervention arm 139 participants completed the study (93%). In the SMBG arm, 62 participants completed the study (83%). Data analysis included all randomised participants and last observation carried forward methods were used to impute missing data.

All participants wore the Freestyle Libre® glucose sensor in masked mode to capture 14 days of baseline data after which the Freestyle Libre® group participants continued to use the device. The device was again worn in masked mode by the SMBG group participants for 14 days prior to the six month data collection. Key outcomes from the REPLACE trial are reported in Table 2.

For the Freestyle Libre® group, the mean number of SMBG tests reduced from 3.8 (SD 1.4) tests per day to 0.4 (SD 1.0) by the end of the study. The mean number of Freestyle Libre® sensor scans per day was 8.3 (SD 4.4). There was no correlation between frequency of Freestyle Libre® sensor scanning and time in hypoglycaemia or change in HbA1c. There were no differences detected in total daily dose of insulin between study groups.

The primary outcome was difference in HbA1c between study groups at six months. HbA1c values decreased in both study groups, however there was no statistically significant difference between groups in the extent of the change. For a prespecified sub-group of participants aged <65 years (n=142, 95 Freestyle Libre® and 47 SMBG) HbA1c was reduced by a greater amount in the Freestyle Libre® group and this was a statistically significant difference (p=0.0301). For participants aged ≥65 the opposite pattern was noted, with HbA1c reducing more in the SMBG group (p=0.0081).

A large number of related secondary outcomes were derived from sensor glucose values. No adjustment was made for multiple testing. The rate of hypoglycaemic events <3.1mmol/L (55 mg/dL) in the Freestyle Libre® group was reduced by 44.3% over 24 hours and by 53% at night-time compared with the SMBG group. For events <2.5mmol/L (45 mg/dL) the reduction was 48.8% over 24 hours and 57.8% at night, whilst for events <2.2mmol/L (40 mg/dL) there was reduction in event rates over 24 hours of 52.6% in the Freestyle Libre® group compared with the SMBG group. All the differences were statistically significant. There were no statistically significant differences between groups in time (hours) in hyperglycaemia >13.3mmol/L (240 mg/dL) or overall mean time in range 3.9–10mmol/L (70–180 mg/dL).

There were no statistically significant differences between study groups in Diabetes Distress Scale (DDS), or overall Diabetes Quality of Life (DQoL) scores at six months. Patient satisfaction with treatment as measured by the total treatment satisfaction aspect of the Diabetes Treatment (change) Satisfaction Questionnaire (DTSQc) was statistically significantly improved in the Freestyle Libre® group compared with the SMBG group (13.1±0.50 vs 9±0.72, p<0.0001).

Table 2: key outcomes from the REPLACE RCT[5]

	Baseline: Freestyle Libre® n=149 Mean (SD)	Baseline: SMBG n=75 Mean (SD)	6 months: Freestyle Libre® n=149 Mean (SD)	6 months: SMBG n=75 Mean (SD)	Difference in adjusted means (SE)
HbA1c					
HbA1c (%)	8.65 (1.01)	8.75 (0.98)	8.37 (0.83)	8.34 (1.14)	0.03 (0.114) p=0.8222
HbA1c (mmol/mol)	71.0 (11.1)	72.1 (10.7)	68.0 (9.0)	67.7 (12.4)	0.3 (1.25) p=0.8259
HbA1c (age <65 years)					
HbA1c (%)	8.81 (1.06)	8.93 (1.08)	8.38 (0.88)	8.60 (1.24)	-0.33 (0.149) p=0.0301
HbA1c (mmol/mol)	72.8 (11.5)	74.1 (11.7)	68.1 (9.6)	70.5 (13.5)	-3.6 (1.63) p=0.0300
Hypoglycaemia					
Time (hours) in glucose <3.9mmol/L (70mg/dL) per 24 hours	1.30 (1.78)	1.08 (1.58)	0.59 (0.82)	0.99 (1.29)	-0.47 (0.134) (-43.1%) p=0.0006
Number of hypoglycaemic events <3.9mmol/L (70mg/dL) per 24 hours	0.64 (0.63)	0.63 (0.66)	0.38 (0.45)	0.53 (0.59)	-0.16 (0.065) (-27.7%) p=0.0164
Hyperglycaemia					

Time (hours) in glucose >13.3mmol/L (240mg/dL) per 24 hours	3.1 (3.3)	3.9 (4.5)	3.5 (3.7)	3.9 (4.2)	0.1 (0.46) (2.1%) p=0.8729
Time in range					
Time (hours) in glucose 3.9–10mmol/L (70-180 mg/dL) per 24 hours	13.9 (4.5)	13.5 (5.2)	13.6 (4.6)	13.2 (4.9)	0.2 (0.58) 1.1% p=0.7925

A total of 139 Freestyle Libre® group participants completed the six month treatment period and continued into a prespecified open access phase which continued for a further six months[6]. Of this cohort, 125 participants completed the additional six month period. However, 17 participants' data were incomplete, so only 108 participants were included in the analyses. The study results suggest that improvements in hypoglycaemia noted at six months persist at one year follow-up as shown in table 3.

Table 3: hypoglycaemia outcomes from the REPLACE trial extension period (Freestyle Libre® group only)[6]

	Baseline n=108 Mean (SD)	**Six months n=108 Mean (SD)**	**12 months n=108 Mean (SD)**	**% change from baseline to 12 months**
Time (hours) in glucose <3.9mmol/L (70mg/dL) per 24 hours	1.40 (1.91)	0.47 (0.57)	0.70 (0.94)	-49.9 p=0.0002
Number of hypoglycaemic events <3.9mmol/L (70mg/dL) per 24 hours	0.67 (0.66)	0.33 (0.36)	0.40 (0.44)	-40.8 P<0.0001

Patient social aspects

A patient organisation submission was received from Diabetes Scotland (Appendix 1). Diabetes Scotland was asked to provide this submission to SHTG after their patient submission to the EUnetHTA for the review on continuous glucose monitoring (CGM real-time) and flash glucose monitoring.

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 with the submission.

Diabetes Scotland advise 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 advise 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.

Safety

In the IMPACT trial examining the use of Freestyle Libre® by patients with T1 DM (n=241) over a six month period, there were five serious adverse events recorded in each study group[3]. Six serious hypoglycaemic adverse events requiring hospitalisation or third party intervention were reported: two in the Freestyle Libre® group and four in the SMBG group. The study was not statistically powered to detect differences in the incidence of adverse events associated with hypoglycaemia. One serious adverse event, in the SMBG group, was

related to hyperglycaemia. The remaining three serious adverse events were related to cardiac or gastrointestinal disorders. Seven Freestyle Libre® group participants withdrew from the study due to device related adverse events or sensor insertion symptoms. There were 242 Freestyle Libre® sensor insertion-site symptoms experienced by randomised patients across the study groups – categorised as erythema, itching, rash, pain, bleeding, bruising, oedema and induration.

The REPLACE trial in patients with T2 DM over a six month period recorded 42 serious adverse events: 20 in the Freestyle Libre® group and 22 in the SMBG group[5]. Sixteen participants (11%) in the Freestyle Libre® group experienced a serious adverse event compared with 12 participants in the SMBG group (16%). There were three serious hypoglycaemic events in the Freestyle Libre® group and one in the SMBG group, none were reported to be related to the device. For Freestyle Libre® group participants, 4% (n=6) had device-related adverse events all of which were related to sensor adhesive reactions. In the extension of this study up to 12 months in 139 Freestyle Libre® group participants, seven participants experienced a serious adverse event (5%)[6]. Nine participants (6.5%) experienced device-related adverse events, all of which were sensor adhesive or site reactions.

A 14 day prospective single arm study on the performance of Freestyle Libre® compared with capillary blood glucose readings in 72 adult participants recorded data on adverse events[7]. One participant had a serious hypoglycaemic adverse event prior to insertion of, and not related to, the study device. Skin issues were identified in 202 site exams, with symptoms including severe itching and moderate erythema.

Another prospective 14 day single arm study examined the safety of the Freestyle Libre® device in a UK paediatric population (aged 4–17 years) with T1 DM (n=89)[8]. One participant had a serious adverse event which was unrelated to the study or device. Five participants each had one device-related adverse event, all of which concerned skin reactions (four mild, one moderate).

Within NHS National Services Scotland, the Incident Reporting and Investigation Centre (IRIC) aims to improve the safety of equipment and environments in Scotland's care services. Part of IRIC's role is to receive, assess and analyse adverse incident reports. Since 2014, IRIC received one Freestyle Libre® incident report, for information only, relating to a skin reaction. The report has not been investigated.

Cost effectiveness

Review of published literature

Twelve economic studies were identified including three cost comparison analyses[9-11], one budget impact analysis[12], and several cost-utility analyses[13-20], although the latter were only available as conference abstracts.

In one cost comparison analysis conducted in the UK[9], the annual cost per patient of Freestyle Libre® versus SMBG in people with T1 DM on intensive insulin treatment was estimated; based on acquisition costs of consumables and cost related to severe hypoglycaemic events from an NHS perspective. The study found that Freestyle Libre® was associated with an acquisition cost equivalent to approximately eight SMBG tests per day. Hence, at a testing frequency recommended by NICE[21] of 10 tests per day, Freestyle Libre® would be cost saving; whereas at the frequency observed in the IMPACT trial of 5.6 tests per day, Freestyle Libre® is more costly. However, Freestyle Libre® was assumed to be associated with a 48.5% reduction in severe hypoglycaemic events compared with SMBG testing which, if taken into account, makes Freestyle Libre® cost neutral. Freestyle Libre® was found to be particularly cost effective in people with T1 DM who need to conduct frequent testing. Similar findings have been reported in other cost studies[11, 12].

The cost-utility analyses – only available as conference abstracts[13-20] – estimate the cost-effectiveness of Freestyle Libre® vs SMBG in T1 DM or T2 DM groups across various countries (Europe and Australia, Sweden, UK, or Greece) and perspectives. They draw on data from the IMPACT and REPLACE trials, and other published literature, to estimate the costs and health benefits using the IMS Core Diabetes Model over a 50 year time horizon. In the UK analysis, a base case incremental cost effectiveness ratio (ICER) of £25,045/QALY was estimated in T1 DM and £23,842/QALY in T2 DM. The applicability of this analysis to Scotland is unclear. Costs were reported as aggregate estimates, it is not clear how these were derived, and the Freestyle Libre® price was not available. A different rate of insulin use between the two arms was also assumed, although no significant difference was observed in the trials.

Due to the general lack of transparency of the published analyses it was deemed that a de-novo economic analysis would better inform the cost-effectiveness and use of Freestyle Libre® within NHS Scotland. The model would also facilitate the exploration of a range of scenarios, and can be updated once new data become available.

Healthcare Improvement Scotland de-novo economic analysis

A detailed report of the economic modelling methods and results is presented within Appendix 2.

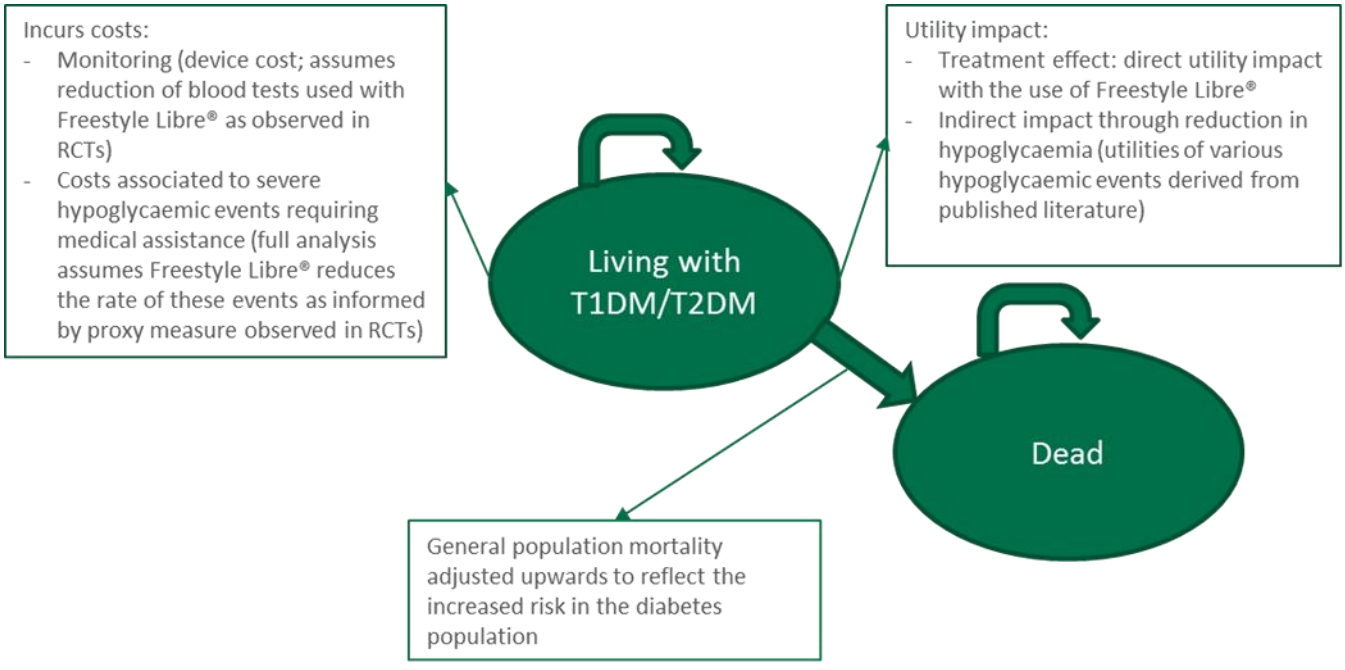
Methodology

Within the economics literature searched as part of this review, a common focus is the impact of Freestyle Libre® on the testing frequency of blood glucose and on the frequency

of hypoglycaemic events[a]; the two outcomes on which Freestyle Libre® had a statistically significant impact compared with SMBG in the IMPACT and REPLACE trials. As such, this de-novo economic analysis is built around these two outcomes, but also incorporates the associated impact on resource utilisation and health utility.

The modelling framework has a simple two state structure as depicted in Figure 1, and is essentially separated into two sub-models for T1 DM and T2 DM. A patient can be either alive or dead (i.e. the two states) in the model, with transition determined by a diabetes-specific mortality rate. One year of living with diabetes is associated with a direct resource use linked to the consumables involved in monitoring blood glucose, but also an indirect resource use due to severe hypoglycaemic events. A key assumption is that Freestyle Libre® monitoring results in a decrease in the number of blood glucose tests used by a patient. The evidence also points to a potential decreased incidence of hypoglycaemia with Freestyle Libre® monitoring compared with SMBG at various levels of severity, which can result in a further impact upon NHS resources for severe hypoglycaemic events requiring medical assistance. These potential savings relating to hypoglycaemic events are offset by an increased cost associated with the Freestyle Libre® sensors. The intervention effect within the model is assumed to persist throughout the full time horizon.

Figure 1: economic model framework



The model does not take into account the impact of HbA1c or other intermediate outcomes linked to diabetes control or management, mainly due to a lack of evidence on the impact of

[a]Non-severe hypoglycaemic events are defined as symptomatic hypoglycaemic events from which the patient can recover without third-party assistance, whereas severe events require third-party assistance

Freestyle Libre® on these outcomes. However, these variables could be included in future modeling once data become available.

The focus of the model is to determine the cost-effectiveness of Freestyle Libre® versus SMBG by considering the impact on cost of glucose monitoring, managing hypoglycaemia and the associated impact on health benefits as measured through health utility scores. All costs and health benefits were aggregated over a lifetime horizon and were discounted using the UK Treasury recommended rate of 3.5%. Only resource utilisation and costs from an NHS perspective were considered in the analysis.

The cohort characteristics in this analysis are detailed in table i in Appendix 2 and were set to reflect the populations in the IMPACT and REPLACE trials. Table ii within Appendix 2 summarises the baseline model inputs used for each type of diabetes.

Key assumptions and inputs are as follows:

- SMBG mean number of blood tests per day 5.5 (T1 DM) and 3.8 (T2 DM).
- Freestyle Libre® leads to a reduction in blood tests of 90.9% (T1 DM) and 89.5% (T2 DM).
- Freestyle Libre® leads to a reduction in non-severe hypoglycaemic events of 25.8% (T1 DM) and 27.7% (T2 DM) and a reduction in severe hypoglycaemic events of 55.0% (T1 DM) and 52.6% (T2 DM).
- Approximately 10% of severe hypoglycaemic events require medical assistance.
- Freestyle Libre® sensors have a lifetime of 14 days use.
- Freestyle Libre® sensors cost £35 each
- National Services Scotland National Procurement data were used to calculate weighted average costs for test strips and lancets involved in finger prick testing.
- Freestyle Libre® use leads to a 0.03 direct utility gain per annum.

Model validation

The model has been externally validated by Edinburgh University colleagues (report available on request). As described within the report, the following uncertainties should be considered when interpreting the results: heterogeneity associated with the evidence sources used within the economic evaluation; use of a surrogate measure from the RCTs for real-life symptomatic hypoglycaemic events; methods used to capture utility gain and patient preference associated with the device.

A panel of clinical experts also met to consider the model and to validate the various assumptions and estimates used. Clinical expert responses to specific questions about the model are available on request.

Results

Two different model structures were used. The first was a restricted model structure which only took into account the relative cost of monitoring and the direct impact of the device on health utility scores. The second model structure builds upon the first, but this time incorporates hypoglycaemic events and the associated impact on utility scores and NHS resource use. Both sets of results are presented in Tables 4 and 5 below.

Table 4: base case results for the restricted analysis

	Freestyle Libre®	SMBG	Freestyle Libre® vs SMBG
T1 DM			
Total costs	£18,074	£12,860	£5,214
Total QALYs*	9.73	7.61	2.12
ICER			**£2,459/QALY**
T2 DM			
Total costs	£10,450	£5,535	£4,916
Total QALYs	6.14	5.04	1.09
ICER			**£4,498/QALY**

Table 5: base case results for the full analysis (incorporating Freestyle Libre® impact on hypoglycaemia)

	Freestyle Libre®	SMBG	Freestyle Libre® vs SMBG
T1 DM			
Total costs	£17,010	£10,496	£6,514
Total QALYs	13.20	12.67	0.53
ICER			**£12,340/QALY**
T2 DM			
Total costs	£9,837	£4,241	£5,596
Total QALYs	7.51	7.20	0.31
ICER			**£18,125/QALY**

**QALY – Quality adjusted life year*

The sensitivity of the results to changes in the model inputs were explored in a one-way sensitivity analysis detailed in the full report. Figure 2 in Appendix 2 illustrates the inputs to which the ICER is most sensitive, these include: annual number of hypoglycaemic events; reduction in blood tests used; hypoglycaemia disutilities; Freestyle Libre® utility; and consumables costs. Various other scenarios and parameter values identified as relevant by the panel of clinical experts were also explored. Freestyle Libre® remained cost-effective across these scenarios.

Probabilistic sensitivity analysis was also carried out to help assess the joint parameter uncertainty surrounding the model. Figure 3 in Appendix 2 illustrates the results of the probabilistic sensitivity analysis and provides cost-effectiveness acceptability curves (CEACs). The CEACs show a high probability of Freestyle Libre® being cost-effective compared with SMBG.

Budget impact model

In addition to the de novo cost-effectiveness analysis, a budget impact model was also estimated which forecasted the potential cost of adopting Freestyle Libre® in NHSScotland. The structure of the budget impact model is illustrated in Figure 4 in Appendix 2. The budget impact model only takes into account the cost of monitoring, although the indirect NHS resource use associated with hypoglycaemia is also included in an optimistic scenario. Prevalence and incidence of various types of diabetes were derived from the Scottish Diabetes Survey and SCI-Diabetes database. The target population was estimated to be 59,167 patients: 28,531 with T1 DM, 32,342 with T2 DM, and 1,129 with other types of diabetes. Owing to the absence of clinical data on other types of diabetes, the model only estimated the budget impact for the T1 DM and T2 DM populations. In addition a Freestyle Libre® adoption rate of 30% in year 1 rising to 50% by year 5 was assumed.

The incremental cost of monitoring per patient of Freestyle Libre® versus SMBG is illustrated in Table 6, as well as the potential resource savings to the NHS related to a reduction in severe hypoglycaemia episodes. Budget impact model results for the base case and optimistic scenarios are presented in Table 7.

Table 6: incremental cost per patient of Freestyle Libre® versus SMBG

	Monitoring cost	Hypoglycaemia cost	Overall impact
T1 DM	£370	-£227	£144
T2 DM	£544	-£49	£495

Table 7: NHSScotland budget impact of introducing Freestyle Libre® as a replacement for self-monitoring of blood glucose

		Year 1 (30% uptake)	Year 2 (35% uptake)	Year 3 (40% uptake)	Year 4 (45% uptake)	Year 5 (50% uptake)
Conservative	**T1 DM**	£3,285,912	£4,066,273	£4,914,691	£5,831,766	£6,818,100
	T2 DM	£5,470,797	£6,770,039	£8,182,591	£9,709,451	£11,351,623
	Both	£8,756,709	£10,836,312	£13,097,282	£15,541,217	£18,169,723
Optimistic	**T1 DM**	£1,274,785	£1,577,529	£1,906,677	£2,262,460	£2,645,113
	T2 DM	£4,981,418	£6,164,439	£7,450,635	£8,840,913	£10,336,188
	Both	£6,256,203	£7,741,969	£9,357,312	£11,103,373	£12,981,301

Budget impact model results at the NHSScotland board level are presented in Appendix 3 and are based on the current size of the target population within each of the boards.

Conclusion

There is evidence from two randomised controlled trials - with some risk of bias - that use of Freestyle Libre® safely improves hypoglycaemia outcomes in adults when compared with SMBG. In these studies Freestyle Libre® improved the frequency of monitoring and greatly reduced the need for finger-prick tests. There were no randomised data relating to children or young people.

Cost effectiveness analyses were carried out to model the impact on costs and utility associated with Freestyle Libre® compared with SMBG. Results illustrated that Freestyle Libre® is likely to be cost effective for people with T1 DM and for people with T2 DM who are insulin users and self-monitor their blood glucose levels. The incremental cost-effectiveness ratio of Freestyle Libre® falls within the willingness-to-pay thresholds for an additional quality-adjusted life year. The uncertainty of the results has been captured in the probabilistic sensitivity analysis.

The restricted populations within the two trials and the heterogeneity of the populations across the other evidence sources pose challenges to the generalisability of the economic model results. However, the sensitivity analyses covered a wide range of possible scenarios, Freestyle Libre® appears likely to offer a cost-effective monitoring option for people with DM. Further data collection is encouraged to help ensure the applicability of these conclusions to the Scottish 'real-world' diabetes population.

Identified research gaps

One research gap is the lack of data relating to use of Freestyle Libre® in children or young people. Studies in this population would provide data to inform the economic model that has been created for this assessment.

Further comparative studies are encouraged to help determine the effect of Freestyle Libre® on glycaemic control and longer term diabetes complications.

Further research using data collected within the SCI Diabetes system – a shared electronic patient record to support treatment of NHSScotland patients with diabetes – is encouraged to inform future assessments of Freestyle Libre® and other diabetes-related technologies.

Ongoing research

Three ongoing RCTs were identified as outline in table 8.

Table 8: ongoing RCTs on Freestyle Libre®

Study	Intervention	Comparator	Patient group	Estimated completion date
NCT03175315	Freestyle Libre® with FLASH psycho-educational programme	Freestyle Libre® (wait list for FLASH programme)	T1 or T2 DM Age 16–75 (n=216)	March 2018
NCT02776007	Freestyle Libre®	SMBG	T1 DM Age 12–17 (n=60)	March 2019
NCT03522870	Freestyle Libre®	SMBG	T1 DM Adults (n=76)	December 2019

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

Evidence Notes are produced to inform a decision at a particular point in time and are therefore not routinely updated. They will however be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further information about the evidence note process see:

www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email shtg.hcis@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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- NHS National Services Scotland and National procurement colleagues

Healthcare Improvement Scotland development team:

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- Lucian Gaianu, Senior Health Economist
- James Stewart, Public Involvement Advisor
- Caroline Foulkes, Communications and Publications Co-ordinator
- Shonagh Ramsey, Project Officer
- Jess Kandulu, Project Officer
- Anne O'Connor, Team Support Administrator
- Members of the SHTG evidence review committee

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Appendix 1: Diabetes Scotland patient organisation submission

The Scottish Health Technologies Group
Patient Organisation

Submission Form

Subject of SHTG Assessment

Flash Glucose Monitoring -- Freestyle Libre®

Name of patient organisation

DIABETES SCOTLAND

Health/medical conditions represented

DIABETES

Contact name for this submission

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Date of submission

1 JUNE 2018

1. **Tell us about the sources you used to gather information for this submission.** (See page 6 of guidance.)

DIABETES UK SURVEY 2017
FUTURE OF DIABETES REPORT (SCOTLAND) 2017
FOCUS GROUPS.
ONLINE FORUM
HELPLINE
PATIENT STORIES (Diabetes UK NHS Grampian, NHS Lothian,)

2. What is the health condition and how does it affect the day-to-day lives of patients and their carers? (See page 7 of guidance.)

Diabetes is a serious, life-long health condition that occurs when the amount of glucose in the blood is too high because the body can't synthesise it properly. If left untreated, high and low blood glucose levels can cause serious health complications, even death. There are two main types of diabetes: Type 1 and Type 2. They're different conditions, with differing modes of onset.T1 has a rapid onset and is an auto immune response. T2 has a much more complex, multifactorial manifestation and usually has a slower, more insidious onset. Both conditions are serious and need to be treated and managed properly with a range of interventions.

Families find themselves faced with unexpected hospital stays, constant medication adjustments and lifestyle changes in order to cope with health complications from diabetes. Simple things such as going out, family events, and holidays require more planning which can lead to frustration, anger, resentment and more stress. People living with and affected by diabetes have told us that family dynamics can change due to one family member dominating the attention of others, causing feelings of jealously, abandonment etc. The strain of managing a child with diabetes, especially in the early months and years after diagnosis can cause breakdown of parental relationships. Similarly, a parent diagnosed with diabetes may require help from his or her children thus altering the established family roles.

Those dependent on insulin are required to undertake self-monitoring of blood glucose (SMBG),testing up to 6 – 10 times a day, and self-manage 24 hours a day, 365 days a year. Frequent testing can be painful, inconvenient and difficult to achieve due to the person's daily school or work routine. For example it is not always practical/easy for a teacher to SMBG in front of pupils, leave in the middle of class to SMBG, or take appropriate action if their blood glucose levels are rising/falling. It is not always easy for people to wash their hands in order to test when they are on the move.

> *"Finger prick tests can be painful and as I am testing between 6-10 times per day I am often left with small black scars on my fingertips. It is also very difficult to do a finger prick test discreetly, especially if you are walking or standing and have nowhere to place your equipment while you change lancet, open and insert a test strip, prick your finger, apply blood to the strip and then wait for the result." (T1 male, NHS Grampian)*

One of the most challenging aspects of living with diabetes is the prevention and management of hypoglycaemia (hypos), especially nocturnal (night time) hypos. Hypos are distressing not only for the person living with the condition but also for

parents, spouses and family members. They can be difficult and distressing to manage, the person may become aggressive, irritable, uncooperative, unsteady, confused etc.

Parents of young children frequently report interrupted sleeps for protracted periods (years) because they have to check their child's blood glucose levels during the night to avoid life threatening hypos and, where necessary, take remedial actions such as waking the child for blood testing or treatment.

Not everyone with diabetes comes to terms with the fact that they are living with a long term condition, or are able to sustain the intense daily vigilance required to keep healthy. The need for constant vigilance can lead to 'diabetes burnout', anxiety, obsession and eating disorders such as anorexia and diabulimia.

"Diabetes doesn't just affect someone physically. The effect of varying blood sugar levels on mood – and the relentless need to manage the condition – affects your mental health."(Future of Diabetes: Diabetes UK 2017)

"Managing an invisible condition can be isolating, and other people do not always understand what it's like to live with diabetes."

(Future of Diabetes: Diabetes UK 2017)

3. What do patients and carers want from the health technology? (See page 8 of guidance.)

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 people with diabetes and their families
- Reduce the risk of developing devastating complications such as sight loss, amputation, renal failure, stroke, acute and chronic depression

People living with diabetes and their carers want to be able to manage diabetes effectively, to understand how their conditions is affected by everyday tasks that those without diabetes take for granted. They need to know the actions to take to stay healthy and to avoid excessive high and low blood glucose levels.

Without a having a clear picture of what my glucose levels are doing, I'm essential poking around in the dark. Even with a finger

prick test it's a moment in time rather than a direction. Flash gives an interactive way of managing my diabetes I can watch things unfolding and react accordingly. I am now trying to avoid events rather than avoiding recording the event. It takes away the stress and guesswork around testing and management of my condition". (Male, T1: Diabetes UK Big Conversation 2017)

It's quick and reliable, allows me to get on with my lifestyle and not be impinged by having to finger prick so many times a day. It helped me get hb1c ready for pregnancy and was invaluable to me while pregnant as I checked bloods 3-4 times in the night. Now I have a baby it's essential to me" (T1 female NHS Lothian)

Parents want '**peace of mind** ' knowing their child can have a full night's sleep, without the need for painful 'finger pricks' in-order to avoid debilitating nocturnal hypoglycaemic episodes. The challenges, fear, and anxiety associated with hypos for both carers and people living with diabetes should not be underestimated. This is one of the most talked about topics covered in calls to Diabetes UK Helpline, in focus and support groups, and online forums. If left untreated severe hypo can lead to seizures, coma, lasting neuro deficits, and even death.

To compensate and avoid hypos individuals often test more frequently/ excessively, or run their blood glucose level higher than advised targets – thus increasing the risk of micro and macro vascular damage and serious lasting complications such as blindness, stroke, kidney disease, neuropathy and amputation; and/or withdrawing from social events/ interaction because of the fear of hypoglycaemic episodes and the possible consequences such as loss of control, hospital admission, injury through falling, discrimination and stigma.

"I experienced some terrible hypos and became so terrified that I began to stay in the high blood glucose range which was basically playing Russian Roulette with my own health." (T1 female, NHS Lothian)

The impact and time required to recover from a severe hypo varies from individual to individual. On average it **can take several hours before the person is able to resume normal tasks of daily living.** In some instances the person may not be able to attend school, college or university, thus missing vital education; or, if employed, they may be unable to attend work and potentially face disciplinary action. **All of which can impact on attainment, future prospects or life chances, financial security, mental and physical wellbeing and result in premature mortality.**

This little piece of tech has significantly changed how I manage my diabetes. I now test multiple times a day – typically more than 20 – ***yet it is far easier and more discreet than finger-prick testing****. And I'm able to* ***keep far closer to target levels****… not only by reacting to the current blood glucose reading, but more importantly to the trend arrow." (T1 diabetes using Flash GM since 2016"(Diabetes Big Conversation 2017)*

Flash technology can provide people with the tools to effectively self-mange and improve the quality of life for those living with and affected by diabetes.

With the increased information available from Flash GM I am already able to see visually the effects of food, insulin and exercise on my blood glucose. The trend arrow also allows me to take remedial action to avoid high and low blood sugar and allows me to spend more time in range which will reduce my chances of costly long term complications. It is also great being able to see overnight data which allows me to check my basal insulin dose without having to wake at 3am to do a finger prick test. " (Male T1,NHS Grampian) "

4. What difference did the health technology make to the lives of patients that have used it? (Leave blank if you didn't make contact with anyone who had experience of the health technology.) (See page 9 of guidance.)

While Flash GM (Freestyle Libre) has been approved for prescription on NHS it is not currently available in ALL areas across Scotland. Many people have chosen to self-fund the technology are already reaping the benefits; but this is not an option for others. Access to flash technology should not be governed by the ability to pay but should be based upon individual needs and person centred approaches.

The following statements are from individuals and family members who have personal experience and shared their stories with us in support of this submission:

"*It has as made my life with T1 diabetes better. It gives the freedom and confidence to manage my diabetes and enjoy life.*" (Type 1 Diabetes big conversation)

"My son is very active. He does judo, tennis, football, cricket, swimming and helps to walk the family dog too. At school he is physically and mentally active. ***No day is ever the same.***

"The Flash device has ***allowed my son his freedom and independence to test.*** *The arrows are the most important for us. At six years old my son can read his levels and immediately understand how to take care of himself.* ***We have a better understanding of how to manage his diabetes with his active lifestyle, so he can join in and experience a 'normal' childhood****." (Mother of a child with Type 1 diabetes Diabetes Big Conversation 2017)*

"IT takes away the 'wonder' of what could be going on with blood sugars and gives more detail about the in betweens... Really helpful for adjusting basils on the pump The biggest advantage for me is with exercise. Being able to scan before, during, and after is so handy. I have had less worry about nighttime readings The only thing that annoys me is that the sensors fail in low temperatures and I do a lot of winter climbing in Scottish mountains - taking gloves off can be really risky in the cold so I was looking forward to being able to scan through multiple layers but I found that both sensor and scanner were too cold to take a reading " t1 , NHS Lothian)"

5. Additional information you believe would be helpful for SHTG to consider. (See page 9 of guidance.)

The feedback we hear from people living with diabetes **is that it is life-changing.** It allows them the confidence and freedom to manage their conditions and to get on with life. It allows children to experience a 'normal childhood'. It gives parents peace of mind.

> *"The Flash device has* ***allowed my son his freedom and independence to test.*** *The arrows are the most important for us. At six years old my son can read his levels and immediately understand how to take care of himself.* ***We have a better understanding of how to manage his diabetes with his active lifestyle, so he can join in and experience a 'normal' childhood****." (Mother of a child with Type 1 diabetes Diabetes Big Conversation 2017)*

80% of NHS diabetes spending is spent on treating serious complications. Early intervention to reduce HbA1C has been shown to reduce complications such retinopathy, stroke and amputation. The use of Flash monitoring has been associated with improved glycaemic control (McKnight JA and Gibb FW Diabetes Med. 2017 May; 34(5):732). The potential health benefits through increase in the length of time people remain within 'healthy targets' and subsequent improvement in quality of life for people living diabetes will be felt by NHS Scotland in the long term.

Flash Glucose Monitoring is a relatively new technology. It is a more convenient method for glucose monitoring than capillary blood glucose monitoring for people with insulin-treated diabetes, Flash GM allows people to test as many time as needed without the cost of using test strips and lancet (though there are still occasions when testing is required). If someone with insulin dependent diabetes is currently testing 8 times daily to manage their diabetes the use of Flash GM is cost neutral (Diabetes UK Consensus Guideline for Flash Glucose Monitoring : September 2017).

No day is ever the same living with diabetes, it is a relentless condition which requires constant vigilance and management. Not everyone living with diabetes is the same- Flash GM may not suit everyone; many may feel uncomfortable having equipment /sensors attached 24 hours, or not have the inclinations to change from their present treatment regime, or will meet the criteria for access to Flash GM. Diabetes technology and care is advancing fast, diabetes services must be ready to embrace those advances, be prepared to invest in innovation, have suitably trained Healthcare professionals in place in-order to provide the right treatment, at the right time, by right person in the right setting, to enable people to live well and safely with diabetes.

Booklet : Listening to the patient voice on Flash Glucose Monitoring (Diabetes Scotland: May 2018)

Booklet.pdf

6. Please summarise the key points of your submission in up to 5 statements. When we present your submission, we will present these first. (See page 9 of guidance.)

- People with experience of using Flash GM have reported to us enormous benefits and improved quality of life. (Booklet above).
- People with diabetes have reported how Flash GM supports them to carry on with their daily lives, (sports, work, performances, and exercise) with greater ease and confidence Using Flash GM may benefit people in certain jobs where finger-prick testing is not always practical and they struggle to test regularly.
- Flash GM 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.
- Diabetes technology and care is advancing fast, diabetes service must be ready to embrace those advances, be prepared to invest in innovation, and have an appropriately trained Healthcare professional workforce .**Everyone has the right to the treatment, support and technology that will support them to live a healthy, happy life. We urge Health Boards across Scotland to make Flash Glucose Monitoring available on prescription to all those who can benefit.**

7. **Please give us details of anyone outside your group that had a role in preparing your submission.** (See page 10 of guidance.)

8. **Do you consent for your submission to be posted on the SHTG website?** (See page 10 of guidance.)

Yes	X	**No**	

Thank you for completing this form. It will be given to SHTG members to inform their development of an Advice Statement for this technology.

Appendix 2: Cost-effectiveness analysis of Freestyle Libre® flash glucose monitoring for type 1 and type 2 diabetes patients receiving intensive insulin treatment in Scotland

INTRODUCTION

Flash glucose monitoring is carried out via a small sensor that is worn on the arm. It measures interstitial fluid glucose levels every minute, with the data stored at intervals of 15 minutes for up to 8 hours. These values can be accessed any time by scanning with a reader or mobile phone. Unlike conventional finger-prick self-monitoring of blood glucose (SMBG), once applied, the sensor allows readings to be taken non-invasively, potentially reducing the number of finger-prick blood glucose tests required to appropriately monitor diabetes control.

Two randomised controlled trials (RCTs), the IMPACT[1] and REPLACE[2] trials, showed that using the flash-glucose monitoring device Freestyle Libre® in intensive insulin-treated type 1 diabetes mellitus (T1 DM) and type 2 diabetes mellitus (T2 DM) patients significantly reduced time spent in hypoglycaemia compared with standard SMBG, while substantially decreasing the number of blood glucose test strips used. However, it is not clear whether the improved outcomes observed in the trials justifies the relatively higher cost of this technology, while its relative effectiveness in other diabetes populations is uncertain. Hence, the purpose of this cost effectiveness analysis is to evaluate and explore the relative economic value of Freestyle Libre® versus SMBG in Scotland. The analysis draws on data from the aforementioned RCTs, published evidence relating to the impact of Freestyle Libre® and hypoglycaemia on health utility scores and resource use, and Scottish specific data regarding diabetes demographics, management and costs.

METHODS

Literature review

A literature search was carried out between 5 and 7 March 2018 for economic studies relating to flash glucose monitoring in people with diabetes treated with insulin. Multiple databases were searched (CRD database, Cochrane Library, Medline, Embase, and more) using various search strategies and MeSH terms which are available on request. In addition to searching for existing economic studies, the purpose of this literature search was to inform the model structure and identify potential data sources for resource utilisation, costs, utilities, or other key variables used in this analysis.

The literature search identified 12 economic studies including three published cost comparison analyses[3-5], one budget impact analysis[6], and several cost-utility analyses[7-14], the latter only being available as conference abstracts.

In one cost comparison analysis in the UK[3], the annual cost per patient of Freestyle Libre® versus SBGM in people with T1 DM on intensive insulin treatment are estimated based on acquisition costs of consumables and cost related to severe hypoglycaemic events from an NHS perspective. The study found that the Freestyle Libre® system has an acquisition cost equivalent to performing approximately 8 blood tests per day under SMBG. Hence, at a frequency of 10 (upper limit recommended by NICE[15] in T1 DM), Freestyle Libre® would be cost saving; whereas at the frequency observed in the IMPACT trial of 5.6 tests per day, Freestyle Libre® is more costly. However, Freestyle Libre® was assumed to be associated with 48.5% reduction in severe hypoglycaemic events compared with SMBG testing which, if taken into account, would make Freestyle Libre® cost neutral. Freestyle Libre® was found to be particularly cost effective in people with diabetes who need to conduct frequent testing. Similar findings have been reported in other cost studies[5, 6].

The cost-utility analyses[7-14] looked at the cost-effectiveness of Freestyle Libre® versus SMBG in T1 DM or T2 DM patients across various countries (Europe and Australia, Sweden, UK, or Greece) and adopting different perspectives but were only available as conference abstracts. They utilised data from the IMPACT and REPLACE trials – alongside other published literature – to estimate total costs and health benefit using the IMS Core Diabetes Model over a 50 year time horizon. In the UK analysis, a base case incremental cost effectiveness ratio (ICER) of £25,045 per quality-adjusted life year (QALY) was estimated in T1 DM and £23,842/QALY in T2 DM. The applicability of this analysis to Scotland is unclear. Costs were reported as aggregate estimates and it is not clear how these were derived, and the Freestyle Libre® price was not reported. A different rate of insulin use between the two arms was also assumed, even though no significant difference was observed in the trials. Owing to the general lack of transparency with the analyses it was deemed that a de-novo economic analysis would better inform the cost-effectiveness and use of Freestyle Libre® in Scotland and would facilitate the exploration of a range of scenarios.

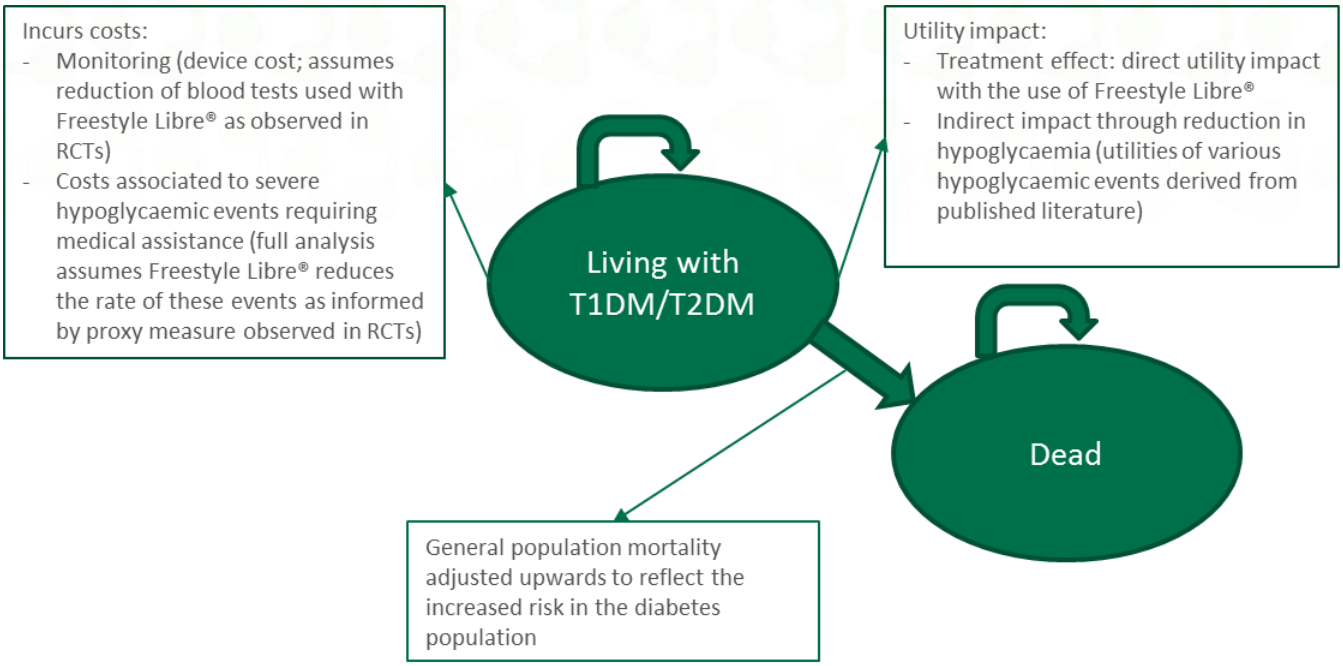
Modelling approach

A common theme across the relevant economic literature is the impact of Freestyle Libre® on blood glucose testing and on frequency of hypoglycaemia, two outcomes on which Freestyle Libre® had a statistically significant impact compared with SMBG in the IMPACT and REPLACE trials. As such, this economic analysis is built around these two outcomes, as well as the associated impact on resource utilisation and health utility.

The modelling framework has a simple two state structure depicted in Figure 1 and is separated into two sub-models, one for each of the largest diabetes types (T1 DM and T2 DM). A patient can be either alive or dead, with transition determined by a diabetes-specific mortality rate. One year of living with diabetes is associated with a direct resource use linked to the consumables involved in monitoring blood glucose, but also an indirect resource use due to severe hypoglycaemic events. The assumption is that use of the Freestyle Libre® results in a decrease in the number of blood glucose

tests used by a patient. The evidence also points to a potential decreased incidence of hypoglycaemia with Freestyle Libre® monitoring compared with SMBG at various levels of severity, which can result in a further NHS resource saving for the type of events requiring medical assistance. These potential savings are offset by an increased cost associated with the Freestyle Libre® sensors. The effect associated with the device is assumed to persist throughout the full time horizon within the model.

Figure 2: Economic model framework



The model does not take into account the impact of HbA1c or other intermediate outcomes linked to diabetes control or management, mainly due to the lack (or statistical insignificance) of evidence on the impact of Freestyle Libre® on these outcomes. Instead the focus of the model is to determine the cost-effectiveness of Freestyle Libre® versus SMBG by considering the impact on cost of monitoring, managing hypoglycaemia and the associated impact on health benefits as measured through health utility scores. All costs and health benefits were aggregated over a lifetime horizon and were discounted using the UK Treasury recommended rate of 3.5%. Only resource utilisation and costs from an NHS perspective were considered in the analysis.

The cohort characteristics in this analysis are detailed in Table i and were set to reflect the populations in the IMPACT and REPLACE trials. This determines the starting age and gender distribution of the model cohort which affects progression through the modelling framework. Use of the trial population characteristics assumes generalisability of trial outcomes, however, the trial populations may not accurately reflect the overall Scottish diabetes population, especially the T1 DM population in the IMPACT trial which had well-controlled diabetes. Also the populations across the rest of the studies used to derive model inputs are heterogeneous. Table ii summarises the baseline model inputs used for each diabetes type.

Table i: cohort characteristics

Patient characteristics	T1 DM (IMPACT)	T2 DM (REPLACE)
Start age (years)	43.7	59.2
Duration of diabetes (years)	22	17
Male (%)	56.9%	67%
Proportion white	99.6%	96.4%
BMI	25	33.2
HbA1c	6.78%	8.68%
MDI (%)	67%	95%
CSII (%)	33%	5%

BMI – Body Mass Index; MDI – multiple daily injections; CSII – continuous subcutaneous insulin infusion

Table ii: base case key inputs

Key input	Point estimate (95% CI, ± SD)	Source
T1 DM population		
Adverse events		
NSHEs (pooled incidence per person-year)	42.89 (34.08 to 51.70)	Donnelly (2005)[16]
SHEs (pooled incidence per person-year)	1.15 (0.10 - 2.19)	Donnelly (2005)[16]
Proportion NSHE nocturnal (%)	35	IMPACT[1]
Proportion SHE nocturnal (%)	40	IMPACT[1]
Resource use		
Incidence SHE requiring medical assistance (per 100 patients-years)	11.5 (9.4 to 13.6)	Leese (2003)[17]
Mean no. blood tests used per day (SMBG)	5.5 (± 2.0)	IMPACT[1]
Freestyle Libre® sensor lifetime (days)	14	Assumption
Freestyle Libre® effect		
Reduction in NSHEs (%)	25.8	Based on proxy measure: reduction in no. of events with glucose <3.9 mmol/L (70 mg/dL) observed in IMPACT[1]
Reduction in SHEs (%)	55.0	Based on proxy measure: reduction in no. of events with glucose <2.2 mmol/L (40 mg/dL) observed in IMPACT[1]
Reduction in blood tests used	90.9	IMPACT[1]
Utilities		

Baseline	0.720 (± 0.30)	Evans (2013)[18]
Disutility daytime NSHE	0.004 (0.001 to 0.006)	Evans (2013)[18]
Disutility nocturnal NSHE	0.008 (0.005 to 0.011)	Evans (2013)[18]
Disutility daytime SHE	0.047 (0.18 to 0.033)	Evans (2013)[18]
Disutility nocturnal SHE	0.051 (0.037 to 0.065)	Evans (2013)[18]
T2 DM population		
Adverse events		
NSHEs (pooled incidence per person-year)	23.31 (0 to 58.98)	Edridge (2015)[19]
SHEs (pooled incidence per person-year)	1.05 (0 to 3.69)	Edridge (2015)[19]
Proportion NSHE nocturnal (%)	45	REPLACE[2]
Proportion SHE nocturnal (%)	50	REPLACE[2]
Resource use		
Incidence SHE requiring medical assistance (per 100 patients-years)	11.8 (9.5 to 14.1)	Leese (2003)[17]
Mean no. blood tests used per day (SMBG)	3.8 (± 1.4)	REPLACE[2]
FSL sensor lifetime (days)	14	Assumption
Freestyle Libre® effect		
Reduction in NSHEs (%)	27.7	Based on proxy measure: reduction in no. of events with glucose <3.9 mmol/L (70 mg/dL) observed in REPLACE[2]
Reduction in SHEs (%)	52.6	Based on proxy measure: reduction in no. of events with glucose <2.2 mmol/L (40 mg/dL) observed in REPLACE[2]
Reduction in blood tests used	89.5	REPLACE[2]
Utilities		
Baseline	0.700 (±0.31)	Evans (2013)[18]
Disutility daytime NSHE	0.005 (0.003 to 0.006)	Evans (2013)[18]
Disutility nocturnal NSHE	0.007 (0.005 to 0.010)	Evans (2013)[18]
Disutility daytime SHE	0.060 (0.051 to 0.069)	Evans (2013)[18]
Disutility nocturnal SHE	0.078 (0.067 to 0.089)	Evans (2013)[18]
Costs (T1 DM & T2 DM)		
Blood glucose test strips (£ per unit)	£0.26 (± 0.06)	Scottish National Procurement Data
Blood glucose test lancets (£ per unit)	£0.03 (± 0.01)	Scottish National Procurement Data
Blood glucose test scanner	£0	Assumption
FSL sensor (£ per unit)	£35	National Drug Tariff Part IX

FSL scanner	£0	Assumption
NHS cost related to SHE requiring medical assistance	£1,034 (£855 to £1,253)	McEwan (2015)[20]

NSHE – non-severe hypoglycaemic event; SHE – severe hypoglycaemic event; FSL – Freestyle Libre; SMBG – self-monitoring of blood glucose; NHS – National Health Service

Model inputs

The base case inputs used in the model were derived based on the IMPACT and REPLACE RCTs, a range of published evidence sources for utility scores and resource utilisation, and national Scottish cost data.

Adverse events

The adverse events included in the model are hypoglycaemic events, which may be non-severe (NSHE) where the individual is able to take remedial action, or severe (SHE) which require third-party assistance, and can occur during the day or night. The incidence of these events in the T1 DM and T2 DM populations have been estimated in a range of observational studies[16, 19, 21].

The rates of hypoglycaemic events for T1 DM used in the model was derived from a random sample of 267 people with insulin-treated diabetes which were recruited from a population-based diabetes register in Tayside, Scotland[16]. The sample contained 94 T1 DM patients experiencing a total of 336 hypoglycaemic events (nine of which were severe events defined as hypoglycaemia requiring external assistance for recovery), with a mean of 3.57 (0-16) hypoglycaemic events per patient during the one month follow-up period. Mean age was 41 years (range 16–74), 49% were males, mean diabetes duration was 19.91 (range 0.56–58.83) years, and 91% of patients had poorly controlled diabetes (HbA1c >7.0%).

For T2 DM the rates were derived from a systematic review and meta-analysis of 46 studies, including the observational study in Tayside, looking at the rate of hypoglycaemic events in people with T2 DM on various treatment regimens. Among the insulin treated patients there were three studies (n=513) reporting mild/moderate events and 11 studies (n=5,851) reporting severe events. There was a very high degree of heterogeneity among the studies indicated by an I^2 statistic above 90%.

The proportion of nocturnal and daytime hypoglycaemic events was derived based on the proportion of events with low blood glucose observed during the night in IMPACT and REPLACE[1, 2].

Resource utilisation

A proportion of SHEs may require medical assistance leading to additional resource use for the NHS. The incidence of emergency treatment of hypoglycaemia in people with T1 DM and T2 DM was determined in an observational study of patient records in Tayside, Scotland[17]. Incidence rates were 11.5 (95% CI 9.4 to 13.6) and 11.8 (95% CI 9.5 to 14.1) events per 100 patient-years for T1 DM and T2

DM patients treated with insulin, respectively. One in three cases were treated solely by the ambulance service with no other contact with health care professionals.

The mean number of blood tests used per day before the introduction of Freestyle Libre® was estimated for each diabetes type in the IMPACT and REPLACE trials. This is the rate of testing assumed to reflect the Scottish real-world setting for people that self-monitor their blood glucose, but different rates are explored in the model in alternative scenarios. The NICE guidelines on diabetes[15, 22] recommend a testing frequency of 10 blood glucose tests per day in people with T1 DM.

The sensor lifetime was assumed to be 14 days in the base case analysis. This is the duration claimed by the manufacturer in the summary of product characteristics, although shorter durations have been observed elsewhere[23]. The manufacturer has confirmed a warranty policy that will replace up to a maximum of three non-defective sensors over a 90 day period. This means that the sensor could in fact last for as short a duration as 9.5 days and, under the current replacement policy, still cost the same per month as if it were to last 14 days.

Device-related effect

Freestyle Libre® is assumed to have a direct impact on the mean number of blood tests carried out and the occurrence of hypoglycaemia as informed by the two RCTs[1, 2]. Self-administered blood tests may still be performed and are in fact recommended to confirm out-of-range values of blood glucose or as a requirement of the DVLA before driving. The IMPACT and REPLACE trials showed a high and significant drop in the number of blood tests used, from 5.5 to 0.5 tests per day (91% drop) in T1 DM and from 3.8 to 0.4 (90% drop) in T2 DM.

Although the trials did not record patient-reported hypoglycaemic events per se, apart from severe ones for which there was no significant difference, there was a significant drop associated with Freestyle Libre® in the number of events with blood glucose levels below certain thresholds (hypoglycaemic states) which are a strong predictor of actual hypoglycaemic events. It is this decrease that was used as a surrogate measure of the impact of Freestyle Libre® on non-severe hypoglycaemic events (NSHEs) and severe hypoglycaemic events (SHEs), which was validated by a panel of clinical experts.

Utilities

The impact on health utility of daytime and nocturnal hypoglycaemia has been investigated in a time trade-off survey in five countries, including the UK[18]. The questionnaire was applied to both a general population and a diabetes population, all of which were adults. For the model baseline values, the results in the diabetes population were considered. This group was comprised of 551 people with T1 DM, 56% male with mean age 39 ± 14, and 1,603 with T2 DM, 56% male with a mean age 54 ± 12 SD. Overall, the disutilities obtained from the populations with T1 or T2 DM were similar to those of the general population. However, the T2 DM population reported a statistically significantly higher disutility for severe nocturnal hypoglycaemia ($p = 0.008$) compared with the general population.

Another time-trade-off study[24] sponsored by the manufacturer of Freestyle Libre® and conducted in 209 participants (51.7% women; mean age 42.1 years) from the UK general population (London and Edinburgh) estimated a statistically significantly greater utility associated with Freestyle Libre® compared with SMBG. Participants valued health states that were drafted and refined on the basis of literature, clinician input, and a pilot study. The two health states had identical descriptions of diabetes and insulin treatment, differing only in glucose monitoring approach. Both health states required checking glucose levels about 3 times per day which is likely to represent an underestimate of the actual real world testing frequency under SMBG. In this respect, the utility increment is likely to be a conservative estimate. However, it should also be noted that the health state associated to Freestyle Libre® monitoring did not include any finger prick testing, which may have led to disutility.

The utility scores were applied to the number of years lived by the cohort of patients to derive quality-adjusted life year (QALY) estimates.

Costs

Consumables costs involved in self-monitoring of blood glucose, namely strips and lancets, have been estimated from Scottish National Procurement data by taking a weighted average that accounts for the distribution of quantities of various brands purchased. The average cost estimated assumes that prices remain constant and that each brand of test would be displaced uniformly following Freestyle Libre® introduction, in line with its current share of the market. This assumption might not necessarily hold in practice and a preference shift towards the Freestyle Optimum brand of blood glucose test strips, which can be readily used with the Freestyle Libre® device, may be observed. A very restrictive approach where all blood glucose tests would be replaced with the Optimum brand, which is more costly than the weighted average, was tested in the sensitivity analysis but it did not have a noteworthy impact. It has also been assumed that a patient would use a ratio of strips to finger-prick lancets of one to one – disposed after a single use.

The price for a single Freestyle Libre® sensor used is the list price included on the Scottish Drug Tariff Part IX[2].

The scanners involved in both types of monitoring have been assumed to be offered at no cost by the manufacturers which is in line with the current arrangements. This has been confirmed by the Freestyle Libre® manufacturer, but it may be worth exploring whether such an agreement would still apply for regular SMBG tests with the prospect of a decreasing market share.

The healthcare resource implications of hypoglycemia-related hospital admissions was investigated in a retrospective record-linked cohort study in England[20]. The cohorts consisted of 1,131 patients aged ≥18 years with a diagnosis of T1 DM or T2 DM between January 1, 2002 and October 30, 2012 in the Clinical Practice Research Datalink database, who had initiated insulin treatment and had a recording of hypoglycemia in the same period. Mean cost per admission was £1,034 (95% CI £855 to

[2] http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/Docs/March-2018/2018-03-SDT-PART9.pdf

£1,253) which is the cost applied in the model to the proportion of SHEs requiring medical assistance.

Costs have been inflated to current prices using a series of gross domestic product (GDP) deflators at market prices from the Office for National Statistics[3].

Mortality

Age and gender specific all-cause mortality rates for the general population – drawn from the National Records of Scotland[4] – were used in the model. These were adjusted using diabetes-specific mortality rates in the general population to obtain all-cause non-diabetes mortality rates in the general population. Owing to the fact no age and gender specific mortality rates were available in the Scottish diabetes population specifically, and because these were needed to inform transition probability in the model, they were estimated by applying an upward adjustment factor to the all-cause non-diabetes mortality rates in the general population. This factor represents the proportional increase in the mortality rate in the diabetes population compared with the general population at the age category given by the mean age of the Scottish diabetes population. This method assumes that the adjustment factor does not vary with age which is a limitation of the model, although it is unlikely to have an important impact on the results. All mortality rates were transformed to one-year probabilities using an approximation[5].

Sensitivity analysis

The structural uncertainty in the model was explored by removing certain inputs. A restricted analysis was considered which removes any effect that Freestyle Libre® might have on hypoglycaemia and the associated impact on resource use and health utility scores. In this restricted analysis only the monitoring costs and the direct utility impact of Freestyle Libre® were included.

One-way sensitivity analyses were performed by varying the key model inputs across their 95% CI range where available, or by ±20% where confidence interval were not available. These analyses identified those parameters to which the cost-effectiveness results were most sensitive.

To explore the joint uncertainty in the model input estimates, a probabilistic sensitivity analysis (PSA) was conducted by assigning a specific probability distribution for each of the key model inputs and running 1,000 simulations of the model results. The shape and form parameters for the model input distributions were estimated from point estimates and standard errors, where available, using the method of moments statistical approach (or assumed where point estimate statistics were not available). The type of distribution attached to each model input and the estimated parameters of the distribution are presented in table iii. Cost-effectiveness acceptability curves (CEACs) were

[3] https://www.gov.uk/government/collections/gdp-deflators-at-market-prices-and-money-gdp
[4] https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/age-standardised-death-rates-calculated-using-the-esp
[5] The approximation used to transform rates to probabilities is: $probability = 1 - e^{(-rt)}$, where r is the mortality rate and t is the desired cycle length

plotted based on the PSA which inform the probability of Freestyle Libre® being cost-effective at various willingness-to-pay thresholds.

Table iii: probability distributions for model inputs used in the PSA

Model input	Assigned distribution	Alpha	Beta
T1 DM population			
NSHE	Gamma*	91.05	0.47
SHE	Gamma	4.70	0.24
NSHE night (%)	Beta**	35.00	65.00
SHE night (%)	Beta	40.00	60.00
SHE* (%)	Gamma	115.20	0.10
No. tests	Gamma	899.94	0.01
Reduction NSHE	Beta	4.13	5.87
Reduction SHE	Beta	5.50	4.50
Reduction tests	Beta	9.09	0.91
Baseline utility	Beta	887.93	345.31
NSHE daytime disutility	Beta	15.30	3809.93
NSHE nocturnal disutility	Beta	27.09	3359.35
SHE daytime disutility	Beta	35.90	727.86
SHE nocturnal disutility	Beta	48.33	899.29
FSL utility	Beta	64.92	2099.22
Strip cost	Gamma	94146.34	0.00
Lancet cost	Gamma	35268.30	0.00
SHE* cost	Gamma	85.64	12.07
T2 DM population			
NSHE	Gamma	1.64	14.21
SHE	Gamma	0.61	1.73
NSHE night (%)	Beta	45.00	55.00
SHE night (%)	Beta	50.00	50.00
SHE* (%)	Gamma	101.12	0.12
No. tests	Gamma	1097.73	0.00
Reduction NSHE	Beta	4.43	5.57
Reduction SHE	Beta	5.26	4.74
Reduction tests	Beta	8.95	1.05
Baseline utility	Beta	2451.34	1050.57
NSHE daytime disutility	Beta	95.55	19015.41
NSHE nocturnal disutility	Beta	20.76	2945.23
SHE daytime disutility	Beta	160.43	2513.46
SHE nocturnal disutility	Beta	178.02	2104.23
FSL utility	Beta	64.92	2099.22
Strip cost	Gamma	94146.34	0.00
Lancet cost	Gamma	35268.30	0.00
SHE* cost	Gamma	85.64	12.07

**Gamma distribution is bounded by 0 and ∞ and is commonly used to model resource utilization and costs*

***Beta distribution is bounded by 0 and 1 and is commonly used to model probabilities and utilities*

Model validation

The model has been externally validated by University of Edinburgh University health economics researchers. All suggestions and limitations reported were implemented and discussed in this report. The checks involved in the technical validation are listed below and a full report is available on request:

- Detection of coding errors
- Sheet by sheet testing, including macros
- Check model parameters, testing of dropdown menus, names of cells, and all switches, including all sensitivity analyses
- Check if any elements seem redundant
- Check intended functionality of macros versus actual functionality and for interpretability
- Run model with extreme values
- Appropriate transition of the conceptual model
- Appropriateness of data and model

In addition to this, a panel of clinical experts considered the model and validated the various assumptions and input estimates used. Clinical expert responses to specific questions about the model are available on request.

RESULTS

Base case

Table iv presents base case results of the full analysis which incorporates the relative impact of Freestyle Libre® on hypoglycaemia and the associated resource use and disutility, as well as the direct impact on the cost of monitoring and utility. These results are based on the key input parameters detailed in table ii and are reported separately for T1 DM and T2 DM.

Table iv: base case results of full analysis (assumes impact of FSL on hypoglycaemic events)

	Freestyle Libre®	SMBG	Freestyle Libre® vs SMBG
T1 DM			
Total costs	£18,074	£12,860	£5,214
Total QALYs	9.73	7.61	2.12
ICER			**£2,459/QALY**
T2 DM			
Total costs	£10,450	£5,535	£4,916
Total QALYs	6.14	5.04	1.09
ICER			**£4,498/QALY**

Based on the incremental cost-effectiveness ratios (ICERs) shown here, Freestyle Libre® seems to offer good value for money compared with SMBG in both T1 DM and T2 DM populations, assuming the populations have the mean testing frequencies and hypoglycaemia rates detailed in table ii, and that Freestyle Libre® directly impacts these two measures as observed in RCTs, plus having a direct impact on utility linked to patients' preference for the device itself.

Restricted analysis

The reduction in frequency of hypoglycaemia was based on a surrogate measure from the two RCTs which estimated the number of events with glucose level below certain thresholds – an approach validated by the clinical experts. However, in order to explore the structural uncertainty in the model, results were estimated in a restricted analysis which discounted any impact of Freestyle Libre® on hypoglycaemia and the associated resource use and disutility. Instead, this analysis only focused on the difference in cost of monitoring and the direct impact of Freestyle Libre® on utility. Results of the restricted analysis are reported in table v.

Table v: restricted analysis results (only considering cost of monitoring and impact of treatment on utility)

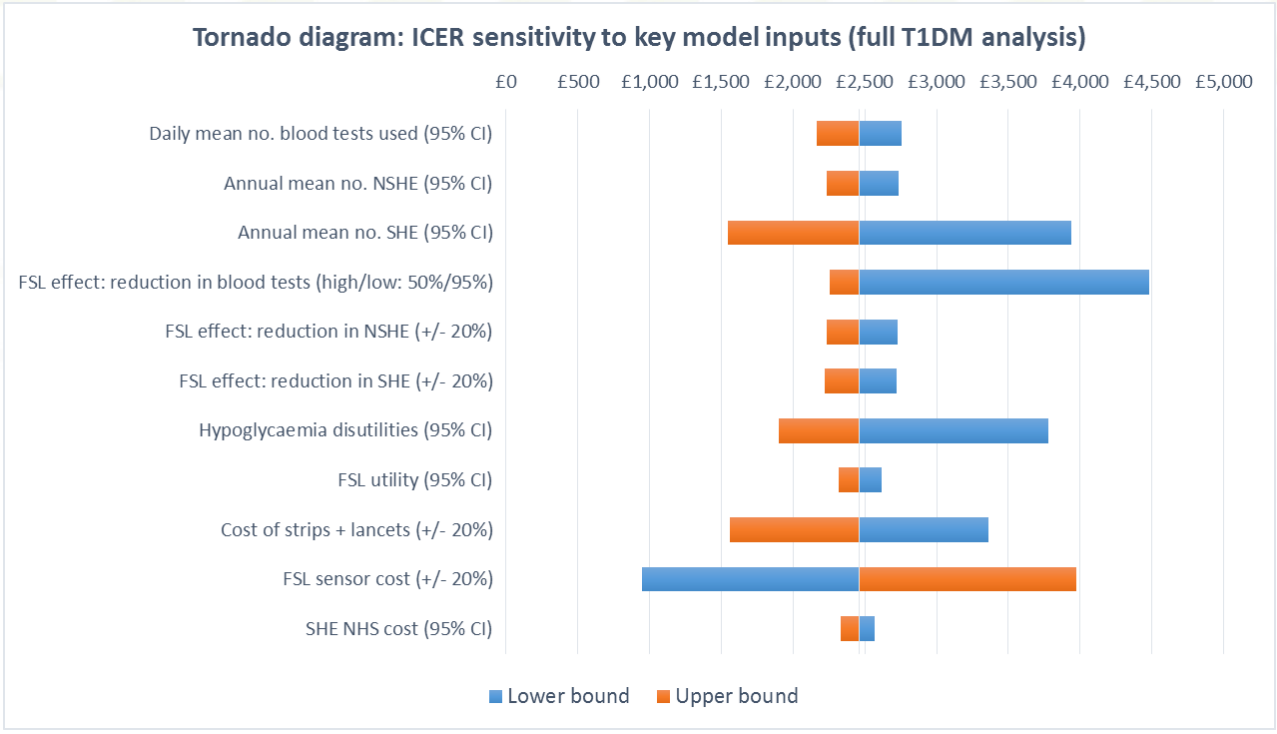
	Freestyle Libre®	SMBG	Freestyle Libre® vs SMBG
T1 DM			
Total costs	£17,010	£10,496	£6,514
Total QALYs	13.20	12.67	0.53
ICER			**£12,340/QALY**
T2 DM			
Total costs	£9,837	£4,241	£5,596
Total QALYs	7.51	7.20	0.31
ICER			**£18,125/QALY**

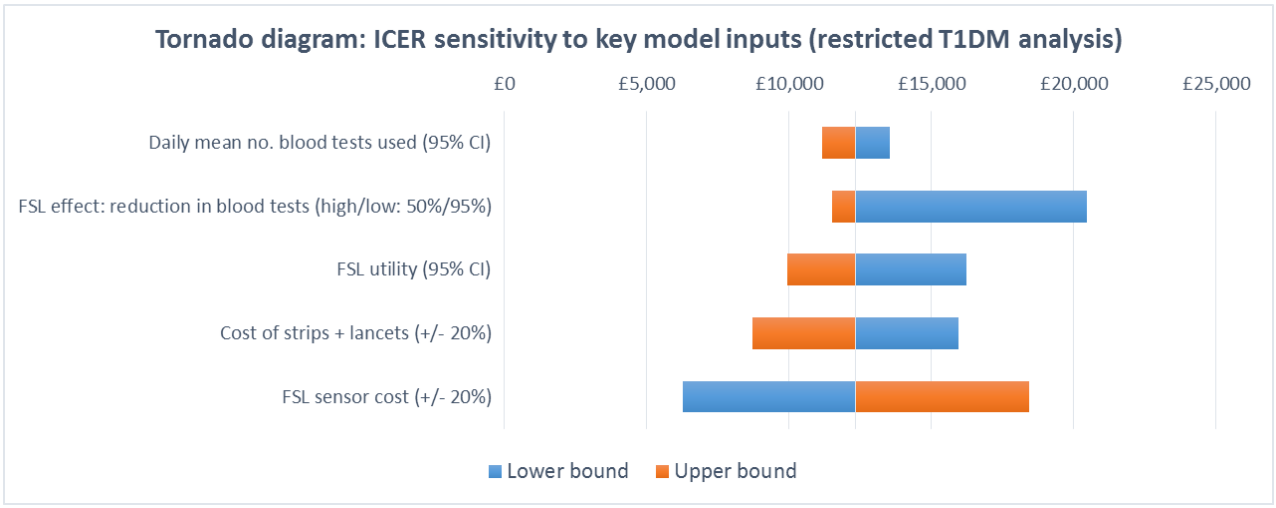
Even at the slightly higher ICER as shown in the restricted analysis, Freestyle Libre® still seems to offer good value for money compared with SMBG based on commonly accepted willingness-to-pay thresholds.

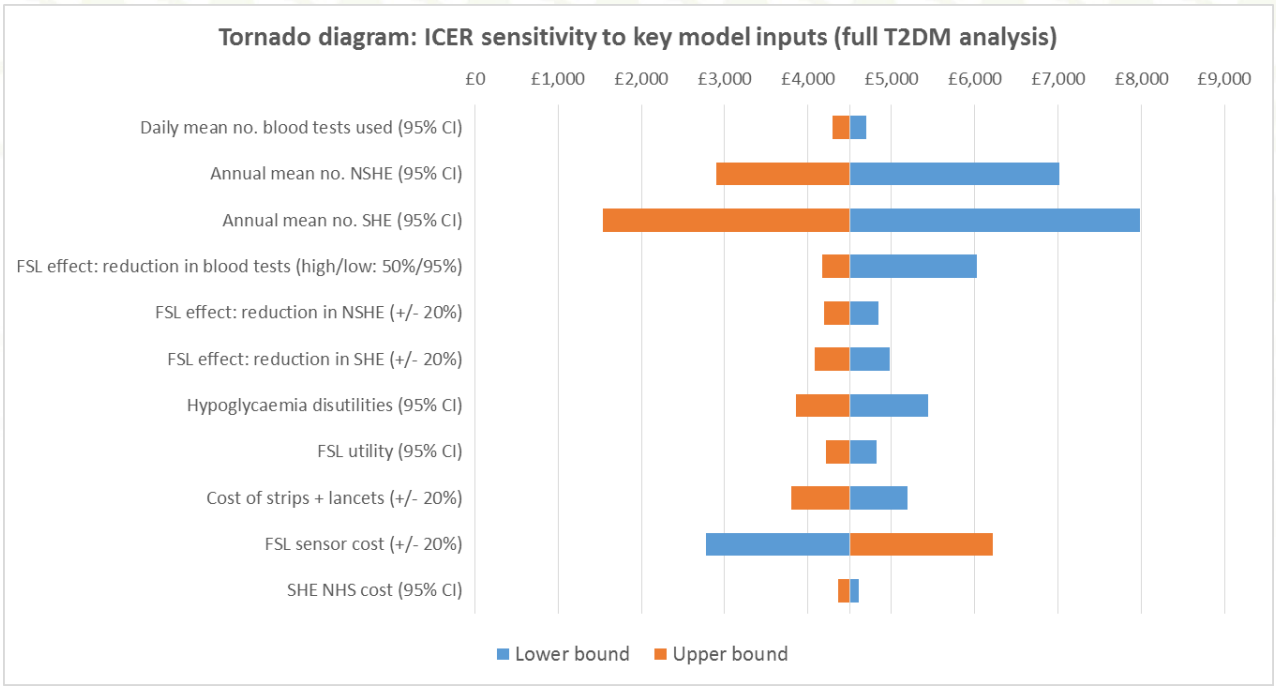
One-way sensitivity analysis

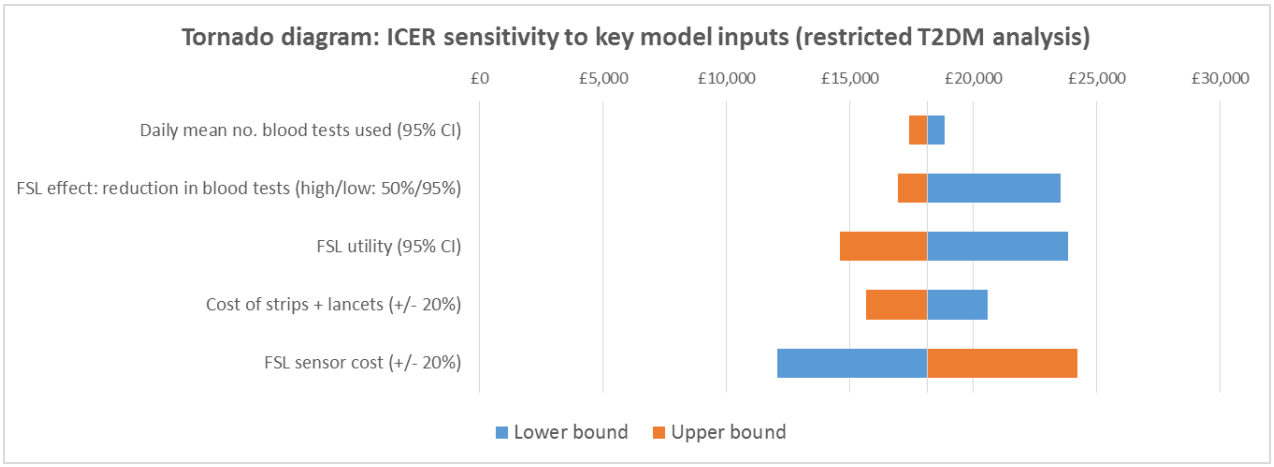
The uncertainty in key model inputs was explored in a one-way sensitivity analysis. Figure 2 presents model inputs to which the ICER is most sensitive in the full and restricted analysis for both T1 DM and T2 DM. Inputs were varied across their 95% confidence interval or by ±20% where this was not available. For inputs in which such a variation was not feasible, such as the reduction in mean number of blood tests used per day, a high/low estimate was used as detailed.

Figure 3: one way sensitivity analysis of key model inputs









FSL – Freestyle Libre

Key parameters affecting model results in the full analysis for T1 DM are the annual number of SHE, the reduction in blood tests used on Freestyle Libre®, hypoglycaemia disutilities, and consumables costs. In addition, the ICER is fairly sensitive to the device-related utility in the restricted analysis. This shows the model results in the full analysis are relatively more reliant on the impact of Freestyle Libre® on hypoglycaemia rather than its direct impact on utility or cost of monitoring. In both scenarios ICERs remain within commonly accepted willingness-to-pay thresholds, with the ICER rising above £20,000/QALY only when Freestyle Libre® is assumed to lead to a low (50%) reduction in the number of blood tests used compared with SMBG in the restricted analysis.

For the T2 DM full analysis key parameters seem to be the annual number of hypoglycaemic events of any type, reduction in blood tests, and Freestyle Libre® sensor cost. Cost of strips/lancets are less important for this patient group since T2 DM patients generally test less. Device-related utility again becomes important in the restricted analysis, yet ICERs remain under £25,000/QALY.

During the clinical expert panel session, key parameters were discussed and debated. Of particular note (also reflected in the expert responses to the questionnaire – available on request):

- The assumptions surrounding the baseline number of finger prick blood tests was assumed to be optimistic. For T1 DM patients, an average of five tests per day was felt to be more realistic, and that 3–4 per day should also be tested. When three tests per day are assumed, the ICER increases to £4,505/QALY in the full analysis and to £20,577/QALY in the restricted analysis. For T2 DM, 3.8 tests per day was assumed to be very optimistic, with two per day a more likely estimate. A testing frequency of two tests per day increased the ICER to £6,142/QALY in the full analysis and to £23,947/QALY in the restricted analysis. The threshold of testing frequency above which Freestyle Libre® becomes less costly and more effective (dominating) compared with SMBG is 8.2 and 8.9 in the full and restricted T1 DM analyses respectively; the equivalent frequencies for the T2 DM population are 8.2 and 8.8 respectively.
- The experts agreed that a strips to lancets ratio of 1:1 is the recommended optimal, however it was recognised that in practice this may be as high as 5:1. In the latter scenario, the ICER increased to £2,866/QALY and £13,973/QALY in the full and restricted T1 DM analysis, and to £4,811/QALY and £19,235/QALY in the full and restricted T2 DM analysis respectively.
- One expert suggested modelling a reduction to two tests per day in order to cover DVLA requirements. This increased the ICER to £3,810/QALY and £17,765/QALY in the full and restricted T1 DM analyses respectively, and to £5,972/QALY and £23,186/QALY in the full and restricted T2 DM analyses respectively.

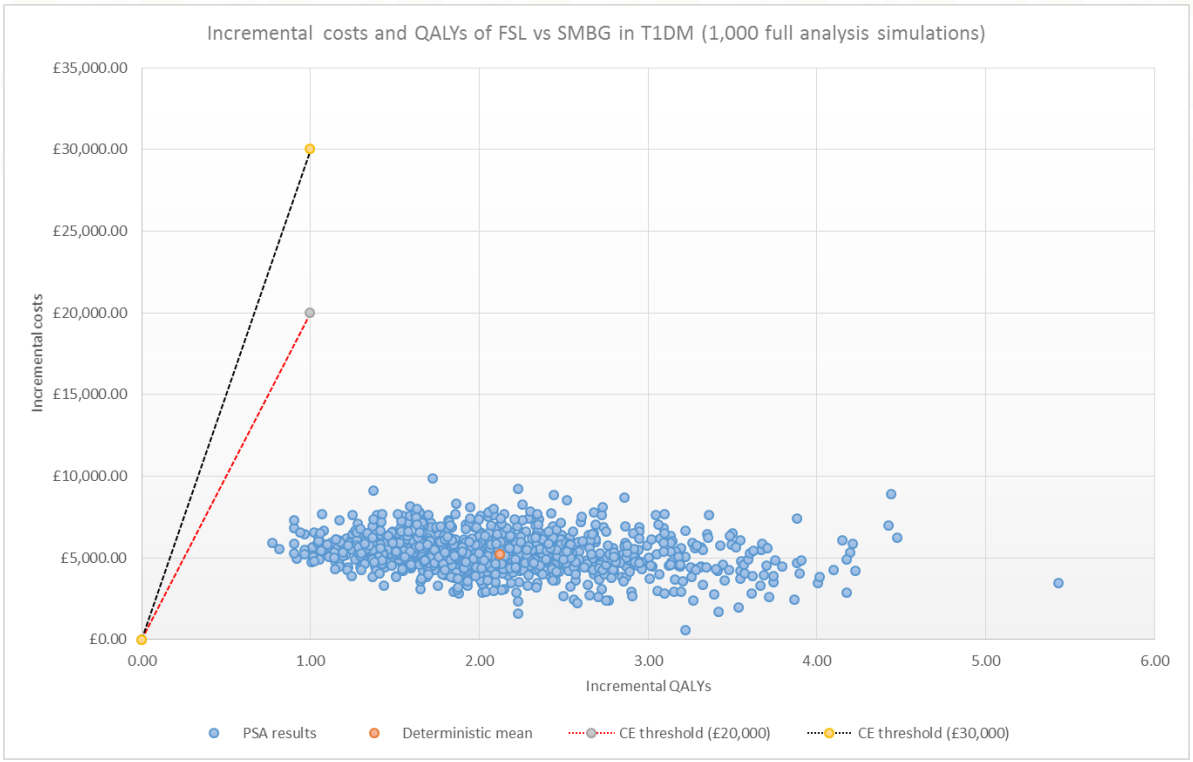
Additionally, the following scenarios (extreme values) were explored:

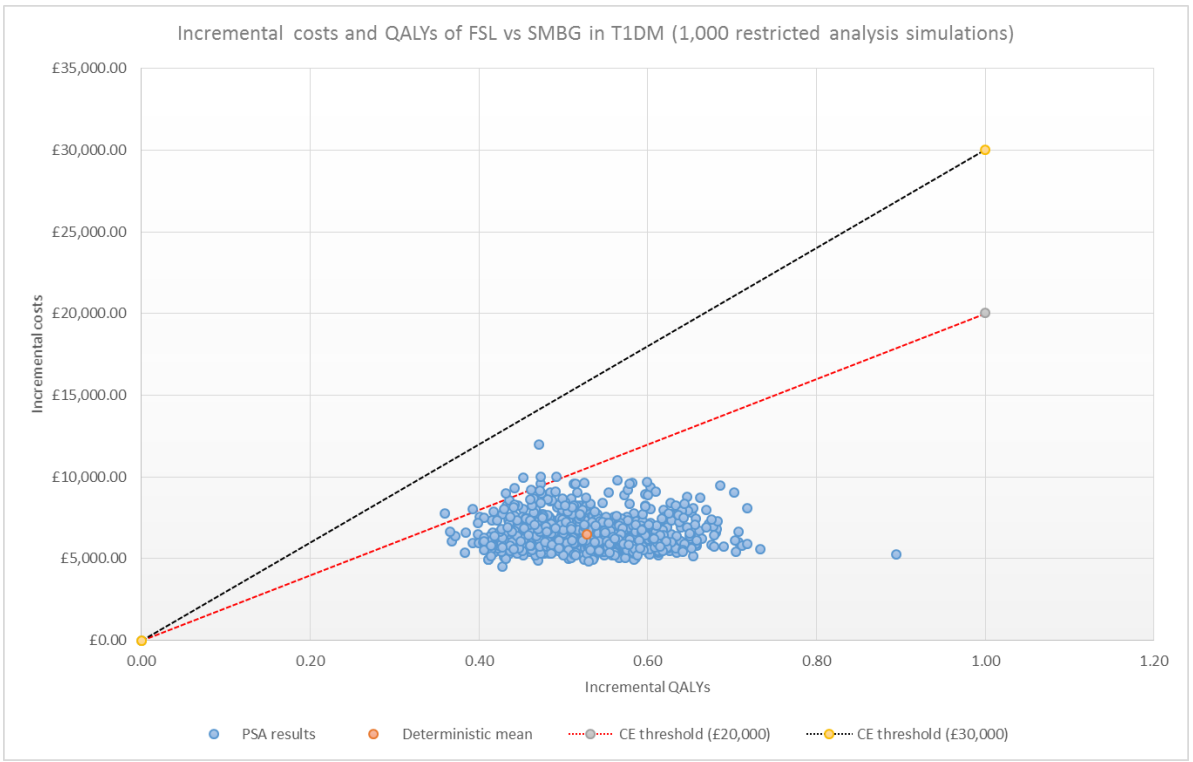
- The proportional reduction in the number of tests used was changed to an absolute reduction, reflecting a drop to 0.5 tests per day in the T1 DM population and to 0.4 tests per day in the T2 DM population as observed in the two RCTs following Freestyle Libre® introduction. Hence this frequency of testing was assumed in the Freestyle Libre® arm regardless of the baseline testing rate in the SMBG arm. This absolute decrease seems more plausible rather than a proportional decrease given the fact that the two Freestyle Libre® arms in the trials have a very similar rate of testing whereas the two SMBG rates have very different rates. Hence, when a drop from three tests per day to 0.5 was considered in T1 DM the ICER further increased to £4,710/QALY in the full analysis and to £21,379/QALY in the restricted analysis. In T2 DM, if a drop from two tests per day to 0.5 was considered the ICER increased to £6,438/QALY in the full analysis and to £24,994 in the restricted analysis.
- Since roughly a third of the events requiring medical assistance only resulted in an ambulance being called out, the overall resource impact might be overestimated since the cost estimate is based on hypoglycaemia episodes treated in hospitals. To account for this a reduction by a third in the cost estimate of treating a severe hypoglycaemia event was explored, which only had a small impact, increasing the full analysis ICER to £2,668 in the T1 DM population and to £4,709 in the T2 DM population respectively.

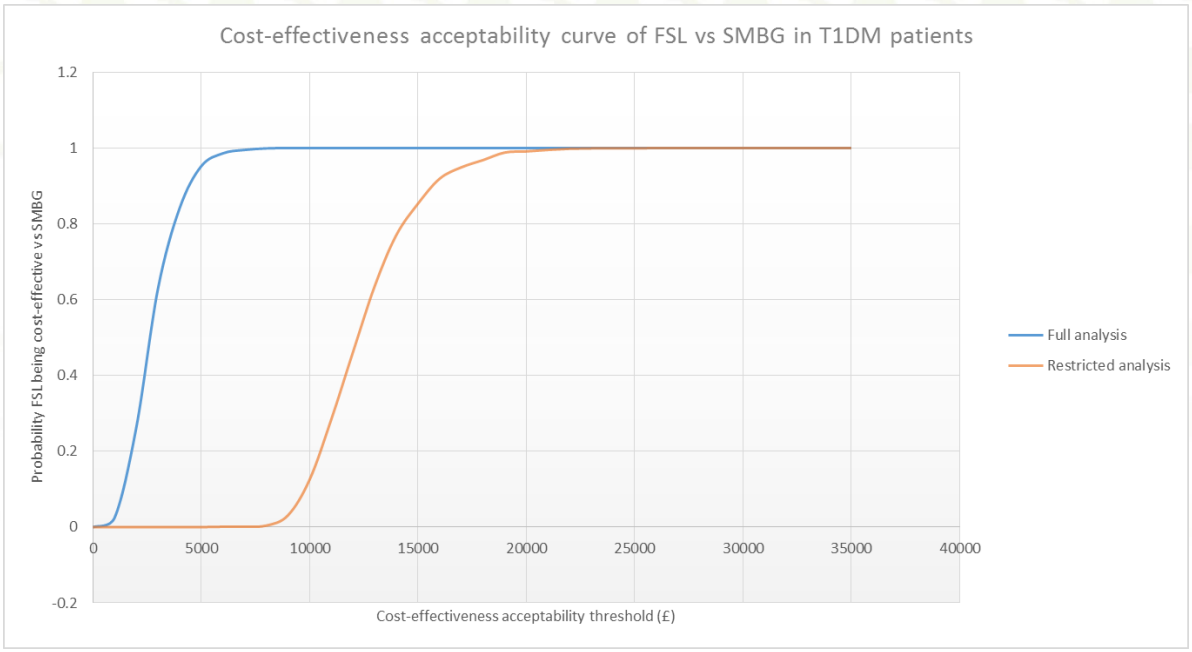
Probabilistic sensitivity analysis

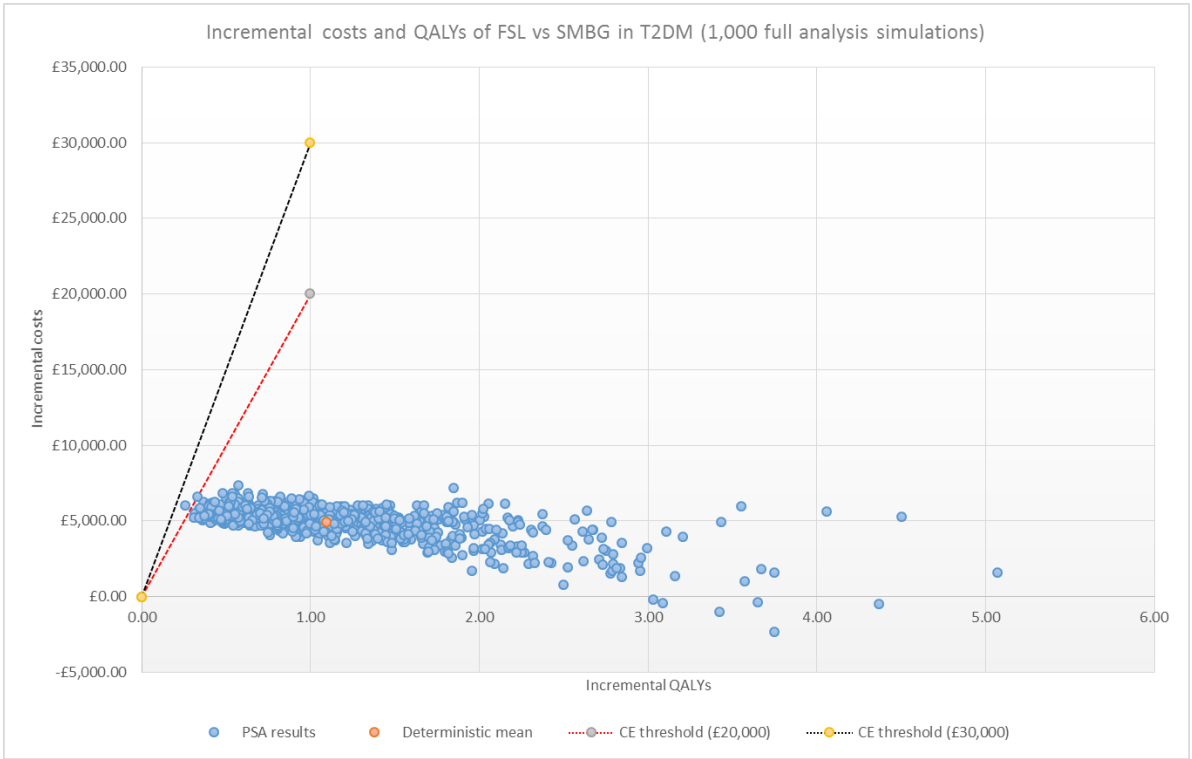
Plots of the PSA results together with CEACs which give the probability of Freestyle Libre® being cost-effective at various levels of the willingness-to-pay threshold are presented in Figure 3.

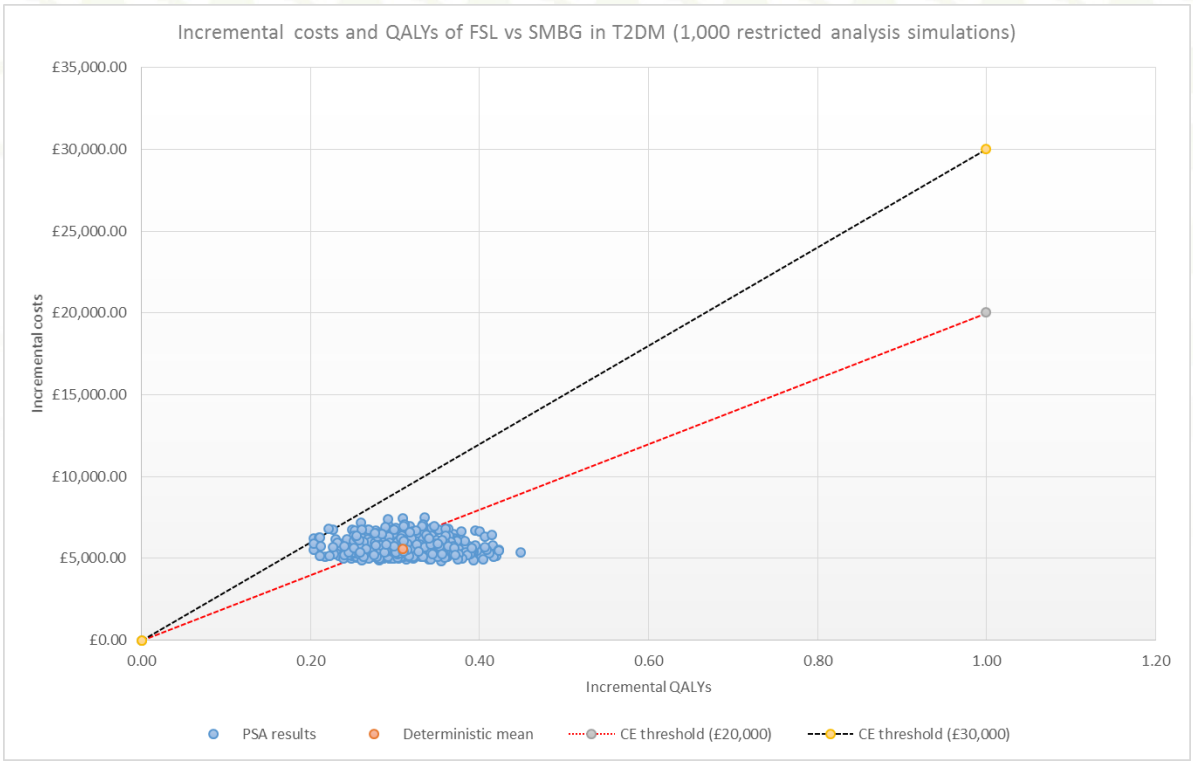
Figure 4: probabilistic sensitivity analysis results

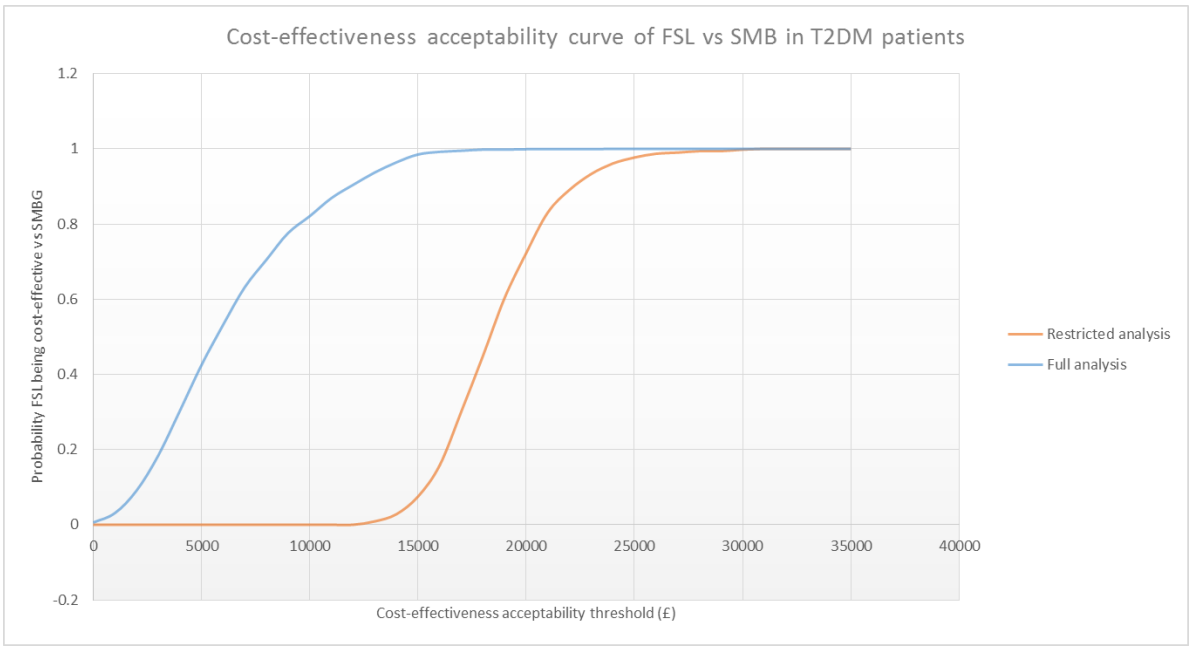





Cost-effectiveness acceptability curve of FSL vs SMBG in T1DM patients
Probability FSL being cost-effective vs SMBG
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
0
5000
10000
15000
20000
25000
30000
35000
40000
Cost-effectiveness acceptability threshold (£)
Full analysis
Restricted analysis


Incremental costs and QALYs of FSL vs SMBG in T2DM (1,000 full analysis simulations)
Incremental costs
£35,000.00
£30,000.00
£25,000.00
£20,000.00
£15,000.00
£10,000.00
£5,000.00
£0.00
-£5,000.00
0.00
1.00
2.00
3.00
4.00
5.00
6.00
Incremental QALYs
PSA results
Deterministic mean
CE threshold (£20,000)
CE threshold (£30,000)





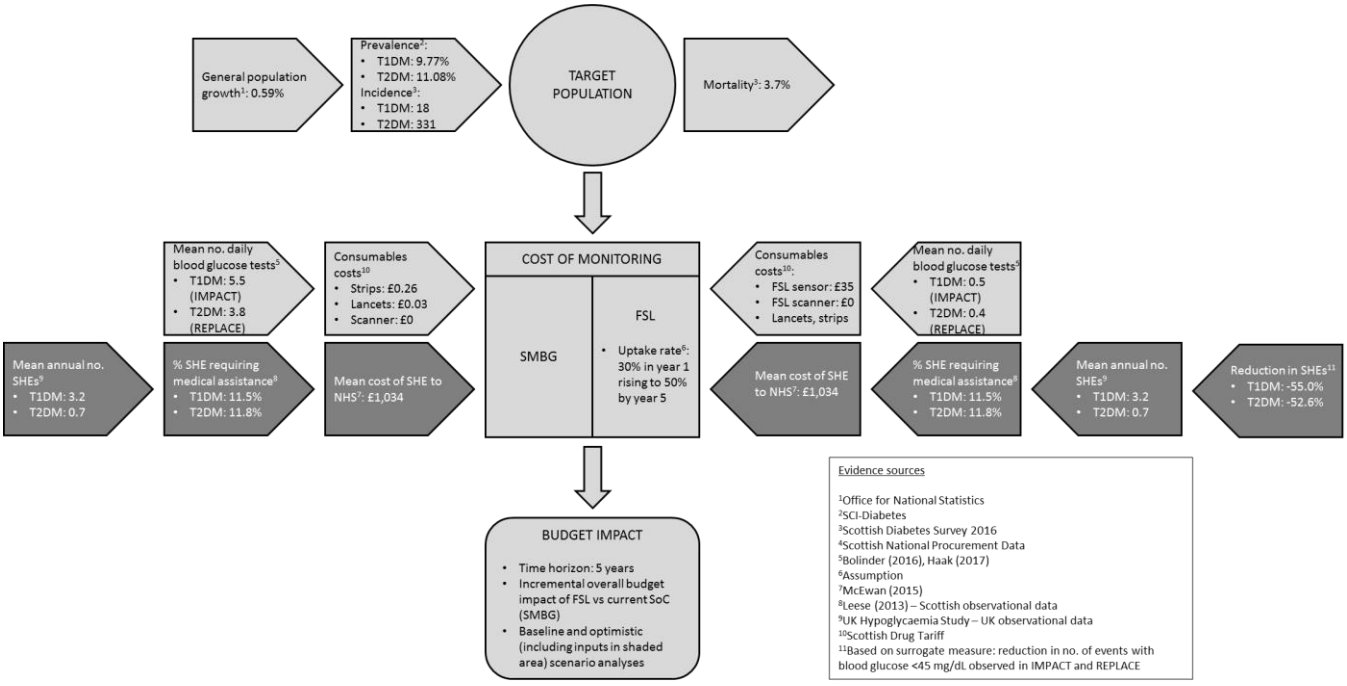
In the full analysis in both T1 DM and T2 DM populations, most simulation points fall to the right of the two lines representing thresholds of £20,000/QALY and £30,000/QALY respectively. This demonstrates a high probability of Freestyle Libre® being cost-effective compared with SMBG in the full analysis which is also indicated by the CEAC curve corresponding to the full analysis which is very steep for low thresholds. When the analysis is restricted, a higher proportion of points cross the first line indicating a lower probability of Freestyle Libre® being cost-effective, which is also indicated by the steepness of the CEAC curves at higher thresholds, but the probability still remains high: 99.1%

of the points fall below the £20,000/QALY threshold in the restricted T1 DM analysis, whereas in the T2 DM restricted analysis this proportion is 72.3%.

Budget impact

In addition to the cost-effectiveness analysis, a budget impact model was estimated which forecasted the potential cost of adopting Freestyle Libre® for NHSScotland. The structure of the budget impact model is illustrated in Figure 4. The budget impact model only takes into account the cost of monitoring (and the indirect resource use to NHS associated to hypoglycaemia in a separate optimistic scenario). Prevalence and incidence of various types of diabetes were derived from the Scottish Diabetes Survey and SCI-Diabetes database. These data show that the target population, namely people with diabetes on intensive insulin who are self-monitoring their blood glucose, is roughly 20% of the overall diabetes population. The target population amounts to 59,167 patients: 28,531 having T1 DM, 32,342 having T2 DM, and 1,129 having other types of diabetes. Due to the absence of clinical data on other types of diabetes, the model only estimated the budget impact in the T1 DM and T2 DM populations. A Freestyle Libre® adoption rate of 30% in year 1 rising to 50% by year 5 was assumed.

Figure 5: budget impact model framework



The incremental cost of monitoring per patient of Freestyle Libre® versus SMBG is given in table vi, as well as the savings to the NHS related to severe hypoglycaemia episodes.

Table vi: incremental cost per patient of Freestyle Libre® vs SMBG

	Monitoring cost	Hypoglycaemia cost	Overall impact
T1 DM	£370	-£227	£144
T2 DM	£544	-£49	£495

Budget impact model results for the base case and optimistic scenarios are presented in table vii. Based on an initial adoption rate of 30%, rising to 50% after five years, and assuming testing frequency drops from 5.5 to 0.5 and from 3.8 to 0.4 in the T1 DM and T2 DM populations respectively, the overall budget impact of introducing Freestyle Libre® flash monitoring technology as a replacement for self-monitoring of blood glucose is approximately £8.8m in year 1, rising to £18.2m by year 5. In the optimistic scenario, when the potential reduction in severe hypoglycaemic events requiring medical assistance is considered, the overall impact is £6.3m rising to £13m by year 5.

Table vii: NHSScotland budget impact of introducing Freestyle Libre® as a replacement for self-monitoring of blood glucose

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	**T1 DM**	£3,285,912	£4,066,273	£4,914,691	£5,831,766	£6,818,100
	T2 DM	£5,470,797	£6,770,039	£8,182,591	£9,709,451	£11,351,623
	Both	£8,756,709	£10,836,312	£13,097,282	£15,541,217	£18,169,723
Optimistic	**T1 DM**	£1,274,785	£1,577,529	£1,906,677	£2,262,460	£2,645,113
	T2 DM	£4,981,418	£6,164,439	£7,450,635	£8,840,913	£10,336,188
	Both	£6,256,203	£7,741,969	£9,357,312	£11,103,373	£12,981,301

Budget impact model results at the NHSScotland board level are presented in Appendix 3 and are based on the current size of the target population within each of the boards.

DISCUSSION

Key limitations

"Essentially, all models are wrong, but some are useful" George Box (1976). There are a number of limitations and key areas of uncertainty attributed to the cost-effectiveness model presented in this report, and these should be considered when interpreting the results.

- Generalisability of model results: The outcomes collected within the two RCTs were not sufficiently comprehensive to populate even a simple cost-effectiveness model like the one developed here. Therefore, a number of additional assumptions and data sources had to be utilised. This imposes a challenge as the model inputs were derived from different populations which are likely to be heterogeneous and not representative of the Scottish target population. The T1 DM population in the IMPACT trial had well-controlled diabetes, which is observed only in

a small proportion of the real world T1 DM population in Scotland. Most of this uncertainty in model inputs in relation to the target population was likely captured in the sensitivity analysis by testing various ranges and extreme values.

- Freestyle Libre® impact on hypoglycaemia: The outcomes relating to hypoglycaemia reported in the trials were the ones recorded by the device, such as time length and number of events with glucose levels below various thresholds. These were used as a proxy for real-life hypoglycaemic events derived from the literature, which were patient reported outcomes. The limitations is that some events recorded by the device as blood glucose below a given threshold, although technically categorised as hypoglycaemia, may not reflect a real-life hypoglycaemia event with the associated symptoms that would be experienced and reported by a patient and hence would not have an impact on utility scores or resource utilisation. Although this proxy measure was considered reasonable by a panel of clinical experts, the uncertainty around it was explored in a restricted scenario of the analysis.
- Model parameters were assumed to be uncorrelated within the probabilistic sensitivity analysis: It was not possible to incorporate potential correlations between the parameters in the PSA due to the unavailability of the required information; hence PSA results may include scenarios that may not be realistic in practice. For example high number of severe adverse hypoglycaemic events but low number of non-severe hypoglycaemic events. Nonetheless, the increased uncertainty resulting from ignoring these correlations will likely only have a small effect on the results.
- Disutility of hypoglycaemic events: The hypoglycaemia disutility in the model was assumed to be additive and constant, not accounting for the potential diminishing marginal disutility in patients experiencing an increased number of events. This may not be plausible if the effects of these events on health related quality of life is not strictly additive, for example if an individual is experiencing 50 NSHE events per cycle, the change to 49 NSHE events per cycle may not fundamentally alter their health. The impact of this assumption is less likely to be of importance for severe events since the baseline mean rates are small. The uncertainty around this assumptions is eliminated in the restricted analysis and lowering the disutility linked to NSHEs in half as a rough method to account for the potential marginal disutility only has a small impact on the results of the model: increasing the ICER to £3,270/QALY in T1 DM and to £5,480/QALY in T2 DM.
- Device-related utility: The direct effect of Freestyle Libre® on utility represents a 'process' utility which was estimated in a time trade-off (TTO) study. Although the vignette-based method appears feasible for estimating utility associated with glucose monitoring and hypoglycaemic events, it should be noted that influential health technology assessment guidelines have stated a preference for utilities derived via generic measures. For example, the NICE Guide to the Methods of Technology Appraisal indicates a preference for utilities derived via the EQ-5D to maximize consistency across appraisals[25]. This guide, however, says that utilities derived via other methods may be acceptable for economic modelling when the EQ-5D is not appropriate. Assessment of process utilities such as a change in the way of monitoring blood glucose, or short term acting states like hypoglycaemic events, are likely to be represent situations when the EQ-

5D might not be appropriate. This is because a generic instrument designed to assess overall health status or quality of life may not be sensitive to utility differences stemming from specific treatment process attributes or short acting states.

- Model simplicity: The model was simplistic in relation to the landscape complexity of diabetes control and management, not including many aspects relating to disease progression and management such as hypoglycaemia-related long-term complications and impact on overall survival. It was not possible to capture such factors due to the lack of published evidence. If indeed Freestyle Libre® helps decrease the incidence of hypoglycaemia it can be expected more long-term health benefits and resource savings to the NHS to be realised. This can be potentially informed by the collection and utilisation of real-world data.

CONCLUSION

Based on the results of the analysis presented, the Freestyle Libre® flash glucose monitoring technology appears likely to be a cost-effective alternative to self-monitoring of blood glucose levels in both T1 DM and T2 DM patients treated with intensive insulin therapy. The incremental cost-effectiveness ratio of Freestyle Libre® falls within reasonable values of the willingness-to-pay thresholds for an additional QALY. The uncertainty of the results has been captured in the probabilistic sensitivity analysis, the results of which support the base case findings. The restricted populations within the IMPACT and REPLACE trials and the heterogeneity of the populations across the other evidence sources pose challenges to the generalisability of the model results to other populations. However, it is reasonable to assume the general conclusions are applicable to the Scottish real-world diabetes population.

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Appendix 3: forecasted budget impact in each NHSScotland board

Table i: NHS Ayrshire & Arran budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£258,787	£320,245	£387,064	£459,289	£536,969
	T2 DM	£449,444	£556,181	£672,226	£797,663	£932,573
	Both	£708,230	£876,426	£1,059,290	£1,256,952	£1,469,542
Optimistic	T1 DM	£100,398	£124,241	£150,163	£178,183	£208,320
	T2 DM	£409,240	£506,429	£612,094	£726,310	£849,151
	Both	£509,637	£630,669	£762,257	£904,493	£1,057,471

Table ii: NHS Borders budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£74,400	£92,069	£111,279	£132,043	£154,376
	T2 DM	£149,702	£185,254	£223,907	£265,687	£310,624
	Both	£224,102	£277,323	£335,185	£397,731	£464,999
Optimistic	T1 DM	£28,864	£35,718	£43,171	£51,227	£59,891
	T2 DM	£136,311	£168,682	£203,878	£241,921	£282,837
	Both	£165,174	£204,401	£247,049	£293,148	£342,728

Table iii: NHS Dumfries & Galloway budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£106,532	£131,832	£159,339	£189,071	£221,049
	T2 DM	£187,762	£232,352	£280,832	£333,235	£389,596
	Both	£294,294	£364,185	£440,171	£522,306	£610,644
Optimistic	T1 DM	£41,330	£51,145	£61,816	£73,351	£85,757
	T2 DM	£170,966	£211,568	£255,711	£303,426	£354,745
	Both	£212,295	£262,713	£317,527	£376,777	£440,502

Table iv: NHS Fife budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£233,219	£288,605	£348,822	£413,912	£483,918
	T2 DM	£439,125	£543,412	£656,793	£779,350	£911,162
	Both	£672,344	£832,017	£1,005,616	£1,193,262	£1,395,080
Optimistic	T1 DM	£90,478	£111,966	£135,327	£160,579	£187,738
	T2 DM	£399,844	£494,802	£598,041	£709,635	£829,656
	Both	£490,323	£606,768	£733,368	£870,214	£1,017,394

Table v: NHS Forth Valley budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£160,662	£198,817	£240,300	£285,139	£333,365
	T2 DM	£278,936	£345,179	£417,200	£495,049	£578,778
	Both	£439,598	£543,997	£657,500	£780,189	£912,143
Optimistic	T1 DM	£62,330	£77,132	£93,225	£110,621	£129,331
	T2 DM	£253,984	£314,302	£379,881	£450,766	£527,004
	Both	£316,314	£391,434	£473,106	£561,387	£656,335

Table vi: NHS Grampian budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£379,830	£470,035	£568,107	£674,115	£788,128
	T2 DM	£493,255	£610,396	£737,754	£875,418	£1,023,478
	Both	£873,085	£1,080,431	£1,305,861	£1,549,532	£1,811,607
Optimistic	T1 DM	£147,357	£182,352	£220,400	£261,526	£305,758
	T2 DM	£449,132	£555,794	£671,760	£797,109	£931,925
	Both	£596,489	£738,147	£892,159	£1,058,635	£1,237,683

Table vii: NHS Greater Glasgow & Clyde budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£708,871	£877,218	£1,060,248	£1,258,088	£1,470,870
	T2 DM	£1,011,883	£1,252,191	£1,513,458	£1,795,867	£2,099,604
	Both	£1,720,753	£2,129,409	£2,573,706	£3,053,955	£3,570,475
Optimistic	T1 DM	£275,010	£340,321	£411,328	£488,081	£570,631
	T2 DM	£921,367	£1,140,179	£1,378,075	£1,635,222	£1,911,789
	Both	£1,196,376	£1,480,500	£1,789,403	£2,123,303	£2,482,420

Table viii: NHS Highland budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£219,859	£272,073	£328,840	£390,202	£456,197
	T2 DM	£365,881	£452,773	£547,243	£649,358	£759,185
	Both	£585,741	£724,846	£876,084	£1,039,560	£1,215,382
Optimistic	T1 DM	£85,295	£105,552	£127,575	£151,380	£176,984
	T2 DM	£333,152	£412,271	£498,291	£591,271	£691,274
	Both	£418,448	£517,823	£625,866	£742,652	£868,257

Table ix: NHS Lanarkshire budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£460,910	£570,370	£689,376	£818,013	£956,364
	T2 DM	£638,897	£790,626	£955,589	£1,133,900	£1,325,678
	Both	£1,099,807	£1,360,996	£1,644,965	£1,951,913	£2,282,043
Optimistic	T1 DM	£178,812	£221,278	£267,447	£317,352	£371,026
	T2 DM	£581,746	£719,903	£870,108	£1,032,469	£1,207,092
	Both	£760,558	£941,180	£1,137,555	£1,349,821	£1,578,118

Table x: NHS Lothian budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£392,384	£485,570	£586,883	£696,394	£814,176
	T2 DM	£855,584	£1,058,774	£1,279,684	£1,518,471	£1,775,292
	Both	£1,247,968	£1,544,343	£1,866,567	£2,214,866	£2,589,469
Optimistic	T1 DM	£152,227	£188,379	£227,684	£270,169	£315,863
	T2 DM	£779,049	£964,063	£1,165,213	£1,382,640	£1,616,487
	Both	£931,276	£1,152,442	£1,392,897	£1,652,809	£1,932,351

Table xi: NHS Orkney budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£13,360	£16,532	£19,982	£23,711	£27,721
	T2 DM	£29,095	£36,004	£43,516	£51,636	£60,370
	Both	£42,454	£52,537	£63,498	£75,347	£88,090
Optimistic	T1 DM	£5,183	£6,414	£7,752	£9,199	£10,754
	T2 DM	£26,492	£32,783	£39,624	£47,017	£54,970
	Both	£31,675	£39,197	£47,376	£56,216	£65,724

Table xii: NHS Shetland budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	T1 DM	£14,051	£17,388	£21,015	£24,937	£29,155
	T2 DM	£26,219	£32,446	£39,215	£46,533	£54,403
	Both	£40,270	£49,833	£60,231	£71,470	£83,558
Optimistic	T1 DM	£5,451	£6,746	£8,153	£9,674	£11,311
	T2 DM	£23,874	£29,543	£35,707	£42,370	£49,536
	Both	£29,325	£36,289	£43,860	£52,045	£60,847

Table xiii: NHS Tayside budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	**T1 DM**	£241,742	£299,152	£361,569	£429,038	£501,601
	T2 DM	£509,832	£630,910	£762,548	£904,838	£1,057,875
	Both	£751,573	£930,062	£1,124,117	£1,333,876	£1,559,476
Optimistic	**T1 DM**	£93,785	£116,057	£140,273	£166,447	£194,599
	T2 DM	£464,226	£574,473	£694,336	£823,898	£963,245
	Both	£558,011	£690,531	£834,608	£990,345	£1,157,844

Table xiv: NHS Western Isles budget impact

		Year 1	Year 2	Year 3	Year 4	Year 5
Conservative	**T1 DM**	£21,306	£26,366	£31,868	£37,814	£44,210
	T2 DM	£35,184	£43,540	£52,624	£62,444	£73,005
	Both	£56,491	£69,906	£84,492	£100,258	£117,215
Optimistic	**T1 DM**	£8,266	£10,229	£12,363	£14,670	£17,151
	T2 DM	£32,037	£39,645	£47,917	£56,858	£66,475
	Both	£40,303	£49,874	£60,280	£71,528	£83,626