2017

REPORT

A SINGLE-TECHNOLOGY ASSESSMENT

# FreeStyle Libre Flash Glucose Self-Monitoring System

Norwegian Institute of Public Health

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| **Title** | FreeStyle Libre Flash Glucose Self-Monitoring System: A Single-Technology Assessment |
| **Norwegian title** | FreeStyle Libre systemet for egenmåling av blodsukker: en hurtigmetodevurdering |
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Norwegian Institute of Public Health (NIPH)
Oslo, August 2017

# Executive summary

**Background**

Diabetes mellitus (DM) has become one of the most common public health problems world-wide. According to the 2014 Norwegian Public Health report, diabetes affects an estimated 4.3% of the Norwegian population. Diabetes is a metabolic disorder resulting from a defect in insulin production, secretion, action, or all. Type 1 and 2 are the two main types, with the prevalence of type 2 accounting for the majority (>85%) of diabetes. This assessment will focus on FreeStyle Libre, flash glucose monitor for insulin treated individuals with type 1 and 2 diabetes ("Type 1 and 2 DM").

To achieve proper quality of life and reduce long-term problems, people are increasingly encouraged to take an active role in the management of their condition. Adequate treatment management, aimed at tight control of blood glucose, reduces the risk of the long-term complications of diabetes such as retinopathy, nephropathy, neuropathy, coronary heart disease, ischaemic stroke and peripheral vascular disease. 'Management' of the disease should be understood as a package including testing of blood glucose, taking insulin (i.e., multiple daily insulin injections, using an insulin pump), using anti hyperglycemic drugs, or adopting lifestyle interventions such as diet and physical activity.

In recent years, and available in Europe since 2014, the FreeStyle Libre System - a 'wireless' method using a sensor for monitoring interstitial fluid glucose - was introduced to help individuals with type 1 and 2 DM achieve better glucose control. The system, unlike others, does not require finger prick calibration, since that functionality is embedded into the core technology. Also, unlike other systems, the individual has to take active action to get access to the real time glucose value, by leading the receiver over the sensor. Similarly to other continuous glucose monitoring options, it relies on the individual to take action on the information retrieved.

**Objective**

Our goal was to assess the clinical effectiveness, cost effectiveness and safety of FreeStyle Libre for individuals with type 1 and 2 DM.

**Methods**

We conducted a systematic review according to standard methods to summarise the evidence. The study populations were insulin treated individuals with Type 1 or 2 DM, the intervention was FreeStyle Libre, and the outcomes were HbA1c, hypo and hyperglycaemia, quality of life, patient satisfaction, pain, and adverse events.

We searched databases, trial registries, health technology assessment agencies websites and grey literature from inception to January 2017 with no language restrictions. Two reviewers independently screened the titles and abstracts of all records identified by searches, discussed any discrepancies and solved them by consensus. We obtained full text copies of all studies deemed potentially relevant and the same two reviewers independently assessed these for inclusion; solving any disagreements by consensus. One reviewer extracted data relating to study details, participants, intervention, and comparator, using a piloted, standard data extraction form. A second reviewer checked data extraction and any disagreements we resolved by consensus. The assessment of the methodological quality of each included study was based on the Cochrane Collaboration risk of bias tool. Quality assessment of evidence was carried out independently by two reviewers. We solved any disagreements by consensus. Meta-analysis was considered a suitable analysis for the data identified, despite heterogeneity. For some outcomes we employed a narrative synthesis.

**Assessment of cost effectiveness**

We assessed the cost-effectiveness estimates provided by the submitter of FreeStyle Libre compared to self-monitoring blood glucose (SMBG) for individuals with type 1 and 2 DM. The submitter used a commercially available cost-effectiveness model, IMS CORE diabetes model (IMS CDM) for this assessment. The model is internet based, with a Markov application, for individuals >18 years. The interactive simulation predicts the long-term health outcomes and costs associated with the management of type 1 and 2 DM. The model consist of 17 sub-models designed to simulate diabetes related complications, nonspecific mortality, and costs over time. As the model simulates individual patients over time, it updates risk factors and complications to account for disease progression. However, this model received from the submitter, lacks transparency, and made it difficult to gain a firm understanding of the factors that determine how patients

progress through the model, assumptions and parameters effect outcomes and to assess the validity of the model. Because the Norwegian Institute of Public Health did not have complete access to the model, it was not possible to perform a full assessment of the model or to modify underlying assumptions and parameters in order to independently assess the impact on reported results. Furthermore, the documentation package did not include any sensitivity analysis, which is essential for considering the validity and robustness of results from economic evaluations.

**Results**

We included two randomized controlled trials (RCTs) in the review. These studies compared FreeStyle Libre to SMBG. Also, we found several publications investigating the accuracy of the device, however, the study designs of these studies (single arm) did not meet the inclusion criteria of this evaluation and, although we compiled them for information, they were excluded from the synthesis. The information derived from these single arm studies are potentially important to validate the sensitivity and specificity estimates of FreeStyle Libre. In addition, we found other European assessments conducted in the past 6 to 8 months. The included RCTs reported data on middle aged adults from European countries with type 1 and 2 DM at 6 months post intervention. We rated the studies' risk of bias as unclear to high risk.

Main findings from these trials are that FreeStyle Libre may slightly improve treatment satisfaction, time spent with glucose in range 3.9 to 10 mmol/L, number of nocturnal events with glucose levels <3.1 mmol/L within 7h, and time spent with glucose levels >13.0 mmol/L in comparison to SMBG. FreeStyle Libre lead to little or no difference in quality of life and HbA1c level in comparison to SMBG. The evidence is uncertain about whether FreeStyle Libre leads to an improvement in time and events with glucose <3.9mmol/L within 24 h, time with glucose <3.1 mmol/L at night within 7 hours, and time with glucose > 10 mmol/L.

The submitted economic model runs a 40-year time horizon. The submitter´s basecase suggested that the technology is dominant for individuals with type 1 DM, i.e. that FreeStyle Libre is a cheaper and more effective technology. According to submitter´s base case, individuals with type 2 DM the incremental cost-effectiveness ratio (ICER) was calculated to be NOK 235,673 per QALY (whole study population) and NOK 243,434 per QALY (under 65 years). As the model received by the submitter was neither sufficiently transparent nor sufficiently flexible to allow changes, we have not been able to produce alternative incremental cost-effectiveness ratios (ICERs). From a healthcare

perspective, the submitter has calculated a budget impact for type 1 DM to have a total added cost the fifth year after adoption of the technology. Further, the submitter calculated a budget impact for type 1 and 2 DM that lead to a cost saving on the fifth year after adoption of the techonology. The submitter did not calculate a budget impact for type 2 DM only.

We estimated that, from a healthcare perspective, the annual costs five years after introduction would be NOK 186 million added cost and NOK 91,7 million saved cost for type 1 and 2 DM alone, respectively, and NOK 94 million added cost for type 1 and 2 DM combined.

**Conclusions**

Overall, the evidence for the intervention of interest was limited but suggests that FreeStyle Libre increases treatment satisfaction, reduces some hypo- and hyperglycaemic measures (increases time with glucose in range 3.9 to 10 mmol/L, reduces time and number of events with glucose <3.9 in 24 hours, number of glucose <3.1 night events and time with glucose >13 mmol/L) and has similar serious adverse events than SMBG, without differences in other outcomes including HbA1c and quality of life.

The quality of the included studies was generally low and there were only two small studies including middle aged adults.

Several inconsistencies lead us to question the result of the submitted health economic report. Specifically, the submitted model included several input data that did not match the input data described in the submitted documentation package, and nor did it match the input data found in other literature.

The most challenging issue is that the model is not sufficiently transparent or flexible, since we did not have access to the complete model. Therefore, we were not able to assess how the possible adjustments would affect the results provided by the submitters.

**Suggested research priorities**

- Independent research for FreeStyle Libre will be important
- Diabetes affects the life of children, adolescents and their caregivers in many ways, as well as pregnant women. Independent research including these groups is warranted

- The clinical effectiveness of FreeStyle Libre needs to be investigated in different conditions, for example, among individuals with poor self-monitoring adherence, newly diagnosed, impaired awareness of hypoglycaemia, and in addition to training and education components
- FreeStyle Libre compared to other continuous monitoring systems is warranted
- Pain is a major determinant of diabetes treatment adherence, especially for children, and it should be included as an individual outcome in future trials
- Future trials should include longer term follow up and quality of life outcome assessments at various points to inform improved clinical and cost effectiveness modelling

# **Sammendrag** (norsk)


**Bakgrunn**

På verdensbasis er diabetes mellitus (DM) i dag blant de mest vanlige helseproblemene. I følge Folkehelserapporten fra 2014 regner man med at 4.3% av Norges befolkningen er rammet. DM er en metabolsk sykdom forårsaket enten av manglende insulinproduksjon eller manglende insulinrespons eller en kombinasjon av disse. DM type 2 står for flerparten av tilfellene (>85%). I denne rapporten har vi vurdert bruk av FreeStyle Libre-systemet for måling av blodsukker (glukose) hos personer med type 1 og 2 DM som behandles med insulin.

For å oppnå bedre livskvalitet og forhindre komplikasjoner over tid er det en fordel at pasienten tar en mest mulig aktiv rolle i å overvåke og behandle egen sykdom. God oppfølging og kontroll av glukosenivå reduserer nemlig risikoen på lang sikt for komplikasjoner grunnet diabetes, som for eksempel retinopati, nefropati, nevropati, (sykdom/skade i netthinne, nyre og perifere nerver), samt hjerte- og karsykdommer og hjerneslag. Behandlingen av diabetes består i en «pakke» av ulike tiltak, som innebærer testing av glukosenivå i blod, inntak av insulin (for eksempel ved å injisere insulin flere ganger per dag eller ved bruk av insulinpumpe), bruk av blodsukkersenkende medikamenter og endring i livsstil med hensyn til diett og fysisk aktivitet.

I de siste par årene, og siden 2014 i Europa, har FreeStyle Libre-systemet vært tilgjengelig på markedet. Dette nye systemet er en metode som benytter en sensor for å måle glukosenivået i den interstitielle væsken, som leses av trådløst. Hensikten er å oppnå bedre kontroll av blodsukkernivået hos personer med type 1 og 2 DM. Til forskjell fra andre målemetoder krever ikke dette systemet fingerstikk for kalibrering, da denne funksjonen er integrert i selve teknologien. I tillegg, også ulikt andre metoder, må brukeren selv føre avleseren nær sensoren og skanne denne for å få vite aktuelt glukosenivå. Metoden er altså avhengig av at brukeren bidrar selv, og i så måte er dette systemet tilsvarende andre metoder for kontinuerlig glukosemonitorering.

**Mål**

Målet med denne rapporten var å vurdere klinisk effekt og sikkerhet, samt kostnadseffektivitet av FreeStyle Libre hos personer med type 1 og 2 DM.

**Metode**

Vi utførte en systematisk oversikt i henhold til standard metodikk for å oppsummere kunnskapsgrunnlaget. Vi inkluderte studier hvor populasjonene hadde type 1 eller type 2 DM og hvor intervensjonen innebar bruk av FreeStyle Libre. De predefinerte utfallsmålene var HbA1c, hypo- og hyperglykemi, livskvalitet, pasienttilfredshet, smerte og uønskede hendelser.

Vi søkte i databaser og studieregistere, men også på nettsidene til andre organisasjoner som gjør metodevurderinger, samt etter grå litteratur publisert frem til januar 2017 uten begrensning med hensyn til språk. To forskere gikk uavhengig av hverandre gjennom titler og abstrakter på alle treffene identifisert via litteratursøket. Uoverensstemmelser ble diskutert inntil konsensus var oppnådd. Vi innhentet mulig relevante publikasjoner i fulltekst. Etter at to forskere hadde lest gjennom disse uavhengig av hverandre bestemte vi om vi skulle inkludere studien i metodevurderingen. Også på dette trinnet løste vi uenigheter gjennom diskusjon. Mens én medarbeider ekstraherte informasjon om studiene, det vil si om deltakerne, intervensjonen, komparatoren, utfall og effektestimater ved bruk av et velutprøvd standard ekstraksjonsskjema, sjekket en annen medarbeider de ekstraherte dataene. Vi løste uoverensstemmelser som beskrevet for de tidligere trinnene i prosessen. Vurdering av den metodologiske kvaliteten på hver av de inkluderte studiene ble utført ved bruk verktøyet for å vurdere risiko for systematiske skjevheter utviklet av Cochrane Collaboration (Risk of Bias). Bedømmelsen av kvaliteten av kunnskapsgrunnlaget ble gjort av to forskere hver for seg. Også her var uenighet løst som beskrevet tidligere i avsnittet. Vi vurderte at dataene egnet seg til å inngå i metaanalyser, til tross for heterogenitet mellom effektestimatene. For noen utfallsmål var syntesen gjort narrativt.

**Evaluering av kostnadseffektivitet**

Vi evaluerte kostnadseffektiviteten til FreeStyle Libre sammenlignet med selvkontrollert blodsukkermåling (SMBG) for personer med type 1 og 2 DM. Abbott brukte en kommersielt tilgjengelig kostnadseffektivitetsmodell, IMS CORE diabetesmodellen (IMS CDM) for evalueringen. Modellen er internettbasert og Markov-basert, for personer over 18 år. Den interaktive simuleringen predikerer de langsiktige helsemessige utfallene og kostnadene knyttet til administreringen av type 1 og 2 DM. Modellen består av

17 delmodeller designet for å simulere diabetesrelaterte komplikasjoner, uspesifisert dødelighet og kostnader over tid. Siden modellen simulerer individuelle pasienter over tid, oppdaterer den risikofaktorer og komplikasjoner for å ta hensyn til sykdomsprogresjon. Modellen vi mottok fra Abbott er ikke transparent, og derfor var det vanskelig å få en solid forståelse av faktorene som bestemmer en kohorts fremgang gjennom modellutviklingen, antagelsene og parametereffektresultatene og for å vurdere modellens validitet. Folkehelseinstituttet hadde ikke tilgang til den fullstendige modellen, og det var derfor umulig å utføre en fullstendig evaluering av modellen eller å endre underliggende forutsetninger og parametere for å kunne vurdere effekten av rapporterte resultater. Videre inkluderte ikke dokumentasjonspakken noen sensitivitetsanalyse.

**Resultater**

I denne hurtigmetodevurderingen inkluderte vi to randomiserte kontrollerte studier (RCTer). Disse studiene har sammenlignet FreeStyle Libre med SMBG. I tillegg fant vi flere publikasjoner som omhandlet utstyrets målenøyaktighet, men grunnet studiedesignet (single-arm) og rapportens formål ble ikke disse inkludert. Dog erkjenner vi betydningen av disse single-arm studiene med tanke på at de viser sensitiviteten og spesifisiteten av FreeStyle Libre som metode for å måle glukosekonsentrasjon. De inkluderte RCTene rapporterte funn på middelaldrende voksne fra ulike europeiske land med type 1 og 2 DM seks måneder etter at intervensjonen påbegynte. Etter vår vurdering hadde studiene fra «uklar» til «høy» risiko for systematiske skjevheter (risk of biases).

Hovedfunnene fra de inkluderte studiene er at FreeStyle Libre muligens forbedrer brukers tilfredshet, tid tilbrakt med glukosenivå mellom 3,9 og 10 mmol/l, antall nattlige hendelser med glukosenivåer <3.1 mmol/l i løpet av 7 timer og tid med nivåer >13.0 mmol/l sammenlignet med SMBG. Imidlertid medfører FreeStyle Libre liten til ingen forskjell med hensyn til livskvalitet og nivå av HbA1c sammenlignet med SMBG. Vi er usikre på om FreeStyle Libre fører til forbedring av tid og hendelser med glukosenivå <3.9mmol/L i løpet av ett døgn, tid med nivåer <3.1 mmol/L målt på natten (7 timer), samt tid tilbrakt med glukosenivå > 10 mmol/l.

Den økonomiske modellen, innsendt av Abbott, hadde en 40 års tidshorisont. Den innsendte modellen tyder på at FreeStyle Libre er dominant for individer med type 1 DM, det vil si kostnadseffektiv. I følge Abbott, for personer med type 2 DM ble den inkrementelle kostnadseffektivitetsratioen (ICER) beregnet til 235 673 kroner per QALY (hele studiepopulasjonen) og 243 434 kroner per QALY (under 65 år). Siden modellen

levert av Abbott ikke var transparent, har vi ikke hatt mulighet til å produsere alternative inkrementelle kostnadseffektivitetsratioer (ICER). Med utgangspunkt i et helsetjenesteperspektiv, estimerte Abbott budsjettkonsekvens for type 1 DM til å gi merkostnader femte år etter teknologien blir innført. Videre estimerte Abbott budsjettkonsekvens for type 1 og 2 DM til å være kostnadsbesparende femte år etter teknologien blir innført. Abbott estimerte ikke budsjettkonsekvens for type 2 DM separat. Fra et helsetjenesteperspektiv estimerte vi imidlertid at den totale årlige kostnaden fem år etter introduksjon av FreeStyle Libre henholdsvis vil gi 186 millioner kroner merkostnader for type 1 DM alene og 91,7 millioner kroner sparte kostnader for type 2 DM alene. Ved kombinasjon av type 1 og type 2 DM vil introduksjonen av FreeStyle Libre gi omkring 94 millioner kroner merkostnader fem år etter introduksjonen.

**Konklusjoner**

Generelt sett var kunnskapsgrunnlaget begrenset, men resultatene kan tyde på at FreeStyle Libre øker pasienttilfredsstillelse og at det reduserer noe varighet og hyppighet av hypo- og hyperglykemi-episoder. FreeStyle Libre øker muligens tid tilbragt med glukosenivå mellom 3.9 og 10 mmol/l, reduserer tid og antall hendelser med glukosenivå <3.9 mmol/l over et døgn, hendelser med glukosenivo <3.1 mmol/l- i løpet av natten og tid tilbagt med nivåer glukose >13 mmol/l. FreeStyle Libre medfører tilsvarende antall uønskede hendelser som SMBG. Det er små eller ingen forskjeller med hensyn til de andre utfallene, som HbA1c og livskvalitet. Kvaliteten på de to inkluderte studiene var generelt sett lav og inkluderte voksne middelaldrende deltakere.

Det er flere uoverensstemmelser mellom forutsetningene nevnt i den skriftlige dokumentasjonspakken, i annen literatur og antakelsene som faktisk er brukt i den helseøkonomiske modellen. I tillegg er den innsendte helseøkonomiske modellen ikke transparent. Vi hadde ikke fullstendig tilgang til hele modellen, og det førte til stor usikkerhet omkring modellens struktur og kvaliteten av innholdet. På grunn av dette er det ikke mulig å se hvordan våre justeringer og korreksjoner hadde påvirket resultatet.

**Forslag til videre forskning**

- Det er viktig at det gjøres uavhengig forkning på FreeStyle Libre
- Diabetes rammer også barn og ungdom og de som har omsorg for dem, og gravide kvinner. Det er derfor behov for uavhengig forskning, som inkluderer disse gruppene
- Effekt av FreeStyle Libre må undersøkes under ulike aktuelle forhold, som for eksempel blant personer som ikke følger opp sin sykdom eller som har

vanskeligheter med utførelsen av sin blodsukkerkontroll, hos dem som nylig er blitt diagnostisert med diabetes og hos personer som ikke er klar over eller ikke føler eventuell hypoglykemi. Forhold knyttet til trening og opplæring er det også viktig å få mer kunnskap om.

- FreeStyle Libre må sammenlignes med andre metoder for kontinuerlig blodsukkermonitoring
- Smerte er vesentlig med tanke på tilslutning til ethvert behandlingsprogram for diabetes, spesielt hos barn, og dette bør inkluderes som et separat utfallsmål i fremtidige studier
- Videre bør studiene følge opp deltakerne over lengre tid, samt måle livskvalitetsutfall ved ulike tidspunkt for å bidra til bedre modellering av klinisk effekt og kostnadseffektivitet.

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# Abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary (see Appendix 1) is provided for the non-specialist reader.

| | |
|---|---|
| CI | Confidence interval |
| CPI | Consumer price index |
| DM | Diabetes mellitus |
| DRGs | Norwegian diagnoses-related groups |
| GP | General practitioner |
| HELFO | The Norwegian Health Economics Administration. |
| HRQL | Health related quality of life |
| HTA | Health technology assessment |
| ICER | Incremental cost effectiveness ratio |
| IMS CDM | IMS Core Diabetes Model |
| MD | Mean difference |
| Mmol | Milimoles |
| Mol | Moles |
| SMBG | Self monitored blood glucose |
| NIPH | Norwegian Institute of Public Health |
| NOK | Norwegian Kroner |
| QALY | Quality adjusted life year |
| RCT | Randomised controlled trial |
| RR | Risk ratio |
| SD | Standard deviation |

# Preface

## What is a single-technology assessment?

A single-technology assessment is one of a series of health technology assessment (HTA) products that can be mandated in "The National System for Introduction of New Health Technologies" within the Specialist Health Service in Norway (https://nyemetoder.no/).

Within this system, the Commissioner Forum RHA ("Bestillerforum RHF"), where the four Regional Health Authorities are represented, evaluates submitted suggestions and decides on which technologies should be assessed and the type of assessment needed. In a single-technology assessment, the technology (a pharmaceutical or a device) is assessed based on documentation submitted by the company owning the technology, or their representatives ("the submitter").

The HTA unit of the Norwegian Institute of Public Health (NIPH) receives and evaluates the submitted documentation, but is not the decision-making authority. Single-technology assessments conducted at NIPH are published on our website (www.fhi.no) and on https://nyemetoder.no/

## Objective

To assess the clinical effectiveness, cost-effectiveness and safety of FreeStyle Libre (interstitial measurement of glucose) for insulin treated individuals with diabetes type 1 and 2.

## Log

We received the FreeStyle Libre comission, ID2016_044, on December 23, 2016. The Commission Forum requested the NIPH HTA Unit to perform a clinical effectiveness and safety assessment along with a cost-effectiveness analysis of this single-technology for the management of insulin dependent individuals with diabetes type 1 and 2. Information on the commission can be seen here https://nyemetoder.no/metoder/system-freestyle-libre-for-egenmaling-av-blodsukker

| Date | Correspondence |
|---|---|
| September 23, 2016 | Publication of horizon scanning report on this device |
| October 24, 2016 | The commissioning forum commissioned a single technology assessment |
| Oct. 2016 – Dec 2016 | Dialogue and meeting with technology manufacturer |
| December 23, 2016 | Valid submission acknowledged |
| April 26 – 27, 2017 | Clinical experts, and stakeholders draft reviewing |
| May 12, 2017 | Norwegian Institute of Public Health external review process |
| May 25, 2017 | Norwegian Institute of Public Health internal review process |
| June 2, 2017 | End of 180 days evaluation period –Report Submitted |
| June 8, 2017 | Report available at FHI website |
| July-Aug 2017 | Amendments to report considered (i.e. health economic) |
| August 21th 2017 | Amended report available at FHI website |

## History

Report first submission to commissioner forum: June 2nd, 2017

Amended version: August 21th 2017: the methods used in original report remain intact. Amendments were done as follow: removal of information deemed confidential by the submitter, further explanation of transparency issues encountered with the IMS Core model, and elaboration of discrepancies between the cost-effectiveness analysis and budget impact analysis. Inclusion of in-text evidence derived from single arm study designs (previously in appendices), and updated information on European countries HTAs.

## Project team, consultants and stakeholders

| Norwegian Institute of Public Health team | |
|---|---|
| Julia Bidonde (project leader), Researcher | *Acknowledgements* |
| Beate C. Fagerlund, Health Economist | Torunn Tjelle, Researcher |
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External consultants

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Member of board of medical advisors for the Norwegian Diabetes Association
Sven Magnus Carlsen, Professor, NTNU.

Stakeholders who provided feedback on this assesment

Norwegian Diabetes Association
Ragnhild and Andreas Jansson

| | | |
|---|---|---|
| Signe Agnes Flottorp | Ingvil Sæterdal | Julia Bidonde |
| *Department director* | *Acting Head of Unit* | *Project leader* |

# Background

## The technology

Name of the technology: FreeStyle Libre, Flash Glucose Sensor Monitor System ("Free-Style Libre")

Manufacturer which submitted the application and provided the documentation package: Abbott Norge AS (Leverandør), Postboks 1, 1360 Fornebu, Norge ("submitter").

## Regulatory status (CE-marking) and market access of the technology

FreeStyle Libre has European Conformity (Conformité Européenne) or CE-marking Class IIb, notification by the British Standards Institution (No 597686), United Kingdom. Clarification of CE Marking of Medical Devices can be found at http://www.ce-marking.com/medical-devices-class-IIb.html

FreeStyle Libre is available in Norway, but is not reimbursed by the Norwegian health care system (Specialist Health Care) or through the National Social (Security) Insurance (Folketrygden).

## Description and use of the technology

### FreeStyle Libre (information below taken from the submitter's package and website)

FreeStyle Libre flash glucose monitor is a system that relies on a subcutaneous glucose sensor, usually placed on the upper arm, that measures and continuously stores glucose readings day and night (see Figures 1 and 2 below). Glucose levels are checked by 'scanning' the sensor with a reader obviating the need for regular self-monitor blood glucose (SMBG) testing. It reports current glucose concentration, glucose trend and displays the previous 8 hours as a trend; FreeStyle Libre updates readings every minute and stores data every 15 minutes. A hand-held reader is used to scan and retrieve information from the sensor. The reader can capture data from the sensor when it is within 1 to 4 cm distance of the sensor. Various reports are available from the reader:

- Logbook: individual glucose readings and user-entered notes

- Daily graph: daily overview of glucose readings, including how they fall within the target glucose range
- Average glucose: average glucose readings along with four 6-hours periods during the day
- Daily patterns: indicates when glucose levels are in the target range and the variability of glucose levels
- Time in target: indicates the percentage of time glucose readings are in the target range and above or below the target range
- Low glucose events: indicates the number of low glucose events at four different times of the day
- Sensor usage: indicates average number of scans per day and what percentage of glucose data has been captured by these scans

FreeStyle Libre is factory-calibrated, and the sensors can be worn for up to 14 days. The sensor is water resistant in up to 1 meter of water for a maximum of 30 minutes; it can be worn while bathing, showering, swimming and exercising.


**Figure 1.** FreeStyle flash glucose system (image used with submitter's permission)

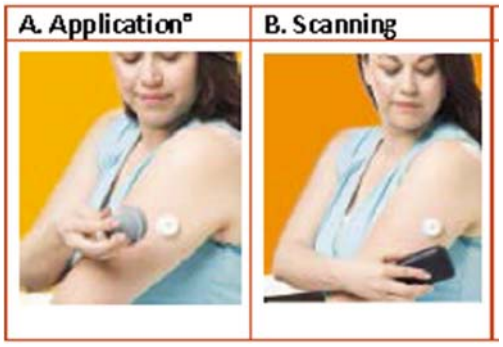



**Figure 2.** FreeStyle application and scanning (image used with submitter's permission)

FreeStyle Libre initial package includes the following components:
A reader Kit

- 1 FreeStyle Libre Reader
- 1 USB cable
- 1 Power adapter
- 1 Quick Start Guide
- User Manual

A Sensor Kit

- Disposable Sensor: it has a thin, sterile filament (0.4 mm wide, inserted approximately 5 mm under skin) attached to a small disk (30 mm x 5 mm)
- Medical grade adhesive is used to keep the sensor in place on top of the skin once applied
- 1 Sensor applicator
- 1 Alcohol wipe
- Product Leaflet

Optional sofware

Specially designed software, gives people the possibility to download data to a computer and to create a series of reports that provide a full glycemic picture across various timeframes. Reports are presented in graphical formats that are easy for people to interpret.

The reports are as follow:

- Snapshot
- Daily Patterns
- Glucose Pattern Insights
- Mealtime Patterns
- Monthly Summary
- Weekly Summary
- Daily Log
- Reader Details

**Context for Use (from the submitter's package)**

FreeStyle Libre is indicated for measuring interstitial fluid glucose levels in people aged 4 and older with diabetes mellitus. The indication for children (age 4-17) is limited to those *who are supervised by a caregiver who is at least 18 years of age*. FreeStyle Libre is designed to replace SMBG of diabetes with the exceptions listed below.

- During times of rapidily 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 rapidily, 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.
- In order to confirm hypoglycaemia or impending hypoglycaemia as reported by the sensor.
- If symptoms do not match FreeStyle Libre reading. Do not ignore symptoms that may be caused by low blood glucose or high blood glucose.

**Advantages and disadvantages of FreeStyle Libre**

The advantage of the FreeStyle Libre is the continuous provision of information about interstitial glucose concentration that can facilitate adjusting insulin dosage. The technology is factory calibrated, which means the individual does not have to perform daily SMBG by finger prick, the sensor is small and can easily be hidden under clothing, and it is water resistant which can be seen as an advantage for those who enjoy water activities.

Disadvantages of FreeStyle Libre are potential skin irritation, and associated costs (sensor has to be replaced every 14 days); there can be some delay in the measurement, which may impede optimal monitoring. Although a high body mass index may not influence readings, according to clinical experts opinion, a very narrow subcutaneous space in underweight individuals may perhaps put limitations to the sensor use. Unlike other real time monitors, FreeStyle Libre does not have an alarm, and it does not work in synchronisation with an insulin pump.

## Description of the health condition

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin production, secretion, action, or all. The number of people with DM is high and rising in every country - with the number of adults with DM having more than doubled over nearly three decades (1). The latest estimates show a global prevalence of 382 million people with DM in 2013, a number that is expected to rise to 592 million by 2035 (2). Across Europe there are about 60 million people with DM and the number is expected to increase to 71 million by 2040 (3).

In Norway (4):

- Approximately 200,000 - 220,000 people (4.3% per cent of the Norwegian population) have been diagnosed with diabetes,
- Based on calculations from the Norwegian Prescription Database, in Norway, approximately 28,000 people (0.6% of the population) have type 1 diabetes,
- Approximately 28% of people with type 2 diabetes are treated with diet and exercise,
- International studies and unpublished data from Norway suggest that many people are living with undiagnosed diabetes,
- The prevalence and incidence of type 2 increases with age to a peak at 80 years,
- Norway is among the countries with higher new cases of type 1 DM in children per year.

The aetiological classification of diabetes has been accepted worldwide; type 1 and type 2 DM are the two main types, with the prevalence of type 2 accounting for the majority (>85%) of total diabetes. Type 1 is the most common form of diabetes among children, but it can also develop among adults. Type 1 DM requires insulin; people with type 2 DM can be treated with oral medication but may also require insulin. Often modifications in diet and lifestyle help to manage the disease for individuals with type 2 DM. Other types of DM are monogenic, secondary and gestational. Monogenic diabetes occurs when there is a change in a single gene. Together monogenic diabetes account for 1-2% of all diabetes cases, and dependent on the gene involved the treatment is either insulin or sulfonylurea tablets (5). Secondary forms of diabetes (secondary to pancreatic disease or administration or certain drugs) account for 1 to 2% of all diabetes (6). Gestational diabetes (5 - 10% of pregnancies) represents a risk factor for future development of DM (7-9).

*Children and adolescent*

Type 1 diabetes is the most common type seen in children, and is most commonly first diagnosed in the teenage years. Type 2 diabetes in children and adolescents is a relatively novel disease facing paediatric health care providers (10). Type 2 is becoming increasingly more prevalent in younger people, and may be more in people of South-Asian, African Caribbean or Middle Eastern descent. Children with a diagnosis of diabetes often present to the health service with issues such as hypoglycaemia, hyperglycaemia, or diabetic ketoacidosis (11). Diabetes affects children's life including school life, daily activities, their academic achievements and personal aspirations. For example, they may be affected by lack of full time school nurses, lack of teacher knowledge of diabetes, lack of access to diabetes tools, lack of freedom to perform diabetes self-care, lack of nutritional information in cafeterias, or lack of communication between parents and school personnel (12).

Children with type 1 DM need multiple daily measurements of their blood glucose. In small children, parents or other caregivers are responsible for the treatment and the monitoring of their diabetes which can interfere with daily activities and work. Furthermore, blood glucose may be measured after the child has gone to bed. This can affect the quality of sleep, in particular if the child needs to eat due to low blood glucose level.

Time of youth is a challenging period of life; adolescents with diabetes face unique age-specific demands. Some difficulties are learning about the new disease and managing

disease knowledge, maintaining a positive health behaviour and ensuring treatment regime adherence. Young people face difficulties in the transition from childhood to adulthood, and problems coping with a chronic disease are common. Managing emotions, navigating social relationships with peers including the disclosure of the disease are some of their difficulties (13). A period of disease neglect is often seen, resulting in a reduced number of daily measurements and poor diabetes control. This will lead to several years with elevated blood glucose, thus increasing the risk of developing diabetes related complications later in life.

*Management of the condition*

Without proper disease management the individual is likely to become progressively ill and debilitated. Management of blood sugar levels - hypoglycaemia and hyperglycaemia - is extremely important in diabetes care. If blood glucose is uncontrolled it can lead to complications such as retinopathy, nephropathy, neuropathy, or heart disease, stroke and peripheral vascular disease. Hypoglycaemia occurs when the level of blood glucose falls below 3.5 millimoles per litre (mmol/L). Indications include hunger, nervousness, shakiness, perspiration, dizziness, sleepiness and confusion, and if unattended it may lead to unconsciousness. Fear of recurrent hypoglycaemia can decrease quality of life in the short term, but can also hinder adherence to treatment and the achievement of good glycaemic control. Hyperglycaemia occurs when the level of blood glucose is higher than 11 millimoles per litre. Hyperglycemia together with insulin depletion can lead to ketoacidosis. This is a feared condition that untreated has a high mortality. Admission to hospital is necessary, often at an intensive care unit. Long-term consequences of chronic hyperglycaemia may be nerve damage, kidney damage or failure, damage to the blood vessels of the retina and other eye complications. Premature morbidity, mortality, reduced life expectancy and financial and other costs of diabetes make it an important public health condition (14).

Glucose is generally measured in three ways:

a) first, blood glucose can be tested by a drop of blood with a glucose meter (capillary blood glucose testing), also known as self-monitoring of blood glucose or SMBG;
b) second, continuous glucose monitors (CGM) provide frequent automated testing of interstitial tissue glucose, calibrated to reflect blood plasma glucose; and
c) third, longer term control is measured by glycated haemoglobin (HbA1c) which reflects the average blood glucose levels over 2 to 3 months.

Psychosocial and cultural aspects of the disease are also important considerations in successful diabetes management. Positive factors, e.g., good coping skills, family support, effective weight control programs, etc., can increase interest in disease management and improve adherence to medication, resulting in better glycaemic control and improved quality of life. Individuals lacking positive influences may find disease management more difficult, resulting in poor glycaemic control and an increased likelihood for long-term complications (15;16).

Self-monitoring of blood glucose is an essential part of diabetes management and is used to optimise glycaemic control. Management of diabetes requires lifelong integration of many factors such as, life circumstances, daily adherence to dietary and exercise plans, frequent blood glucose monitoring and adherence to medications. Training for self-management improves the knowledge of diabetes, glucose levels and glycated haemoglobin. It can also lead to improved systolic blood pressure levels, body weight and can reduce the need for DM medication for type 2 DM. Effective control of blood glucose levels allows individuals with DM to adjust therapy (insulin dosage) appropriately.

*Impaired awareness of hypoglycaemia*

Recognizing symptoms of hypoglycaemia (being 'aware') at their onset is fundamental for timely self-management of blood sugar levels. Impaired awareness of hypoglycaemia means the individual's ability to perceive the onset of hypoglycaemia, or to recognize warning symptoms, is diminished or absent. The counter regulatory hormone response (insulin) is deficient or lacking in individuals with impaired awareness (17). Impairment in the ability to recognize the onset of hypoglycaemia can have serious consequences and constitutes a significant problem commonly seen in individuals with type 1DM, and less often seen in individuals with type 2 DM. CGM is a useful system that helps individuals to detect asymptomatic hypoglycaemia, as it provides real-data time and alerts for the individual (18). Hypoglycaemia is the main cause of individuals getting a continuous glucose monitoring system in Norway today.

Norway implemented a national diabetes strategy (2006-2010 later prolonged to 2012) which aimed to improve the primary prevention of diabetes, improve the cooperation between the primary and secondary health care and increase the resources of health care in the local municipalities. Norway published the latest national diabetes clinical guideline in 2016. The clinical guideline has its main focus on secondary and tertiary prevention of diabetes. Although both documents emphasise lifestyle and self-management of the disease, the use of FreeStyle Libre is not included (19).

# Clinical effectiveness and safety

## Issue addressed

According to the submitter, by using FreeStyle Libre, people with DM may improve glucose control management and consequently reduce the number of diabetes related complications and improve their quality of life. Moreover, the technology could make it easier for people to adhere to treatment. FreeStyle Libre may help reducing the incidence of severe and nocturnal hypoglycaemia and its associated anxiety. FreeStyle Libre may offer benefits through cost and resource savings by reducing the number of hospital admissions and consultations for diabetes related complications, and by achieving optimal blood glucose levels more quickly.

## Objective

The objective of this document was to assess the clinical effectiveness, cost-effectiveness and safety of FreeStyle Libre for insulin treated individuals with type 1 and 2 DM ("type 1 and 2").

## Methods

### Inclusion and exclusion criteria

We used the population, intervention, comparison, outcome, and design (PICO –D) framework to evaluate the suitability of evidence for inclusion (see Table 1).
We selected these outcomes in collaboration with the clinical experts and the Norwegian Diabetes Association via communication and consultation mechanisms.

***Table 1.*** *PICO –D framework*

| | |
|---|---|
| Population | Insulin dependent individuals (of any age) diagnosed with diabetes type 1 or 2 |
| Intervention | FreeStyle Libre flash glucose monitor |
| Comparator | Any other glucose monitoring system or procedure including conventional self-monitoring of blood glucose plus multiple insulin injections, pen device use, insulin syringe, etc. |
| Outcomes | Change in HbA1c (glycosylated haemoglobin),<br>Hypoglycemia or hyperglycemia – day, night time, and episodes<br>Quality of life<br>Patient / treatment satisfaction<br>Pain<br>Adverse events (related to the device or not, withdrawals, etc.) |
| Design | Randomised control trials (RCTs)* or controlled studies (i.e., controlled before and after with at least two intervention and two control sites; or interrupted time series with at least three data points before and three after the time point of the intervention). |

* Hierarchies of evidence rank research according to its validity. RCTs are commonly viewed as providing the highest level of evidence. This type of design minimises the risk of confounding factors influencing the results and it has been the 'gold standard', or optimal research design, for evaluating effectiveness.

We excluded studies if:

- Population of interest / focus of the publication was other than insulin dependent diabetes type 1 and 2 DM
- The glucose monitoring system in the intervention was done by an instrument other than FreeStyle Libre
- None of the outcomes in Table 1 were assessed
- Data for type 1 and 2 DM were not presented/available independently
- Type of study were clinical practice guidelines, conference abstracts and proceedings, books, book chapters, animal or modelling studies

### Literature search and selection of studies

The search strategy was designed, peer reviewed and executed by two experienced information specialists. The search was adapted to each database and had no language restrictions. We searched systematically in the following databases: MEDLINE and Embase via the Ovid interface, Cochrane Library: Cochrane Database of Systematic Reviews, Other Reviews, Central Register of Controlled Trials, Economic Evaluations database, Centre for Reviews and Dissemination: Database of Abstracts of Reviews of Effects, Health Technology Assessment database up to January 18, 2017. We also searched the *The International Network of Agencies for Health Technology Assessment (INAHTA)* members' website for other FreeStyle Libre assessment.

We supplemented the database search by consulting other sources such as Google scholar, HTA agencies' homepages, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform and by hand-searching reference lists of relevant papers. We used a combination of subject terms and text words (see Appendix 2 for detailed search strategy).

Pair of authors (JB, KF, TT or IS) independently scanned title and abstract of the retrieved records. We investigated all potentially relevant articles as full text regarding eligibility compliance as per criteria mentioned in Table 1. Differences in opinion were resolved by a third reviewer. The results of this process are presented in a PRISMA (preferred reporting items for systematic reviews and meta-analysis) flow chart (Figure 3 in the results section).

All data was extracted independently by one reviewer (JB) into a standardised data extraction form, which was then been checked for accuracy by another reviewer (KF or TT). We extracted the following data (see Table 2):

***Table 2.*** *Data extracted*

| Data | Details to be extracted (if available) |
|---|---|
| Publication Summary | Author & year, title, publication type, inclusion/exclusion, country (use first author affiliation) of origin |
| Population | Total sample size, age, gender, diagnosis, years since diagnosis, type of diabetes |
| Intervention | Length, follow up |
| Comparator | Blood capillary glucose monitoring, other system (Navigator, MiniMed) etc. |
| Outcomes | Same as in table 1 |

We extracted data from included studies as far as possible. We contacted primary studies' authors to request data provided in graphical form for two of the outcomes. Primary authors sent our request to the submitter; due to a delay in the response, we estimated data from the graph using a graphical data software (Engauge Digitizer). We eventually received a response from the submitter.

### Risk of bias assessment in included studies

Two reviewers (JB and KF) independently evaluated the risk of bias using the Cochrane "Risk of bias tool" (20). The risk of bias tool addresses specific domains related to the study's internal validity: sequence generation and allocation concealment (selection

bias), blinding of participants, study personnel or staff (performance bias), blinding of study assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. A brief description of these biases is presented in Table 3 below.

***Table 3:*** *Assessment of Risk of Bias in included RCTs*

| Domain-Item | Description |
|---|---|
| Sequence Generation<br>Was the allocation sequence adequately generated? | The method used to generate the allocation sequence should be described in sufficient detail to allow an assessment of whether it should produce comparable groups. |
| Allocation Concealment<br>Was allocation adequately concealed? | The method used to conceal the allocation sequence should be described in sufficient detail to determine whether intervention allocations could have been foreseen in advance or during enrolment. |
| Blinding of participants, personnel and outcome assessors<br>Was knowledge of the allocated intervention adequately prevented during the study?<br>*Assessments will be made for each main outcome (or class of outcomes).* | All measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received, should be described. Any information relating to whether the intended blinding was effective should also be reported. |
| Incomplete outcome data<br>Was incomplete outcome data adequately addressed?<br>*Assessments will be made for each main outcome (or class of outcomes).* | The completeness of outcome data for each main outcome should be described, including attrition and exclusions from the analysis. The authors should report any attrition and exclusions, the numbers in each intervention group (compared with total randomized participants), and reasons for attrition/exclusions and any re-inclusions in analyses. |
| Selective Reporting*<br>Were results of some outcomes not reported because the results were not statistically significant<br>*Assessment will be made by comparing trial registry record or published protocol to the study publication* | The authors should not select and report outcomes in full text publications based on their results. All of the study's prespecified outcomes should be reported (by checking the trial protocol if available) |

| | |
|---|---|
| Other sources of bias<br>Was the study apparently free of other problems that could put it at a high risk of bias? | Overall, the study should be free from any important concerns about bias (i.e. bias from other sources not previously addressed by the other items). |

*Between studies reporting biases: due to a lack of sample studies (i.e., more than 10) we were not able to produced funnel plots (20) to investigate publication reporting bias.

Within studies reporting biases: when a published study protocol was available, we compared outcomes in the study protocol with the outcomes in the published report. We documented the trial number or the availability of a published protocol.

Each criterion was rated as being at low, high, or unclear risk of bias according to the information provided in the studies. We classified studies as 'low risk of bias' if all key domains had low risk of bias and no serious flaws. The criterion 'unclear risk' was assigned when the absence or ambiguity of the information hindered the assessors' ability to determine the potential for bias. If the criterion was not fulfilled we classified it as 'high risk'. Disagreements were resolved through consensus meetings by consulting a third team member.

The results of the risk of bias assessments were used for descriptive purposes to provide an evaluation of the overall quality of the included studies and a transparent method of devising recommendations for the design of future studies.

### Data synthesis

When two or more studies reported the same outcome, we pooled the data (meta-analysis) using RevMan 5.3 2014 (21). For continuous data, we used the group post-test means and standard deviations to calculate the effect size. Effect sizes were expressed preferentially in the form of mean difference (MD) and 95% confidence interval (CI). Dichotomous data was analysed by calculating relative risk (RR) and the corresponding 95% CI. For graphical data, standard errors were transformed to standard deviations. We organised the data by outcome and reported the results for the outcomes of interest in text and tables.

*Assessment of Heterogeneity*

Statistical heterogeneity was assessed by visual inspection of the forest plot to assess obvious differences in results between the studies, and using the $I^2$ and $chi^2$ statistical

tests. As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (22), we followed the interpretation of an $I^2$ value from 0% to 40% as 'might not be important'; from 30% to 60% as representing 'moderate' heterogeneity; from 50% to 90% as representing 'substantial' heterogeneity; and from 75% to 100% as representing 'considerable' heterogeneity. Because $I^2$ has overlapping categories (i.e., 0% to 40%, 30% to 60%) or "ambiguous" zones, when moderate to substantial statistical heterogeneity was found (i.e., $I^2$ between 50% and 60%) we explored it thoroughly. In addition, clinical and methodological diversity was assessed in terms of participants, outcomes, and study characteristics to determine whether a meta-analysis was appropriate.

Given that values between 50% and 60% fall in an 'ambiguous' zone, when there were no apparent causes of heterogeneity, we kept the trial in the analysis and documented our decision. The $chi^2$ test was interpreted with a p value ≤ 0.10 indicating evidence of statistical heterogeneity.

### Grading of the evidence

One reviewer (JB ) used the GRADE tool (Grading of Recommendations Assessment, Development and Evaluation) developed by the GRADE working group (23) to determine the certainty of the effects of interventions reported in the included reviews, i.e. to what degree we could trust the results. A second reviewer (KF) independently checked the assessment. If disagreements were found, they were solved by discussion. We considered the compiled documentation for each of the main outcomes using GRADE and prepared summary of findings tables for the outcomes of interest. In the tables we integrated the certainty of evidence and the magnitude of effect of the intervention. We made the GRADE ratings separately for each of the outcomes of interest.

We used the five GRADE considerations for downgrading (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence as high, moderate, low or very low. The table below (see Table 4) presents what GRADE means by each of these four categories.

Evidence from randomised controlled trials (RCTs) started as high quality evidence but may have been downgraded depending on the five criteria in GRADE that are used to determine the certainty of the evidence.

***Table 4.*** *GRADE*

| Quality Level | Significance |
|---|---|
| High | We are very confident that the true effect lies close to that of the estimate of the effect |
| Moderate | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| Low | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect |
| Very low | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

### Presentation of results in relation to the submitter's package

Some results (i.e., search and risk of bias) from the submitter's and the NIPH have been compared in tabular form. In the discussion chapter, we incorporate the clinical effectiveness implications of the results and present agreements or disagreements with the submitter's file.

### Stakeholder involvement

As stated in the literature, there is not a conventional model to involve stakeholders' in HTAs (24). Nevertheless, the NIPH followed a consultation process aiming to incorporate the experience and knowledge of clinical experts, consumers or users of the device, and patient organizations. Clinical and external review experts were designated by the Regional Health Authorities.

First, the PICO framework was agreed upon in collaboration and with the feedback from clinical experts and the Norwegian Diabetes Associaton. Second, we asked clinical experts to provide feedback during the assessment to validate our understanding of the disease and initial findings. Third, all stakeholders (clinical experts, users' and patients' organization) were invited to provide feedback on the first draft of the assessment. The project leader contacted them and provided initial information. Following an invitation to take part in the assessment, everyone agreed to the confidentiality terms and conditions and signed correponding forms. Users' experts were invited following a snowballing technique, and the Norwegian Diabetes Association, the main stakeholder in this report, was sent an email invitation. The NIPH requested clarification when needed on the key evidence responses submitted. Lastly, following the first draft, we incorporated feedback into the manuscript and prepared it for external content experts. Then, methodologists at NIPH and external content experts peer-reviewed the second and final draft.

## Results

### Literature search

The search identified 1665 citations, which included 1622 journal records and 43 trial registry records. We excluded 1576 records based on screening of titles and abstracts. We assessed 89 full text articles and trial registry records for eligibility. This resulted in the final inclusion of 2 RCTs and corresponding registry records. See Figure 3 for details.

Several single-arm studies, which provide evidence of initial explorations of FreeStyle Libre accuracy, compared sensor readings to blood glucose capillary measurements or venous and capillary-paired measurements. Given the availability of randomized control trials and lack of a comparison group on this type of design, the team decided to focus on the evidence provided by the RCTs. A summary of completed *(published and unpublished)* single-arm studies (e.g., population studies, author & year, country of origin, duration, and outcomes) is presented in Appendix 3.

*FreeStyle Libre registry records*

We found several registry records for FreeStyle Libre. Among these, seven single arm studies have been completed, three are ongoing RCTs, and seven are ongoing single arm studies. We reported details (e.g., registry number, study title, study status, country of origin, outcomes, and study duration) of ongoing studies in Appendix 4.

*Other European assessments*

We found five completed and one ongoing FreeStyle Libre assessments. Also, we found a Government claim, a peadiatric guideline and a Swedish report using FreeStyle Libre as an example. We present the results of these reports in the discussion.

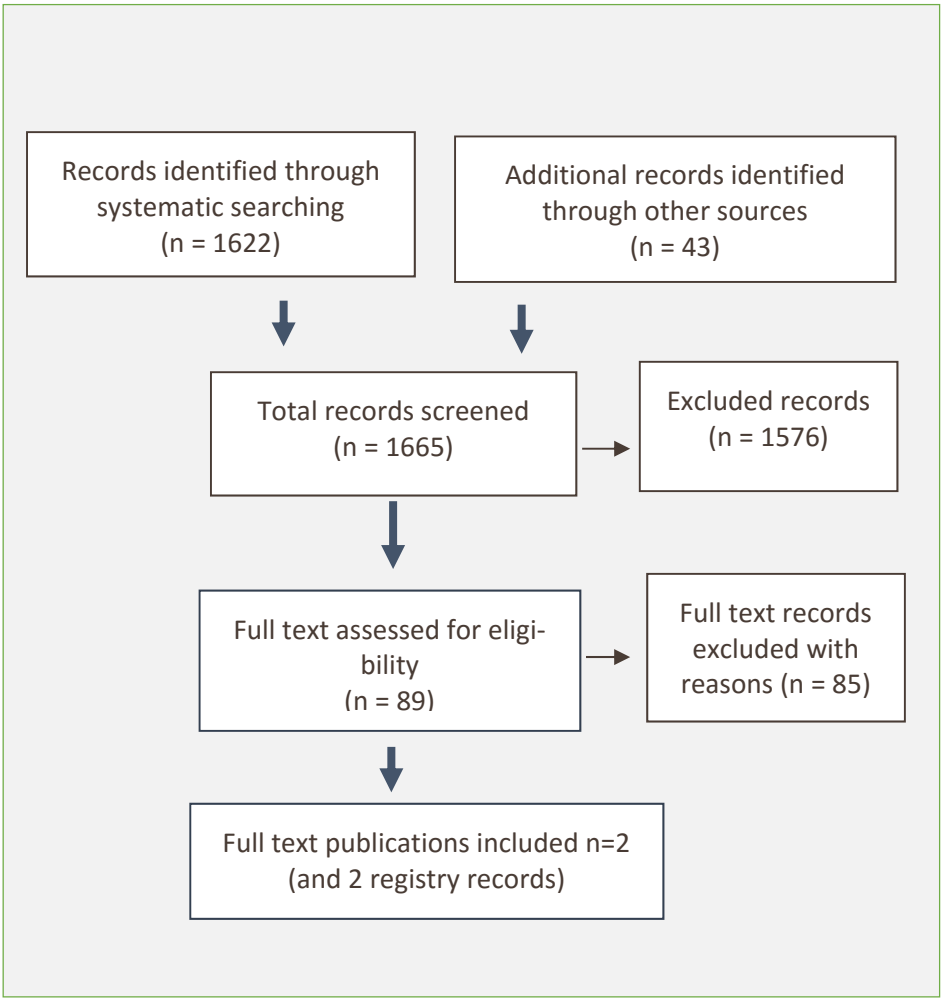



**Figure 3.** *A flow chart of the literature selection*

Table 5 (below) presents the comparison between the search strategy of NIPH and the submitter: the number of databases searched differed greately, and so were the number of full text retrieved and screened, other HTA European assessments, and ongoing studies and records included.

***Table 5.*** *NIPH and submitter search findings*

| Norwegian Institute of Public Health | Submitter |
|---|---|
| Database search:<br>MEDLINE, Embase (Ovid), Cochrane Library, Technology Assessments, Economic Evaluations database, Centre for Reviews and Disseminations, Database of Abstracts of Reviews of Effects, Health Technology Assessment, and PubMed databases up to January 18, 2017. | Database search: (pg 11)<br>www.ncbi.nlm.nih.gov/gov/pubmed<br>www.cochranelibrary.com<br>up to Nov 11, 2016 |
| Full text records screened: 89 | Full text records retrieved: 4 |

| | |
|---|---|
| Reports from other HTA agencies: 1 ongoing and 4 published | Reports from other HTA agencies: 1 |
| Registry records: 18 | Ongoing: "to be supplied" |
| Records included in the analysis: 2 RCTs and 2 registry records | Records included: 1 article and 1 abstract/poster |

## Characteristics of included trials

### Included Studies

Two RCTs (and corresponding registry records – hereafter "protocols") were included in this appraisal. The studies were published in 2016 and 2017, and were conducted across 23 (25) and 26 European diabetes centres (26) (IMPACT and REPLACE studies respectively) in seven countries (France, Germany, United Kingdom, Sweden, Austria, Spain and the Netherlands). In both trials, the length of the treatment was 6 months, the trials used a randomised clinical trial with parallel group study design, and the FreeStyle Libre group was compared to SMBG. Individuals' insulin administration method was primarily multiple daily injections (25;26).

### Participants

The studies included a total of 463 adults, of reported white ethnicity (177 females, 286 males). Details of inclusion and exclusion criteria to the trials can be seen in Appendix 5. Table 6 shows some important baseline characteristics. The IMPACT study included individuals with type 1 DM who showed good glycaemic control at baseline, while the REPLACE study included individuals with type 2 DM with bad diabetes control, HbA1c of 8.74%.

***Table 6*** *Baseline characteristics of included studies*

| Study (Diabetes type) | BMI (SD) | Age (range) | Baseline HbA1c % (SD) | Years since diagnosis | SMBG per day (SD) |
|---|---|---|---|---|---|
| Bolinder (25): Type 1 DM | 25 (4) | 43 years (33-57) | 6.7 (0.6) | 20 years (range 12-31), | 5.5 (2.2) |
| Haak (26): Type 2 DM | 33 (6) | 59 years (22-81) | 8.74 (1.04) | 17 years (range 2-43) | 3.8 (1.3) |

BMI: body mass index; DM: diabetes mellitus; SMBG: self monitor blood glucose; SD: standard deviation;

### FreeStyle Libre vs SMBG

SMBG includes self monitoring and the follow up use of insulin in the form of a pen device, or continuous subcutaneous insulin infusion. In both studies participants wore

FreeStyle Libre technology into masked mode for 14 days baseline period; measurements were blinded for participant and investigator at this time. Participants supported their glucose management by SMBG. They used the strip port built into the FreeStyle Libre and compatible test strips made by the Abbott. Participants were asked to keep record of capillary glucose concentrations in a glucose diary and to log other events in an event diary. Those that had sensor data for 50% of the blinded wear period, or more than 650 individual sensor readings, were then centrally randomised into two groups.

After randomisation, the technology was unblinded for participants in the intervention group who then continuously used sensor glucose data for self-management of glucose levels throughout the duration of the study. Participants in the intervention group were given access to the technology software, which they could use at home to review their sensor data if they wished. No training was provided to these participants for interpretation of glucose sensor data in neither of the studies. Participants in the control group self-monitored glucose concentrations using the FreeStyle Libre meter and test strips.

SMBG=self-monitoring of blood glucose.

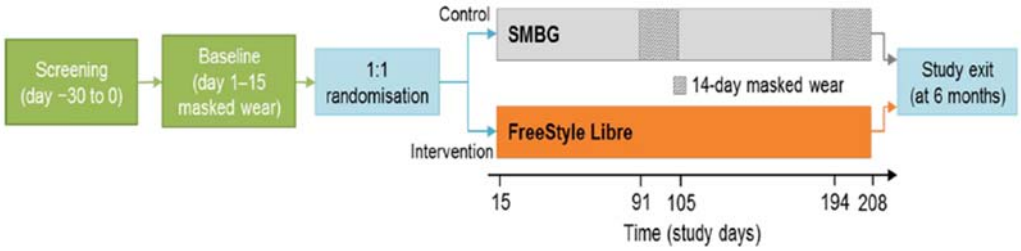



***Figure 4.*** *Study design (reprinted from Bolinder 2016 with submitter's permission)*

## Risk of bias in included studies

Two reviewers evaluated the 'risk of bias' using the Cochrane Handbook tool (20) based on the primary article and corresponding protocol. Results of the risk of bias for the two RCTs are presented below in Figures 5 and 6. Some concerns in the risk of bias were the unclear information about allocation concealment – although there were no obvious baseline imbalances no information is provided on concealment allocation - and lack of blinding in the included studies (participants, personnel, and staff). We understand that for participants and personnel it is almost impossible to perform a trial with true blinding with this type of intervention. However, this does not mean that potential biases can be ignored. The fact that participants and personnel were not blinded

may bias the results and outcome assessment.

Detection bias for subjective outcomes (i.e., quality of life, treatment satisfaction) was assessed as high risk, as it is possible that the non-blinded assessor (the individual) overestimated the effect of the intervention. Detection bias for some objective outcomes (i.e. adverse event) were the observer judgement was involved was assessed as high risk; for outcomes were no judgement was involved (i.e., blood test) we considered the assessment of the outcome was not likely to be influenced by the lack of blinding. Furthermore, we are unclear how the data was transferred and analysed from the FreeStyle Libre for analysis. It is clear, however, that all study personnel was unmasked and therefore the non-blinded assessor could overestimate the effect being assessed. Selective outcome reporting was assessed as unclear, as there are differences between the protocol, the journal publication, and the submitter package, which we could not explain. Overall, our assessment had a higher number of high risk and unclear risks domains than the submitter's assessment. Table 7 below compares results regarding risk of bias:

***Table 7.*** *Norwegian Institute of Public Health and submitter's risk of bias*

| Norwegian Institute of Public Health | Submitter |
|---|---|
| Tool utilized: Cochrane Handbook Tool (20) | Tool utilized: no information provided |
| Selection bias (randomization): Low risk<br>Selection bias (allocation): Unclear risk<br>No information on how this was done | Selection bias (randomization & allocation): Low risk<br>Central interactive web response WRS using the biased coin minimisation method; study centre and type of insulin administration were prognostic factors |
| Performance bias (blinding of personnel and participants): High risk – no blinding | Performance bias: Unclear risk - no blinding |
| Detection bias (subjective outcomes): High risk – self reported<br>Detection bias (objective outcomes): low to high risk – outcomes requiring judgement high risk, outcomes not requiring judgement are low risk | Detection bias: Low risk<br>Detection of hypoglecemia was done by sensor and not subject to human evaluation |
| Attrition bias: Low risk – data accounted for, appropriate statistical methods | Attrition bias: Low risk<br>Minimal missing data. Missing data is accounted for |

| | |
|---|---|
| Reporting bias: Unclear risk | Reporting bias: Low risk<br>All outcomes accounted for |
| Other sources of bias: High risk -sponsor studies | Other sources of bias: not evaluated |

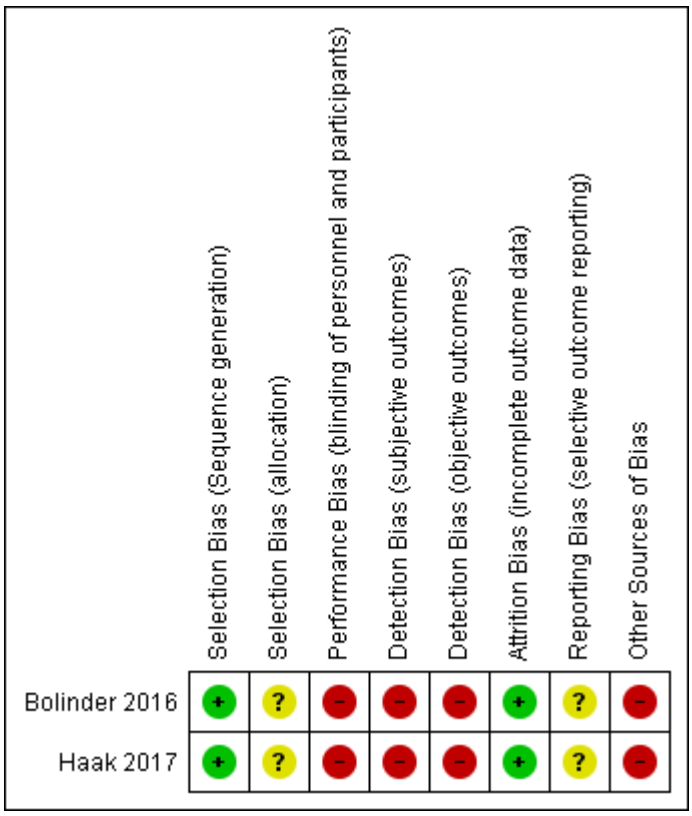



***Figure 5.*** *Risk of Bias: Bolinder and Haak*

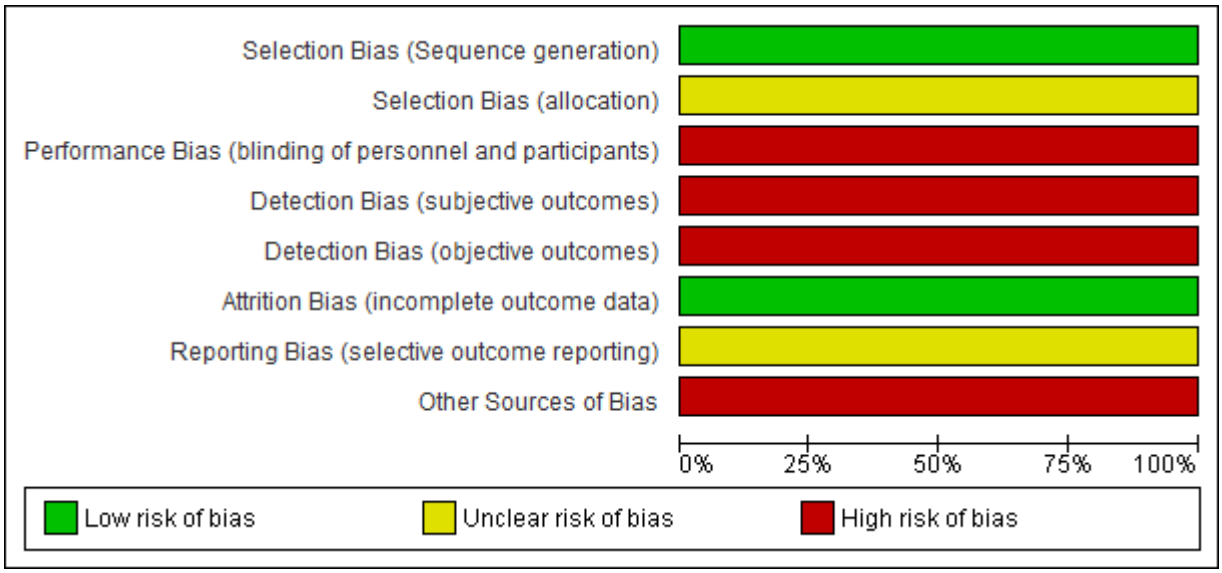



***Figure 6.*** *Risk of Bias: studies combined*

## Effect of FreeStyle Libre

The included studies provided data for health related quality of life, treatment satisfaction, HbA1c, glycaemic measures, and adverse events. The studies did not assess pain as a separate outcome, but recorded pain as part of adverse events. The RCTs specified the evaluation of the self-management of DM was in the home setting. The results related to the effects of the intervention from the meta-analysis are presented below corresponding to the objectives of the assessment.

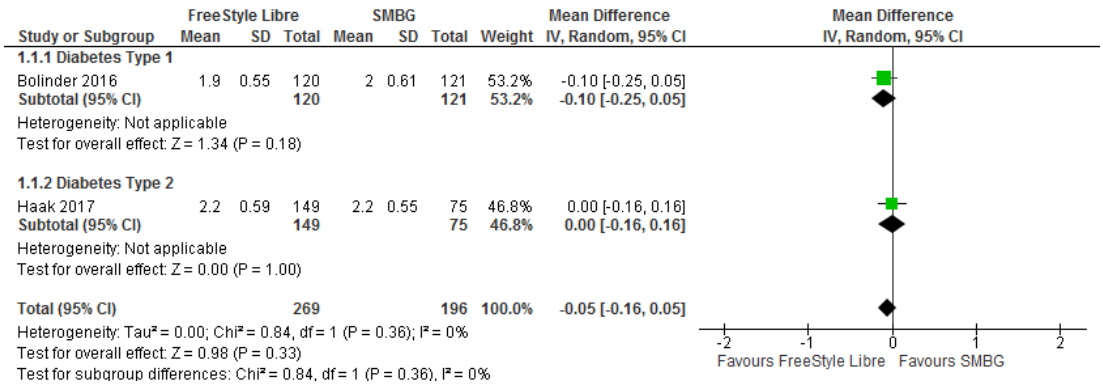
Following the feedback from clinical experts, we present the effect estimates of each group i.e. type 1 DM and type 2 DM for the glycaemic measures for each of the two studies separately in the forest plots and in Appendix 6. The forest plots are followed by the "summary of findings" table, which is the key information concerning the certainty (quality) of evidence and the magnitude of effect of the intervention.

### Outcomes

All outcomes, with the exception of adverse events, were measured at baseline and 6 months end points. Adverse events were measured at baseline and 6 months end point for the intervention group, and baseline and 4 weeks, divided in two sets of 14 days at 3 months and 6 month, in the control group.

### Health Related Quality of Life

This outcome was measured with a diabetes specific scale (self-report, Diabetes Disease Questionnaire); the scale is a 1-5 point Likert scale with high scores indicating dissatisfaction, frequent impact, or frequent worry. The MD was -0.05 (95% CI -0.16 to 0.05; $I^2$ 0% indicating no heterogeneity; p=0.36).



The GRADE quality of evidence for this outcome was low which means FreeStyle Libre may lead to little or no difference in health related quality of life for individuals with type 1 or 2 DM.

***Table 8.*** *Summary of findings table -health related quality of life*

FreeStyle Libre compared to self-monitoring of blood glucose in insulin-treated diabetes individuals

Patient or population: individuals with diabetes type 1 and 2 insulin dependent
Setting: home setting
Intervention: FreeStyle Libre technology
Comparison: SMBG
Outcome: measured at 6 months (end of intervention)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with SMBG | Risk with FreeStyle Libre technology | | | |
| Health Related Quality of Life<br>DQoL Likert scale (self-reported) from 1 to 5, lower scores are best | The mean health related quality of life ranged across control group from 2 to 2.2 points | The mean health related quality of life in the intervention group was 0.05 lower (0.16 lower to 0.05 higher) | - | 465<br>(2 RCTs) | ⊕⊕◯◯<br>LOW [a] |

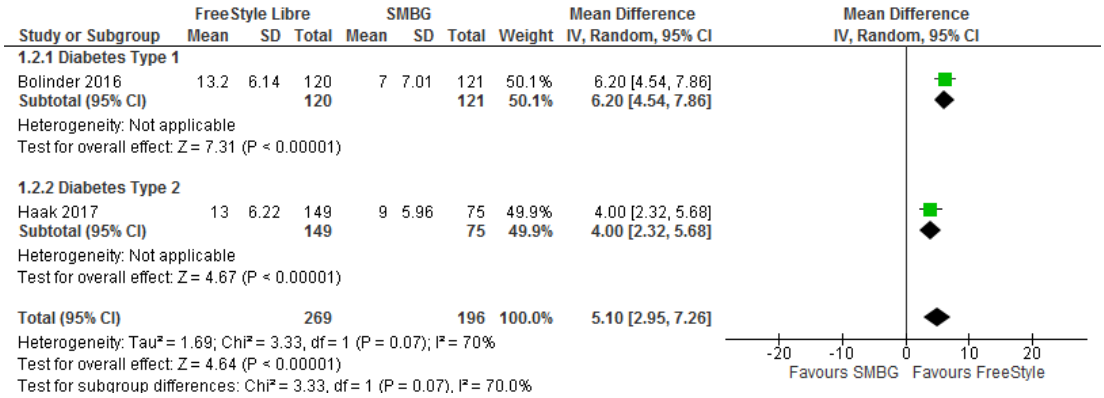
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RCT: randomised control trial:

a. Issues related to unclear or high risk of selection, performance and detection biases (subjective outcome) (downgraded twice)

### Patient Treatment Satisfaction

This outcome was measured with the (self-report) Diabetes Treatment Satisfaction Questionnaire; scores range from -18 to 18 with higher scores indicating higher treatment satisfaction. The MD was 5.10 (95% CI 2.95 to 7.26; $I^2$ = 70% indicating substantial heterogeneity; P=0.07 also indicating statistically significant heterogeneity).

Due to statistical heterogeneity ($I^2$ = 70%), clinical heterogeneity was explored. On evaluation, daily life of individuals with Type 1 and 2 DM is very different. But even when diabetes management imposes considerable demands on individuals, treatment method used has an impact on treatment satisfaction. Despite high heterogeneity both groups considerably improved their treatment satisfaction at the end of intervention.




The GRADE quality of evidence (see table 9) for this outcome was low, which indicates that FreeStyle Libre may improve treatment satisfaction for individuals with type 1 or 2DM.

***Table 9.*** *Summary of findings - patient treatment satisfaction*

FreeStyle Libre compared to self-monitoring of blood glucose in insulin-treated diabetes individuals

Patient or population: individuals with diabetes type 1 and 2 insulin dependent
Setting: home setting
Intervention: FreeStyle Libre technology
Comparison: SMBG
Outcome: measured at 6 months (end of intervention)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with SMBG | Risk with FreeStyle Libre technology | | | |
| Patient satisfaction<br>Satisfaction score (self-reported), scale from: -18 to 18, high scores are best | The mean patient satisfaction ranged across control groups from 7 to 9 points | The mean patient satisfaction in the intervention group was 5.1 higher (2.95 higher to 7.26 higher) | - | 465<br>(2 RCTs) | ⊕⊕◯◯<br>LOW [a] |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RCT: randomised control trial:

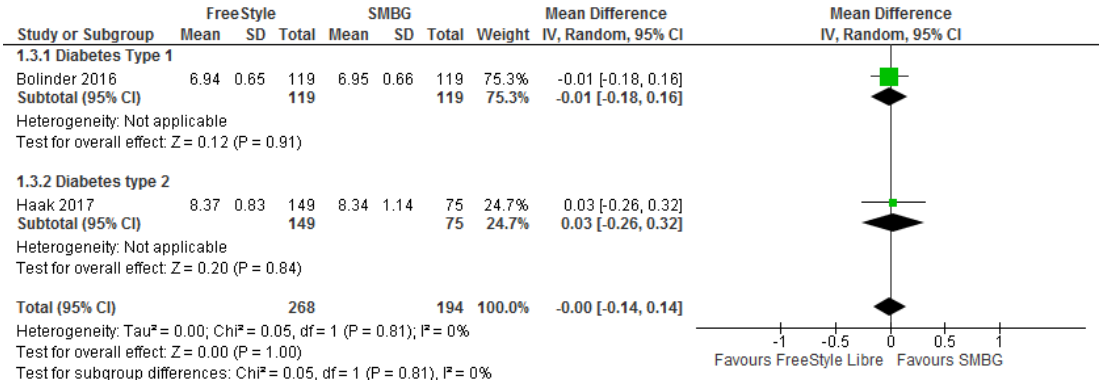
Sponsored studies but not further downgraded
a. Issues related to unclear or high risk of selection, performance and detection biases (subjective outcome) (downgraded twice)

**Pain:**

Pain was recorded among adverse events

**HbA1c:**

**HbA1c:** (target level of 7% or less, analysed by ICON Laboratories, Dublin, Ireland). The hemoglobin A1c MD was -0.00 (95% CI -0.14 to 0.14; $I^2$ = 0% indicating no heterogeneity; P=0.81 also indicating no statistically significant heterogeneity).




The GRADE quality of evidence (see table 10) for this outcome was low, which indicates that FreeStyle Libre may lead to little or no difference on HbA1c changes for individuals with type 1 or 2DM.

***Table 10.*** *Summary of findings table - HbA1c %*

FreeStyle Libre compared to self-monitoring of blood glucose in insulin-treated diabetes individuals

Patient or population: individuals with diabetes type 1 and 2 insulin dependent
Setting: home setting
Intervention: FreeStyle Libre technology
Comparison: SMBG
Outcome: measured at 6 months (end of intervention)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with SMBG | Risk with FreeStyle Libre technology | | | |
| HbA1c<br>Target level 7% or less | The mean HbA1c (%) ranged across control groups from 7 to 8% | The mean HbA1c (%), target level 7% or less in the intervention group was 0 (0.14 lower to 0.14 higher) | - | 462<br>(2 RCTs) | ⨁⨁◯◯<br>LOW [b] |

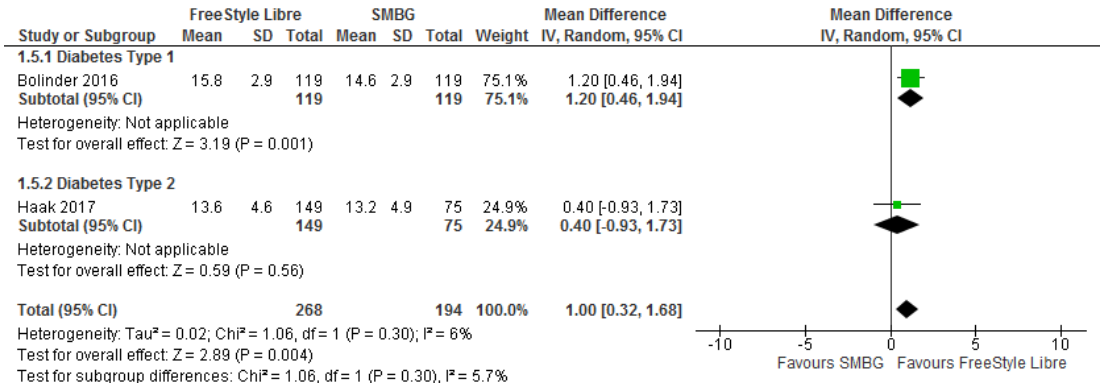
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RCT: randomised control trial:

b. Issues related to unclear or high risk of selection and performance biases (downgraded twice)

## Glycaemic Measures (time in range, without hypoglycaemia and hyperglycaemia)

*Time in range - glucose 3.9-10mmol/L*

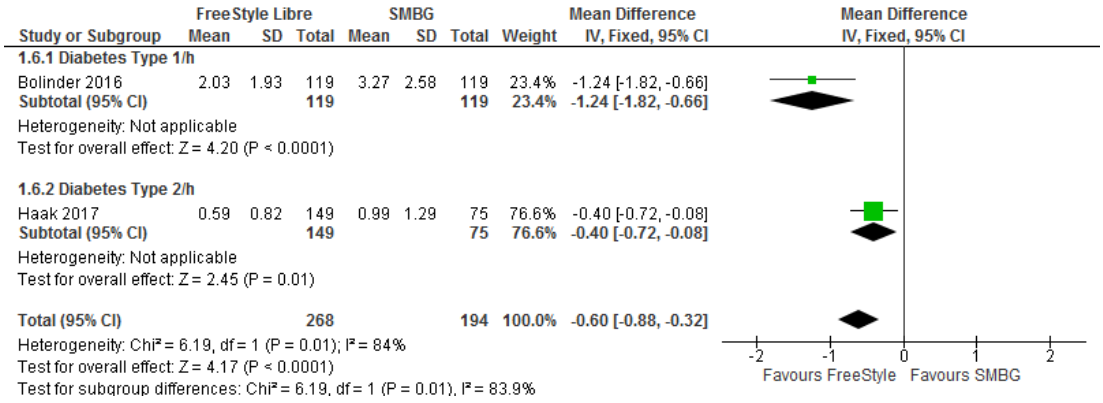
The time (in hours) spent with glucose range 3.9-10mmol/L, shows a statistically significant result in favor of FreeStyle Libre. The overall MD was 1.00 (95% CI 0.32 to 1.68; $I^2$ = 6% indicating no heterogeneity; p=0.30). Results showed statistically significant effect for type 1 DM (238 participants, MD 1.20 95% CI 0.46 to 1.94) and not statistically significant effect for diabetes type 2 (224 participants, MD 0.40, 95% CI -0.93 to 1.73). The GRADE quality of evidence for this outcome was low (see Table 11) which means FreeStyle Libre may slightly improve time with glucose in range 3.9-10ml/L for insulin dependent individuals with type 1 and 2 DM.




Glucose <3.9 mmol/L within 24h

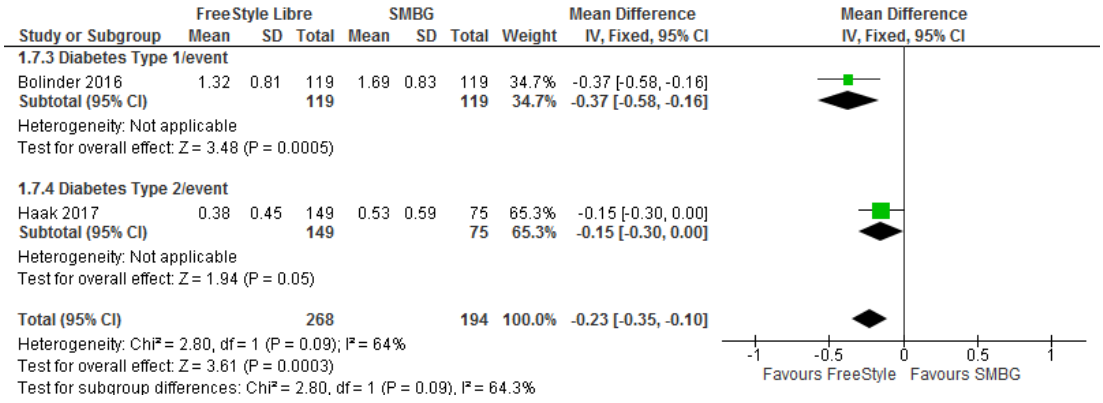
*Time/hours*

The time (in hours) spent with glucose <3.9 mmol/L within 24 hours decreased in the FreeStyle Libre group. The total MD was -0.60 (95% CI -0.88 to -0.32; $I^2$ = 84% indicating considerable heterogeneity, p=0.01). The high heterogeneity in glycaemic measures is not surprising and can be explained by considering the physiopathology of each type of diabetes. The GRADE quality of evidence for this outcome was very low (see Table 11) which means we are uncertain whether FreeStyle Libre leads to less time with glucose <3.9 mmol/L within 24h for individuals with type 1 or 2DM




*Events*

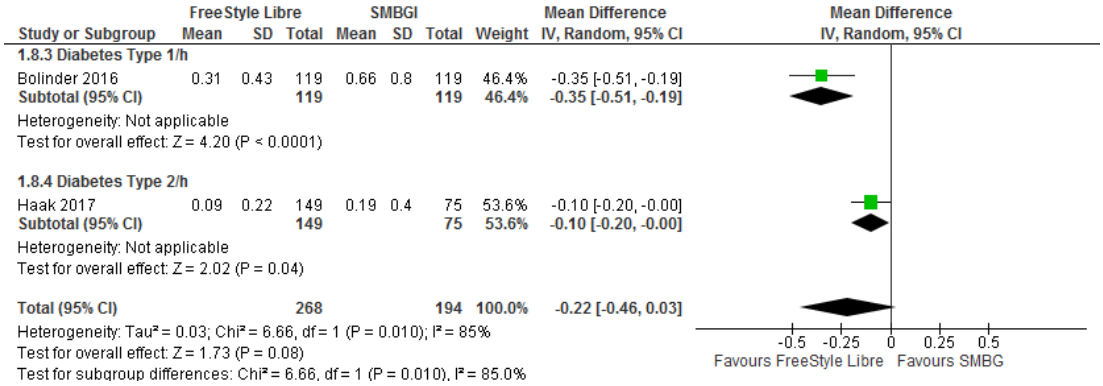
The mean number of events with glucose <3.9mmol/L decreased for participants in the intervention. The total MD was -0.23 (95% CI -035 to -0.10; $I^2$ = 64% indicating substantial heterogeneity; p=0.09). The GRADE quality of evidence for this outcome was very low (see Table 11) which means we are uncertain whether FreeStyle Libre decreases the number of events with glucose <3.9 mmol/L within 24h for individuals with type 1 or 2DM




Glucose <3.1 mmol/L at night (23:00-06:00) within 7h

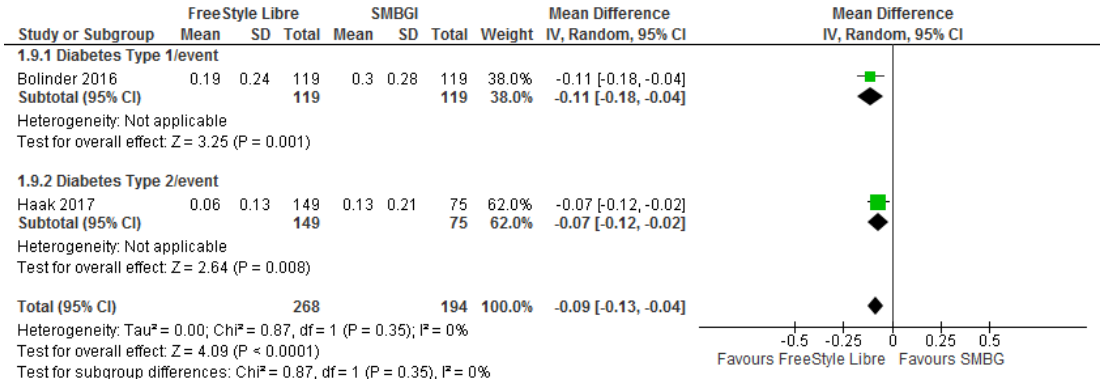
*Time /hours*

The time spent in hypoglycemia during the night showed a non-statistically significant result. The overall MD was -0.22 (95% CI -0.46 to 0.03; $I^2$=85% indicating considerable heterogeneity; p=0.010). Results, however, showed statistically significant effect for type 1 DM (MD -0.35 95% CI -0.51 to -0.19) and statistically significant effect, however smaller, for type 2 DM (MD -0.10 95%CI -0.20 to 0.00). The GRADE quality of evidence for this outcome was very low (see Table 11) which means we are uncertain whether FreeStyle Libre decreases nocturnal time with glucose <3.1 mmol/L within 7h




*Events*

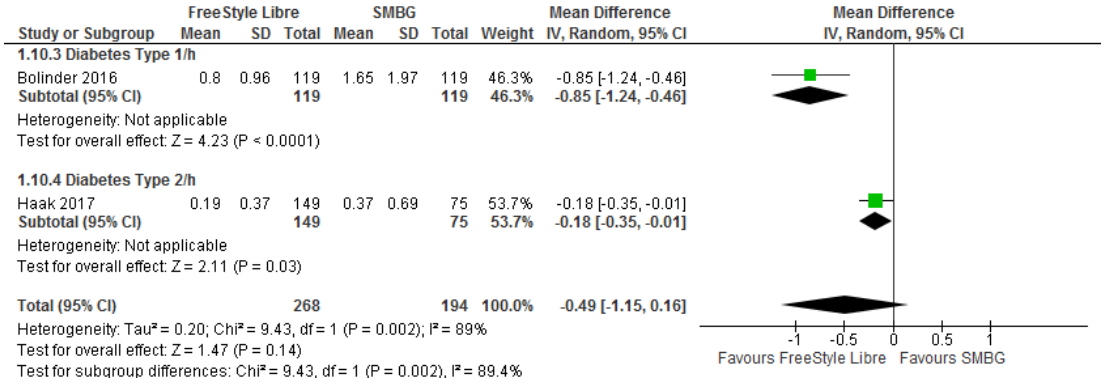
The number of hypoglycemic night events showed a statistically significant decrease in in favour of the intervention. The MD was -0.09 (95% CI -0.13 to -0.04, $I^2$ = 0% indicating no heterogeneity; p=0.35). The GRADE quality of evidence for this outcome was low (see Table 11) which means FreeStyle Libre may slightly decrease nocturnal events with glucose <3.1 mmol/L within 7h




Glucose <3.1 mmol/L within 24h

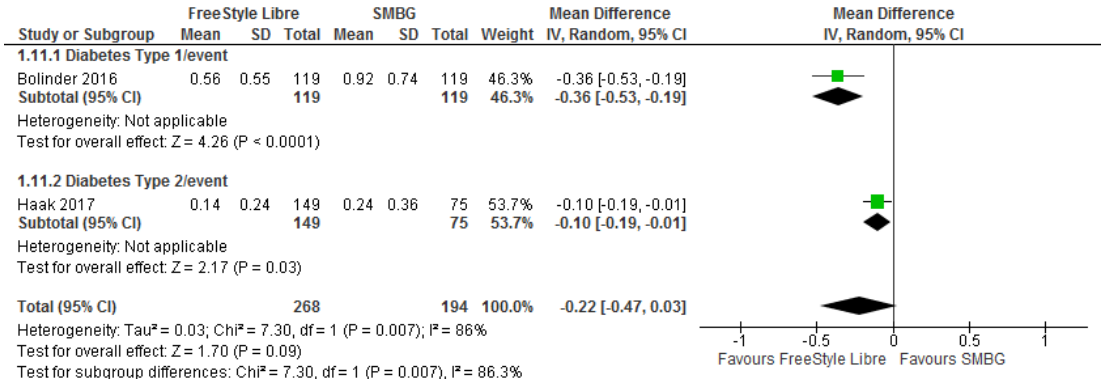
*Time /hours*

The time spent with glucose <3.1 mmol/L within 24 h was not statistically significant. The pooled MD was -0.49 (95% CI -0.35 to 0.16; $I^2$= 89% indicating considerable heterogeneity, p=0.002). Results however, showed statistically significant effect for type 1 DM (MD -0.85 95% CI -1.24 to -0-46) and however smaller results, they are also statistically significant for diabetes type 2 (MD -018 95% CI -0.35 to -0.01). The GRADE quality of evidence for this outcome was very low (see Table 11) which means we are uncertain whether FreeStyle Libre leads to less time with glucose <3.1 mmol/L within 7hours.



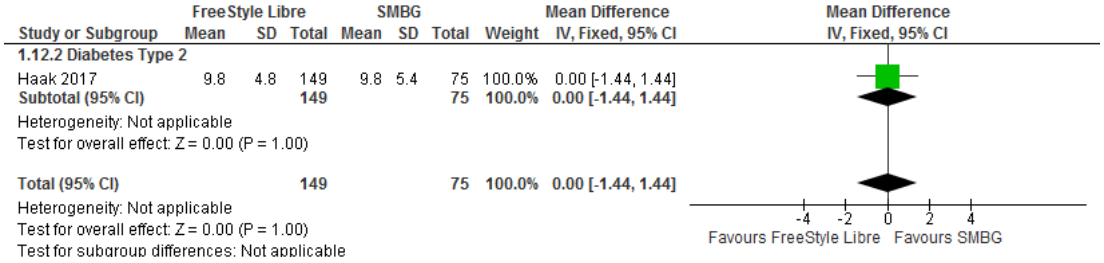

*Events*

Similarly, results of the meta-analysis showed non-statistically significant effect size in the number of events participants had with glucose <3.1 mmol/L. The MD was -0.22 (95% CI -0.47 to 0.03; $I^2$ = 86% indicating substantial heterogeneity; p=0.007). Likewise, results showed a statistically significant effect for type 1 DM (MD -0.36 95% CI -0.53 to -0.19) and a smaller effect for type 2 DM (MD -0.10 95% CI -0.19 to -0.01). The GRADE quality of evidence for this outcome was very low (see Table 11) which means we are uncertain whether FreeStyle Libre leads to fewer events with glucose <3.1 mmol/L within 7hours.




Time with Glucose >10.0mmol/L (h)

One study (N=224) provided data for this outcome. There was evidence of no effect on time spent with glucose >10mmol/L in individuals with type 2 DM. The MD was 0.00 (95% CI -1.44 to 1.44) The GRADE quality of evidence for this outcome was very low (see Table 11) which means we are uncertain whether FreeStyle Libre leads to less time with glucose >10.0 mmol/L for individuals with type 2 DM.




Time with Glucose >13.3 mmol/L (h)

Time spent with a glucose concentration >13.3 mmol/L detection favoured the intervention. The overall MD was -0.39 (95%CI -0.75 to -0.03; $I^2$ 0% indicating no heterogeneity, p=0.03). However results showed statistically significant effect only for type 1 DM (MD -0.39 95%CI -0.77 to -0.01) but not for diabetes type 2 (MD -0.40 95%CI -1.52 to 0.72). The GRADE quality of evidence for this outcome was low (see Table 11) which means FreeStyle Libre may slightly decrease time with glucose >13.3 mmol/L for individuals with type 1 and 2 DM.

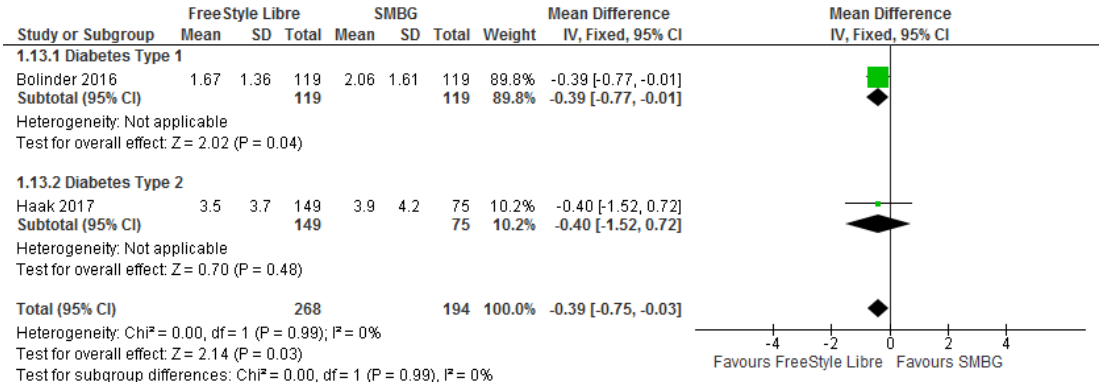



***Table 11.*** *Summary of findings table - glycaemic measures*

FreeStyle Libre compared to self-monitoring of blood glucose in insulin-treated diabetes individuals

Patient or population: individuals with diabetes type 1 and 2 insulin dependent
Setting: home setting
Intervention: FreeStyle Libre technology
Comparison: SMBG
Outcome: measured at 6 months (end of intervention)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with SMBG | Risk with FreeStyle Libre technology | | | |
| Time in range (hours) 3.9-10 mmol/L | The mean time with glucose range 3.9-10 mmol/L across control groups was 15 to 13 hours | The mean time (hours) with glucose range 3.9-10 mmol/L in the intervention group was 1 higher (0.32 higher to 1.68 higher) | - | 462 (2 RCTs) | ⨁⨁◯◯ LOW [b] |
| Hypoglycaemia<br>Time (hours): glucose < 3.9 mmol/L within 24h | The mean time with glucose < 3.9 mmol/L within 24h ranged across control groups from 3 to 1hours | The mean time (hours) with glucose < 3.9 mmol/L within a period of 24h in the intervention group was 0.6 lower (0.88 lower to 0.32 lower) | - | 462 (2 RCTs) | ⨁◯◯◯ VERY LOW [b,c] |
| Events (number): glucose < 3.9 mmol/L within 24h | The mean of glucose < 3.9 mmol/L within a period of 24h ranged across control groups from 0.5 to 2 events | The mean events (number) of glucose < 3.9 mmol/L within a period of 24h in the intervention group was 0.23 lower (0.35 lower to 0.1 lower) | - | 462 (2 RCTs) | ⨁◯◯◯ VERY LOW [b,d] |
| Nocturnal Hypoglycaemia<br>Time (hours): glucose < 3.1 mmol/L during a period of 7h (23:00-06:00) | The mean nocturnal time with glucose < 3.1 mmol/L in the control groups range from 0.2 to 0.7 events | The mean nocturnal time with glucose < 3.1 mmol/L in the intervention group was 0.22 lower (0.46 lower to 0.03 higher) | - | 462 (2 RCTs) | ⨁◯◯◯ VERY LOW [b,e] |

FreeStyle Libre compared to self-monitoring of blood glucose in insulin-treated diabetes individuals

Patient or population: individuals with diabetes type 1 and 2 insulin dependent
Setting: home setting
Intervention: FreeStyle Libre technology
Comparison: SMBG
Outcome: measured at 6 months (end of intervention)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with SMBG | Risk with FreeStyle Libre technology | | | |
| Nocturnal Hypoglycaemia<br>Events (number): glucose < 3.1 mmol/L during a period of 7h (23:00-06:00) | The mean glucose < 3.1 mmol/L in the control groups ranged from 0.1 to 0.3 events | The mean glucose < 3.1 mmol/L in the intervention group was 0.09 lower (0.13 lower to 0.04 higher) | - | 462<br>(2 RCTs) | ⊕⊕◯◯<br>LOW [b] |
| Hypoglycaemia<br>Time (hours): glucose < 3.1 mmol/L within a period of 24h | The mean glucose < 3.1 mmol/L within a period of 24h ranged from 0.37 to 1.65 hours | The mean events (number) of glucose < 3.1 mmol/L within a period of 24h in the intervention group was 0.49 lower (1.15 lower to 016 higher) | - | 462<br>(2 RCTs) | ⊕◯◯◯<br>VERY LOW<br>[b,f] |
| Events (number) of glucose < 3.1 mmol/L within a period of 24h | The mean events (number) of glucose < 3.1 mmol/L within a period of 24h ranged across control groups from 0.24 to 0.92 | The mean events (number) of glucose < 3.1 mmol/L within a period of 24h in the intervention group was 0.22 lower (0.47 lower to 0.03 higher) | | 462<br>(2 RCTs) | ⊕◯◯◯<br>VERY LOW<br>[b,g] |
| Hyperglycemia<br>Time (hours): glucose > 10.0 mmol/L | The mean time (hours) with glucose > 10.0 mmol/L in the control groups was 10 | The mean time (hours) with glucose > 10.0 mmol/L in the intervention group was 0 (1.44 lower to 1.44 higher) | - | 224<br>(1 RCT) | ⊕◯◯◯<br>VERY LOW<br>[b,h] |
| Time (hours): glucose > 13.3 mmol/L | The mean time (hours) with glucose > 13.3 mmol/L ranged across control groups from 2 to 4 | The mean time (hours) with glucose > 13.3 mmol/L in the intervention group was 0.39 lower (0.75 lower to 0.03 lower) | - | 462<br>(2 RCTs) | ⊕⊕◯◯<br>LOW [b] |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RCT: randomised control trial:

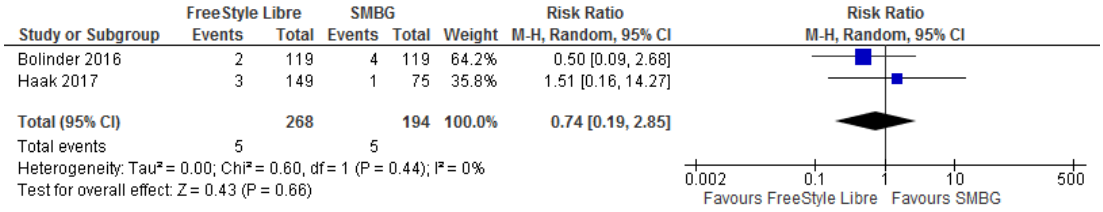
b. Issues related to unclear or high risk of selection and performance biases (downgraded twice)
c. <3.9 mmol/L within 24hours/h: substantial heterogeneity ($I^2$ 84%)
d. <3.9 mmol within 24hours /event: substantial heterogeneity ($I^2$ 64%)
e. Nocturnal <3.1mmol (h): substantial heterogeneity ($I^2$ 85%)
f. <3.1 mmol within 24hours/h: substantial heterogeneity ($I^2$ 89%)
g. <3.1 mmol within 24hours/event: substantial heterogeneity ($I^2$ 86%)
h. Imprecision: single study with small sample size (number of participants bellow 300 rule of thumb)

### Adverse Events

Non-device related adverse events were measured at baseline and 6 months end point for the intervention group, and baseline and 4 weeks (14 days at 3 months and again at 6 month) in the SMGB group.

### Serious adverse events (non-device related)

Both included studies provided data on severe non-device related adverse events. Compared to SMBG, FreeStyle Libre was associated with similar number of serious adverse events, RR 0.74 (95% CI 0.19 to 2.85), $I^2$ = 0% indicating no heterogeneity.




The GRADE quality of evidence for this outcome was low (see Table 12) which means FreeStyle Libre may lead to little or no difference in serious adverse events for individuals with Type 1 and 2 DM.

***Table 12.*** *Summary of findings table - adverse events*

FreeStyle Libre compared to self-monitoring of blood glucose in insulin-treated diabetes individuals

Patient or population: individuals with diabetes type 1 and 2 insulin dependent
Setting: home setting
Intervention: FreeStyle Libre technology
Comparison: SMBG
Outcome: measured at 6 months (end of intervention)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| Adverse Events Moderate to Severe | 26 per 1000 | 19 per 1000 (5 to 73) | RR 0.74 (0.19 to 2.85 | 462 (2 RCTs) | ⊕⊕◯◯ LOW [b] |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RCT: randomised control trial:

b. Issues related to unclear or high risk of selection and performance biases (downgraded twice)

### Device related adverse events

Bolinder 2016: "13 adverse events, reported by 10 participants in the intervention group, were related to wearing the sensor…there were 248 sensor insertion-site signs and symptoms experienced by 65 participants across both groups (26% of participants). Signs can be subdivided into those expected due to sensor insertion: pain (38),

bleeding (25), oedema (8), induration (5), and bruising (5), and those associated with sensor wear: erythema (85), itching (51), and rash (31)." page 2260

Haak 2017: "six (4.0%) intervention participants reported 9 device-related adverse events (2 severe, 6 moderate, and 1 mild). These were sensor-adhesive reactions, primarily treated with topical preparations…there were 158 anticipated sensor insertion site symptoms observed for 41 (27.5%) intervention and 9 (12%) control participants. These symptoms were primarily due to sensor adhesive (erythema, itching, and rash) and resolved without medical interventions."

Seven cardiac events were reported for 4 (2.7%) intervention and three (4.0%) control participants (none considered to be related to study procedures or the device).

**Withdrawal device related**

Bolinder 2016: "Seven participants withdrew from the study due to device-related events or repetitive occurrences of sensor insertion-related symptoms".

Haak 2017: "Three participants (1 intervention, 2 controls) experienced an adverse event leading to withdrawals from the study; none were associated with the device".

In regards to adverse events, The Lancet published correspondence between Brahimi (27) and Bolinder (25) regarding concerns about skin adverse events which might affect individuals using the FreeStyle Libre device. As some information provided by Bolinder was not addressed in the submitter's package or the journal publications (i.e., use of a different body site for the sensor, design changes in the technology) we considered it important to present it here.

(Brahimi) "…the authors reported 13 cutaneous adverse events related to the use of FreeStyle Libre. These adverse events occurred in ten patients, and were categorised as mild (three cases), moderate (four cases), and severe (six cases). Two patients with severe skin adverse events were treated by drug therapy and two were discontinued from the study. All seven cases with mild or moderate skin adverse events required drug therapies, and three of them were discontinued from the study. It seems reasonable that patients with skin adverse events might decide to continue or discontinue their participation in the trial, but the management of these adverse events during this study remains unclear and not proportional to the severity of the adverse events. It would be helpful for both practitioners and patients if the authors can determine clearly what

type of device-related skin adverse events require treatment or device discontinuation, or both."

Bolinder's reply:
… the number and type of events reported for FreeStyle Libre in the IMPACT trial were similar to those for other systems in which a device is worn on the skin for a period of time using a medical-grade adhesive… Skin symptoms can occur with high skin temperature and humidity, along with long duration of exposure, all of which might be contributing factors to adverse events. Sensor-wear-related symptoms were recorded as adverse events in the IMPACT trial if the effects were severe and lasted for more than 7 days, or if the patient required prescription medication for the event to resolve. Adverse event severities were recorded on the basis of a health-care professional's assessment of mild, moderate, or severe events.

According to the study protocol, individuals with known sensitivity to medical-grade adhesives were excluded from participation. However, we reasonably expected that a few participants might have been unaware of their sensitivity ... For participants with adverse events involving skin symptoms during this trial, symptoms (including severe) were resolved by use of barrier products (e.g., Cavilon spray) or drug therapy (e.g., zinc ointment, Fenistil gel, or hydrocortisone cream) as prescribed, or simply by relocating the device to another area of the skin such that the effects were maintained at a tolerable, background level. In other cases, although the adverse events were generally mild or moderate, the longevity of the symptoms, despite use of treatment, contributed to the participant's decision to withdraw from the trial. None of the participants withdrew because of health-care professional advice to stop wearing the sensor.

Since completion of the IMPACT trial, minor design changes have been made to FreeStyle Libre. These changes are expected to improve breathability of the skin that is in contact with the sensor and to facilitate the exclusion of moisture between the sensor–skin interface.

# Cost-effectiveness analysis

## Methods for evaluating submitted cost-effectiveness models

### Cost-effectiveness analysis

The primary objectives of health economic modelling are to evaluate the incremental cost-effectiveness of the specified health intervention(s) compared to standard treatment, using the best available evidence, and to assess the most important sources of uncertainty surrounding the results and the robustness of the results. In order to make comparisons across different types of treatments and multiple health outcomes, economic models typically measure treatment benefits in terms of quality-adjusted life years (QALYs), a measure designed to capture the utility of both life extension and health improvement. QALYs, by definition, take on a value of 1 for perfect health and 0 at death (28). The output of a cost-effectiveness model is expressed as an incremental cost-effectiveness ratio (ICER), which can be thought of as the extra cost of obtaining an extra life-year in perfect health. The ICER is defined as

$$Cost_{Intervention} - Cost_{Comparator} \Big/ QALY_{Intervention} - QALY_{Comparator}$$

### Evaluating cost-effectiveness models

There is no single correct way to build an economic model to estimate the cost-effectiveness of a specific health initiative. Modelling requires consulting with clinical experts to gain an understanding of normal disease progression, and to determine, based on the research question, the relevant treatment population, relevant comparator, and important health outcomes and adverse events connected to treatment. This informs the basic model structure, and also determines which clinical effect data is most important to retrieve in the systematic literature search. Once the model structure is in place, systematic searches and evidence grading are used to provide the most reliable risk information for the model, but must also to collect all of the relevant cost and quality of life data that is needed for cost-effectiveness calculations.

A model is rarely meant to capture every potential detail of the treatment landscape; rather the goal is to include enough detail to provide a realistic view of the most significant pathways in disease progression, given the research question(s) one is trying to answer. Evaluating any given model is primarily about determining whether the choices made by the submitter regarding model structure and treatment comparator are reasonable given the research question; whether baseline epidemiological data reflect the population in which the analysis is being performed; whether the clinical effect data used in the model are of adequate quality; whether resource use and costs reflect the conditions of the healthcare system in question; whether there has been sufficient sensitivity and scenario analysis to determine the degree and source of uncertainty in the model results; and whether the model displays external and internal validity. Checklists are available to help researchers systematically examine these issues (28).

We proceed by first describing the health economic model used in the submission and the results generated by the model. We then provide our evaluation of the model, focusing on the following issues: model structure, choice of model parameters, use of appropriate sensitivity and/or scenario analysis to examine the extent of uncertainty in model results, and relevance of the model for the Norwegian context (28).

## Published cost-effectiveness evaluations identified by the submitter

The submitter identified and provided two published cost-effectiveness evaluations of flash glucose monitoring systems. One economic analysis examined European and Australian individuals receiving intensive insulin treatment for type 1 DM (29). The second economic analysis focused on European individuals receiving intensive insulin treatment for type 2 DM (30). Both studies were funded by the submitter and were used the IMS Core Diabetes Model (Table 13). The NIPH searched for other published economic evaluations of Free Style Libre, withouth finding any relevant ones.

***Table 13.*** *FreeStyle Libre cost-effectiveness evaluations for type 1 and 2 DM*

| Study | Bilir et al (29) | Li et al (30) |
|---|---|---|
| Model Analysis | CEA | CEA |
| Population | Individuals >18 years with well-controlled Type 1 diabetes, HbA1c of ≤7.5% (58 mmol/mol) treated by multiple daily insulin injections or continuous subcutaneous insulin infusion for at least 6 months (25). Glucose levels were self tested by individuals at least 10 times per week. Individual characteristics in the analyses reflect the IMPACT trial population and estimates from the published literature were used for CDM inputs unavailable from the IMPACT study. | Individuals >18 years with poorly controlled Type 2 diabetes, HbA1c of ≥7.5% (58 mmol/mol) treated by multiple daily insulin injections or continuous subcutaneous insulin infusion for at least 6 months (REPLACE trial). SMBG was done by individuals at least 10 times per week. Individuals' characteristics in the analyses reflect the REPLACE trial population and estimates from the published literature were used for inputs unavailable from the REPLACE study. |
| Intervention | FreeStyle Libre | FreeStyle Libre |
| Comparison | SMBG | SMBG |
| Incremetal QALY | 0.80 | 0.56 |
| Incremental costs | SEK192,973 | SEK144,360 |
| ICER/QALY | SEK240,826/QALY | SEK258,108/QALY |

CEA: Cost-effectiveness analysis, CDM: Core diabetes model, SEK: Swedish crones, ICER: incremental cost effectiveness ratio, QALY: quality adjusted life year, SMBG: self-monitoring blood glucose

### Description of the published cost-effectiveness evaluations identified by the submitter

Bilir et al. (29) estimated the cost-effectiveness of FreeStyle Libre compared to SMBG through the IMS Core Diabetes Model (IMS CDM) for intensive insulin-treated Type 1 DM. The IMS CDM combines Markov model structures with a Monte Carlo simulation. HbA1c progression was based on data from the Diabetes Control and Complications Trial study (31), while other physiological parameters progression were taken from the Framingham Heart Study (32). Sweden was the core case, with additional results for Germany, Italy, France, the Netherlands and Australia. For the core case, cost-effectiveness was modelled from a societal perspective with a 50- year time horizon. The estimated ICER for FreeStyle Libre compared to blood glucose monitoring was 240,826 Swedish crones (SEK)/QALY.

Li et al. (30) estimated the cost-effectiveness of FreeStyle Libre compared to SMBG through the IMS CDM for intensive insulin-treated Type 2 DM using the same IMS CDM model as Bilir et al. They also used Sweden as the core case, with additional results for Germany, Italy, France and the Netherlands. The Swedish National Diabetes Register risk equation was used for HbA1c value prediction, while the CDM default risk equation (based on United Kingdom Prospective Diabetes Study (33)) was used for other countries. Other physiological parameters progresion data were taken from the Framingham Heart Study (32). The core case, cost-effectiveness was modelled from a societal perspective with a 40-year time horizon. The ICER for FreeStyle Libre compared to blood glucose monitoring was 258,108 SEK/QALY.

Scenario analyses performed for the other countries, in both studies, showed smiliar results as the Swedish core case.

## Population and comparator in the submitted report

The cost-effectiveness analysis population are individuals with type 1 and type 2 DM. The main characteristics of individuals with type 1 DM are age ≥ 18 years, HbA1c lower than 7.5%, and performed SMBG at least 3 times each day on average (25). The main characteristics of individuals with type 2 DM are age ≥ 18 years, HbA1c between 7.5% and 12%, and SMBG performed at least 10 times a week on average (26) (Appendix 5).

The submitter presented the analysis of FreeStyle Libre compared to SMBG. The latter is the current reference treatment for insulin dependent individuals with type 1 and 2 DM in Norway.

## Type of analysis and decision model of the submitted report

The submitted report used the IMS CDM, which was designed to assess lifetime health outcomes and economic consequences of various measures for DM. The model determines the ICER per QALY. The analysis was conducted from the perspectives of both the healthcare services and society more broadly, and used a 40-year time horizon. Costs and clinical outcomes are extrapolated in the model beyond the study follow-up period of 6 months. The discount rate in the analysis was set to 4% for both costs and QALYs. The model included two arms: the FreeStyle Libre and SMBG arm. The analysis assumed that the individuals with diabetes used either only SMBG or FreeStyle Libre continuously throughout the lifetime. The model is Markov-based with annual cycles

meaning that an individual's health state with cost and effect implications is evaluated at annual intervals.

According to the submitter the model quantifies the development of complications, life expectancy, quality-adjusted life-years and total costs for the cohort in the study over the 40-year projection time. Baseline characteristics for individuals with type 1 DM are from the IMPACT study and reflect the mean baseline characteristics of the study's treatment and control groups: age of 44 years, HbA1c of 6.78%, and mean diabetes duration of 22 years (25). Similarly, baseline characteristics for type 2 DM cohort are from the REPLACE study: age of 59, HbA1c of 8.70%, and mean duration of diabetes of 17.5 years (26) (see Table 6).

The model structure comprises 17 sub-models, independent of each other, that simulate the complications of diabetes (Figure 7). Each sub-model is a Markov model using Monte Carlo simulations to predict outcomes. Transition probabilities represented by distributions predict occurrence of complication during a year, and depend on time and the current health status. The model uses different transition probabilities and procedures for type 1 and type 2 DM. For type 1 DM the most important data sources are the diabetes control and complications trial and the Framingham Heart Study studies (31). For type 2 DM the most important data source is the United Kingdom Prospective Diabetes Study (33). Because eight of the 17 diabetic complications may result in a fatal outcome, the model also calculates background mortality.

According to the submitter the model uses the C++ (Microsoft® Visual Studio 2005) program to form the basis of the calculations required to run each simulation (31).

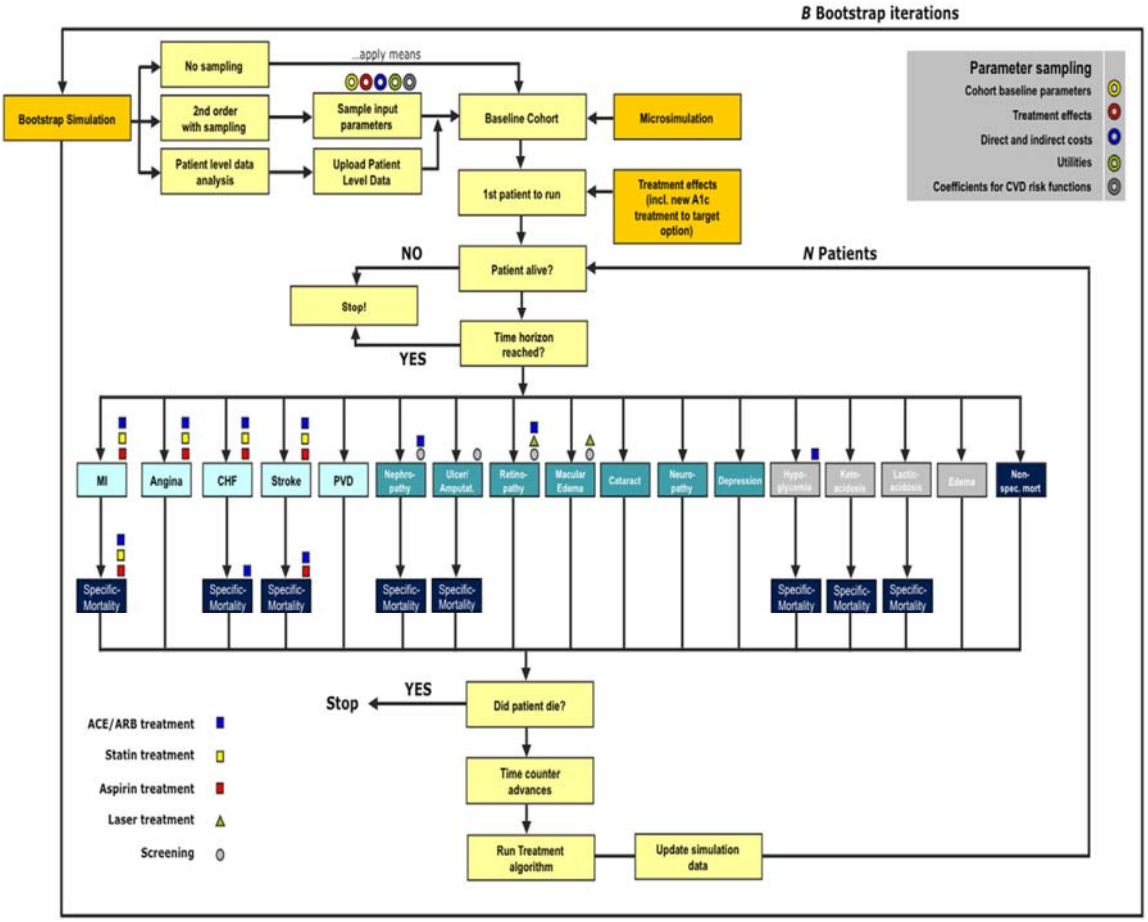



Figure 7. Flow diagram of the IMS Core Diabetes Model. PVD: peripheral vascular disease, MI: myocardial infarction, CVD: cardiovascular disease, CHF: congestive heart failure, ARB: angiotensin receptor blocker, ACE: angiotensin-converting enzyme (34).

## General comments on the submitted health economic analysis

The model utilised by the submitter lacks transparency, this shall be understood as the difficulty for the NPIH to gain a firm understanding of the factors that determine how a single patient progress through the model, which assumptions are made and which parameters affect the model´s outcomes. Specifically:

- we did not have information about several key equations and assumed relationships in the model,
- we lacked access to a micro simulation module where it should be possible to run sensitivity analyses (35),
- we lacked access to the assumed distribution of variables, which is crucial for the assessment of a Monte Carlo probabilistic model.

Patient level data are missing from the model that we have access to (35).

The problem with lack of transparency is reinforced by the unexpected behavior of the model. The model generated results that were hard for us to explain given the information provided by the submitter about the model. For example, the submitter stated in a meeting that HbA1c was the main driver for the analysis linked to type 1 and 2 DM. We found that changes in HbA1c made little change in the ICERs.

It was also difficult to assess the internal validity of the model. Because of our lack of full access to the model, it was imposible to perform a full assessment or to modify underlying assumptions and parameters in order to independently assess the impact on reported results. Our access was limited to a web-based model, which only allowed us to examine the model's input data.

The submitter argues that the IMS Core Diabetes Model has been used in many peer reviewed publications, and has also been validated in an article published in a high quality journal (34;36). For validation purposes , McEwan et al used the model to predict clinical outcomes in 112 clinical diabetes studies based on baseline characteristics from the studies, and then compared the model's results with the "gold standard" clinical trial outcomes. The resulting $R^2$ values of 0.90 and 0.88 for type 1 and 2 DM respectively, indicate that the model was able to explain a large portion of the variation in results of the 112 clinical studies. They therefore conclude that the IMS Core Diabetes Model is a credible tool for predicting the absolute number of clinical episodes in the populations from the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study (33). Our clinical experts found the assumed patient population of the submission to be reasonable for Norwegian conditions.

Although the submitted analysis examined both a health care perspective and a societal perspective, our assessment focused on the health care perspective. A health care perspective is appropriate when decision-making occurs with a fixed budget, as is the case for the Norwegian Regional Health Authorities.

## Clinical and epidemiological data

The submitted IMS Core Diabetes Model uses separate transition probabilities and strategies of management for type 1 and type 2 DM. Model parameters are based on data from several published clinical and epidemiological studies from different countries.

The model is described to capture the natural course of diabetes, associated with the relationship between risk factors and specific events, mortality from complications and long-term mortality. The model includes incidence data for the following adverse events among patients with type 1 and type 2 DM: fatal cardiovascular events (stroke, myocardial infarction, heart failure and angina), non-fatal cardiovascular events, microvascular complications, foot ulcer and amputation, depression and other mild or severe adverse events (i.e., hypoglycemia, ketoacidosis, lactic acidosis).

In the default scenario the amount of insulin consumed or required is not intensified over time. This is based on 30 months of dosing data from Buse and colleagues (37).

## Efficacy

The efficacy data in the submitted model is taken directly from the IMPACT and RE-PLACE clinical studies (both evaluated over a 6-month period). Efficacy data based on intention-to-treat analysis from the clinical studies are assumed to reflect the intervention effect in the model. This effect is believed to persist throughout the study's time horizon.

The clinical effectiveness of FreeStyle Libre for individuals with type 1 DM was measured as the difference between the groups in time per day spent in hypoglycaemia (glucose < 70 mg/dL [3.9 mmol/L]), and in the model applied by adjusting the baseline values. In the IMPACT trial, the primary endpoint of time spent in hypoglycaemia was significantly reduced in the intervention arm compared to the control group. At baseline, the mean time spent in hypoglycaemia was 3.38 hours per day in the FreeStyle Libre arm and 3.44 hours in the blood glucose arm, representing a 2% reduction. After adjustments for baseline hypoglycaemia, the adjusted mean difference between the groups was −1.24 hours per day, corresponding to a 38% reduction of time with hypoglycaemia with FreeStyle Libre compared with SMBG (25).

For individuals with type 1 DM in the SMBG arm, the rate for mild hypoglycaemic events is 6,760 per 100 person-year (27 % of these events were nocturnal hypoglycemic events). For individuals with type 1 DM in the FreeStyle Libre arm, the rate for mild hypoglycaemic events was calculated based on 25.5 % and 33.2 % reduction in the frequency of daily and nocturnal hypoglycemic events, respectively (glucose < 70 m/dL). The rate of what turned out to be 4,897 per 100 person-years, (25 % of these events were nocturnal hypoglycemic events) (25).

According to the United Kingdom Hypoglycemia Study Group (2007) (38) the rates for severe hypoglycemia are the same in both arms. The analysis is based on this.

Individuals with type 1 DM in both the FreeStyle Libre and SMBG arm, had the same mean change in HbA1c (0.12 %) at baseline. This was presented in the IMS Core Diabetes Model.

The clinical effectiveness of FreeStyle Libre for individuals with type 2 DM was measured as the difference between the changes in HbA1c. The study was powered to detect a difference in the change in HbA1c at 6 months of 0.35%. The primary endpoint of the REPLACE study, reduction in HbA1c, was similar for both arms. The adjusted mean change in HbA1c from baseline was −0.29% in FreeStyle Libre compared to −0.31% in the SMBG group with no significant difference between groups (26).

Information about the number of mild hypoglycaemic events for individuals with type 2 DM in the SMBG arm were found in a recently published meta-analysis study for SMBG. For individuals with type 2 DM using FreeStyle Libre, the number of mild hypoglycemic events were calculated based on the relative difference between the treatment arms. The rate of mild hypoglycemic events was 27.7 % lower in the FreeStyle Libre arm compared to the SMBG arm presented in the online-based model for individuals with type 2 DM (26). Further, no difference was assumed in severe hypoglycemic events between the arms. These rates are assumed to be constant during the 40-year time horizon.

The submitter has also incorporated an additional utility rate of 0.03 in the IMS Core Diabetes Model for the use of FreeStyle Libre compared with SMBG in all their scenarios, to account for the assumed improvement in user-friendliness. The utility value of 0.03 (and other utility values) for FreeStyle Libre is based on a Time Trade Off study, performed by Evidera and sponsored by Abbott Diabetes Care. The EQ-5D has limited sensitivity to utility benefits associated with glucose monitoring devices, and is therefore not included in the REPLACE or IMPACT studies (25;26).

## Costs

The submitter identified resource use and cost data by searching in published Norwegian cost studies and administrative databases. All costs are from the year 2016 and measured in Norwegian kroner (NOK) and the consumer price index (CPI) is used

to adjust costs from different years (39). The submitted documentation package contains direct costs related to the health care perspective, and indirect costs related to a social perspective.

The cost of FreeStyle Libre includes the cost of the intervention, the cost of treatment for complications, the cost related to side effects and other treatment costs.

### Cost of the intervention

The submitter calculated the total yearly costs related to FreeStyle Libre and standard SMBG for individuals with type 1 and 2 DM (see Table 14). The calculated cost of FreeStyle Libre is listed in table 14.

***Table 14:*** *Calculated cost of FreeStyle Libre*

| Item | Cost (NOK) | Unit | Source (REF) |
|---|---|---|---|
| Insulin | 0.34 | IU/ml | (40) |
| Metformin | 0.38 | 500 mg x 3 per day | (40) |
| FreeStyle Libre | 599 (excl. VAT) | Per sensor | ((41), read June, 2017) |
| Test strips | 4.82 | Per strip | (42) |
| Lancets | 0.53 | Per lancet | (43) |
| Additional GP visit | 284<br>(x 2 for FreeStyle Libre year one) | Per consultation | (44) |

GP: general practitioner, mg: miligram; SLV: The norwegian medicines agency; IU/ml: international units per milimiter; VAT: Valute-Added Tax

The unit price of the FreeStyle Libre sensor (NOK 599) is taken from the website of FreeStyle Libre (41). The price stated in the submission was lower, but claimed by the sumbitter to be confidential.

- Diabetes type 2 < 65 years old:

For resource use calculation, the following assumptions observed in the REPLACE study (26) were used. *General:* an individual with type 2 DM uses metformin in addition to insulin.

*FreeStyle Libre:* The submitter assume that the individual needs 109.5 SMBG strips per year, 85.2 insulin units per day and 0.65 lancets per day. Further, the submitter suggests that the individual needs two GP consultations the first year and one consultation in subsequent years. The cost for FreeStyle Libre users would be about NOK 24,954 the first year, and NOK 24,670 the second year. According to the website of

FreeStyle Libre a sensor works up to fourteen days (41). Our clinical experts considered that an individual needs between 26 to 29 sensors per year.
*SMGB:* The submitter assumes that the individual needs three SMBG strips per day, 87.8 insulin units per day and 1.26 lancets per day. Further, the submitter suggests that the individual needs one GP consultation per year. The annual cost for SMBG users would be about NOK 17,116.

- Diabetes type 1:

The following assumptions lay behind the data in the IMPACT study (25).
*FreeStyle Libre:* Continuous glucose monitoring systems in Norway are mainly used by those individuals with impaired awereness of hypoglycaemia.

The submitter assumes that the individual needs 182.5 SMBG strips per year, 45.8 insulin units per day and 267.4 lancets per year (25). According to the submitter's website FreeStyle Libre sensor works up to fourteen days (41). Our clinical experts considered that an individual needs between 26 to 29 sensors per year.
Further, the submitter suggests that one individual needs two GP consultations in the first year and one consultation in subsequent years. The total cost for FreeStyle Libre users would then be about NOK 23,446 in the first year and NOK 23,162 in the second and subsequent years.
*SMBG:* The submitter assumes that one individual needs 1,971 SMBG strips per year, 34.8 insulin units per day and 657.6 lancets per year (25). Further, the submitter suggests that one individual needs one GP consultation each year. The annual cost for SMBG users would be about NOK 14,904.

**Cost of complications**

The submitter obtained costs related to myocardial infarction, angina, stroke and peripheral vascular disease based on Norwegian diagnoses-related groups (DRGs) (45). The first year costs related to myocardial infarction (NOK 53,311), angina (NOK 21,840), heart failure (NOK 47,299) and peripheral vascular disease (NOK 39,259) are based on DRGs (45). The cost related to stroke in the first year is about NOK 91,266 and based on several published sources (45-47).

The submitter adopted the assumption of the reimbursement report for Pradaxa that the costs related to myocardial infarction will decline by 69 % from the first year to the second year and beyond (45;48). According to the reimbursement report by Levemir (46) and adjustments by CPI from 2007 to 2016 on cost data (39), the cost related to

stroke and peripheral vascular disease will both decline to NOK 9,320 in year two and beyond. Death due to stroke within 30 days is given the same cost in the first year, but regardless of the costs related to rehabilitation. The cost related to angina in year two and beyond are NOK 415 (40;44;45). The submitter does not mention any source for the costs assigned to heart failure in year two and beyond (NOK 2,443).

The costs of dialysis in year one (NOK 792,887) (49) and the cost of peritoneal dialysis in year one (NOK 629,085) are also used in year two and beyond, minus the costs related to training of health professionals. DRG, immunosuppressive drugs and corticosteroids, according to the indication of the drug mycophenolate are used to estimate the transplantation costs (NOK 539,558) (40;45).

### Cost of the side effects

In the submitted model, mild hypoglycaemic events are assumed to have no cost. Severe hypoglycaemic events are given a cost of NOK 31,583 because the submitter assume that individuals having severe hypoglycaemia need help from a third party. Help from a third party also applies to individuals affected by ketoacidosis, which the submitter considers to cost NOK 48,022. Edema is given a cost of NOK 3,787 (45).

### Other treatment costs

The input costs related to medications were derived from the Norwegian Medicines Agency (40) and the costs related to screening and cataract surgery were obtained from the Norwegian Medical Association and Unilabs (44;50). The cost related to laser treatment, treatment for blindness, neuropathy, amputation (event based), healed wound and infected wound were taken from the Norwegian Directorate of Health (45). The cost related to gangrene treatment and amputation prosthesis were obtained from the study by Ghatnekar et al. (51).

## Health related quality of life (HRQL)

HRQL utility values, based on scores from the generic EuroQol instrument (EQ-5D), were available for all health states. Most of the utility values were taken from European studies. The health state “Diabetes type 2, with no complications” was given a utility value of 0.785 (52) and the health state “Diabetes type 1, with no complications” was given a utility value of 0.9. In the submitted model, the HRQL change over time, depending on disabilities related to complications or events that may occur for an individual with diabetes. An individual starts with the same baseline HRQL utility value in both

study groups (FreeStyle Libre and SMBG), and experience disutility associated with the various minor and major diabetes related events.

The utility values for mild hypoglycaemia and the frequency of hypoglycaemia are based on calculations from Lauridsen et al (53). The first individual experience with hypoglycaemia will be perceived as severe. The disutility per event decrease as the individual experiences hypoglycaemic episodes more often and adapt to the situation. Similarly, the average disutility per event depends on the rate of hypoglycaemia. Taking this into account, the disutility per hypoglycaemic event was estimated in each treatment arm.

## NIPH comments on submitter parameters and input data

There is great uncertainty connected to the efficacy data. Input data for the model is taken from several studies, from different countries with various study populations. Thus, the study populations may not be comparable and may not represent the current Norwegian population. According to our clinical experts, when using old data it should be pointed out as a possible source of biased results. Historic data often overestimate treatment effects. A lot of the data used for input in the health economic model are old. Using data from the 50s, 60s, 70s' (32) and mostly 80s' (33) would, for instance, greatly overestimate cardiovascular disease in individuals with DM, and hence the potential for savings by decreasing glucose levels. Further, at that time primary prevention with lipid lowering drugs was not invented and the borders for initiation of antihypertensive treatment were higher.

The submitted clinical studies extrapolate the effect of 6 months over a 40-year period (25;26). A 6-month period was chosen, because it is long enough to detect differences in duration spent in hypoglicaemia that may result from participants and health care professionals responding to the more comprehensive glucose data provided by FreeStyle Libre (25;26). The long term effects of treatment of hypoglicaemia, and the long term effects of hypoglicaemia incidence, are less known, which increase the uncertainty regarding the efficacy data in the model. Patient fatigue in wearing FreeStyle Libre is not taken into account. Neither is the fact that initial studies, in particularly those involving dedicated individuals, tend to overestimate treatment effects compared to when the treatment is used in a general disease population (clinical expert).

The clinical input data used for cost-effectiveness calculations presented in the model deviate substantially from the clinical input data presented in the submitted documentation file for both type 1 and type 2 DM. For individuals with diabetes type 1, the online-based model used clinical input data from the REPLACE study (this study includes individuals with type 2 DM, under 65 years) in one simulation, and clinical input data related to a Swedish data collection in another simulation. These constitute considerable deviations regarding clinical risks and probability data from the clinical inputs found in IMPACT and REPLACE. The model did not have any HbA1c adjustments related to type 1 DM for the control group, but only for the intervention group. In the submitted model, the change in baseline HbA1c were different between the intervention group and the control group. According to the literature, the change in baseline hbA1c should be the same.

Although the rate related to mild hypoglycemic events were somewhat lower in FreeStyle Libre arm compared to the SMBG arm presented in the online-based model for individuals with type 2 DM, the severe hypoglycemic events were similar in each arm. The cost related to severe hypoglycemic events were much higher than mild hypoglycemic events. The submitter assumes that every severe hypoglycemic event needs a third party intervention (involving a hospital/doctor) and then generates a cost. However, one of our clinical experts states that several patients may have episodes of severe hypoglycemia that they handle themselves without intervention from a third party. And when a third party is needed that would most often be relatives at home.

The submitter considered a difference in change HbA1c between FreeStyle Libre and SMBG. However, the studies from Bolinder and Haak (25;26) show no statisticaly significant change in HbA1c between intervention and control. The lack of statistical significance is not an error per se, but introduces uncertainty that merits further consideration in one-way sensitivity analysis. This was not performed by the submitter and was not possible to explore by the reviewers because of the rigidity of the IMS online model.

Regarding the cost and resource use, our clinical experts consider that the insulin consumption should be the same if Freestyle Libre is used, given that diabetes is correctly treated. In children and youth under 18 years old the consumption of strips would, according to our clinical experts, be higher than 5.4 per day which was assumed by the submitter. In their opinion, several children use more than 10 strips a day.

## Cost-effectiveness results

The submitter provided separate cost-effectiveness results for type 1 and type 2 DM.

The submitters results for type 1 DM were based on an equal change in HbA1c in both arms (0.12%), however results are driven by the assumption that individuals in the FreeStyle Libre arm had a utility gain of 0.03. The submitter's result consequently show that the use of FreeStyle Libre gives a higher QALY and a lower cost, resulting in a dominant ICER.

***Table 15.*** *Cost-effectiveness results (type 1 DM) of FreeStyle Libre versus SMBG according to submitter's model*

| Population | Incremental Cost (NOK) | Incremental Effect (QALYs) | ICER |
|---|---|---|---|
| Type 1 DM | -1 ,225 ,067 | 1.17 | dominant |

NOK: Norwegian Kroner; QALYs: quality adjusted life year; ICER: incremental cost effectiveness ratio

The submitters' results for type 2 DM were given in two scenarios, one for all individuals in the REPLACE study and one for individuals aged under 65 years (Table 16). The submitter assumed utility gain was 0.03 for FreeStyle Libre use. According to the submitter, the use of FreeStyle Libre gives a higher QALY and higher costs, which results in an ICER of NOK 235,673 per QALY gained. According to the submitter, the scenario with individuals under 65 years, the resulting ICER is NOK 243,434.

***Table 16.*** *Cost-effectiveness results (type 2DM) of FreeStyle Libre versus SMBG according to submitter's model*

| Population | Incremental Cost (NOK) | Incremental Effect (QALYs) | ICER (NOK) |
|---|---|---|---|
| Type 2 DM | 88731 | 0.38 | 235673 |
| Type 2 DM < 65 years | 103119 | 0.42 | 243434 |

NOK: Norwegian Kroner; QALYs: quality adjusted life year; ICER: incremental cost effectiveness ratio

### NIPH comments in the results

We were not able to make our own results or adjust submitters results, i.e. we were not able to make our own incremental cost-effectiveness ratios (ICERs). This was because the submitter's model was not fully transparent regarding input, and we have not been able to evaluate the intervention using alternative assumptions. Also the output is not reported in adequate detail. The submitter has reported incremental costs, incremental

effects and ICERs, while absolute levels of direct costs and utilities were not reported, which is good practice including for validation purposes.

The submitter did not perform a sensitivity analysis, which leads to lack of information about the uncertainty associated with the data incorporated in the model. The lack of one way sensitivity analyses also makes it difficult to consider the internal validity of the model.

The overall comments in the sections above regarding the low quality of the effectiveness input data make the submiters model´s results very uncertain. The lack of sensitivity analysis and the fact that we were not able to perform our own sensitivity analysis due to de model constraints make the submitted results of cost effectiveness (ICER) even less reliable.

## Budget impact analysis

The submitter calculated a budget impact, from a Norwegian health care perspective, for introducing FreeStyle Libre as a second-line treatment for individuals with diabetes type 1 or type 2 compared to SMBG. The budget impact was estimated as the net cost difference between a scenario in which FreeStyle Libre is adopted for a full cohort of eligible individuals relative to a scenario in which the device is not adopted. The budget impact was estimated as the yearly cost five years after adoption of the technology.

The submitter created two budget impact scenario analyses, one scenario analysis limited to type 1 DM only and another scenario analysis which included both type 1 DM and type 2 DM. The submitter did not create a budget impact for type 2 DM only.

### The submitted budget impact analysis

According to data from the Norwegian Diabetes Association 2015 (54), there were 28,000 individuals with type 1 DM and 8,220 individuals with type 2 DM, using insulin, in Norway (54). Based on these numbers, the submitter assumed a 0.9% increase in individuals having diabetes type 1 for each year and a 3% increase in individuals having diabetes type 2 each year. Table 17 below shows the prediction of individuals with year 1 as being 2017 as assumed by the submitter. It states the annual number of individuals using FreeStyle Libre if this new technology was adopted. If the new technology was not adopted, all of these individuals would receive SMBG (see Table 17). The submitter assumed that an individual would change their sensor every 14$^{th}$ day (41).

***Table 17.*** *Annual and increased number of individuals with adopted technology according to submitter's model*

| Number of individuals if the new technology is adopted | | | | | |
|---|---|---|---|---|---|
| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
| Annual number of individuals with type 1 DM | 28,506 | 28,763 | 29,022 | 29,283 | 29,546 |
| Increased number of individuals (type 1 DM) | | 0.9% | 0.9% | 0.9% | 0.9% |
| Annual number of individuals with type 2 DM | 8,721 | 8,982 | 9,252 | | |
| Increased number of individuals (type 2 DM) | | 3% | 3% | 3% | 3% |
| Annual number of individuals (type1 + type 2 DM) | 37,227 | 37,745 | 38,273 | | |
| Increased number of individuals (type 1 + type 2 DM) | | 1.4% | 1.4% | 1.4% | 1.4% |

The cost of type 1 and 2 DM was estimated by the submitter to be NOK 239,515,116 in 2015 (55). The submitter assumed that the cost related to SMBG is equally distributed between individuals with type 1 and 2 DM. Further, the submitter assumed that the cost of FreeStyle Libre also includes an additional cost of 9% of the total costs related to SMGB. The submitter assumed that an increased number of individuals with both type 1 and 2 DM would switch from SMBG to FreeStyle Libre during the five first years.

The submitted budget impact analysis also includes additional resource use related to emergency reception, ambulance and hospital stays. Number of annual events per person were taken from the two trials, IMPACT (25) and REPLACE (26). These rates showed more events, which led to more resource use, by using SMGB only instead of FreeStyle Libre.

The submitter estimated that the total added costs would be about NOK 748 million for the first five years after adoption of FreeStyle Libre for individuals with type 1 DM in Norway. The submitter calculated, however, a potential cost saving of NOK 75 million for the first five years after adoption of FreeStyle Libre for individuals with type 1 and type 2 DM in Norway. The submitter's concerns for confidentiality did not allow presentation of these results disaggregatedly.

### NIPH comments on the budget impact analysis

The submitter's budget impact analysis was based on an Excel-based model, which is different from the IMS-CDM model used for cost-effectiveness analysis. The budget impact model includes study data on resource utilisation that where not used in the model. Based on expert opinions, the acute events with severe hypoglycaemia and

ketacidosis applies both to individuals with type 1 and type 2 DM who use insulin. FreeStyle Libre may lead to more stable glucose levels among these individuals because of more frequent blood glucose measurement. Therefore, these individuals may decrease the number of emergency receptions, ambulance and hospital stays, and then reduce the resource use related to these complications.

However, according to our clinical experts, the additional cost related to SMBG while using FreeStyle Libre may have been underestimated in the submitted calculations. We therefore recalculated the budget impact analysis based on the assumption that 20% of the total costs related to SMBG is more reasonable than the 9% applied by the submitter. We based the recalculation on the submitter's model, which is Excel based and allowed us to modify input parameters. Further, our experts assumed that 60 % of the individuals with type 1 DM and about 30 % of the individuals with type 2 DM insulin users would start using the FreeStyle Libre instead of SMBG only. Our clinical experts assumed that an individual would likely have to use 29 sensors per year, a somewhat higher number than found on the submitter's website (41). In our alternative analysis we also used the public price, NOK 599 (excl. VAT), found on the submitter's FreeStyle Libre website June, 2017 (41), since the price stated in the submission was claimed by the submitter to be confidential.

Based on the submitters' model and assumptions we created three budget impact scenario analyses, one scenario analysis related to type 1 DM only, a second scenario analysis related to type 2 DM only, and a third scenario analysis which included both type 1 DM and type 2 DM insulin users. The submitter did not create a budget impact for type 2 DM only.

Table 18 shows the budget impact for individuals with diabetes type 1. The budget impact includs the two scenarios: (1) cost related to adoption of the FreeStyle Libre and (2) cost without adoption of the FreeStyle Libre. The calculations show the difference between the two scenarios in each of the five years of the analysis. The comparisons between the two scenarios shows an increase in total added costs for each year. We estimated that the total added costs would be about NOK 913,000,000 for the first five years after adoption of FreeStyle Libre for individuals with diabetes type 1 in Norway, or about NOK 186 million per year five years after implementation.

***Table 18.*** *NIPH's budget impact estimates for type 1 DM*

| Annual budget Impact | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| + Cost if the New technology is adopted (NOK) | 358,457,802 | 361,683,922 | 364,939,077 | 368,223,529 | 371,537,540 |
| - Cost without adoption of the new technology, i.e. current situation (NOK) | 179,074,804 | 180,686,477 | 182,312,655 | 183,953,469 | 185,609,051 |
| Total added cost (NOK) | 179,382,998 | 180,997,445 | 182,626,422 | 184,270,059 | 185,928,490 |

* Based on number of individuals estimated in Table 17; NOK: Norwegian Kroner

Table 19 shows the budget impact for individuals with type 2 DM insulin users. The calculations show the difference between the two scenarios in each of the five years of the analysis. The comparisons show a decrease in total costs of about NOK 433,000,000 for the first five years after adoption of FreeStyle Libre for individuals with type 2 DM insulin users in Norway, or a decrease of NOK 91,7 million per year five years after implementation.

***Table 19.*** *NIPH's budget impact estimates for type 2 DM*

| Annual budget Impact | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| + Cost if the New technology is adopted (NOK) | 29,801,725 | 30,695,777 | 31,616,650 | 32,565,150 | 33,542,104 |
| - Cost without adoption of the new technology, i.e. current situation (NOK) | 111,308,554 | 114,647,811 | 118,087,245 | 121,629,862 | 125,278,758 |
| Total cost (NOK) | (81,506,829) | (83,952,034) | (86,470,595) | (89,064,713) | (91,736,654) |

* Based on number of patients estimated in Table 17; NOK: Norwegian Kroner

In our third budget impact scenario analysis, we assessed the total added cost of introducing FreeStyle Libre to both individuals with type 1 DM and type 2 DM. Based on our calculations, the total added cost would be the difference between the total added costs for individuals with type 1 DM (NOK 913,000,000) and the total cost savings for individuals with type 2 DM insuline users (NOK 433,000,000). The total

added cost for introducing FreeStyle Libre to both populations would be about NOK 480 million , or about NOK 94 million per year five years after introduction.

As mentioned, the submitter applied two different models for the cost-effectiveness and budget impact analyses. These two tools produced some results that are counterintuitive, seen in combination. Most importantly, for type 2 DM, the cost-effectiveness analysis and the IMS-CDM produced positive incremental costs for FreeStyle Libre compared to SMBG (Table 16), while the budget impact analysis gave the result that introducing FreeStyle libre is cost-saving for these patients. Inversely, the IMS-CDM produced negative incremental costs for type 1 DM (Table 15), while the budget impact analysis showed substantial cost increases related to introduction of FreeStyle Libre. These results in sum appear non-consistent. Whether this is due to the utilisation of different data in de model and in the budget impact calculations is uncertain.

# Discussion

We have performed an independent clinical systematic review and assessed the submitted cost-effectiveness information of FreeStyle Libre for individuals with type 1 and 2 DM. We conducted an independent review of the clinical evidence using a PICO framework; the PICO components were selected in collaboration with the Norwegian Diabetes Association and clinical experts. Our main outcomes are clinical outcomes, and we did not evaluate the sensitivity or specificity of the device – i.e., measuring how well the device does what it is supposed to do.

## Clinical effectiveness and safety: summary of main results

The submitter's literature search identified two records (one RCT and one poster). These two records reported clinical trials of FreeStyle Libre for individuals with type 1 and 2 DM respectively. The submitter indicated other publications provided useful information for the accuracy of the device (i.e. single arm studies). The submitter also included an authority evaluation conducted in France (July 2016) in the documentation package (56).

We considered that only the RCTs were relevant to respond to the clinical effectiveness and safety research question (25;26); the results of these trials were used in the main analyses in this assessment. We regarded the submitter's information to be fair and the submitter's interpretation to be mostly appropriate. After reviewing the (small amount of) evidence available, we considered the value placed on the benefits of FreeStyle Libre by people with the condition, those who represent them, and clinical experts.

The meta-analysis of FreeStyle Libre versus SMBG provided low to very low quality evidence on outcomes post intervention. There were no differences in serious adverse events with FreeStyle Libre compared with SMBG. There were clear differences in the effects of FreeStyle Libre versus SMBG for individuals with Type 1 vs type 2 DM for some outcomes.

Traditional methods of meta-analysis suggest studies are combined in one analysis if they compare similar populations and similar interventions at similar follow up time points, using similar outcomes. However, the answer to the feasibility to conduct a meta-analysis or not may also depend *on the question being asked*.

The meta-analysis was carried out despite clinical differences in Type 1 and 2 DM, as we believed the synthesis matched our research question. Our analysis aimed to prove the submitter's claim ("the technology is indicated for measuring interstitial fluid glucose levels in people (age 4 and older) with diabetes mellitus"). As Gøtzche (57) points out there is a debate between "lumpig" and "splitting" results of clinical trials while considering meta-analyses. Clinical experts and stakeholders believed the characteristics of the individuals differ in a way they did not recommend to pool the data from the studies found; in this way they advocated for "splitting". After further consultation with the NIPH team statistician and experts, we decided to combine the data as we believe this statistical approach matches the research question being asked. The rational we followed when we decided to "lump" the included RCTs was that FreeStyle Libre should reflect the objective of the report. This approach, of course, did not prevent us from looking at, explore and present the results or any resons for heterogeneity in subgroups when necessary. Nevertheless, the reader should be aware that the synthesis is based on two small submitter initiated RCTs; this in itself brings difficulties estimating between-studies variance, which has implications for many aspects of the analysis.

## Overall completeness and applicability of evidence

Given the small number of RCTs included in this assessment, we believe it is likely that new trials may alter the estimated effects of FreeStyle Libre for diabetes.

RCTs included only adults, individuals with well controlled type 1 and poorly controlled type 2 DM. Thus, our conclusions are limited to adults with these characteristics and further generalizations are not recommended.

We considered the information regarding adverse events (e.g., safety and harm) imprecise and of uncertain validity, primarily because of the incomparable times utilized, but also the small number of participants in these trials.

The number of studies is still not sufficiently large to draw firm conclusions on the clinical effectiveness of FreeStyle Libre, nor is the literature sufficiently explicit or large

enough to answer clinical questions about the ideal routine or combination of FreeStyle Libre for (all) individuals with DM.

We acknowledge the evidence for FreeStyle Libre is increasing and evolving rapidily. We identified a number of ongoing and completed (published/unpublished) studies. Among the ongoing studies there are 3 RCTs: one including youth 12 to 17 years, another adults with type 2 DM, and one adults with severe hypoglycaemia. The results from these ongoing RCTs will aid our understanding of the clinical effectiveness of FreeStyle Libre, and will provide better information for decision makers and those planning services for individuals with diabetes.

## Quality of the evidence

Risk of bias assessments highlighted concerns regarding insufficient information on allocation concealment, blinding of participants and care providers, and detection bias related to self reported instruments and one objective outcome.

Other issues to consider when interpreting these results are: a) the studies assessed a large number of outcomes (more than presented in this report), increasing the probability of finding statistically significant differences for outcomes by chance; and b) important clinical heterogeneity was present among the studies which remains a major challenge.

The included studies were sponsored by the submitter. Studies were registered in the trial registry for randomized control trials, which ensured public access to the full study protocol. The submitters' role and responsibilities were fully disclosed in the published studies. However, financial relationships among industry, scientific investigators and academic institutions have been seen to influence research in important ways (58). Industry sponsored research is a topic of concern that is continuously being investigated. The concern relates to industry sponsored research being more likely to favour the product developed by the company than research funded by other sources (59;60). It will be important for further assessment to have independent studies to compare these results with.

## Other European assessments

FreeStyle Libre assessment have been published in other European countries (see Table 20). One of these assessments was included in the submitted documentation pack-

age (*) and the others were retrieved by our search. Overall, we found their results similar to our assessment. After considering similarities in the methods and reporting, we chose to comment on the results of Haute Autorité de Santé (HAS, France), and SESCS (Spain). We then briefly comment on TLV report as the Swedish HTA assesement has not yet been published (e-mail correspondence).

***Table 20.*** *European HTA FreeStyle Libre assessments*

| Agency | Title (date) |
|---|---|
| AQuAS – Agència de Qualitat i Avaluació Sanitàries de Catalunya, Spain (61). | Dispositiu Flash FreeStyle Libre® per al monitoratge de la glucèmia (October 2016) |
| SESCS – Informes de Evaluacion de Technologias Sanitarias (62), Spain (translated document) | Efectividad, seguridad y coste-efectividad del sistema flash de monitorizacion de glucosa en liquido intersticial (FreeStyle Libre) para diabetes mellitus tipo 1 y 2 (June 2016) |
| *HAS – Haute Autorité de Santé, France (56) | Systeme FreeStyle Libre, Systeme flash d'autosurveillance du glucose (July 2016) |
| HTA-centrum Göteborg – Sweden (translated document) | Kontinuerlig glukosmätning med FreeStyle Libre: effekt på HbA1c hos typ 1 diabetiker (2015) |
| Agenas, Agenzia nazionale per i servizi sanitari regionali, Italy | Under appraisal |

**In addition to the above FreeStyle Libre assessments**

- **ZIN** – Zorginstituut Nederland, The Netherlands (63) Flash glucosemonitoringsysteem (FreeStyle Libre) (February 2016). This is an individual's claim for financial compensation. The applicant did not receive it due to FreeStyle not meeting ZIN's scientific criteria (translated document).
- **Swedish Paediatric Society**: The document does not mention "FreeStyle Libre", but refers to CGM. It includes a set of recommendations of use of continuous glucose monitoring in children and youth with type 1 DM. **(64).**
- **The Dental and Pharmaceutical Benefits Agency (TLV)** – Sweden (65)

The French national committee for the evaluation of medical devices and health technologies reviewed FreeStyle Libre *clinical effectiveness* and *accuracy* July 2016. In total, the review included two non-RCT studies (66-68) for the accuracy and precision of the technology, and two RCTs not published at time of evaluation (IMPACT and REPLACE studies). HAS recommended the inclusion of the technology as follows: "Measurement of interstitial glucose levels for the treatment of patients with type 1 and 2 diabetes

(adults and children aged 4 years) undergoing intensified insulin therapy (using external insulin pump or >3 injections per day) and performing the SMBG several times a day (>3 per day). FreeStyle Libre is especially designed for individuals who have received therapeutic education and specific training on the use of the flash interstitial glucose monitoring system." The report indicates that the initial prescription of FreeStyle Libre must be ensured by a diabetologist or a paediatric diabetologist; they further indicate there needs to be a provision of a trial period of a minimum of one month for eligible individuals and those who continue using FreeStyle Libre should undergo a 3 month evaluation to assess whether or not to continue using the system. In addition, prior to prescription, individuals should receive specific education to provide them with the skills and knowledge to apply the sensor and to interpreter and use the information provided by the system. Renewal is ensured by any doctor. The commission emphasised that individual comfort and improved quality of life due to lower capillary blood glucose by finger prick test improved with FreeStyle Libre. HAS' assessment provides a guidance for the reimbursement decision. No cost-effectiveness assessment analysis was carried out for this product (e-mail correspondence) as it is the Ministry of Health that takes the decision. In May 2017 the French Health Ministry granted national reimbursement of the technology for insulin dependent individuals with Type 1 and 2 DM.

The assessment by the Canary Government, Spain conducted in June 2016 focused on the effectiveness, safety and cost-effectiveness of FreeStyle Libre for individuals with type 1 and 2 DM. The assessment included one RCT for individuals with Type 1 DM (IMPACT study), and also mentions the REPLACE study, which was not published at the time the report was conducted. Researchers were not able to identify published economic evaluations; thus Abbott provided one. The agency concluded there is limited scientific evidence regarding the safety and effectiveness of FreeStyle Libre; similarly to our assessment, they stated the available studies are industry funded and the overall GRADE quality of the evidence was low. However, time spent in hypoglycemia was graded a moderate. Also in agreement with our report, the assessment mentioned the lack of serious adverse events and recommends the use of FreeStyle Libre should be done with the individual, providing training and education regarding adverse events, benefits and risks. Similarly to our experience, the economic assessment present uncertainties and limitations associated with the use of certain parameters and points out to the lack of a sensitivity analysis. The agency states the results should be interpreted

with caution. In summary, the agency makes a conditional recommendation for FreeStyle Libre use for individuals with type 1 DM with controlled HbA1c levels (<7.5%), and with a good prior adhesion in the use of self-monitoring glucose in blood.

The Dental and Pharmaceutical Benefits Agency (TLV) in Sweden, has recently published a report entitled "National assessment of medical devices for increase equity in health care" (65). This report describes a process which is about to be established for assessing medical devices before deciding on introducing into the Swedish health care. FreeStyle Libre is used as example on how a medical device has been introduced before any assessment on clinical effectiveness and cost-effectiveness has been carried out. According to the report, this has caused significant budget impact and led to unequal access to FreeStyle Libre to individuals, which vary significantly between the Swedish regions today. Prescriptions of FreeStyle Libre has kept on increasing since spring 2016 in all regions of Sweden despite the high costs, and it is estimated that use of continuous glucose monitors (such as FreeStyle Libre) will lead to a total cost of 600.000.000 SEK per year. Therefore, in May 2016, TLV was asked to assess the cost-effectiveness of continunous glucose monitoring. In the mean time, the New Technologies Council (NT-Rådet) has chosen to put on hold the recommendation on using FreeStyle Libre for individuals with type 2 DM until the assessment is completed in May 2017. The NT-Council is expected to give their recommendation the 7th of June (69). The full Swedish HTA report has not been published at time of our submission (e-mail correspondence).

## Implications for clinical practice

We have used the EPICOT approach to describing implications of the presented evidence (70)

*Evidence*

Diabetes is a chronic disease with a duration of decades that requires long-term treatment. Current evidence (derived from two RCTs) is inadequate to evaluate the benefit and harms of FreeStyle Libre in comparison with standard treatment (SMBG).

Nevertheless, the evidence seems to suggest that FreeStyle Libre may improve treatment satisfaction, and slightly improve time in range, glucose <3.9 mmol/L within 24 hours and number of events, nocturnal events and time spent with glucose <13.0mmol/L when compared to SMBG, however the quality of evidence is low. Individuals in the intervention had similar number of serious adverse events as those in the

comparison group. There were no other statistical differences in other outcomes including quality of life or change in HbA1c. None of the studies, although conducted in Europe, included individuals from Norway.

Many studies conducted to date (some provided by the submitter, retrieved by our search, and recommended by the Norwegian Diabetes Association) were excluded because they did not meet our PICO criteria (eg, lack of a comparator group). However, with the aim of presenting a complete listing of all FreeStyle Libre evidence, we provide information on single arm completed studies (published and unpublished) in Appendix 3 and trial registry records (ongoing studies recruiting or not yet recruiting) in Appendix 4. We summarized FreeStyle Libre completed and ongoing studies in table 21.

***Table 21.*** *Summary of completed and ongoing studies for FreeStyle Libre*

| Population | **Completed (C) or Ongoing (O)** | |
|---|---|---|
| | RCTs | Single arm |
| Type 1 DM – Children | -- | 3 (C) – 1 (O) |
| Type 1 DM - Adolescent | 1 (O) | -- |
| Gestational diabetes | -- | 1 (C) |
| Type 1 - adults | 1 (C) | 4 (C) – 1 (O) |
| Type 2 - adults | 1 (C) – 1 (O) | 1 (O) |
| Type 2-≥ 75 yrs of age | -- | 1 (O) |
| Type 1 & 2 - adults | -- | 4 (C) – 2 (O) |
| Adults - insulin dependent | -- | 1 (C) |
| Adults with severe hypoglycaemia | 1 (O) | -- |
| Children, adults, seniors | -- | 1 (O) |

Some single arm studies present evidence for population groups not addressed by the included RCTs. For example, three single arm tudies (66;71;72) included children 0 to 18 years old, and one study focused on Type 1 and 2 pregnant women (73). In addition, four studies have focused exclusively on adults with type 1 DM (74-77) and another four included adults with both Type 1 and 2 DM (68;78-80). Ish Shalom (79) focused on individuals with diabetes difficult to control. One unpublished trial registry record (81) does not specify type of diabetes (insulin dependent adults).

Simlarly, among the trial registry records (or ongoing studies recruiting or not yet recruiting) we found evidence that will serve updating this assessment. There are three RCTs: one for type 1DM adolescents (82), one involving individuals with type 2 DM (83), and the last one for individuals with severe hypolgycaemia (84). We also found 7 single arm studies: one involving children (85), one involving individuals 4yrs+ (children, adults and seniors) (86), one involving adults with Type 1 DM (87) two involving adutls with type 2 DM (88;89), and two involving adutls with both type 1 and 2DM (90;91).

*Population*

The empirical evidence included in this report is limited to two studies with less than 500 white middle-aged adult participants living in Europe. Our clinical experts stressed the interpretation of the results must be linked to the characteristics of the studies' participants (e.g., IMPACT study individuals' HbA1c levels, REPLACE study individuals' age of diagnosis of 40 years). Therefore, the generalizability of the results to the Norwegian population/context is subject to discussion.

Although single arm studies have involved children and pregnant women these important groups were not included in the included RCTs. Also, there is a lack of evidence (derviced from RCTs) for individuals who may require the support of a caregiver or experienced team to use the technology.

It will be important to obtain information on long term use of the technology in children. The information will be important as Norway has a high number of new cases of type 1 diabetes in children per year (4). According to one of the clinical experts consulted, children and adolescents will likely benefit highly from using FreeStyle Libre. Future studies focusing on children, pre-teenagers and teenagers are important, as this cohort behaves in a different way than adults and FreeStyle Libre is after all, a behavioural management intervention.

*Intervention*

Individuals with diabetes (and/or their caregivers) must obtain, process, and understand basic health and diabetes specific disease management information to make appropriate decisions. The submitter suggest the point of using FreeStyle Libre is to increase the patient's glycaemic insight and diabetes management. We agree with the submitter that the intervention may create an opportunity to encourage and empower more suitable diabetes management. But evidence presented in the studies is limited to

clinical outcomes and a selected group of individuals who have lived with the disease for many years and were habituated to (self) manage the disease. We agree to the unique potential the technology has to make an impact, but cannot assume based on this assessment or submitters' package, the technology is barrier free and adherence and proper self management are guaranteed. Before technology can aide behavioral management and adherence, ongoing diabetes education, health and diabetes literacy, and support systems may need to be established so that providers and individuals can use the technology successfully.

Interactions between individuals and health care providers present with considerable differences in different countries, which will affect individual's behaviour and therefore the effectiveness of the technology of interest. Thus, the results from the included studies may not be representative for the Norwegian context.

The submitter argues that FreeStyle Libre may change diabetes treatment as "it is the patient that makes the day to day decisions concerning treatment." Treatment decisions were not assessed in this report. For example, the amount of insulin per day or other lifestyle changes like diet and exercise were not considered, and therefore we are uncertain whether FreeStyle Libre contributes to change these or other aspects of diabetes treatment.

No training was provided to these participants for interpretation of glucose sensor data. This is an important issue as one would expect greater effect if the individuals in the REPLACE study had received such training. In the assessment of cost, extra consultations are included, thus giving the possibility for correct education.

Training and educational tools may be needed to teach users and their caregivers how to manage glucose levels. Data interpretation and competence managing glucose levels can involve a lot of time and dedication.

Last, compatibility regarding technology software and technological systems at home for people with diabetes and for healthcare professionals in Norway could be a point of issue.

*Comparison*

There is currently a lack of evidence for comparisons other than capillary blood testing. It is very important to be aware that none of the included studies used continuous glucose monitoring (with or without continuous subcutaneous insulin infusion) as a comparator.

*Outcomes*

*Quality of Life and Treatment Satisfaction*

Quality of life is mentioned as one of the main features perceived by users of FreeStyle Libre. Our assessment showed an effect size crossing the line of no effect, which is telling us we are uncertain that one intervention is better than the other for this outcome. The results were surprising for some members of the team, but were not for some of our clinical experts.

One possible explanation for the results is that the participants were already dedicated to use new technologies, and the length of time the individuals have lived with the disease has influenced their views on quality of life. This in addition to a perhaps 'short' intervention not allowing to perceive further improvements in their quality of life. Also, some studies have found that better glycaemic control is associated with better quality of life, but other studies have failed to show this relationship (92;93). One of our clinical experts added, participants realization of changes in blood glucose with FreeStyle Libre, even when they do what they are told by health practicioners, may affect their quality of life as they may feel not being the master of the situation.

Another possible explanation is the tool used by researchers. The Diabetes Quality of Life scale was developed for use in the diabetes control and complications trial (DCCT) to compare two treatment regimens for chronic complications in patients with Type 1 diabetes. As one of our stakeholders pointed out, the scale does not seem to cover important psychological aspects such as motivation and coping. One explanation, is that the tool is not sensitive enough to measure changes in this type of trial.

Nevertheless, we felt it was importat to add the comment of one of the stakeholders consulted (a young man living with diabetes Type1) on the impact of FreeStyle Libre on his quality of life. He told us:

*The life of a diabetes 1 patient is characterized by a high degree of limitations and Freestyle Libre takes away some of these limitations (e.g., soccer training, swimming, skiing and at school). When you have a chronic disease that you will have for 70-80 years, even small improvements in quality of life have a major impact in the long run!!!*

Treatment satisfaction, however, had a change of 5 points (on a scale -18 to 18 points) which, according to our clinical experts, is clinically significant improvement. Type of insulin regimen, the frequency of blood glucose self-monitoring and perceived frequency of hyperglycaemia can have a significant association with treatment satisfaction. One can argue that treatment satisfaction is part of quality of life, thus confirming that FreeStyle Libre improves the lives of individuals with diabetes.

*HbA1c (%)*

The submitter suggested the REPLACE and IMPACT trials were designed to reflect routine clinical practice and that the end points used in the trials were relevant, in particular HbA1c. We disagree with the submitter's statement, and as one of our clinical experts suggested, the population in the trials may have been selected purposefully
In other words, in the IMPACT trial population charachteristics (i.e., well controlled HbA1c) it was likely researchers would find changes in hypoglycemia (main endpoint of the study). Similarly, we founded noteworthy main goal of the REPLACE study (changes in HbA1c) and the participants' characteristics (i.e., not well controlled HbA1c).

There was evidence of a lack of an effect for HbA1c, however, this was not a surprising result. Individuals in the IMPACT study were well controlled, with a mean level of 6.7% (25). One of our clinical expert argued that the individual's disease was extremely well regulated in this study, and it would even not be recommended for them to reduce their HbA1c < 6.5%. Participants in this study were rather dedicated and measured blood sugar regularly and often. It is likely that if they were not that well regulated, it would be more likely to see a reduction in HbA1c. For individuals with HbA1c of 7.5% it would be necessary to reduce their HbA1c. This scenario hardly reflects clinical practice.

Individuals with Type 2 DM were different, and less prone to hypoglycaemia. The group studied was not well regulated with an HbA1c of 8.8% (Haak), indicating that they even from the beginning of the study were not dedicated individuals.

In addition, the study by Haak et al. included older participants, mean age 59 years. Participants younger than 65 years of age had a larger fall in HbA1c level in the intervention group compared with the control group. Furthermore the mean BMI was very high, 33.1, indicating that several of the participants had a metabolic syndrome even though those with insulin consumption over 1.75 units/kg/day were excluded. Those with poor diabetes control and signs of metabolic syndrome need combined interventions to achieve good diabetes control. The submitter indicated "A focus on prevention of hypoglycaemia in this group may explain why HbA1c levels were not significantly reduced" but we have not indication of what this means.

This highlights the difficulties in identifying and including individuals for the trials relevant to the technology. Based on this, we are unsure how FreeStyle would perform on individuals with poorly controlled HbA1c. The submitter acknowledges limitations of the technology for situations of rapidly changing glucose levels, confirmation of hypoglycaemia or impending hypoglycaemia, or when symptoms do not match FreeStyle Libre reading. As one of our clinical experts mentioned, these are situations when individuals are in greatest need of knowing exactly what their present glucose level is. These limitations have to be taken into consideration.

*Pain*

We have not been able to report on this outcome as it was not directly measured in the studies. Individuals' adherence to insulin therapy is an ongoing challenge in clinical care. Pain is obviously a very relevant outcome, in children in particular, and a reason for choosing one treatment (or type of technology) over another. Injection/needle related discomfort continues to bear heavily in the individual, the caregiver and sometimes the healthcare provider.

*Glycaemic control*

We do not agree with the submitters' claim that the users of FreeStyle Libre decreased most aspects of hypoglycemia. Results of our analysis show only half of the outcomes were statistically significant.

There were some clear, and expected, differences in glycaemic control outcomes for type 1 and 2 DM. As a clinical expert pointed out, in type 1 DM a more rapid rise and fall in blood glucose is observed since these individuals do not produce any insulin and thus depend completely on insulin supplied subcutaneously. It is therefore not so strange that, when looking at the forest plots, the effect of FreeStyle Libre is greatest in

the type 1 DM group. While looking at the pooled results, our analysis showed no statistically significant results *for time and events* with glucose <3.1 mmol/L, and <3.1 mmol/L at night. This was also the case for hyperglycaemia time >10 mmol/L (type 2DM). A clinical expert mentioned a reduction in hypoglycaemia (especially in the low group <3.1mmol/L) is of clinically significance, and the importance of this as it may reduce morbidity and mortality due to loss of consciousness and secondary cardiovascular incidents. Further, our results showed only a reduction of number of *events* with glucose <3.9 mmol/L within 24 hours.

*Adverse events*

We disagree with the submitter's favourable interpretation of adverse events related to the device and withdrawals compared with SMBG. Adverse events were measured at uncomparable times (i.e., baseline and 6 months end point for the intervention group, and baseline and 4 weeks - 14 days at 3 months and 14 days at 6 month - in the control group) constituting a major threat in the interpretation of the results. As such, the current results may be misleading and need to be read with caution. In addition, the low number of participants and the short length of the intervention do not justify, in our opinion, such optimistic conclusions.

Issues related to the technology, like scaring or irritability of the skin in the areas where sensor is worn may need to be taken into consideration as alternative areas to sensor wearing as it was needed in at least one of these RCTs (25). The trial period is not long enough to understand the associations between consequences in subcutaneous skin and intersticial reading.

Some sensors fail and consistent supply of sensors is necessary; this can cause the user to have to use other methods for management of the disease. As one of our clinical experts mentioned, individuals will still need some SMBG to check if the FreeStyle show correct values.

Non-device related, device-related and withdrawals from the study were noted in both trials. In agreement with our clinical experts, we concluded that FreeStyle has a tolerable short term adverse event profile, enphasazing that even that information has to be taken with caution.

One of our clinical experts mentioned that individual's fatigue in wearing the FreeStyle Libre is not taken into account. Neither is the fact that initial studies in particularly dedicated patients tend to overestimate treatment effects compared to when the treatment is used in a general disease population.

**Limitations of the assessment/technology**

- The main uncertainties regarding clinical effectiveness are the general lack of data (including children, youth, and special populations) and low quality of available data.
- Due to inherit difference in disease characteristics it was difficult to evaluate and interpret the data in this assessment.
- One of the clinical experts suggested there is a very clear relationship between time spent in hypoglycaemia and risk of severe hypoglycaemia. This is especially important in individuals with impaired awareness of hypoglycaemia. These individuals will /should often chose a technology with an alarm that will indicate the glucose level is approaching hypoglycaemia. FreeStyle Libre is unable to provide such alarm, and this is therefore a limitation of the technology.
- The FreeStyle Libre glucose sensor is situated under the skin and therefore measures the glucose levels in the fluid between blood capillaries and the body's cells (interstitial fluid) rather than capillary blood glucose levels. Because glucose moves from the capillaries to tissues, there is a lag between blood and interstitial glucose levels of at least 6-7 minutes, but on top of this comes a delay in the sensor (94). The lag increases when glusoe is increasing and decreases when glucose is decreasing, and the effect is larger when the speed of change in glucose levels are larger. To know the delay and the absolute difference one must do test with the actual glucose sensor. Further, confirmatory capillary blood glucose tests may therefore be required to confirm the value displayed by the continuous glucose monitor before making any adjustments to diabetes therapy or driving a vehicle.

## Cost-effectiveness

The submitter provided a cost-effectiveness analysis over a time horizon of 40-years. The submitter calculated an incremental cost-effectiveness ratio for FreeStyle Libre compared with SMBG. The health economic evaluation was conducted using a web-based model, being the IMS CDM. The model was built upon Markov modelling of 17 sub-models of complications associated with Type 1 and 2 DM.

We have highlighted some weaknesses in the model that we think should be addressed. First, the model received from the submitter lacks transparency, making it difficult to gain a firm understanding of the factors that determine a cohort's progress through the model, assumptions and parameters effect outcomes and to assess the validity of the model. This made us unable to evaluate the model structure, and track what's influenced the results (internal validation). The model has been considered for its external validity, latest performed by McEwan et al. 2014 (34). According to McEwan et al. 2014 (34) a review method used in long term cost-effectiveness models of diabetes interventions also confirmed the prominent role that the diabetes control and complications trial and the United Kingdom Prospective Diabetes Stud (31;33) play in providing data on efficacy and disease progression, particularly for defining the relationship between HbA1c and complications.

However, some issues are not sufficiently commented by the submitter. First, the model and validation focus on the disease, diabetes, but not particuarly the technology and procedure represented by FreeStyle Libre. Input is thus not validated. Secondly, the submitted model shows an improvement in HbA1c for use of FreeStyle Libre compared to blood glucose monitoring. This is not the case with our efficacy findings in our single technology assessment, which shows that there were approximately no difference in HbA1c for the intervention versus the comparator. The submitter has based the results on 6 months data, which is a very short period of time, as HbA1c is something that influences diabetes through a lifetime period. Evidence for a longer time period is not present, which leads to large uncertainty about the results. Third, the submitter did not provide references to several sources of the input data and quality of life improvements. For example, the utility value related to type 1 DM, with no complications of 0.9. In addition, the submitter use different values in the efficacy part and in the model. Regarding the costs, the price of FreeStyle Libre were based on the price found on the official web-side related to the device (41), which is another price than used by the submitter. The price and the other costs did not include value added tax (VAT). VAT should have been included in this analysis since it applies the perspective of the health care provider.

Based on input given by the clinical experts and thorough review, we believe that the health economic model captured the outcomes that are clinically relevant for the defined population and intervention. According to our clinical experts, the study population in IMPACT and REPLACE were said to be comparable to the Norwegian population.

On the other hand, various input data in the model is taken from studies with different inclusion criteria (for example about the study population and diabetes type), which leads to a great uncertainty about how well the data fit to the use of FreeStyle Libre in Norway. The clinical input data related to individuals with type 1 DM were based on different references. In one simulation their clinical inputs were based on the REPLACE trial, which includes patients with type 2 DM, under 65 years. In another simulation the included clinical input data were based on Swedish findings. Several of the clinical input data incorporated in the submitted model, did not correspond to the clinical input data listed up in the submitted document. Further, it is uncertain how comparable the input data are to each other, since most of the complications are from separate studies. The time horizon in the IMPACT and REPLACE trials was only 6 months, and in the model the outcomes are extrapolated over 40 years assuming continuous benefits.

The calculated incremental cost-effectiveness ratio (ICER) based on the submitted economic model over a 40-year time horizon was dominant for patients with type 1 diabetes, meaning that FreeStyle Libre according to the manufacturer is both cost saving and more effective. For patients with type 2 diabetes the ICER was calculated to be NOK 235,673 per QALY (whole study population) and NOK 243,434 per QALY (under 65 years). As the submitted model was not transparent and not sufficiently flexible, we were not able to run a model with adjusted input data.

The submitter estimated that FreeStyle Libre would be potentially cost saving the first five years after its adoption for patients with diabetes type 1 and diabetes type 2 insuline users in Norway. However, we adjusted some of the calculations related to the budget impact analyses, based on input data from our clinical experts. Our results indicated that the total added costs would be about NOK 913 million the first five years after a doption of FreeStyle Libre for only patients with diabetes type 1, and about NOK 480 million total added costs the first five years after adoption of FreeStyle Libre for patients with diabetes type 1 and diabetes type 2 insuline users. The annual costs five years after introduction would be NOK 186 million added cost and NOK 91,7 million saved cost for type 1 and 2 DM alone, respectively, and NOK 94 million added cost for type 1 and 2 DM combined.

We found it strange that the submitter's cost-effectiveness results and budget impact results deviates from each other, i.e. a dominanted ICER and a high total added cost in the budget impact.

No sensitivity analyses were provided by the submitter, which is a crucial part of an economic evaluation, and it was therefore not possible to assess how robust the results are to variation in uncertain single parameters. We can thus not see how prices and other aspects might influence the results. One way sensitiveity analyses are in addition important for considering the internal validity of the model. The submitter has only done one scenario analysis with a small price difference.

## Key Conclusions

All of the existing diabetes technologies have advantages and disadvantages, and per se none enable everyone with diabetes to achieve target HbA1c levels. FreeStyle Libre may be used to inform individuals regarding their interstitial glucose level to allow decision making regarding treatment and to give the person information on the impact of changes in lifestyle, diet and physical activity, which could influence the long-term control of their disease.

### Efficacy

There is limited and low quality scientific evidence on the clinical efficacy of FreeStyle Libre; this brings limitations to the generalization of the results. The two trials we have evaluated indicate that FreeStyle Libre may improve treatment satisfaction, time spent in hypoglycaemia and number of hypoglycaemic events, but the studies were too few and small to support the clinical efficacy of FreeStyle Libre to the broader community of individuals with diabetes. In addition, the studies included represent only a part of the population of people with diabetes in Norway, and it is therefore difficult to make generalizations to the Norwegian context.

FreeStyle Libre may slightly improve treatment satisfaction, time in range, number of nocturnal events <3.1 mmol/L within 7h, and time with glucose >13.0 mmol/L in comparison to SMBG; FreeStyle Libre lead to little or no difference in quality of life and HbA1c in comparison to SMBG. We are uncertain whether FreeStyle Libre leads to an improvement in time and events with glucose <3.9mmol/L within 24 h, time with glucose <3.1 mmol/L at night within 7 hours, and time with glucose > 10 mmol/L. This applies only to individuals 18 years or older, and individuals under 65 years with type 2 DM, as well as individuals 18 years or older with type 1 DM

Our search found several FreeStyle Libre registry records of ongoing studies (see Appendix 4). Among these ongoing trials, three have a randomized controlled design and

can further our knowledge on the clinical effectiveness of FreeStyle Libre. The results of this assessment will likely change when new evidence becomes available.

**Cost-effectiveness**

The results of submitters' analysis showed that FreeStyle Libre is a cost-effective alternative to SMBG. However, we were not able to control the submitted results and to make our own cost-effectivness results (ICERs). There are several problems with the model that lead us to question the submitted result. The most challenging issue is that the model is not transparent. Other challenging issues are the short term data used in the model, which should capture the difference in efficacy between the FreeStyle Libre users and individuals who are using SMBG only. Also, the submitted model included several input data that neither matched the input data described in the submitted documentation package nor matched the input data found in other literature.

Because we did not have access to the complete model we were not able to assess the validity of the submitters' estimates, nor how adjustment of the model with alternative assumptions would affect the results provided by the submitters. Taking in account the comments above the NIPH finds the ICER estimates unreliable. The NIPH is therefore not able to consider whether or not FreeStyle libre is cost-effective based on the submitted documentation.

According to the budget impact analysis performed by NIPH the annual costs five years after introduction would be NOK 186 million added cost and NOK 91,7 million saved cost for type 1 and 2 DM alone, respectively, and NOK 94 million added cost for type 1 and 2 DM combined.

Overall FreeStyle Libre does not seem to provide a higher efficacy or fewer adverse events or increased quality of life measures for insulin treated patiens than other SMBG devices, thus it makes difficult to support the lower costs associated with FreeStyle Libre.

# Appendices

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## Appendix 1. Glossary of terms

**Cost-effectiveness analysis:** an economic analysis that converts effects into health terms and describes the costs for additional health gain.

**HbA1c:** the term HbA1c refers to glycated haemoglobin. The HbA1c test measures diabetes management over two to three months.

**HELFO:** The Norwegian Health Economics Administration. HELFO is responsible for direct payments to various health service providers, individual reimbursement for certain medicines, dental services and health services abroad.

**Health-related quality of life:** is an individual's or a group's perceived physical and mental health over time.

**Hypocalcaemia:** this is a term that refers to low blood calcium level.

**Hyperglycaemic and hypoglycaemic AUC:** the area under the curve is the product of the magnitude and duration of the sensor measured glucose level above or below a specified cutoff level. Higher values for this calculation indicate more numerous, severe, or protracted glycemic events.

**Impaired awareness of hypoglycaemia:** a term used to describe a situation where people with diabetes, usually type 1 diabetes, are frequently unable to notice when they have low blood sugar.

**Incremental cost-effectiveness ratio (ICER):** the difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.

**Millimole:** a figure that is a part of the International System of Units and equal to 1/1,000 of a mole (SI). A mole is a unit of measurement commonly used in chemistry to denote amounts of atoms and molecules.

**Nephropathy:** this is a term that refers to damage to or disease of a kidney.

**Neuropathy:** this is a term that refers to disease or dysfunction of one or more peripheral nerves, typically causing numbness or weakness.

**Retinopathy:** Diabetic retinopathy is a common complication of diabetes. It occurs when high blood sugar levels damage the cells at the back of the eye (known as the retina). If it isn't treated, it can cause blindness.

**Type 1 diabetes:** Diabetes where the body does not produce insulin.

**Type 2 diabetes**: the body usually still produces some insulin, but this is not enough to meet demand and the body's cells do not properly respond to the insulin.

## Appendix 2. Search strategy

**Literature search – FreeStyle Libre**

Date Run: 2017.01.18

Databases: Ovid MEDLINE, Embase (Ovid), Cochrane Library; Cochrane Database of Systematic Reviews, Other Reviews; Central Register of Controlled Trials); Technology Assessments; Economic Evaluations Database, Centre for Reviews and Dissemination; Database of Abstracts of Reviews of Effects; Health Technology Assessments, PubMed.

Other sources: Google scholar, HTA agencies, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform.

All results: 1662 records of which 40 ongoing trials (2197 including duplicates)

Searched by: Ingrid Harboe, peer reviewed by Ingvild Kirkehei

**Search strategies**

**Database: Cochrane Library**

All Results: Cochrane Reviews (2); Other Reviews (8); Trials (175); Technology Assessments (11)

| ID | Search | Hits |
|---|---|---|
| #1 | MeSH descriptor: [Diabetes Mellitus] explode all trees | 19557 |
| #2 | diabet*:ti,ab,kw<br>in Cochrane Reviews (Reviews and Protocols) | 418 |
| #3 | diabet*<br>in Other Reviews, Trials, Technology Assessments and Economic Evaluations | 48765 |
| #4 | #1 or #2 or #3 | 49246 |
| #5 | MeSH descriptor: [Blood Glucose Self-Monitoring] this term only | 599 |
| #6 | ((glucose) and (monitor* or scan*)):ti,ab,kw<br>in Cochrane Reviews (Reviews and Protocols) | 31 |
| #7 | ((glucose) and (monitor* or scan*))<br>in Other Reviews, Trials, Technology Assessments and Economic Evaluations | 4937 |
| #8 | #5 or #6 or #7 | 4968 |
| #9 | (flash* or interstitial* or real-time or realtime):ti,ab,kw<br>in Cochrane Reviews (Reviews and Protocols) | 56 |
| #10 | (flash* or interstitial* or real-time or realtime)<br>in Other Reviews, Trials, Technology Assessments and Economic Evaluations | 7494 |
| #11 | #9 or #10 | 7550 |

| | | |
|---|---|---|
| #12 | #4 and #8 and #11 | 196 |
| #13 | (freestyle and (flash* or libre)):ti,ab,kw i<br>n Cochrane Reviews (Reviews and Protocols) | 0 |
| #14 | (freestyle and (flash* or libre))<br>in Other Reviews, Trials, Technology Assessments and Economic Evaluations | 6 |
| #15 | ((guardian and (real-time or realtime)) and diabet*):ti,ab,kw<br>in Cochrane Reviews (Reviews and Protocols) | 0 |
| #16 | ((guardian and (real-time or realtime)) and diabet*):ti,ab,kw<br>in Other Reviews, Trials, Technology Assessments and Economic Evaluations | 9 |
| #17 | #13 or #14 or #15 or #16 | 15 |
| #18 | #12 or #17 | 196 |

**Database: Embase** <1974 to 2017 January 17>,
Epub Ahead of Print, In-Process & Other Non-Indexed Citations, **Ovid MEDLINE**(R) Daily and Ovid MEDLINE(R) <1946 to Present>

**Search Strategy:**

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes mellitus/ | 1212267 |
| 2 | diabet*.tw. | 1292593 |
| 3 | or/1-2 | 1524496 |
| 4 | Blood Glucose Self-Monitoring/ | 20461 |
| 5 | blood glucose monitoring/ | 21246 |
| 6 | (glucose and (monitor* or scan*)).tw. | 74233 |
| 7 | or/4-6 | 90759 |
| 8 | (flash* or interstitial* or real-time or realtime).tw. | 727888 |
| 9 | 3 and 7 and 8 | 2547 |
| 10 | (freestyle and (flash* or libre)).tw. | 38 |
| 11 | (guardian and (real-time or realtime) and diabet*).tw. | 112 |
| 12 | or/10-11 | 150 |
| 13 | 9 or 12 | 2551 |
| 14 | remove duplicates from 13 | 1747 |
| 15 | 14 use oemezd [Embase] | 1573 |
| 16 | 14 use ppez [MEDLINE] | 174 |

**Database**: Centre for Reviews and Dissemination: DARE (Database for Reviews and Dissemination) and HTA (Health Technology Assessment Database)

**Results**: 22 records

| Line | Search | Hits |
|---|---|---|
| 1 | MeSH DESCRIPTOR Diabetes Mellitus EXPLODE ALL TREES | 2427 |
| 2 | (diabet*) | 4453 |
| 3 | #1 OR #2 | 4459 |

| | | |
|---|---|---|
| 4 | MeSH DESCRIPTOR Blood Glucose Self-Monitoring EXPLODE ALL TREES | 110 |
| 5 | ((glucose and (monitor* or scan*))) | 371 |
| 6 | #4 OR #5 | 371 |
| 7 | ((flash* or interstitial* or real-time or realtime)) | 411 |
| 8 | #3 AND #6 AND #7 | 22 |
| 9 | ((freestyle and (flash* or libre))) | 0 |
| 10 | ((guardian and (real-time or realtime) and diabet*)) | 1 |
| 11 | #9 OR #10 | 1 |
| 12 | #8 OR #11 | 22 |

**Source: ClinicalTrials.gov**

**WHO ICTRP (International Clinical Trials Registry Platform)**
Results: 40 records
Search: "Glucose Monitoring System" AND flash; Diabetes AND flash; freestyle libre

**HTA agencies** (or similar):
AHRQ (Agency for Healthcare Research and Quality), AHTA (Adelaide Health Technology Assessment), (CADTH, Queensland Health, DIMDI (German Institute of Medical Documentation and Information) ECRI, IHE (Institute of Health Economics), NICE (National Institute for Health and Care Excellence), McGill Technology Assessment Unit, SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services).
Results: 7 records
Search: "Glucose Monitoring System" AND flash; Diabetes AND flash; freestyle libre

**Google scholar:**
Results: 2 records
Search: Search: "Glucose Monitoring System" AND flash; Diabetes AND flash; freestyle libre

## Appendix 3. Completed (published and unpublished) single arm studies

| Population | Author | Study Design (country) | Duration | Outcomes |
|---|---|---|---|---|
| Type 1- Children 4 to 17yr | Edge 2017 BEAGLE NCT02388815 (66;95) | Single arm (UK) | 14 days | Accuracy, safety and acceptability |
| Type 1- Children 0 to 18yr | Rai 2016 (72) | Single arm (India) | 14 days | Feasibility and acceptability |
| Type 1- Children 4 to 17yr | NCT02821117 (completed) SELFY (71) | Single arm (Germany, Ireland, UK) | 10 weeks | Change in time in range, time in range |
| Type 1 or 2 Pregnant women, | NCT02665455 (completed) FLIPS (73) | Single arm (Austria, UK) | 14 days | Accuracy |
| Type 1 - adults | Olafsottir 2017 NCT02677454 (77;96) | Single arm (Sweden) | 10-14 days | Accuracy and treatment experience |
| Type 1 - adults | Aberer 2017 NCT02614768 (74;97) | Single arm (Austria) | 12 hours | 3 systems performance |
| Type 1 – adults | Bonora 2016 (75) Ethics approval prot no 74889 | Single arm (Italy) | 14 days | FreeStyle Libre and CGM Dexcom G4 Platinum performance |
| Type 1- adults | Dover 2016 (76) | Single arm (UK) | 16 week | Impact of FreeStyle to patients attending diabetes clinic in a university teaching hospital |
| Type 1 & 2 adults | Ji 2016 (80) | Single arm (China) | 14 days | Performance in Chinese patients |
| Type 1 & 2 adults | Ish Shalom 2016 (79) | Single arm (Israel) | 12 weeks | Experiences in difficult to control diabetes |
| Type 1 & 2 adults | Fokket et al (TC5348) (78;98) | Single arm (The Netherlands) | 14 days | Performance |
| Type 1 & 2 adults | Bailey 2015 NCT02073058 (68;99) | Single arm (US) | 14 days | Performance and usability |
| Adults on insulin treatment | UMIN000018692 (completed) (81) | Single arm (Japan) | 14 days | WHO-5 questionnaire, DTSQ, safety |

## Appendix 4. FreeStyle Libre registry records

| Population | Registry number-(country)-Title | Duration | Outcomes |
|---|---|---|---|
| Randomized controlled trials | | | |
| Type 1<br>Adolescents 12-17yr | NCT02776007 (82) – (Israel) -<br>Patients Perceptions of Using the "Libre" System Compared With Conventional SMBG in Adolescents With Type 1 Diabetes The Libre Sat Trial<br><br>Recruiting | 12 weeks | Treatment satisfaction, HbA1c change, average fasting blood glucose, sensor readings at week 12 and 24 hours, number of measurements on intervention and each arm, percentage of readings with 70 to 180 mg/dl, below 60mg/dl, above 240mg/dl |
| Type 2<br><br>Adults | NCT02809365 (83) – (Israel) -<br>FreeStyle Libre-effect on QOL in Type 2 diabetes patients<br><br>Not yet recruiting | 10 weeks | QoL, treatment satisfaction, HbA1c change, percentage to reach HbA1c as per physician prescription, reduction in hypoglycemic events |
| Adults with severe hypoglycaemia | ACTRN12616001695493 (84) – (Australia)- Assessment of the utility of the Flash Libre subcutaneous glucose monitoring system to prevent recurrent severe hypoglycaemia in patients with diabetes<br><br>Recruiting | 24 weeks | Recurrence or occurrence of severe/non-severe hypoglycaemia, time to first recurrence or occurrence severe/non-severe hypoglycaemia, time between recruitment and first occurrence/recurrence of severe and non-severe hypoglycaemia |
| Single Arm/Non Randomized | | | |
| Type 1<br><br>Children 4 to 18 yr | NCT02824549 (85) – (Belgium)<br>An Evaluation of the FreeStyle Flash Glucose Monitoring System<br><br>Recruiting | 24 weeks?<br><br>“0.5 yr” | Usability, skin reactions to sensor, accuracy |
| Type unspecified<br><br>children, adults, seniors | NCT02898714 (86) – (Belgium)<br>Flash Glucose Monitoring Study for Diabetes (FUTURE)<br><br>Recruiting | 3 years | Quality of life, change in HbA1c |
| Type 1 -Adults<br><br>Recruiting | NCT02734745 (87) – (Italy)<br>Accuracy of FreeStyle Libre<br><br>Recruiting | 14 days | Accuracy |
| Type 2 – ≥ 75 yrs of age | NCT03020264 (89) – (France)<br>Frequency of hypoglycemia inpatients with type 2 diabetes under insulin therapy older than 75 years in real life (HYPOAGE) | 4 weeks | Number of confirmed or severe hypoglycemia, events/patient/month of severe hypoglycemia, number of hospitalizations due to hypoglycemia, death, falls, transition to ER, |

| | | | |
|---|---|---|---|
| | | | hypoglycemia in subroups, fear of hypoglycemia, pseudo hypoglycemia and unconfirmed hypoglycemia, nocturnal hypoglycemia, threshold blood glucose <0.54g/L, number of elderly admitted to EHPAD |
| Type 2 -adults | UMIN000023593 (88) – (Japan)<br>Use of FreeStyle Libre Flash Glucose Monitoring System and the Effect on Hypoglycaemia in People with Type 2 Diabetes in Japan<br><br>Pre-initiation | 12 weeks | Change from baseline in time in hypoglycaemia (<3.9 mmol/L [70 mg/dL]), time in range, hyper/hypo glygaemic episodes, accuracy, variability measures, glucose rate change, TDD of insulyne, body weight, blood pressure, treatment satisfaction, hypoglycemia patient questionnaire, number of scans performed, user questionnaire, HCP questionnaire |
| Type 1 and 2 - adults | ISRCTN12543702 (90) – ( UK)<br>Masked performance check of the Abbott FreeStyle Libre Flash glucose monitoring system.<br><br>Recruiting | 14 days | Accuracy, precision within sensor lot |
| Type 1 and 2 - adults | ISRCTN87654534 (91) – (UK)<br>Performance check of the Abbott FreeStyle liver flash glucose monitoring system<br><br>Recruiting | 14 days | Accuracy, precision within sensor lot, relationship between HbA1c levels and glycaemic variability |

## Appendix 5. Included studies inclusion and exclusion criteria

Inclusion Criteria

| Bolinder 2016 | Haak 2017 |
|---|---|
| • Adults 18 years or older<br>• diagnosed with type 1 DM for 5 yrs or longer,<br>• on their current insulin regimen for at least 3 months before study entry,<br>• had a screening HbA1c concentration of 58mmol/mol (7.5%) or lower,<br>• reported self monitoring of blood glucose levels on regular basis (equivalent to > 3 times/day) for 2 months or more before study entry,<br>• considered technically capable of using the flash sensor base glucose monitoring system | • adults 18 years or older<br>• individuals with type 2 DM treated with insulin for at least 6 months,<br>• on thier current regime (prandial only or prandial and basal intensive insulin therapy or CSII therapy) for 3 months or more,<br>• had a screening HbA1c concentration level 58-108mmol/mol (7.5-12%)<br>• reported self monitoring regular blood glucose testing (more 10/week for at least 2 months prior to study entry)<br>• were considered by the investigator to be technically capable of using the flash sensor based glucose monitoring system. |

Exclusion criteria

| Bolinder 2016 | Haak 2017 |
|---|---|
| • currently diagnosed with hypoglycemia unawareness;<br>• diabetes ketoacidosis or myocardial infraction in the preceding 6 months;<br>• known allergy to medical grade adhesives,<br>• used continuous glucose monitoring within the preceding 4 months,<br>• currently using sensor augmented pump therapy,<br>• pregnant or were planning pregnancy, or<br>• receiving oral steroid therapy for any disorder | • if they had any other insulin regime to that described in inclusion;<br>• ketoacidosis or hypersmolar-hypoglycemia state in the preciding 6 months,<br>• if the had a total insulin >1.75 units/kg on study entry;<br>• known allergy to medical grade adhesives<br>• had severe hypoblycemia (requirieng third party assistance),<br>• were pregnant or planning pregnancy,<br>• used continuous glucose monitoring within the previous 4 months,<br>• were receiving steroid therapy for any condition<br>• considered by the investigator unsuitable to participate |

## Appendix 6. Results from Meta-Analysis

| Outcome | Type 1 DM MD[95%CI][1] | Type 2 DM MD[95%CI][1] | Overall MD[95%CI][1] |
|---|---|---|---|
| Health Related Quality of life[2] | -0.10 [-0.25, 0.05] | 0.00 [-0.16, 0.16] | -0.05 [-0.16, 0.05] |
| Treatment Satisfaction[3] | 6.20 [4.54, 7.86] | 4.00 [2.32, 5.68] | 5.10 [2.95, 7.26] |
| Pain | n/a | n/a | |
| HbA1c | -0.01 [-0.18, 0.16] | 0.03 [-0.26, 0.32] | -0.00 [-0.14, 0.14] |
| Glycemic Measures | | | |
| Time in Range 3.9-10mmol/L[3] | 1.20 [0.46, 1.94] | 0.40 [-0.93, 1.73] | 1.00 [0.32, 1.68] |
| <3.9mmol/L within 24 hours[2] | -1.24 [-1.82, -0.66] | -0.40 [-0.72, -0.08] | -0.60 [-0.88, -0.32] |
| <3.9mmol/L within 24 hours-events[2] | -0.37 [-0.58, -0.16] | -0.15 [-0.30, 0.00] | -0.23 [-0.35, -0.10] |
| <3.1mmol/L at night within 7 hours[2] | -0.35 [-0.51, -0.19] | -0.10 [-0.20, -0.00] | -0.22 [-0.46, 0.03] |
| <3.1mmol/L night within 7hr/events[2] | -0.11 [-0.18, -0.04] | -0.07 [-0.12, -0.02] | -0.09 [-0.13, -0.04] |
| <3.1mmol/L within 24 hours[2] | -0.85 [-1.24, -0.46] | -0.18 [-0.35, -0.01] | -0.49 [-1.15, 0.16] |
| <3.1mmol/L within 24 hours/events[2] | -0.36 [-0.53, -0.19] | -0.10 [-0.19, -0.01] | -0.22 [-0.47, 0.03] |
| >10mmol/L – time[2] | n/a | 0.00 [-1.44, 1.44] | |
| >13mmol/L – time[2] | -0.39 [-0.77, -0.01] | -0.40 [-1.52, 0.72] | -0.39 [-0.75, -0.03] |
| Moderate to severe adverse events | 0.50 [0.09, 2.68][4] | 1.51 [0.16, 14.27][4] | 0.74 [0.19, 2.85][4] |

[1]MD: mean difference; [95% CI: confidence interval]; [2] lower scores are best, [3] higher scores are best; [4]RR: risk ration; n/a: not assessed.

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