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CADTH TECHNOLOGY REVIEW

# Flash Glucose Monitoring System FreeStyle Libre to Monitor Glycemia in Patients With Diabetes


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**Authors:** Michel Boucher, Sirjana Pant, Ashna Jinah, Bernice Tsoi, Melissa Walter

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# Abbreviations

| | |
|---|---|
| **A1C** | glycated hemoglobin |
| **BIA** | budget impact analysis |
| **CGM** | continuous glucose monitor |
| **CMA** | cost-minimization analysis |
| **CSEMI** | Comité scientifique de l'évaluation des médicaments aux fins d'inscription / Standing Scientific Committee on Entry on the List of Medications |
| **EUnetHTA** | European Network for Health Technology Assessment |
| **FGMS** | flash glucose monitoring system |
| **HTA** | health technology assessment |
| **IIT** | intensive insulin therapy |
| **INESSS** | Institut national d'excellence en santé et en services sociaux |
| **MDI** | multiple insulin injection |
| **NIPH** | Norwegian Institute of Public Health |
| **NMA** | network meta-analysis |
| **ODB** | Ontario Drug Benefit |
| **OHTAC** | Ontario Health Technology Advisory Committee |
| **PICOS** | population(s), intervention(s), comparators(s), outcome(s), study design(s) |
| **QoL** | quality of life |
| **RAMQ** | Régie de l'assurance maladie du Québec |
| **RCT** | randomized clinical trial |
| **rt-CGM** | real-time continuous glucose monitoring |
| **SAPs** | sensor-augmented pumps |
| **SMBG** | self-monitoring of blood glucose |
| **SR** | systematic review |
| **T1D** | type 1 diabetes |
| **T2D** | type 2 diabetes |

# Executive Summary

## Rationale and Policy Issues

Devices to monitor glycemia have recently evolved to reduce the number of steps required, compared with the traditional approach of self-monitoring of blood glucose (SMBG) using test strips. One of these devices is FreeStyle Libre. This device uses a technology called flash glucose monitoring system (FGMS). FGMS enables patients to measure their glycemia without routine pricking of their finger. It measures glycemia indirectly through interstitial fluid. Patients wear a disposable sensor on the back of their upper arm; this sensor needs to be changed every 14 days. In retail, the FreeStyle Libre reader costs $54.00 and each sensor is sold at a unit price of $97.00; the cost of a sensor reimbursed to pharmacists in Ontario and Quebec is $89.00. Recommendation from Diabetes Canada indicate that flash glucose monitoring may be offered to people with diabetes to decrease time spent in hypoglycemia.

Given the recent commercial availability of FreeStyle Libre in Canada, an increasing number of Canadian jurisdictional drug plans are evaluating the option of reimbursing this FGMS device. Two Canadian jurisdictions (Ontario and Quebec) have commissioned their own health technology assessment (HTA) of this technology; funding recommendations were also developed by these two jurisdictions. Although recommendations from Ontario and Quebec indicate that access to FGMS may be associated with some criteria, there are differences in the characteristics of patients who may be candidates for this technology. There is also interest among the other jurisdictional drug programs to compare current assessments and recommendations for the public coverage of FGMS in Canada to inform decision-making in individual jurisdictions.

The objective of this Technology Review is to synthesize the key findings of the two recent Canadian provincial HTA reports on FGMS (Ontario and Quebec), including clinical, economic, and budget impact analysis (BIA) results. Recommendations from jurisdictional committees were also summarized. This information was considered by members of an ad-hoc Implementation Advice Panel to develop advice on the implementation of the recent recommendations for public funding of FGMS in Canada. Of note, the implementation advice process was a second phase of this project; the advice is reported in a companion report. These reports are intended to help facilitate funding discussions for FGMS in jurisdictions that have not commissioned HTAs.

## Methods

To summarize the available evidence, the clinical and economic sections of the two available Canadian HTA reports (i.e., the joint CADTH/Health Quality Ontario [HQO] and the Institut national d'excellence en santé et en services sociaux [INESSS]), along with the provincial funding recommendations (i.e., the Ontario Health Technology Advisory Committee [OHTAC] and the Comité scientifique de l'évaluation des médicaments aux fins d'inscription / Standing Scientific Committee on Entry on the List of Medications [CSEMI]) were synthesized.

## Clinical Evidence

The systematic reviews (SRs) of clinical effectiveness, conducted by INESSS and jointly by HQO with CADTH concluded that FGMS is superior to SMBG with respect to some glycemic outcomes (i.e., time in target glucose range, frequency and duration of daytime and nocturnal hypoglycemia, and treatment satisfaction) but not others (i.e., A1C and severe hypoglycemic events). There are, however, variations in the clinical benefits according to the type of diabetes; in particular for the time-in-range outcome.

There are few studies comparing FGMS with SMBG, and there was significant overlap in the studies included in the two HTA reports. The HTA reports also generally evaluated the quality of the evidence to be very low to moderate (GRADE). Available studies were noted to have methodological limitations; that is, they have small sample size, potential for bias, and lack long-term data to assess the impact of FGMS on diabetes complication and health care resources.

The two provincial HTAs also consulted with patients and clinicians to gather their perspective and experience with the disease and the device. There was wide support for the use of FGMS which was reported to have physical, emotional, and social benefits. Reduction in, and alternative to finger pricks, and the ability to see blood glucose trends to better manage their diabetes was widely recognized by patients. Cost was the largest barrier to use. Education for patients and care teams was considered a necessary condition for optimal and beneficial use of the FGMS.

## Economic Evidence

The economic evidence presented in this report is based on the two Canadian HTA reports on FGMS conducted by INESSS (Quebec perspective); and HQO/CADTH (Ontario perspective). Each HTA conducted an economic literature review to address specific research questions pertaining to the cost-effectiveness of the FGMS for the management of insulin-dependent diabetes. However, a de novo economic evaluation was not undertaken by HQO; the INESSS reported a cost-minimization analysis (CMA) (i.e., a cost comparison of total health care costs between technologies assumed to have the same clinical efficacy) comparing the FGMS to SMBG in adults with type 1 diabetes (T1D) or type 2 diabetes (T2D) requiring insulin therapy. The use of this approach by INESSS was due to limitations of the clinical evidence.

Both HTA reports included BIAs to address the question on the affordability of FGMS for the target populations identified in their clinical evidence reviews and were undertaken from the perspective of its respective provincial public health care payer. The BIAs for Ontario and Quebec compared the budget difference (i.e., net impact on the budget) between two scenarios: the current environment or “world without FGMS” (i.e., SMBG), and the new environment or “world with FGMS” (i.e., the introduction of FGMS).

While an economic evaluation was not undertaken by HQO, the INESSS’ CMA found that FGMS was more costly than SMBG for all eligible populations due to the differences in the costs of technologies. With respect to the findings of both reports’ BIAs, caution is required in comparing the results between reports given differences in the analytical time frame (i.e., three years versus five years), the market share distribution over the time horizon, and the definition of the target population eligible for FGMS. Nonetheless, both reviews found that the introduction of FGMS would be expected to increase spending on public health budgets regardless of the population studied and the time frame of the analysis.

## Provincial Funding Recommendations

Both CSEMI and OHTAC recommend funding FGMS with conditions or criteria. The OHTAC recommendation specifies that patients with T1D need to perform SMBG frequently and attempt optimal diabetes management to qualify for FGMS, while patients with T2D must in addition be on intensive insulin therapy (IIT); the latter is defined in the HQO report as a method of controlling blood glucose levels that involves multiple daily insulin injections or a continuous subcutaneous insulin infusion (CSII). The CSEMI originally recommended to add FreeStyle Libre to the list of the prescription drug insurance plan for self-monitoring of glycemia in patients on insulin therapy provided the economic burden is lessened. If the economic burden of funding FreeStyle Libre is not reduced for the province, CSEMI recommended that this FGMS be listed as an exceptional drug product for adults aged 18 years and older who have at least two years of experience in self-managing their diabetes and who meet the following three criteria of having:

- IIT
- frequent or severe hypoglycemia events
- necessity for blood glucose self-monitoring at least eight times daily.

Further, CSEMI specified the maximum duration for funding, that is initially three months, to be extended to 12 months only after confirming the appropriated use of the device. It also recommended that patients be trained on the use of the device as a consideration for implementation. In April 2020, part of this recommendation was updated based on a change to Health Canada's labelling of August 2019 that no longer requires patients to have at least two years of experience in diabetes self-management. The updated recommendations also clarified IIT to be the use of insulin pump therapy or the use of three of more insulin injections per day. In addition, the updated recommendation authorizes the initial funding request for six months, instead of three.

Although evidence of the therapeutic value of FGMS, compared to SMBG, was limited in terms of quantity and quality — that is there was a small number of published comparative studies and these studies were noted to have methodological limitations — there was significant support for the use of the device by patients and clinicians consulted by HQO and INESSS. The perceived social, physical, and emotional benefit; and the greater autonomy offered by FGMS in the management of diabetes, were among the key reasons considered in the recommendations.

## Conclusion

FGMS is a new option recently available to monitor glycemia for Canadians living with diabetes. Publicly funded drug programs in Canada are considering information from HTA work to guide their reimbursement decisions for this technology. Information from HTAs conducted by two provincial organizations, HQO in Ontario and INESSS in Quebec, reveals that evidence supporting the effect of FGMS is still limited in quantity and quality; the latter generally ranged from very low to moderate. The therapeutic benefits of FGMS revealed by this evidence mainly consist of improvement in the frequency and duration of hypoglycemia events in patients with T1D, and patients with T2D using IIT, as well as an improvement in the time spent within the target glucose range in patients with T1D. Other important benefits from FGMS reported in the provincial HTAs are in terms of increased comfort (avoidance of finger pricking), convenience of use, ability to easily perform multiple tests per day and conduct trend analysis of test results to improve disease management, as well as increased treatment satisfaction.

From an economic perspective, compared to reimbursing test strips for SMBG, public funding of FGMS is most likely expected to be associated with increased expenditures for drug programs. An estimate derived from the HQO's BIA suggests that drug programs considering reimbursing FGMS could expect an added annual cost ranging from $627 per patient with T1D to $1,241 per patient with T2D who switches to FGMS, compared to if patients were to remain on SMBG to monitor their glycemia. Both HTA reports concluded that the budget impact of introducing FGMS is sensitive to the frequency of self-testing associated with SMBG, such that the incremental costs of FGMS is lower in scenarios in which SMBG users would require a higher frequency of self-testing.

Committees from the two provinces that conducted these HTAs, OHTAC in Ontario and CSEMI in Quebec, both recommended funding FGMS. These recommendations were generally assorted with some clinical criteria. Specifically, FGMS is recommended only for patients with T1D, and patients with T2D requiring IIT, who are at risk of frequent and severe hypoglycemia. Frequent glycemia testing is also generally needed, and one province, Quebec, includes the necessity of testing glycemia at least eight times per day to be eligible for FGMS. This same province further noted that a price reduction would be required to reimburse the FreeStyle Libre FGMS device as a full benefit item to persons with diabetes using insulin. Of note, education and training were considered necessary for optimal use of FGMS in both Ontario and Quebec.

# Introduction and Rationale

## Background and Rationale

Individuals with diabetes need to monitor their glycemia to ensure they reach their glycemic target and avoid hypoglycemia.
The frequency of measurements may vary from person to person. While it is usually recommended that people on insulin monitor their glycemia regularly, especially those with T1D, benefits of regular monitoring of glycemia for persons with T2D not using insulin is less established. For these people, it is usually recommended that the frequency of measurements be individualized based on the type of drugs, the level of glycemic control and the risk of hypoglycemia.[1] The traditional approach to measuring glycemia involves people collecting a small amount of blood from their fingertips and using a blood glucose meter. This approach requires individuals performing a series of steps, namely pricking their finger with a lancet, putting a drop of blood on a test strip, and placing the strip into a glucose meter that displays the glycemic result.[2] It may be referred to as SMBG.

Devices to monitor glycemia have recently evolved to reduce the number of steps required, compared with the traditional approach. One of these devices is FreeStyle Libre. This FGMS uses a technology called flash glucose sensing.[3,4] FGMS enables patients to measure their glycemia without routine pricking of their finger.[5] It uses a sensor filament inserted five millimetres under the skin which accurately measures glucose in the interstitial fluid. The FreeStyle Libre sensors are calibrated at the factory.[3] There is a five to 10 minute delay in interstitial fluid glucose response to changes in glycemia; glucose readings on interstitial fluid reliably reflect blood glucose levels.[5] The FreeStyle Libre system measures glucose every minute and requires no blood glucose testing for calibration.[6] The disposable sensor is worn on the back of the upper arm for 14 days and can read glucose levels through clothing. The reader can hold up to 90 days of data. With each scan, the reader displays a real-time glycemia result, an eight-hour historical trend as well as the direction the glycemia is heading.[7] The FreeStyle Libre reader costs CAD$54.00 in retail and each sensor is sold at a unit retail price of CAD$97.00;[8] the cost reimbursed to pharmacists in Ontario and Quebec is $89.00 per sensor.[9,10] Recommendations from Diabetes Canada indicate that flash glucose monitoring may be offered to people with diabetes to decrease time spent in hypoglycemia.[1]

## Policy Issue

Given the recent commercial availability of FreeStyle Libre in Canada, an increasing number of Canadian jurisdictional drug plans are evaluating the option of reimbursing this FGMS device. Two jurisdictions have commissioned their own HTA of this technology:

- HQO, now Quality business unit at Ontario Health, in collaboration with CADTH, recently assessed FGMS. The final science report was posted on HQO website in December 2019.[11] The recommendation report, which involved guidance from the OHTAC, was also posted in December 2019.[12] The recommendation makes some distinction between T1D and T2D with respect to funding of the FreeStyle Libre FGMS:
  - People with T1D who experience recurrent hypoglycemia despite frequent SMBG and efforts to optimize insulin management.
  - People with T2D requiring IIT (multiple daily injections of insulin or CSII) who experience recurrent hypoglycemia despite frequent SMBG and efforts to optimize insulin management.

Of note, the Ontario Drug Benefit (ODB) Program started to reimburse FreeStyle Libre on September 16, 2019 for persons using insulin; patients residing in Ontario are eligible to have 33 sensors reimbursed each year provided they have a valid prescription from a physician or nurse practitioner.[9]

- In Quebec, INESSS evaluated FreeStyle Libre in 2018. At that time, CSEMI recommended to add FreeStyle Libre to the list of the prescription drug insurance plan for self-monitoring of glycemia in patients on insulin therapy provided the economic burden is lessened. If the economic burden of funding FreeStyle Libre is not reduced for the province, CSEMI recommended that this FGMS device be listed as an exceptional drug product for adults aged 18 years and older who have at least two years of experience in self-managing their diabetes and who meet the following three criteria:
  - ITT
  - frequent or severe hypoglycemia events
  - the necessity of blood glucose self-monitoring a minimum of eight times per day.[13,14]

Initial request is authorized for three months to evaluate patient capacity to use FreeStyle Libre and wear the sensor. Request to pursue treatment is authorized for maximum of twelve months if patients show a capacity to make an optimal use of FreeStyle Libre, that is at least 70% of the time.[13] Of note, FreeStyle Libre is reimbursed in Quebec since July 2019; the Régie de l'assurance maladie du Québec (RAMQ) authorization form must be completed by the attending physician.[15] In April 2020, part of the original recommendation was updated based on a change to the Health Canada labelling in August 2019 and no longer requires patients to have at least two years of experience in diabetes self-management. The updated recommendations also clarified ITT to be the use of insulin pump therapy or the use of three of more insulin injections per day. In addition, the updated recommendation authorizes the initial funding request for six months, instead of three.[16] The updated coverage criteria were implemented by RAMQ on April 29, 2020.[17]

Although recommendations from Ontario and Quebec indicate access to FGMS may be associated to some criteria, there are differences in the characteristics of patients who may be candidates for such technology. There is also interest among the other jurisdictional drug programs in comparing current assessments and recommendations for public coverage of FGMS in Canada in order to inform local decision-making in each jurisdiction.

## Objective

The objective of this Technology Review is to synthesize the key findings from two recent Canadian HTA reports (HQO/CADTH and INESSS) on FGMS, including clinical, economic, and BIA results. Recommendations from the related jurisdictional committees (OHTAC and CSEMI) are also summarized in this report.

Note: As part of a second phase to this project, information from a draft version of the Technology Review report was considered by members of an ad-hoc Implementation Advice Panel. This Panel was tasked with developing an advice for the implementation of the recent jurisdictional recommendations for public funding of FGMS in Canada. The Implementation Advice is reported in a distinct report.

## Policy and Research Questions

### Policy Questions

Two key policy questions were identified for this evaluation. These are:

- Is there a group of patients with T1D or T2D who may particularly benefit from using FGMS device FreeStyle Libre, versus using a more traditional glycemia monitoring method such as using test strips?
- If so, what criteria should be used to determine patients to whom such technology will be reimbursed by public drug programs?

### Research Questions

Four research questions were developed to address the two policy questions of this project:

- In patients with T1D or T2D experienced with self glucose monitoring, what is the comparative clinical effectiveness of using FGMS device FreeStyle Libre, compared to measuring glycemia with test strips?
- Are there patient subgroups, based on medication used or other demographic characteristics, that may derive more clinical benefits from using the FGMS device FreeStyle Libre, compared to measuring glycemia with test strips?
- In patients with T1D or T2D experienced with self glucose monitoring, what is the comparative cost-effectiveness of using the FGMS device FreeStyle Libre, compared to measuring glycemia with test strips?
- Are there patient subgroups, based on medication used or other demographic characteristics, for whom the cost-effectiveness of using FGMS device FreeStyle Libre may be more attractive, compared to measuring glycemia with test strips?

# Methods

## Clinical Evidence

The clinical evidence presented in this report is based on the following two HTA reports:

- INESSS; Système flash de surveillance du glucose (FreeStyle Libre, Abbott), October 2018.[13] In addition, the April 8, 2020 updated recommendation from CSEMI was also considered.[16]
- HQO; Flash Glucose Monitoring System for People with Type 1 or Type 2 Diabetes: A Health Technology Assessment, December 2019[11] as well as the December 2019 Flash Glucose Monitoring System for People with Type 1 or Type 2 Diabetes: Final Recommendation report.[12]

The clinical evidence synthesized in this Technology Review report is limited to the content of the above-cited reports. No review of the individual clinical studies included in the HTA reports was performed nor was a supplemental literature search (published or grey literature) conducted. In addition, CADTH did not conduct a primary economic analysis nor a formal literature search for economic evidence. It was also determined that the two provincial HTAs provide information relevant to the Canadian context. Since these are relatively recent HTA reports, they provide reasonably up-to-date information. Given INESSS and HQO both apply current quality standards for the conduct of HTA, no critical appraisal of their reports was performed.

### Methods Used by the HTA Reports

**Clinical Evidence:** Both the HQO and INESSS HTA reports included a SR of clinical effectiveness of FGMS and these reports compared FGMS with SMBG.[11,13] Table 1 presents the inclusion criteria for the SR of clinical effectiveness in these HTA reports.

## Table 1: Inclusion Criteria for the Systematic Review of Clinical Effectiveness in the HTA Reports

| HTA report | Inclusion criteria |
|---|---|
| INESSS[13] | **Population**: insulin-dependent type 1 or type 2 diabetes; adults (> 18 years) population<br>**Intervention**: FGMS (FreeStyle Libre)<br>**Comparator**: SMBG<br>**Outcomes (Clinical)**: A1C, episodes of hypoglycemia or hyperglycemia (day, night), pain, adverse events (technology related or not), patient satisfaction, and QoL<br>**Study Design**: SR, meta-analysis, RCTs<br>**Language**: English and French<br>**Time Period**: 2014 to January 2018 |
| HQO[11] | **Population**: patients diagnosed with T1D or T2D; all ages<br>**Intervention**: FGMS (FreeStyle Libre)<br>**Comparator**: SMBG<br>**Outcomes (Clinical)**: time spent in the target glucose range (3.9 -10.0 mmol/L); time spent in hypoglycemia (< 3.9 mmol/L); hypoglycemia events (< 3.9 mmol/L); quality of life[a]; glucose variability[b]; A1C; severe hypoglycemic events (hypoglycemia that requires assistance from another person to treat); device-related adverse events<br>**Study Design**: RCTs, observational cohort studies (before-after or parallel groups designs)<br>**Language**: English<br>**Time Period**: January 1, 2014 to April 6, 2018 |

A1C = glycated hemoglobin; FGM = flash glucose monitoring system; HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; QoL = quality of life; RCT = randomized clinical trial; SMBG = self-monitoring of blood glucose; SR = systematic review; T1D = type 1 diabetes; T2D = type 2 diabetes.

[a] As measured using the following tools: Pediatric Quality of Life Inventory (PedsQL), Hypoglycemia Fear Survey (HFS), Diabetes Distress Scale (DDS), Diabetes Quality of Life (DQoL), and World Health Organization Five Well-Being Index (WHO-5).

[b] As measured using the following scales: Mean Amplitude of Glycemic Excursions (MAGE), Coefficient of Variation (CV), Blood Glucose Risk Index (BGRI), Low Glucose Risk Index (LGRI), standard deviation (SD), and Continuous Overall Net Glycemic Action (CONGA).

**Patient and Clinical Perspective:** Both HTA reports included consultation with patients, caregivers, or health care professionals to contextualize the value of FGMS and gather experiential information. These consultations took place through in-person and phone interviews, panel discussions, focus groups, and online surveys. These consultations were limited to patients from the respective provinces, that is, the INESSS HTA consulted Quebec residents and the HQO HTA consulted residents of Ontario.[11,13] Table 2 provides details of patient and clinician engagement method of each the HTA reports.

## Table 2: Details of Patient and Clinician Engagement[11,13]

| HTA report | Patient and clinician perspective |
|---|---|
| INESSS | • Patient panel discussions (nine participants with T1D and T2D), including both users and non-users of FGMS.<br>• Clinician panel discussions (nine participants), including endocrinologists, general practitioners, nurses, nutritionists, and pharmacists.<br>• A multiple-criteria questionnaire was used at both panel meetings to gather information based on the same analysis framework. INESSS also consulted Diabetes Quebec and CNIB. Participants were from the province of Quebec. |
| HQO | • Patient Interviews (25 participants).<br>• Patient focus groups (two six-person groups).<br>• Ontario-wide patient survey (344 participants). Participants included adults with diabetes and parents of children with diabetes. Interviews and focus groups were loosely structured and consisted of series of open-ended questions that were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment. Patients were from Ontario. |

CNIB = Canadian National Institute for the Blind; INESSS = Institut national d'excellence en santé et en services sociaux; HQO = Health Quality Ontario.

## Economic Evidence

Similar to the clinical evidence, the economic evidence presented in this report is restricted to the work presented in two provincial HTA reports. Both reports evaluated the economic value of FGMS for both T1D and T2D populations.

### Economic Evaluation

The review conducted by HQO aimed to address cost-effectiveness; however, a de novo economic evaluation on FGMS was ultimately not conducted as part of its HTA since their review of the clinical evidence found there was insufficient evidence to suggest that FGMS was associated with an improvement in clinical outcomes and health-related quality of life outcomes that would be relevant for modelling the cost-effectiveness of FGMS in adult patients with T1D and T2D.[11]

For the INESSS review, due to uncertainty associated with the clinical evidence, INESSS re-analysis of the sponsor's submitted economic evaluation involved a CMA comparing FGMS to SMBG by capillary blood glucose testing for adults with T1D or T2D on insulin therapy.[13] CMA is a type of economic evaluation that specifically compares the costs between alternative interventions as it assumes the technologies have the same clinical efficacy profile.

### Budget Impact Analyses

Both reviews included a BIA to address the question on affordability. The budget impact of the introduction of FGMS was evaluated by both HTAs from the perspective of their provincial public health care payer, for adult and pediatric patients with diabetes requiring insulin therapy in Ontario[11], and only adult patients in Quebec.[13] Specifically, findings from the clinical evidence review for Ontario suggested that FGMS (plus SMBG) may be used off-label in children; the pediatric population was deemed outside of scope in INESSS review.

The BIAs for Ontario and Quebec compared the cost difference (i.e., net budget impact) between two scenarios: 1) the current environment or "world without FGMS" (i.e., SMBG) and 2) the new environment or "world with FGMS" (i.e., introduction of FGMS) to report the incremental impact on the budget with the funding of FGMS. The analysis was conducted

under a time horizon of three years in Quebec, and five years in Ontario. Of note, at the time these evaluations were done, SMBG was the only publicly funded method of monitoring blood glucose in Ontario and Quebec. A series of scenario analyses were further conducted in Ontario to examine the impact of varying assumptions and input values on the budget impact of FGMS[11] while no additional scenario analyses were reported in Quebec's review.[13] An overview of the BIA methodology undertaken by each province is presented in Table 3.

## Table 3: Overview of the BIA Methodology Undertaken by Ontario and Quebec

| | ON[11] | QC[13] |
|---|---|---|
| **Target population** | Patients with diabetes undergoing IIT who use SMBG, covered by ODB program. This would include all individuals < 25 years and > 65 years covered by ODB and 11.2% of patients between 25 and 64 years of age. Excluded: people with hypoglycemic unawareness, and people at high risk for glycemic variability because CGM, with alerts to prevent high or low blood glucose levels, would be more suitable for these people. (i.e., 35% T1D and 20% T2D treated with IIT) . | Patients with T1D or T2D, aged 18 years and older on insulin therapy (age restriction aligned with Health Canada indication). |
| **Approach to estimate eligible population(s)** | • Population-based (i.e., epidemiological) approach<br>• Assumption to derive proportion of patients with T1D (6%); remainder (94%) was T2D | • Population-based approach (based on RAMQ billing data for 2017) |
| **Time horizon** | Five years (2018 to 2022) | Three years (unspecified) |
| **Perspective** | Provincial public health care payer (i.e., Ministry of Health and Long-Term Care) | Provincial public health care payer (i.e., RAMQ) |
| **Interventions under review** | • SMBG<br>• FGMS | • SMBG<br>• FGMS<br>Note: INESSS report states no CGM is currently reimbursed by RAMQ |
| **Current environment** | No introduction of FGMS (i.e., SMBG) | |
| **New environment** | Introduction of FGMS | Introduction of FGMS |
| **Uptake of new intervention** | Assumed uptake of FGMS is the same for each population (T1D IIT and T2D IIT) from 15% in year 1 to 35% in year 5 (manufacturer's data) | Assumed uptake of FGMS varies by population (from year 1 to 3):<br>• all adults with diabetes (T1D and T2D) on insulin therapy: 25%, 35% and 50%<br>• T1D IIT: 20%, 60% and 80%<br>• T2D IIT: 40%, 60% and 80%<br>• IIT (using more than 8 strips/day): 40%, 60% and 80% |

BIA= budget impact analysis; CGM = continuous glucose monitoring; FGMS = flash glucose monitoring system; INESSS = Institut national d'excellence en santé et en services sociaux; IIT= intensive insulin therapy; ODB = Ontario Drug Benefit; ON = Ontario; RAMQ = Régie de l'assurance maladie du Québec; QC = Quebec; SMBG = self-monitoring of blood glucose; T1D = type 1 diabetes; T2D = type 2 diabetes.

## Market Size

The approach to estimate the market size (i.e., the number of patients eligible for coverage) is presented in detail in Appendix 3. A population-based (i.e., epidemiological) approach was used to estimate the market size for FGMS, with slight variations in how the eligible population size was derived between reviews (Table 4). The prevalence of diabetes was estimated using provincial surveillance databases in Quebec while in Ontario, the prevalence of diabetes was based on data from the Canadian Diabetes Cost Model developed by the Canadian Diabetes Association (now Diabetes Canada).[18] The approach to estimate market growth over time differed by province. In Ontario, the market growth rate was assumed to be equal to the projected annual increase in diabetes prevalence (0.31%)[11] while in Quebec, the market growth rate was assumed to be the same as the growth rate for the population with coverage for RAMQ, although it remained unspecified in the INESSS report.[13]

The population eligible for FGMS differed by province (Table 4). In Ontario, two eligible populations were defined individuals with T1D who received IIT (T1D IIT) and individuals with T2D who received multiple daily insulin injections or CSII.[11] In Quebec, the four eligible populations assessed were all individuals on insulin therapy, individuals with T1D on IIT (T1D IIT), individuals with T2D on ITT (T2D IIT), and individuals on IIT who required more than eight test strips daily.[13] Importantly, IIT was defined differently in the two reports. In Ontario, IIT for patients with T2D was defined as the population treated with multiple daily insulin injections or CSII but was unspecified for patients with T1D.[11] In Quebec, IIT was defined as the population treated with multiple injections of insulin for both patients with T1D and T2D.[13]

## Market Share

Once market size was estimated, the next step was to forecast the market share. The market share distribution for FGMS was assumed to increase yearly though the uptake rate of FGMS and the distribution of patients across the diabetes interventions within the eligible populations were different for each province (Table 3). In both provinces, SMBG was assumed to have the greatest market share in the first year, with increased uptake of FGMS in subsequent years.[11,13] In Ontario, it was assumed that market shares for the current and new environment would remain the same for all eligible populations evaluated, and in the scenario analyses, while in Quebec, the uptake of FGMS differed for different eligible populations (i.e., market shares in the new environment differed in subgroup analyses).

### Table 4: Definition of Target Eligible Population Sizes for Ontario and Quebec (Year 1)

| ON[11] | QC[13] |
|---|---|
| **Target Population:** patients with T1D and T2D requiring IIT<br><br>**Subgroups:**<br>• T1D on IIT (unspecified); (n = 28,537)<br>• T2D on IIT (via multiple daily insulin injections or CSII); (n = 61,263) | **Target population:** patients with diabetes, aged 18 years and older, on insulin therapy<br><br>**Subgroups:**<br>• all adults with diabetes (T1D and T2D) on insulin therapy (n = 74,213)<br>• T1D on IIT; (n = 10,597)<br>• T2D on IIT; (n = 33,300)<br>• all individuals on IIT who required ≥ 8 daily test strips; (n = unspecified). |

CSII = continuous subcutaneous insulin infusion; IIT = intensive insulin therapy; n = sample size; ON = Ontario; QC = Quebec; T1D = type 1 diabetes; T2D = type 2 diabetes.

## Costs

Costs associated with the method of monitoring blood glucose (i.e., costs of technologies) aligned with the perspective of the analysis. Costs associated with SMBG and FGMS did vary by province (Table 5).

The cost components of SMBG may include costs of a glucose meter (or SMBG monitor), a glucose meter battery, insulin, blood glucose testing strips, and lancets. The annual cost of testing strips was the only component of SMBG cost components explicitly listed and considered in both HTA reviews. The daily number of blood glucose tests performed by patients differed between the two provinces (Ontario: six per day [T1D] and four per day [T2D][11]; Quebec: 8.2 per day[13]).

The main cost components of FGMS may include costs of a flash glucose meter (or flash glucose monitor/reader) and sensors. While the flash sensor does not require finger prick calibration with SMBG, Ontario and Quebec similarly recommended occasional finger prick testing (i.e., SMBG) with FGMS using test strips to ensure accuracy of readings in certain situations such as during times of rapidly changing glucose levels, if symptoms do not match the device reading, or to confirm hypoglycemia or impending hypoglycemia.[11,13] In Ontario, calibration of FGMS with SMBG is associated with an additional per strip cost that was assumed to be the same as SMBG; whereas, these costs were not specified in the INESSS report.

### Table 5: Costs of Technologies

| Component | | ON[11] | QC[13] |
|---|---|---|---|
| | | Cost/Assumption | Cost/Assumption |
| Self-Monitoring of blood glucose | Glucose meter (i.e., SMBG monitor) | • Excluded | • Not specified |
| | Glucose meter battery | • Not specified | |
| | Insulin | • Excluded | |
| | Testing strips (i.e., glucose tests) | • Annual cost = $1,620.06[c] (T1D) and $1,080.40[c] (T2D) (based on cost of a single test trip = $0.74; and assumption of 6 test strips per day for T1D; and 4 test strips per day for T2D) | • Annual cost = $2,125.03 (based on cost of a single test strip = $0.71; and assumption of 8.2 test strips per day) |
| | Lancets | • Cost per lancet = $0.10 | • Not specified |
| Flash glucose meter | Flash glucose meter (i.e., flash glucose monitor / reader) | • Excluded[a] | • Cost of monitor = $49.00 (assume 3-year service life) |
| | Sensor | • Cost of sensor is $89.00 every 2 weeks<br>• Assumed calibration is required every 2 days; assumed same per strip costs of SMBG[b] | • Cost of sensor is $89.00 every 2 weeks |
| | Insulin | • Not included | • Not specified |

ON = Ontario; NA = not applicable; QC = Quebec; T1D = type 1 diabetes; T2D = type 2 diabetes.

[a] The cost of the blood glucose meter was assumed to be absorbed by the FGMS and SMBG groups because of its relatively low cost; therefore this cost item was excluded from the analysis.[11]

[b] FGMS users may require calibration with SMBG to confirm hypoglycemic readings, once every two days.[11]

[c] CADTH cost calculation based on information within the HTA report.

### Assumptions

Each of the provincial BIAs made several common assumptions for the reference case, with some exceptions. Importantly, the provinces assumed that the reimbursement policies for SMBG would remain the same over the time horizon and furthermore, no new methods of monitoring blood glucose would be developed. Patient adherence with the methods of monitoring blood glucose levels was assumed to be 100% without switching between methods for a given fiscal year.

## Provincial Funding Recommendations

The two HTAs were conducted to provide recommendations for provincial funding decision regarding FreeStyle Libre. The INESSS HTA report was used by the CSEMI to deliberate on the therapeutic values of the FGMS and to formulate recommendations for the prescription drug insurance plan (RAMQ) in Quebec. The HQO/CADTH HTA report was used by the OHTAC to make funding recommendation in Ontario. The committee used multiple decision criteria to deliberate on the value of FGMS, including overall clinical benefit (effectiveness, safety, burden of illness and need); consistency with expected societal and ethical values; cost-effectiveness; and economic and organizational feasibility of adoption into health systems.[11,13]

# Clinical Evidence

## Key Findings From Clinical Evaluations of the HTA Reports

The following section provides key findings from the HQO and INESSS HTA reports. FGMS was found to be superior to SMBG with respect to some glycemic outcomes (i.e., time in target glucose range, frequency and duration of daytime and nocturnal hypoglycemia, treatment satisfaction) but not others (i.e., A1C, severe hypoglycemic events). The quality of the evidence was evaluated to be very low to moderate (GRADE). Further details on specific outcomes are provided below. Table 6 provides a list of studies included in each of the two HTAs. As such there is considerable overlap in the studies included in these reports.

### Table 6: Studies Included in the HTA reports[11,13]

| First author (name of study, if applicable) | Included in HTA reports | Population |
|---|---|---|
| **RCTs** | | |
| Bolinder (IMPACT) (2016) | INESSS; HQO | T1D; adults (> 18 years) |
| Haak *(REPLACE)* (2017) | INESSS; HQO | T2D; adults (> 18 years) |
| Oskarsson (2018)[a] (subgroup analysis of Bolinder et al.) | HQO | T1D; adults (> 18 years) (only patients on MDI) |
| **Observational Studies** | | |
| Mitsuishi (2017)[a] | HQO | T1D and T2D; adults (18-80 years) |
| Al Hayek (2017) | HQO | T1D; 13-19 years |
| Moreno-Fernandez (2018)[a] | HQO | T1D; adults (18-65 years) |

HQO = Health Quality Ontario; HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; MDI = multiple insulin injection; RCT= randomized clinical trials; T1D = type 1 diabetes; T2D = type 2 diabetes.

[a] Findings from these studies were used by INESSS to complement the findings of the two RCTs (IMPACT and REPLACE). Other studies (observational) used by INESSS to complement the findings of the two RCTs include Ish-Shalom et al., 2016; McKnight and Gibb, 2017; Dover et al., 2016; Herman et al., 2017; Ji et al., 2017; Bailey et al., 2015; Etienne, 2017; and Dunn et al., 2018. No detailed information about these studies was provided in the INESSS HTA report.

## Overview of Clinical Findings of the HTA reports

**INESSS:** The SR of clinical effectiveness in this HTA report is mainly based on two multicenter non-blinded randomized controlled trials (RCTs) (as cited in the INESSS report: IMPACT [Bolinder et al., 2016] and REPLACE [Haak et al., 2017]).[13] Both studies were funded by the manufacturer and involved a six-month intervention period, with data being collected in the first and last 14 days of the study period. In addition to the two RCTs, six HTAs and several other observational studies were also identified, which were used to complement the findings of the two RCTs. These studies were conducted on patients with T1D and T2D. No improvement in A1C was observed in the FGMS group after six months in patients with T2D who have poor blood glucose control and are undergoing insulin treatment. Use of FGMS led to a significant reduction in both number and duration of daytime and nighttime hypoglycemic events in patients with T1D and T2D. No difference was observed for severe hypoglycemic events. An increase in time spent in normal glucose range was observed with FGMS group for patients with T1D but not for patients with T2D. Improvement in quality of life was noted only with respect to treatment satisfaction. Adverse events related to injection-site reactions such as erythema, pain, itching, bleeding, edema, bruising, were reported by FGMS group based on duration. Quality of the evidence were rated to be low to moderate using GRADE.[13]

**HQO:** The SR of clinical effectiveness in this HTA report is based on six studies: two RCTs, both of which were also included in the INESSS HTA report (as cited in the HQO report: Bolinder et al., 2016 and Haak et al., 2017); a subgroup analysis of Bolinder et al. (as cited in the HQO report: Oskarsson et al., 2018); and three observational studies (as cited in the HQO report: Mitsuishi et al., 2017; Al Hayek et al., 2017 and Moreno-Fernandez et al., 2018).[11] These studies were conducted on patients with T1D and patients with T2D. FGMS was shown to be more effective than SMBG among adults with well-controlled T1D and adults with T2D requiring IIT with respect to increasing the time spent in target glucose range (T1D only), and reducing glucose variability, time spent in hypoglycemia, and number of hypoglycemic events. Adverse events related to injection-site reactions such as erythema, itching, allergy, rash and edema, were reported by FGMS group. Quality of the evidence were rated to be very low to moderate using GRADE.[11,13] Table 7, Table 8 and Table 9 outline the risk of bias assessment of the included studies from both the HQO and INESSS HTA reports.

### Table 7: INESSS Risk of Bias Assessment of Included Studies — Randomized Controlled Trials (Cochrane Risk of Bias Tool)[13]

| Author, year | Domain A bias arising from the randomization process | Domain B bias due to deviations from intended interventions | Domain C bias due to missing outcomes | Domain D bias in the measurement of the outcome | Domain E bias in selection of the reported result | Total |
|---|---|---|---|---|---|---|
| Haak, 2017 | Some concerns | Low risk | Low risk | High risk | Some concerns | High |
| Bolinder, 2016 | Some concerns | Low risk | Low risk | High risk | Low risk | High |

## Table 8: HQO Risk of Bias[a] Assessment of Included Studies — Randomized Controlled Trials (Cochrane Risk of Bias Tool)[11]

| Author, year | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|
| Haak, 2017 | Low risk | Low risk | Low risk | High risk | Unknown risk | Low risk |
| Bolinder, 2016 | Low risk | Low risk | Low risk | High risk | Unknown risk | Low risk |

[a] Possible risk of bias level: low, high, and unclear.

## Table 9: HQO Risk of Bias[a] Assessment of Included Studies — Non-randomized Trials (Risk of Bias in Non-Randomized Studies of Interventions [ROBINS-I] Tool)[11]

| Author, year | Pre-intervention | | At intervention | | | Post-intervention | |
|---|---|---|---|---|---|---|---|
| | Confounding | Study participation Selection | Classification of interventions | Deviations from intended intervention | Missing data | Measurement of outcomes | Selection of reported Results |
| Mitsuishi et al., 2018 | Low to moderate risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unknown risk |
| Al Hayek et al., 2017 | Low to moderate risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unknown risk |
| Moreno-Fernandez et al., 2018 | Low to moderate risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unknown risk |

[a] Possible risk of bias levels: low, moderate, serious, critical, and no information.

### Details on the Outcomes Assessed in the SR of Clinical Effectiveness of the HTA Reports

The following section provides details on the outcomes assessed by the INESSS and HQO HTA reports, followed by a table with GRADE evidence profile with the included studies for each outcome (Table 10 to Table 22).

*Glycated Hemoglobin (A1C)*

In general, the SR conducted by INESSS and HQO concluded that no improvement in A1C was observed in the FGMS groups, compared to the SMBG groups, after six months of use in patient with either T1D (IMPACT; secondary data) or T2D (REPLACE; primary outcome). Both HTAs noted that A1C level was a secondary variable in IMPACT since these T1D patients had adequate disease control at the start. Both HTAs noted that, in the REPLACE study, FGMS had favourable effects on A1C in T2D patients younger than 65 years (0.53% FGMS versus –0.20% for the control arm, P = 0.0301), but unfavourable effects in patients 65 years and older (–0.05% FGMS versus –0.49% for the control arm, P = 0.0081).[11,13] The HQO HTA report indicated that the point estimates in both groups (< 65 years and > 65 years) exceeded the recommended cut-off point for clinically meaningful difference (i.e., 0.5%). But it also noted that the generalizability of these results depends on the age distribution of the target population and that the study reported imputing missing values for this outcome in a way that could introduce biases.[11] Both HTAs included a secondary analysis of IMPACT study carried out in patients with T1D on multiple insulin injections (n = 82) that did not demonstrate any effect of the FGMS on A1C levels.[11,13]

Although the INESSS HTA report included several observational studies that showed improvement in A1C levels (0.2% to 1.3%) with FGMS use, in both in adult T2D patients (one study) and T1D patients (four studies), it was highlighted that these studies involved a small number of patients and had significant risk of bias. These studies suggest that individuals (primarily T1D patients) with inadequate diabetes control (A1C ≥ 7.5%) can benefit from using the FGMS to reduce their A1C levels. Similarly, a non-masked RCT (Reddy et al., 2018) of 40 patients with T1D with mean A1C of 7.3%, and hypoglycemia unawareness, concluded that FGMS decreases A1C (0.35% reduction) after eight weeks of use. However, SMBG was not the comparator in this study.[13] One observational study included in the HQO HTA reported a statistically significant decrease in A1C with use of FGMS in patients with T1D, versus use of SMBG, which exceeded the recommended threshold of 0.5% for a minimum clinically important difference. This effect persisted when confined to people using multiple daily injections of insulin but was small and imprecise among those using CSII. However, the HQO HTA noted inconsistency in results across studies and differing interpretations of A1C results.[11]

## Table 10: GRADE Evidence Profile — A1C

| HTA reports | Studies<br>First author (year) — study design | Quality of evidence |
|---|---|---|
| INESSS[13] | Bolinder (2016) — RCT<br>Haak (2017) — RCT | Moderate<br>ΘΘΘ |
| HQO[11] | T1D<br>Bolinder (2016) — RCT<br>Al Hayek (2017) — Observational<br>Moreno- Fernandez (2018) — Observational | Very low<br>Θ |
| | T2D<br>Haak (2017) — RCT | Low<br>ΘΘ |

HQO = Health Quality Ontario; HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RCT = randomized clinical trial T1D = type 1 diabetes; T2D = type 2 diabetes.

### *Glucose Variability*

HQO reported a statistically significant improvement in glucose variability for FGMS, compared with SMBG, for patients with T1D; the results were consistent across scales. HQO reported inconsistent results across scales of glucose variability for T2D patients. However, none of the scales used are considered the gold standard for glucose variability, and the authors were unable to determine the clinically important cut-off points for other scales of glucose variability. Hence, it was impossible to determine whether FGMS is more effective than SMBG in reducing glucose variability in both T1D and T2D patients. Of note, glucose variability was measured using the following scales: Mean Amplitude of Glycemic Excursions, Coefficient of Variation, Blood Glucose Risk Index, Low Glucose Risk Index, standard deviation, and Continuous Overall Net Glycemic Action.[11]

## Table 11: GRADE Evidence Profile — Glucose Variability

| HTA reports | Studies<br>First author (Year) – study design | Quality of evidence |
|---|---|---|
| HQO[11] | T1D<br>Bolinder (2016) – RCT | Moderate<br>ΘΘΘ |
| | T2D<br>Haak (2017) – RCT | Low<br>ΘΘ |

HQO = Health Quality Ontario; HTA = health technology assessment; RCT = randomized clinical trial; T1D = type 1 diabetes; T2D = type 2 diabetes.

*Time in Range*

Both the INESSS and HQO HTA reports noted that T1D patients using the FGMS had statistically significant increase in time spent in the target glucose range (3.9 to 10.0 mmol/L); and a statistically significant decrease in time spent above the target glucose range (> 13.3 mmol/L); compared with using SMBG. On average, T1D patients using FGMS spent an hour more in the target glucose range (95% confidence interval [CI] 0.41 to 1.59; P = 0.0006) and 22 minutes less (–0.37 hours) in a high glucose range (95% CI, −0.69 to −0.05; P = 0.0247).[11,13]

In patients with T2D, a statistically non-significant increase in the time spent in the target glucose range was observed for FGMS, compared with SMBG. The results appeared imprecise and even more so when the analysis was partitioned by age group.[11]

## Table 12: GRADE Evidence Profile —Time in Target Glucose Range (3.9 to 10.0 mmol/L) in 24 Hours

| HTA reports | Studies<br>First author (Year) — study design | Quality of evidence |
|---|---|---|
| INESSS[13] | Bolinder (2016) — RCT<br>Haak (2017) — RCT | Low<br>ΘΘ |
| HQO[11] | T1D<br>Bolinder (2016) — RCT | Moderate<br>ΘΘΘ |
| | T2D<br>Haak (2017) — RCT | Low<br>ΘΘ |

HQO = Health Quality Ontario; HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RCT = randomized clinical trial; T1D = type 1 diabetes; T2D = type 2 diabetes.

## Table 13: GRADE Evidence Profile — Time Above the Target Glucose Range (> 13.3 mmol/L) in 24 Hours

| HTA reports | Studies<br>First author (Year) — study design | Quality of evidence |
|---|---|---|
| INESSS[13] | Bolinder (2016) — RCT<br>Haak (2017) — RCT | Low<br>ΘΘ |
| HQO[11] | T1D<br>Bolinder (2016) – RCT | Moderate<br>ΘΘΘ |
| | T2D<br>Haak (2017) – RCT | Low<br>Θ |

HQO = Health Quality Ontario; HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux;RCT = randomized clinical trial; T1D = type 1 diabetes; T2D = type 2 diabetes.

*Severe Hypoglycemia Events*

The INESSS HTA report noted no significant differences between FGMS and capillary blood sampling (i.e., SMBG) for patients with T1D or T2D with regard to severe hypoglycemic events. These were defined as events requiring assistance from another person to treat and with proven clinical and economic effects. INESSS did not rate the quality of the evidence. INESSS noted that severe hypoglycemic event is a parameter with a greater degree of objectivity and independent of FGMS. However given the rare occurrence of the event and the size of the study populations being too low, the statistical power of these studies were inadequate to observe any differences.[13] HQO report drew similar conclusion.[11]

## Table 14: GRADE Evidence Profile — Severe Hypoglycemia Events

| HTA reports | Studies<br>First author (Year) — study design | Quality of evidence |
|---|---|---|
| HQO[11] | T1D<br>Bolinder (2016) - RCT<br>Moreno- Fernandez (2018) — Observational | Very Low<br>Θ |
| | T2D<br>Haak 2017 — RCT | Very Low<br>Θ |

HQO = Health Quality Ontario; HTA = health technology assessment; RCT = randomized clinical trial; T1D = type 1 diabetes; T2D = type 2 diabetes.

*Hypoglycemia (duration and number of events)*

Based on the same two RCTs, both the INESSS and HQO HTA reports indicated a statistically significant reduction in the duration and number of daytime and nighttime hypoglycemic events (glucose values below 3.1 mmol/L) at six months in patients with T1D or T2D using FGMS, compared with using SMBG. The average daily time spent with glucose values below 3.1 mmol/L was reduced by 50% for T1D patients (48 minutes FGMS versus 99 minutes SMBG [$P < 0.0001$]); and 53% for T2D patients (11 minutes FGMS versus 22 minutes SMBG; $P = 0.0014$). Time spent in nocturnal hypoglycemia (over seven hours) was reduced by 49% in T1D patients (19 minutes FGMS versus 40 minutes SMBG; $P < 0.0001$) and by 58% in T2D patients (5 minutes FGMS versus 11 minutes SMBG; $P = 0.0032$). The reduction in daytime and nocturnal time spent in hypoglycemia remained similar when the RCT in patients with T2D included a subgroup analysis for people 65 years of age and younger and for people older than 65 years of age.[11,13] However, the HQO report noted that although recurrent hypoglycemia can impair awareness of such events, any single episode of severe hypoglycemia can be dangerous; authors were unable to determine from the study how low the glucose level dropped after crossing the hypoglycemia threshold for both RCTs. Additionally, for the RCT on T1D patients, the authors reported that the study imputed missing values for this outcome by carrying forward the last observation, which potentially introduced bias.[11]

Similarly, results favoured FGMS with respect to the daily mean number of hypoglycemic events reported in patients. A hypoglycemic event is defined as a value below glycemic targets, which is maintained for two consecutive readings done 15 minutes apart. Compared to SMBG, the mean number of hypoglycemic events (glucose value less than 3.1 mmol/L) occurring in the same day with FGMS declined by 41% in patients with T1D (0.96 to 0.56 events; $P < 0.0001$), and by 44% in T2D patients (0.34 to 0.14 events; $P = 0.0017$). The mean number of nocturnal events also dropped at six months with the use of FGMS in patients with T1D (0.30 to 0.19; $P = 0.0005$) and in patients with T2D (0.13 to 0.06; $P = 0.0012$).[11,13] The HQO report noted that the observed reduction is slightly lower than the

minimum threshold set by one of the RCT (30% threshold set by RCT versus 25.5% reduction for T1D, and 27.7% for T2D), introducing uncertainty about the importance of this reduction.[11]

## Table 15: GRADE Evidence Profile — Glucose Values ≤ 3.1 mmol/L

| HTA reports | Studies<br>First Author (year) – study design | Quality of evidence |
|---|---|---|
| INESSS[13] | Bolinder (2016) - RCT<br>Haak (2017) - RCT | Low<br>ΘΘ |

HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RCT = randomized clinical trials.

## Table 16: GRADE Evidence Profile — Time in Hypoglycemia (< 3.9 mmol/L Within 24 Hours)

| HTA reports | Studies<br>First author (Year) — study design | Quality of evidence |
|---|---|---|
| HQO[11] | T1D<br>Bolinder (2016) — RCT | Moderate<br>ΘΘΘ |
| | T2D<br>Haak (2017) — RCT | Moderate<br>ΘΘΘ |

HQO = Health Quality Ontario; HTA = health technology assessment; RCT = randomized clinical trials;

T1D = type 1 diabetes; T2D = type 2 diabetes.

## Table 17: GRADE Evidence Profile — Time in Hypoglycemia (< 3.9 mmol/L at Night[a] Within 7 Hours)

| HTA reports | Studies<br>First author (year) —study design | Quality of evidence |
|---|---|---|
| HQO[11] | T1D<br>Bolinder (2016) — RCT | Moderate<br>ΘΘΘ |
| | T2D<br>Haak (2017) — RCT | Moderate<br>ΘΘΘ |

HQO = Health Quality Ontario; HTA = health technology assessment; RCT = randomized clinical trials; T1D = type 1 diabetes; T2D = type 2 diabetes.

[a] Night in this case indicates 11:00 p.m. to 6 a.m.

## Table 18: GRADE Evidence Profile — Number of Hypoglycemic Events

| HTA reports | Studies<br>First author (year) — study design | Quality of evidence |
|---|---|---|
| INESSS<br>(≤ 3.1 mmol/L)[13] | Bolinder (2016) — RCT<br>Haak (2017) — RCT | Low<br>ΘΘ |
| HQO<br>(< 3.9 mmol/L [70 mg/dL] within 24 hours)[11] | T1D<br>Bolinder (2016) — RCT | Moderate<br>ΘΘΘ |
| | T2D<br>Haak (2017) — RCT | Moderate<br>ΘΘΘ |

HQO = Health Quality Ontario; HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RCT = randomized clinical trial; T1D = type 1 diabetes; T2D = type 2 diabetes.

*Safety*

The INESSS and HQO reports noted adverse events related to injection-site reactions such as erythema, pain, itching, bleeding, edema, bruising, in duration with FGMS group in the RCTs. Thirteen and eight adverse events in the intervention arm required medical attention in the RCTs on T1D and T2D patients, respectively. In total, seven T1D patients (six from the intervention arm and one from the control arm) and three T2D patients (one from the intervention arm and two from the control arm) discontinued the study due to sensor-related symptoms. The number of adverse events unrelated to the sensor was similar in the two arms in the two studies.[11,13] The HQO report also mentioned that a comparative safety assessment in the two RCTs was not possible due to the sparsity events. Additionally, the HQO report identified an observational study that found 34 adverse events related to the use of FGMS in T1D and T2D patients. These events included itching, scar at the insertion site, erythema, bruising, bleeding, epidermolysis, pain, and subcutaneous bleeding. However, the HQO HTA was unable to compare safety of FGMS versus SMBG as data on SMBG were missing in this study.[11]

## Table 19: GRADE Evidence Profile — Safety

| HTA reports | Studies<br>First author (Year) — study design | Quality of evidence |
|---|---|---|
| INESSS[13] | Bolinder (2016) — RCT<br>Haak (2017) — RCT | Moderate<br>ΘΘ |
| HQO[11] | T1D<br>Bolinder (2016) — RCT | Very Low<br>Θ |
| | T2D<br>Haak (2017) — RCT | Very Low<br>Θ |
| | Combined T1D and T2D<br>Mitsuishi (2017) — Observational | Very Low<br>Θ |

HTA = health technology assessment; HQO = Health Quality Ontario; INESSS = Institut national d'excellence en santé et en services sociaux; RCT = randomized clinical trial ; T1D = type 1 diabetes; T2D = type 2 diabetes.

*Satisfaction With Treatment*

Based on the two RCTs, the INESSS HTA report noted significant improvement in treatment satisfaction (measured by Diabetes Treatment Satisfaction Questionnaire [DTSQ]) as reported by all intervention group patients for both T1D and T2D patients, compared to the control group participants ($P < 0.0001$). With respect to the four quality of life subscales, treatment satisfaction improved in the FGMS arms (T1D: $P < 0.0001$; T2D: $P = 0.0259$). Similar adult patient satisfaction with FGMS were noted in four other observational studies and one qualitative study (enhanced convenience, practicality and safety, for them as well as their family/friend).[13]

## Table 20: GRADE Evidence Profile — Satisfaction With Treatment

| HTA reports | Studies<br>First author (year) — study design | Quality of evidence |
|---|---|---|
| INESSS[13] | Bolinder (2016) — RCT<br>Haak (2017) — RCT | Low<br>ΘΘ |

HTA = health technology assessment; INESSS= Institut national d'excellence en santé et en services sociaux; RCT = randomized clinical trial.

*Quality of Life and Fear of Hypoglycemia*

Based on findings of the two included RCTs, both the INESSS and the HQO HTA reports noted no statistically significant increase in quality of life for people using FGMS versus SMBG (T1D: P = 0.0524; T2D: P = 0.3863). Although treatment satisfaction improved (see above), there were no significant impact on the other three subscales of quality of life as measured by DTSQ: social worry, diabetes worry, and impact of treatment. Further, no difference was observed for distress associated with the disease.[11,13] HQO identified two observational studies that demonstrated statistically significant improvement in the quality of life (one for T1D; and one for T1D and T2D combined) using FGMS, compared with SMBG. However, the results of only one (for T1D) out of the two studies exceeded the recommended minimum clinically important difference. The effect persisted among people using multiple daily injections of insulin but diminished and was imprecise among people using CSII.[11]

The HQO report identified one observational study that reported a statistically significant reduction in the fear of hypoglycemia in T1D patients when they switched from SMBG to FGMS, but this reduction did not meet the recommended threshold for clinical significance. However, the RCT on T1D patients did not find any difference in the fear of hypoglycemia between SMBG and FGMS (mean difference in the Hypoglycemia Fear Survey [HFS] scale 0.0; 95% CI, −1.41 to 1.41). Further, a subgroup analysis yielded similar results in people using multiple daily injections of insulin. However, it should be noted that this RCT excluded people who would be most likely to experience the fear of hypoglycemia (e.g., those with hypoglycemia unawareness), making it unlikely to demonstrate an effect.[11]

INESSS found no change in the perceived frequency of periods of hypoglycemia (T1D: P = 0.0713; T2D: P = 0.2295) or of hyperglycemia (T2D, P = 0.6095). System unreliability, particularly with respect to hypoglycemia, was identified as a limitation. A reduction in the average number of test strips used daily in the intervention arm was noted (T1D: 5.5 test strips daily at the start of the study and 0.5 test strips after six months; T2D: 3.8 test strips daily at the start and 0.3 test strips daily at the end of the study).[13]

## Table 21: GRADE Evidence Profile — Quality of Life

| HTA reports | Studies<br>First author (year) – study design | Quality of evidence |
|---|---|---|
| INESSS[13] | Bolinder (2016) — RCT<br>Haak (2017) — RCT | Low<br>ΘΘ |
| HQO[11] | T1D<br>Bolinder (2016) — RCT<br>Al Hayek (2017) — Observational<br>Mitsuishi (2017) — Observational | Very Low<br>Θ |
| | T2D<br>Haak (2017) — RCT<br>Mitsuishi (2017) — Observational | Low<br>ΘΘ |
| | Combined T1D and T2D<br>Mitsuishi (2017) — Observational | Very Low<br>Θ |

HTA = health technology assessment; HQO = Health Quality Ontario; INESSS = Institut national d'excellence en santé et en services sociaux; RCT = randomized clinical trial; T1D = type 1 diabetes; T2D = type 2 diabetes.

## Table 22: GRADE Evidence Profile — Fear of Hypoglycemia

| HTA reports | Studies<br>First author (year) — study design | Quality of evidence |
|---|---|---|
| HQO[11] | T1D<br>Bolinder (2016) — RCT<br>Al Hayek (2017) — Observational | Moderate<br>ΘΘΘ |

HQO = Health Quality Ontario; HTA = health technology assessment; RCT = randomized clinical trial; T1D = type 1 diabetes.

**Overview of Patient and Clinician Perspective**

The following section provides an overview of the patient and clinician perspectives gathered through consultation as a part of the HTAs performed by HQO and INESSS. Although concerns were raised about some aspects of FGMS, overall there was a strong support for this technology with respect to improving quality of life. Patients and clinicians noted physical, emotional, and social benefits of using FGMS such as reduction in finger pricks and ability to monitor blood glucose trends. Cost was the largest barrier to use. Education for patients and care teams was considered a necessary condition for optimal and beneficial use of the FGMS.[11,13]

**HQO**

Most patients consulted by HQO had experience in multiple methods of diabetes management (diet and exercise, multiple daily injections, continuous glucose monitoring [CGM] and FGMS) allowing an extensive discussion and varied perspective. There was an overwhelming support for FGMS, and patients reported its medical, social, and emotional benefit over SMBG. Patients thought that FGMS was more useful than SMBG in stabilizing glucose levels to avoid dangerous highs and lows. They noted that the ease of using FGMS led them to check their blood glucose more frequently. Two most common responses to the online survey question regarding the most liked aspect of FGMS were the reduction in finger pricks (96%) and the ability to see blood glucose trends (92%). Patients reported that the ability to monitor glucose levels resulted in decreased stress and anxiety concerning their condition; thus, providing both physical and emotional benefits. FGMS device was considered to be more discreet and less socially obtrusive. This reduced the barrier to checking blood glucose levels, keeping them or their children safer. Although the patient consultation did not intend to compare CGM with FGMS, patients did report the advantage of FGMS over CGM in some respects. Compared to CGM, FGMS were considered to be more accessible because of its lower cost; this allowed patients to trial FGMS on a limited basis without the large commitment needed to try CGM. However, the cost of FGMS was still the largest barrier to use. As opposed to CGM, FGMS does not have an alarm system (for low glucose levels), which was noted by patients as an extremely valuable feature, especially for parents concerned about the glucose levels of young children. This was cited as a disadvantage of FGMS by several participants. Another commonly noted disadvantage of FGMS (compared to newer version of CGM) — especially by parents of children with diabetes — was the lack of a feature that allowed for remote monitoring or connection to smart phones. Other concerns of FGMS reported by patients were related to the device accuracy, comfort, and specific features of each type of device. Despite these concerns, the overwhelming opinion among participants was that these concerns were relatively minor compared with its benefits. Many patients currently using FGMS stated that it is essential to their diabetes management and that they would never want to return to previous methods of managing their diabetes.[11]

### INESSS

Patients and clinicians consulted by INESSS noted several advantages of FGMS that they feel translated to better diabetes control. These include “optimal frequency for SMBG, portrait of glycemic fluctuations for proactive treatment adjustment, and clearer understanding of positive effects of proper nutrition and life habits on blood glucose.” Further, a better understanding of glycemic fluctuations and their causes was thought to help in reducing hypoglycemic events, especially nocturnal hypoglycemia, which could have a significant impact on quality of life. However, FGMS overestimation of hypoglycemic episodes and the need to validate readings by taking capillary blood glucose measurements led some to lose confidence in the device or create anxiety in others. It was noted that features such as the arrow indicating glucose changes would be a better treatment decision indicator (to detect glycemic excursions that normally would go undetected, that is, hypoglycemia not perceived and extended nocturnal hypoglycemia) and should be used more by patients. As such, there was a consensus that training for patients and the care teams was necessary for optimal and beneficial use of the FGMS in the treatment of diabetes. Patients also discussed that the difference between capillary and interstitial blood glucose readings was a source of confusion in the use of FGMS. Although some users experienced adverse injection-site reactions (e.g., irritation) or pain when removing the sensor, using FGMS was generally considered to be safe. Similar to patients consulted by HQO, the lack of an alarm for low glucose levels was considered a disadvantage. Risk of incorrect readings and patients not realizing the importance of validating certain FGMS data via capillary blood glucose measurements when required, was reported as well as shown by experience. One of the widely noted aspect of FGMS was the reduction in frequency of finger pricks which was considered to improve the quality of life. Further advantages noted by participants were easier glucose self-monitoring, greater flexibility and fewer constraints in terms of participation in certain sports. Additionally, certain populations that would benefit from using FGMS were identified as individuals with visual impairment (e.g., the challenge of putting a drop of blood onto a small test strip; less finger sensitivity to read Braille) and persons whose professional occupations require frequent blood glucose monitoring but having difficulty pricking the tip of their fingers as often as required. However, some patients indicated that FGMS was more complicated to use. Some considered FGMS sensor placement on the arm to be non-discrete, an inconvenience or stigmatizing. Technology dependency, potentially anxiety-producing nature of having to take more frequent glucose measures than necessary, and potential risk of lack of accountability and of non-optimal use were also identified.[13]

# Economic Evidence

## Key Findings from Economic Evaluations of the HTA Reports

The following section reports the key findings on the economic evidence from the two HTA reports. The cost-effectiveness of the FGMS for the management of insulin-dependent diabetes was considered by the two HTAs. However, due to limitations with the clinical evidence, only INESSS reported a CMA since the clinical data required to support a cost-effectiveness model was determined to be highly uncertain. The results of the CMA showed that the FGMS is a more costly option compared to SMBG for all identified subgroups.

Both HQO and INESSS performed an affordability analysis assessing the introduction of FGMS to the current environment. The budget impact of FGMS differed substantially between the two provinces due to important methodological differences in the analytical time frame (i.e., three years versus five years), the market share distribution over the time horizon, and the definition of target population eligible for FGMS. Nonetheless, in both reviews, the introduction of FGMS was expected to increase spending on public health budgets regardless of the population studied and the time frame of the analysis. In Quebec, from the perspective of RAMQ, the net budget impact over three years ranged from $380,658 for the most restrictive population (i.e., adults with diabetes on IIT using at least eight test strips daily) to $129.7 million for the most liberal population (i.e., all adults with diabetes on insulin therapy). The introduction of FGMS in Ontario for patients with T1D, and patients with T2D who require IIT, would lead to a five-year net budget impact of $131 million for the Ontario Ministry of Health.

## Overview of the Cost-Effectiveness Results of the HTA Reports

**INESSS:** The CMA results showed that the estimated cost of FGMS was higher than the cost of SMBG regardless of which eligible population was funded: all adults with diabetes on insulin therapy (FGMS: $2,717; SMBG: $803), adults with T1D on IIT (FGMS: $2,748; SMBG: $1,080), adults with T2D on IIT (FGMS: $2,717; SMBG: $895), and all adults with diabetes on IIT using eight or more test strips daily (FGMS: $2,748; SMBG: $2,397). Therefore, the INESSS concluded that FGMS would not be cost-effective in all subgroups analyzed.[13]

**HQO:** HQO did not conduct a de novo economic analysis. Their economic evidence review included a systematic literature review on the topic. One cost-utility analysis was identified from the perspective of Scotland's health care system, which compared FGMS with SMBG in patients with T1D or patients with T2D requiring IIT; however, several methodological limitations were identified with the study that may have overestimated the cost-effectiveness of FGMS.[11]

## Overview on Affordability from the BIAs Results of the HTA Reports

**INESSS:** The net budget impact of introducing FGMS in Quebec for each of the identified subpopulations was calculated as the cost difference between the current environment and the new environment. The eligible populations considered in the current and new environments included (i) all adults with diabetes (T1D and T2) on insulin therapy (the most liberal population); (ii) adults with T1D on IIT; (iii) adults with T2D on IIT; and (iv) all adults with diabetes on IIT who required eight or more daily test strips (the most restrictive

population). Over a three-year period, the introduction of FGMS in Quebec would result in an increase in expenditure of $380,658 to $129.7 million depending on how the eligible population is defined. For all individuals with diabetes on insulin therapy (i.e., subgroup i), the annual net budget impact was estimated to increase from $18.6 million in year 1 to $65.6 million in year 3. The introduction of FGMS in Quebec for patients with T1D on IIT (i.e., subgroup ii) would lead to an annual net budget impact of approximately $3.5 million in year 1 to $12.5 million in year 3. The introduction of FGMS in Quebec for patients with T2D on IIT (i.e., subgroup iii) would lead to an annual net budget impact of approximately $12.4 million in year 1 to $34.8 million in year 3. With funding limited to the most restrictive population in which patients were defined as adults with diabetes on IIT requiring eight or more daily test strips (i.e., subgroup iv), the annual net budget impact would only increase from $53,970 in year 1 and to $191,133 in year 3. The detailed results are presented in Table 23. No additional scenario analyses were undertaken.

## Table 23: Summary of Results for INESSS

| Eligible populations | Quebec: Results summary | | | |
|---|---|---|---|---|
| | Total cost of current scenario (i.e., SMBG only) | Total cost of new scenario (i.e., Introduction of FGMS) [b] | Annual budget impact | 3-year budget impact |
| • All individuals (T1D and T2D) on insulin therapy (n = 74,213) | Years 1 to 3: NR | Year 1: $81,155,927<br>Year 2: $109,301,908<br>Year 3: $131,076,127 | Year 1: $18,638,466<br>Year 2: $45,336,619<br>Year 3: $65,687,224 | $129,662,308 |
| • T1D – IIT (n = 10,597) | Years 1 to 3: NR | Year 1: $15,136,895<br>Year 2: $20,565,800<br>Year 3: $24,236,484 | Year 1: $3,569,979<br>Year 2: $8,948,345<br>Year 3: $12,576,050 | $25,094,375 |
| • T2D – IIT (n = 33,300) | Years 1 to 3: NR | Year 1: $43,027,140<br>Year 2: $59,140,633<br>Year 3: $66,150,334 | Year 1: $12,445,846<br>Year 2: $28,190,692<br>Year 3: $34,851,591 | $75,488,130 |
| • All individuals on IIT who required ≥ 8 daily test strips[a] | Years 1 to 3: NR | Year 1: $1,899,444<br>Year 2: $1,995,385<br>Year 3: $2,064,119 | Year 1: $53,970<br>Year 2: $135,554<br>Year 3: $191,133 | $380,658 |

Source: Adapted from INESSS BIA report (Table 5).[13]

BIA = budget impact analysis; FGMS = flash glucose monitoring system; IIT = intensive insulin therapy; NR = not reported; SMBG = self-monitoring of blood glucose; T1D = type 1 diabetes; T2D = type 2 diabetes.

[a] Unspecified total subpopulation.

[b] The INESSS finds that introducing the FGMS would result in additional expenditures (i.e., reported budget impact of including the FGMS on the list of medications for adults with T1D or T2D treated with insulin therapy [page 25-26]).

**HQO:** The net budget impact of introducing FGMS in Ontario for all patients with T1D and patients with T2D who require IIT was calculated as the cost difference between the current environment and the new environment. The eligible populations considered in the current and new environments included (i) persons with T1D on IIT (unspecified method) and (ii) persons with T2D on IIT (via multiple daily insulin injections or CSII). With a combined population of individuals with T1D and persons with T2D on IIT, the introduction of FGMS in Ontario would result in an annual expenditure of $14.6 million (year 1) to $38.6 million (year 5). Among individuals with T1D requiring IIT, the annual net budget impact was estimated to be $2.9 million in year 1 and would increase to $7.7 million in year 5. Among individuals with T2D requiring IIT, the annual net budget impact was $11.7 million in year 1 and increased to $30.9 million in year 5. The total five-year budget impact for the combined population of persons with T1D and individuals with T2D was approximately $146 million. The detailed results are presented in Table 24.

## Table 24: Summary of Results for HQO

| Eligible populations | Ontario: Results summary | | | |
|---|---|---|---|---|
| | Total cost of current scenario (i.e., SMBG only) | Total cost of new scenario (i.e., Introduction of FGMS) | Annual budget impact | 5-year budget impact[a] |
| (i) T1D on IIT (unspecified method) (n = 28,537) | Year 1: $7,640,943<br>Year 2: $10,528,830<br>Year 3: $13,577,063<br>Year4: $16,815,072<br>Year 5: 20,211,641 | Year 1: $10,542,979<br>Year 2: $14,527,689<br>Year 3: $18,748,821<br>Year 4: $23,201,450<br>Year 5: $27,888,039 | Year 1: $2,902,036<br>Year 2: $$3,998,858<br>Year 3: $5,160,758<br>Year 4: $6,386,378<br>Year 5: $7,676,398 | $14,062,776 |
| (ii) T2D on IIT (via multiple daily insulin injections or CSII) (n = 61,263) | Year 1: $10,933,991<br>Year 2: $15,068,894<br>Year 3: $19,447,726<br>Year 4: $24,066,917<br>Year 5: $28,926,469 | Year 1: $22,630,095<br>Year 2: $31,188,108<br>Year 3: $40,250,982<br>Year 4: $49,811,329<br>Year 5: $59,869,149 | Year 1: $11,696,104<br>Year 2: $16,119.214<br>Year 3: $20,803,256<br>Year 4: $25,744,411<br>Year 5: $30,942,680 | $105,305,665 |
| | Combined population, T1D and T2D | | Year 1: $14,598,140<br>Year 2: $34,716,212<br>Year 3: $25,964,014<br>Year 4: $32,160,789<br>Year 5: $38,619,078 | $146,058,233 |

Source: HQO BIA Report (Table 14).[11]

BIA = budget impact analysis; CSII = continuous subcutaneous insulin infusion; FGMS = flash glucose monitoring system; IIT = intensive insulin therapy; SMBG = self-monitoring of blood glucose; T1D = type 1 diabetes; T2D = type 2 diabetes.

[a] CADTH calculated the five-year budget impact from Table 15, as this information was not reported in the HTA.

A series of scenario analyses were undertaken to estimate which factors would have the greatest affect on the net budget estimates:

- Expanding the target population to include all patients with T1D, and patients with T2D requiring IIT, on SMBG, with and without, ODB program coverage.
- Reimbursing the maximum number of blood glucose test strips for SMBG at 3,000 strips annually (or eight strips daily).
- Reimbursing blood glucose test strips for SMBG at 730 strips annually (or two strips daily).
- Expanding the target population to include all patients with T1D and patients with T2D requiring any type of insulin therapy (including but not limited to IIT), on SMBG.

- Restricting the target population to include only adults with T1D, and patients with T2D requiring IIT, on SMBG (i.e., excluded patients younger than 18 years of age).
- Including patients with diabetes at high risk of glycemic variability (excluding those with hypoglycemic unawareness).
- Funding four flash sensors yearly (i.e., FGMS used for eight weeks of the year).
- Funding eight flash sensors yearly (i.e., FGMS used for 16 weeks of the year).
- All costs associated with SMBG, beyond the ministry of health perspective.
- Lower price of one flash sensor ($70).
- Higher uptake rate of FGMS (from 50% in year 1 to 70% in year 5).
- Utilization of cheap strips, at $0.40 per test strip.

The analysis was found to be sensitive to inputs that had an impact on the market size (i.e., number of people eligible for FGMS), the frequency of self-testing associated with SMBG, and the price of flash sensors. The net budget impact was greater when patients who were ineligible for coverage by the ODB program were included in the target population and a smaller budget increase was observed when the size of the target population was reduced. In contrast, the net budget impact was smaller when the SMBG group was assumed to use the maximum number of test strips (n = 3,000 strips per patient yearly) allowed for reimbursement (since the incremental costs between interventions would be similar with an increase in costs of the reference scenario) or if funding was restricted to individuals with T1D (since the frequency of self-testing by SMBG is higher in individuals with T1D). Finally, if the number of flash sensors reimbursed were capped at four or eight sensors compared to the base case assumption of 26 sensors, the net budget impact would be reduced as the price of flash sensors would be lowered.[11] Furthermore, HQO conducted scenario analyses for specific populations that may derive important glycemic benefits with the use of FGMS (scenario 5 limiting to only adults with T1D, or with T2D requiring IIT, on SMBG; and scenario 6: expanding to include patients with diabetes at a high risk of glycemic variability [excluding those with hypoglycemic awareness]). The reimbursement of FGMS in scenario 5 resulted in a net budget impact of $13.3 million in year 1 to $35.1 million in year 5. In scenario 6, the reimbursement of FGMS in this specific population resulted in a net budget impact of $16.5 million in year 1 to $43.7 million in year 5.[11]

# Provincial Funding Recommendations

## Recommendations

The following section outlines the recommendation made to the provincial funding bodies with regards to FGMS device FreeStyle Libre. Both CSEMI and OHTAC recommended funding FGMS but have outlined some criteria.[12,13] A price condition was also identified in one of the recommendations.[13] Overall, the committees recommended funding FGMS only for patients aiming to optimize their insulin therapy and experiencing recurrent hypoglycemia despite frequent SMBG.[12,13] The detailed provincial recommendations are described below.

### HQO/OHTAC

Based on the guidance of OHTAC, HQO recommended publicly funding FGMS for the following two groups of patients:

- People with T1D who experience recurrent hypoglycemia despite frequent SMBG and efforts to optimize insulin management.
- People with T2D requiring IIT (multiple daily injections of insulin or CSII) who experience recurrent hypoglycemia despite frequent SMBG and efforts to optimize insulin management.[12]

### INESSS/CSEMI

In October 2018, INESSS evaluated FreeStyle Libre.[13] At that time, CSEMI recommended to add FreeStyle Libre to the list of the prescription drug insurance plan for self-monitoring of glycemia in patients on insulin therapy provided the economic burden is lessened. If the economic burden of funding FreeStyle Libre is not reduced for the province, CSEMI recommended that this FGMS be listed as an exceptional drug product for adults aged 18 years and older who have at least two years of experience in self-managing their diabetes and who meet the following three criteria:

- IIT
- frequent or severe hypoglycemia events
- necessity for blood glucose self-monitoring at least eight times daily.[13,14]

Of note, FreeStyle Libre is reimbursed in Quebec since July 2019; the RAMQ authorization form must be completed by the attending physician.[15] INESSS also added an implementation-related consideration in its recommendation; that is, training so that patients can master sensor application and learn how to interpret and use the information provided by the device. More specifically, the initial request is authorized for three months to evaluate patient capacity to use FreeStyle Libre and wear the sensor. Request to pursue treatment is authorized for maximum of twelve months if patients show a capacity to make an optimal use of FreeStyle Libre; that is at least 70% of the time.[13]

The recommendation from CSEMI was updated in April 2020 based on a change to the Health Canada labelling of August 2019 and that which no longer requires that patients have at least two years of experience in diabetes self-management.[16] The most recent funding recommendations therefore applies to persons with diabetes of minimum 18 years of age who meet the following three criteria:

- ITT (i.e., use of insulin pump therapy or greater than or equal to three insulin injections per day)

- frequent or severe hypoglycemic events
- necessity for blood glucose self-monitoring at least eight times daily.[16]

Initials request would now be authorized for six months (instead of three) to evaluate patient capacity to use FreeStyle Libre and wear the sensor. Requests to pursue treatment would be authorized for twelve months if patients show a capacity to make an optimal use of FreeStyle Libre; that is, at least 70% of the time.[16] The updated coverage criteria were implemented by RAMQ on April 29, 2020.[17]

## Reasons for the Recommendations

Respective provincial committees used specific framework to deliberate on the evidence on FGMS. Although FGMS demonstrated clinical benefit with respect to some glycemic outcomes, these findings were based on limited evidence both in terms of the quantity of available studies as well as their methodological quality which ranged from very low to moderate. However, patients and clinicians were highly supportive of the use of device, particularly due to its other benefits. This aspect was key for recommending the funding of FGMS. At the same time, based on the economic evaluations conducted in the HTA reports, there was acknowledgement of the potential high budget impact of funding FGMS.

### HQO/OHTAC

The OHTAC's decision to recommend funding of FGMS was based on determinants related to overall clinical benefit, consistency with expected societal and ethical values, cost-effectiveness, and feasibility of adoption into health system. Based on moderate quality evidence (GRADE), FGMS likely reduced the mean time spent in hypoglycemia, and the mean number of daily hypoglycemia events compared to SMBG, in adults with T1D and in adults in T2D requiring IIT. Based on moderate quality evidence (GRADE), FGMS likely reduced the mean time spent above the target glucose range, and increase the mean time spent in the target glucose range compared with SMBG, in adults with T1D. These outcomes were considered important to people with diabetes. However, no evidence was identified on the effectiveness of FGMS in reducing diabetes vascular complications such as myocardial infarction or kidney damage. Few adverse events were reported. The lived experience of adults with T1D or T2D and parents of children with T1D or T2D was also considered, as they described the physical, social, and safety benefits of FGMS. Consulted patients believed that FGMS improved their blood glucose control; and they desired an increase access to FGMS for people with T1D and T2D. OHTAC considered that adopting FGMS would be "congruent with societal values for better health management" and "consistent with ethical values, including beneficence." However, the committee noted that cost of FGMS was relatively high, especially for people who do not self-monitor their blood glucose several times daily. It was also recognized that there is lack of evidence regarding long-term outcomes and an inability to accurately estimate cost-effectiveness over the long-term. The committee agreed that FGMS would be useful for people with diabetes who monitor their blood glucose several times daily but still experience hypoglycemia.[12]

### INESSS/CSEMI

The members of the CSEMI recommended funding FGMS (with a price condition and some criteria — see above) based on the economic burden, the clinical evidence, as well as patient and clinician consultation. Consultation data with regard to the many potential advantages of using FGMS included "lesser discomfort caused by finger pricking, professional and personal convenience, and greater flexibility in illness management." It was

also recognized that it is suboptimal and contrary to the current recommendations on good clinical practice, for patients — particularly those under IIT — to conduct capillary blood testing. Although clinical evidence shows statistically significant differences in terms of time spent in hypoglycemia, number of hypoglycemia events and time spent in the glycemic target, the quality of evidence is considered to be low and the actual clinical effects of the results observed are seen as highly uncertain. Further, compared to SMBG, RCTs did not demonstrate any improvement in A1C with the use of FGMS. Neither were the studies able to assess the effect of FGMS on: i) the incidence of severe hypoglycemic events, ii) the long-term effects on preventing diabetes (vascular) complications, iii) the use of health care resources or, iv) demonstrate positive effect on the overall quality of life of patients. FGMS has an acceptable safety profile, but the frequency of injection-site reactions was of concern.[13]

Members concluded that the incremental therapeutic value of FGMS compared to SMBG was not demonstrated, and that the FGMS was more costly that SMBG. Hence, FGMS was not considered an efficient option. The budget impact of FGMS was noted to be very significant. In developing their recommendation, CSEMI determined that the economic burden of this new technology needed to be lessened, otherwise the device would only be considered as an exceptional drug product in the RAMQ formulary. However, members recognized that FGMS, compared with SMBG, offered greater autonomy to patients in the management of their medical condition. The incremental cost of FGMS was considered acceptable for patients under IIT whose diabetes is hard to control or patients who suffer frequent or severe hypoglycemia and require to measure their glycemia at least eight times daily.[13]

## Stakeholder Feedback

The draft version of this Technology Review report was posted for 10 days at the end of May and early June 2020 to solicit feedback from CADTH stakeholders. Feedback from 14 different individuals or organizations, including patient organizations as well as pharmaceutical and medical device companies, were received during this time period. All feedback was reviewed; comments received were considered by the project team if they were related to issues deemed to be within the scope of this report.

In short, two main streams of comments were received. The first related to the publication date of the literature evaluated in this report, given the INESSS and HQO HTA reports were published at the end of 2018 and 2019, respectively. This limitation was acknowledged by CADTH and explanations were provided in the original draft report that was posted for stakeholder feedback. To further clarify, the objective of this report was to synthesize the information contained in the two HTA reports recently released by the only two Canadian jurisdictions that assessed FGMS device FreeStyle Libre for the purpose of public funding. The scope of this report also involved summarizing the reimbursement recommendations from Ontario and Quebec. If CADTH was to update this work, it would mean conducting de novo clinical and economic evaluations, as opposed to synthesizing the content of existing work. Furthermore, CADTH had also participated to the HTA work done by HQO. The current approach was therefore developed in order to avoid duplication of publicly funded work and provide needed information to jurisdictions in a timely fashion as redoing and updating the HTAs would have potentially required several additional months of work. The development of advice by an expert panel to further assist jurisdictional drug programs with the potential implementation of the recent funding recommendations was another important component of this project. Some stakeholders indicated that while there may not be many new RCTs available since the publication of the two provincial HTA reports, a number of real-world effectiveness studies have recently been published. CADTH acknowledges that these studies may provide a supplemental and relevant perspective on the impact of FGMS device FreeStyle Libre on the care of patients with diabetes. However, for the aforementioned reasons, it was not possible to consider these studies for inclusion without redoing the whole evaluation and further delaying the opportunity to provide much needed information to jurisdictional drug plans.

The second stream of feedback received from stakeholders related to the absence of patients engagement process in the CADTH report. CADTH values and fosters engagement of patients in its HTA work and recently developed a *formal framework* for that purpose. However, no formal patient engagement process was conducted by CADTH for this project as HQO and INESSS had already formally collected such information. In addition, the CADTH project did not involve the Canadian Drug Expert Committee (CDEC) developing a new recommendation on the funding of FreeStyle Libre. Rather, CADTH convened a small panel of experts to assist with developing an advice to facilitate the implementation of the existing provincial funding recommendations; this advice is available on CADTH website in the form of an Implementation Advice report. In addition, the original draft version of the Technology Review report did indicate that the patient engagement process respectively conducted by HQO and INESSS revealed that there was wide support among patients and clinicians consulted by HQO and INESSS for the use of FGMS. Use of FGMS was reported by these groups to have physical, emotional, and social benefits. Reduction in the need for, and having an alternative to finger pricks, and the ability to see blood glucose trends to better manage their diabetes was widely recognized by patients. Of note, during the stakeholder feedback solicitation period, CADTH received submissions from several

individual patients and patient groups, including testimonies from practitioners treating Canadian Indigenous patients with diabetes. All feedback received from these individuals and groups supported wider access to FGMS technology and suggested the use of FGMS FreeStyle Libre leads to improved disease management and glycemic outcomes. Some clinicians provided feedback indicating that reducing rates of hypoglycemia is in itself a clinically meaningful outcome for their patients, even if A1C is not lowered. Some stakeholders further commented that hypoglycemia in patients with diabetes is a frequent reason for emergency department visits; some of these visits leading to hospitalization. He noted that such encounters with the health care system can be associated with significant expenditures. Other feedback received from a pharmacist noted reports of overestimation of hypoglycemia (false lows) with FGMS among patients she services; this was also reported by some of the patients consulted by INESSS.

## Discussion

FGMS is a relatively new technology; it is considered to be an alternative to SMBG for the monitoring of glycemia in patients with diabetes. FreeStyle Libre, the first FGMS device to be marketed in Canada, is gaining awareness within the diabetes community. Two publicly funded drug programs in Canada, that is INESSS and HQO (the latter in collaboration with CADTH), have conducted their own HTA to inform their local reimbursement decision on FreeStyle Libre. As awareness of FGMS increases, the other publicly funded drug programs in Canada are also interested in using information from these HTAs to inform their own policy decisions. The purpose of this report was to synthesize the evidence from the two recently completed provincial HTAs that compared FGMS to SMBG as well as summarize the funding recommendations from the related recommending bodies from these two provinces; that is, CSEMI in Quebec and OHTAC in Ontario.

Overall, both HTA reports concluded that FGMS offers additional therapeutic value for some glycemic outcomes, compared to SMBG. Clinical benefits mainly consisted of improvement in the number and duration of hypoglycemic events in patients with T1D and patients with T2D on ITT, as well as improvement in the time spent within the target glucose range in patients with T1D. The clinical benefit was not reported consistently across the two main types of diabetes assessed in these reports. Little to no improvement was seen in A1C, severe hypoglycemia (i.e., requiring assistance), and quality of life. Other important benefits from FGMS reported in these HTAs are in terms of increased comfort (i.e., avoidance of finger pricking), convenience of use, ability to easily perform multiple tests per day and trend results from these measurements, as well as increased treatment satisfaction.

The two provincial HTAs also evaluated the budget impact of funding FGMS. Given it appears that SMBG is currently the method most widely used by patients with diabetes for monitoring glycemia, this method was selected for the reference scenario in the BIAs. With the introduction of FGMS, the expectation is that some patients with diabetes would shift from using SMBG to using FGMS to monitor their glycemia. Estimated treatment costs were found to be similar between the BIAs included in this review. Therefore, based on the costing data presented in the HQO[11] report, drug programs considering reimbursing FGMS could expect an added annual cost ranging from $627 per patient with T1D to $1,241 per patient with T2D if they switched to FGMS, compared to if patients remained on SMBG. This is inclusive of the cost of the flash sensor and SMBG for patients with T1D or T2D. It could be, however, that the total budget impact scenarios included in the HQO report might be exceeded in reality given the current ODB reimbursement criteria are different from the

recommended criteria; that is, FreeStyle Libre is currently reimbursed in Ontario provided patients are on insulin and have a valid prescription from a physician or nurse practitioner.

Based on their respective HTA work, INESSS/CSEMI and HQO/OHTAC recommended funding FGMS, but with a price condition (in Quebec) and some clinical criteria (in Ontario and Quebec [if no reduction of the economic burden of funding FreeStyle Libre in the latter province]). In general, these provinces recommended FGMS for patients with T1D aiming to optimize their insulin therapy, and patients with T2D on IIT who are at risk of frequent and severe hypoglycemia despite frequent testing of their glycemia. The key factor considered in recommending FGMS appears to be related to the perceived physical, emotional, and social benefits of FGMS. These mainly included reduction in finger pricks and ability to monitor blood glucose trends, as described by patients and clinicians who were consulted as part of the provincial HTAs. Patients reported cost as the greatest barrier to accessing FGMS, but it was noted that FGMS was less costly than CGM. The lack of alarm for low glucose level was however highlighted as a disadvantage of FGMS over CGM. Importantly, education and training were considered necessary for the optimal use of FGMS in the two HTA reports.

While this Technology Review report provides a condensed version of currently available Canadian provincial HTAs, it is important to mention a few key limitations of this work. First, this evidence synthesis is solely based on two HTA reports published at the end of 2018 (INESSS) and 2019 (HQO). Additional literature search or appraisal of the studies included in these HTAs was not performed.

There are a limited number of studies comparing FGMS with SMBG. The majority of the clinical evidence included in the HTA reports is based on the same two RCTs, one each for T1D and T2D. A number of observational studies were also identified. However, there is limited detailed information available in the HTA reports for the majority of these studies (discussed in the INESSS report, in particular) and about the quality of these studies. With respect to special populations, there are very little to no included studies on FGMS for pregnant women, people with diabetes who do not use insulin, or children younger than 13 years of age.

There are other HTAs identified by INESSS but none are Canadian. The HQO HTA report identified three ongoing randomized trials (NCT03522870, NCT03570138, NCT02776007) and one completed RCT (NCT03182842), but the results of the latter were not published at the time of the HQO report publication. These studies compared the effectiveness of FGMS with SMBG. Of note, the evidence synthesis presented in this report is on FGMS in general, but the RCTs and the observational studies (included in the HTA reports) were conducted on the first-generation of FreeStyle Libre. Hence, the results may not be generalizable to upcoming versions of FreeStyle Libre or other FGMS devices, as new devices or versions of existing devices may have different accuracy levels (error margins) as well as other features.

The HTAs rated the quality of evidence to be very low to moderate and there was variation in how the same evidence was rated (using GRADE) in the INESSS and HQO HTA reports. The RCTs imputed missing data by last observation carried forward, potentially introducing biases. The HQO report clarified that they were unable to determine the extent of this imputation bias. The report also highlighted that there were gaps in accurately comparing the safety of the FGMS and SMBG given too few events reported in the included studies and the failure of one study to report events with SMBG. Further, the quality of evidence for some of the outcomes was rated to be “very low’ to ‘low;” and there were concerns about the risk of bias of included studies.

There is lack of research on the long-term effectiveness of FGMS and its impact on diabetes complications. Indeed, the INESSS and HQO HTA reports noted that available data did not allow for an evaluation of the effect of FGMS on the long-term complications of diabetes and the use of health care resources. HQO also noted that no studies were identified that assessed the effect on vascular complications of switching from SMBG to FGMS. With respect to glycemic outcomes, studies reported a limited number of severe hypoglycemic events, which are rare events, but constitute a parameter with a greater degree of objectivity. Although no significant difference was observed between FGMS and SMBG with respect to severe hypoglycemic events, this could have been a result of small sample size, as noted by INESSS. There remained uncertainty over the clinical significance or interpretation of surrogate outcomes such as A1C, glucose variability and time in range.

## Conclusion

FGMS is a new option recently available to monitor glycemia for Canadians living with diabetes. Publicly funded drug programs in Canada are considering information from HTA work to guide their reimbursement decisions for this technology. Information from HTAs conducted by two provincial organizations; that is, HQO in Ontario and INESSS in Quebec, reveals that evidence supporting the effect of FGMS is still limited in quantity and quality; the latter generally ranged from very low to moderate. The therapeutic benefits of FGMS revealed by this evidence mainly consist of improvements in the frequency and duration of hypoglycemia events in patients with T1D, and patients with T2D using IIT, as well as improvements in the time spent within the target glucose range in patients with T1D. Other important benefits from FGMS reported in the provincial HTAs are in terms of increased comfort (avoidance of finger pricking), convenience of use, ability to easily perform multiple tests per day and conduct trend analysis of test results to improve disease management, as well as increased treatment satisfaction.

From an economic perspective, compared to reimbursing test strips for SMBG, public funding of FGMS is most likely expected to be associated with increased expenditures for drug programs. An estimate derived from the HQO's BIA suggests that drug programs considering reimbursing FGMS could expect an added annual cost ranging from $627 per patient with T1D to $1,241 per patient with T2D who switches to FGMS, compared to if patients were to remain on SMBG to monitor their glycemia. Both HTA reports concluded that the budget impact of introducing FGMS is sensitive to the frequency of self-testing associated with SMBG, such that the incremental costs of FGMS is lower in scenarios in which SMBG users would require a higher frequency of self-testing.

Committees from the two provinces that conducted these HTAs, i.e., OHTAC in Ontario and CSEMI in Quebec, both recommended funding FGMS. These recommendations were however generally assorted with some clinical criteria. Specifically, FGMS is recommended for patients with T1D, and patients with T2D requiring IIT, who are at risk of frequent and severe hypoglycemia. Frequent glycemia testing is also generally needed, and one province, Quebec, includes the necessity of testing glycemia at least eight times per day to be eligible for FGMS. This same province further noted that price reduction would be required to reimburse the FGMS device FreeStyle Libre as a full benefit item to persons with diabetes who are using insulin. Of note, education and training were considered necessary for optimal use of FGMS in both Ontario and Quebec.

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# Appendix 1: Clinical Evidence

## Table 25: Reports and Studies Included in the Two HTA Reports on FGMS[11,13]

| First author (year) *Country* | Study design | | Diabetes type | Baseline glucose | Age | Sample size | Follow-up period | Other inclusion criteria | Exclusion criteria | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bolinder (2016) (IMPACT)<br><br>*Sweden Austria Germany Spain Netherlands* | non-blinded RCT<br><br>Parallel group<br>1:1 | | T1D 1 | A1C < 7.5% | > 18 yrs | N = 239 | 6 months | diagnosed with T1D > 5 years,<br>on current insulin treatment ≥ 3 months<br>A1C concentration 58 mmol/mol<br>Not hypoglycemia unaware<br>Not having diabetic ketoacidosis or MI in the last 6 months<br>No known allergy to medical grade adhesives<br>Not using CGM within the last 4 months<br>Not currently using sensor-augmented insulin pumps<br>Not pregnant, nor planning to become pregnant<br>Not receiving oral steroid therapy | diagnosed with hypoglycemia unawareness<br>diabetic ketoacidosis<br>MI in last 6 months<br>used CGM within preceding 4 months<br>were pregnant or planning to<br>receiving oral steroid therapy | FGMS<br>(n = 119 at time 0; 110 at 6 months) | SMBG<br>(n = 120 at time 0; 101 at 6 months) | Primary: time < 3.9 mmol/L<br><br>Secondary:<br>A1C at 6 months<br><br>Time spent < 3.1 mmol/L, < 2.2 mmol/L<br><br>Frequency of episodes<br>< 3.9 mmol/L<br>< 3.1 mmol/L<br>< 2.2 mmol/L<br><br>Time spent > 10.0 mmol/L and > 13.3 mmol/L<br><br>Time spent in glycemic target<br>Number of glucose measurements performed<br><br>System utilization<br>Change in treatment satisfaction |
| Haak (2017) (REPLACE)<br><br>*France* | non-blinded RCT | | T2D | A1C 7.5% to 12.0% | > 18 yrs | N = 224 | 6 months | Not pregnant Using insulin for ≥ 6 months (prandial only or prandial and basal intensive | Hypoglycemic unawareness | FGMS<br>(n = 149 at time 0; 139 at 6 months) | SMBG<br>(n = 75 at time 0; 62 at 6 months) | Primary:<br>A1C at 6 months |

| First author (year)<br><br>*Country* | Study design | | Diabetes type | Baseline glucose | Age | Sample size | Follow-up period | Other inclusion criteria | Exclusion criteria | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Germany*<br>*UK* | Parallel group<br>2:1 | | | | | | | insulin therapy or insulin pump therapy)<br>Not having a total daily dose of insulin ≥ 1.75 u/kg at study entry<br>Not having severe hypoglycemia<br>Not having diabetic ketoacidosis<br>Not having hyperosmolar-hyperglycemic state in the last 6 months<br>No known allergy to medical grade adhesives<br>Not using CGM within the last 4 months<br>Not receiving steroid therapy | allergy to medical grade adhesives<br>pregnancy<br>taking oral steroids<br>MI<br>CGM use | | | Secondary:<br>Time spent in glycemic target<br>Time spent<br>< 3.9 mmol/L<br>< 3.1 mmol/L<br>Frequency of episodes<br>< 3.9 mmol/L<br>< 3.1 mmol/L<br><br>Time spent<br>> 10.0 mmol/L<br>and<br>> 13.3 mmol/L<br>Number of glucose measurements performed<br><br>System utilization<br>Change in treatment satisfaction |
| Oskarsson (2018)<br><br>*Sweden*<br>*Austria*<br>*Germany*<br>*Spain*<br>*Netherlands* | | *subgroup analysis of Bolinder 2016*<br>n = 82 (only patients on multiple insulin injections) | | | | | | | | | | |
| Mitsuishi (2017)<br>*Japan* | Observational<br>before – after study | | T1D<br>T2D | Mean A1C 7.8% | 18-80 years | | Not reported | Not pregnant, nor likely to become pregnant<br>Not receiving dialysis<br>Not allergic to medical adhesives | | | | |

| First author (year) *Country* | Study design | | Diabetes type | Baseline glucose | Age | Sample size | Follow-up period | Other inclusion criteria | Exclusion criteria | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Not using insulin pumps equipped with CGM | | | | |
| Al Hayek (2017)<br>*Saudi Arabia* | Observational before – after study | | T1D | not reported | 13-19 years | | 3 months for flash but not reported for SMBG | Not diagnosed with dermatological disorders within the last 6 months<br>No severe or unstable medical conditions<br>No severe hypoglycemia that requires third-party assistance<br>No diabetic ketoacidosis, nor hyperosmolar-hyperglycemic state | | | | |
| Moreno-Fernandez (2018)<br>*Spain* | Observational parallel group study | | T1D | A1C ≤ 7.8% | 18-65 yrs | | 6 months | Diagnosed with type 1 diabetes for at least 6 months<br>Not pregnant or planning pregnancy<br>Not breastfeeding<br>Naive to FGM | | | | |

CGM = continuous glucose monitor; CSII = continuous subcutaneous insulin infusion; DK = diabetic ketoacidosis; DTSQ = Diabetes Treatment Satisfaction Questionnaire; FGMS=flash glucose monitoring system; A1C = glycated hemoglobin; HFS = Hypoglycemia Fear Survey; MDI = Multiple Daily Injections; MI = myocardial infarction; RCT = randomized controlled trial; SMBG = self-monitoring of blood glucose; T1D = type 1 diabetes; T2D = type 2 diabetes; TIR = time in range.

# Appendix 2: Detailed Information on Included RCTs

## Table 26: Study Details and Results from the RCT by Bolinder et al., 2016[13]

| Study | Population | Intervention | Measures |
|---|---|---|---|
| **Bolinder et al., 2016 (IMPACT)**<br><br>**Design**: RCT, comparing FreeStyle Libre to capillary blood glucose testing<br><br>**Non-masked**<br><br>**Context**:<br>23 European diabetes centres<br><br>**Funded by the manufacturer** | **Patients**: adults with type 1 diabetes, A1C < 7.5%, non-impaired awareness of hypoglycemia, on current insulin treatment ≥ 3 months<br><br>**Recruited: n** = 239<br><br>**Discontinued**:<br>Intervention arm: 9<br>Control arm: 19<br>Mean age: 42 years<br>BMI: 25<br>A1C: 6.7%<br><br>**Intervention**<br>Time 0: n = 119<br>At 6 months : n = 110<br><br>**Control**<br>Time 0: n = 120<br>At 6 months: n = 101<br><br>**Exclusion criteria:**<br>Hypoglycemic unawareness, allergy to medical grade adhesives, pregnancy, taking oral steroids, myocardial infarction, CGM use | **Parallel group**<br>**Intervention:** FGMS<br>**Control:**<br>CBG testing<br><br>**Duration of treatment:**<br>6 months | **Primary:** time < 3.9 mmol/L<br><br>**Secondary**: A1C at 6 months<br><br>Time spent<br>< 3.1 mmol/L,<br>< 2.2 mmol/L<br><br>Frequency of episodes<br>< 3.9 mmol/L<br>< 3.1 mmol/L<br>< 2.2 mmol/L<br><br>Time spent<br>> 10.0 mmol/L and 13.3 mmol/L<br><br>Time spent in glycemic target<br><br>Number of glucose measurements performed<br><br>System utilization<br><br>Change in treatment satisfaction |

A1C = glycated hemoglobin; BMI = body mas index; CBG = capillary blood glucose; CGM = continuous glucose monitoring; FGMS = flash glucose monitoring system ; RCT: randomized clinical trial

## Table 27: Glucose < 3.9 mmol/L over 24 hours

| | Time 0 (SD) | | at 6 months (SD) | | P | Difference, % |
|---|---|---|---|---|---|---|
| | FGMS (n = 119) | CBG (n = 119) | FGMS (n = 119) | CBG (n = 119) | | |
| Time (hours) | 3.38 (2.31) | 3.44 (2.62) | 2.03 (1.93) | 3.27 (2.58) | < 0.0001 | –38.0 |
| Events | 1.81 (0.90) | 1.67 (0.80) | 1.32 (0.81) | 1.69 (0.83) | < 0.0001 | –5.8 |

CBG = capillary blood glucose; FGMS = flash glucose monitoring system; SD = standard deviation

## Table 28: A1C

| | Time 0 (SD) | | at 6 months (SD) | | P |
|---|---|---|---|---|---|
| | FGMS (n = 119) | CBG (n = 119) | FGMS (n = 119) | CBG (n= 119) | |
| A1C | 6.79 (0.52) | 6.78 (0.64) | 6.94 (0.65) | 6.95 (0.66) | 0.9556 |

A1C = glycated hemoglobin; CBG = capillary blood glucose; FGMS = flash glucose monitoring system; SD = standard deviation.

## Table 29: Glucose < 3.1 mmol/L over 24 hours

| | Time 0 (SD) | | at 6 months (SD) | | P | Difference, % |
|---|---|---|---|---|---|---|
| | FGMS (n = 119) | CBG (n = 119) | FGMS (n = 119) | CBG (n = 119) | | |
| Time (hours) | 1.59 (1.42) | 1.77 (1.86) | 0.80 (0.96) | 1.65 (1.97) | < 0.0001 | –50.3 |
| Events | 0.96 (0.65) | 0.92 (0.73) | 0.56 (0.55) | 0.92 (0.74) | < 0.0001 | –41.3 |
| Time, night (hour) | 0.62 (0.60) | 0.75 (0.83) | 0.31 (0.43) | 0.66 (0.080) | < 0.0001 | –48.9 |
| Events, night | 0.34 (0.27) | 0.36 (0.34) | 0.19 (0.24) | 0.30 (0.28) | 0.0005 | –34.9 |

CBG = capillary blood glucose; FGMS = flash glucose monitoring system; SD = standard deviation

## Table 30: Glucose 3.9 mmol/L – 10.0 mmol/L over 24 hours

| | Time 0 (SD) | | at 6 months (SD) | | P | Difference, % |
|---|---|---|---|---|---|---|
| | FGMS (n = 119) | CBG (n = 119) | FGMS (n = 119) | CBG (n = 119) | | |
| Time (hour) | 15.0 (2.5) | 14.8 (2.8) | 15.8 (2.9) | 14.6 (2.9) | 0.0006 | NA |

CBG = capillary blood glucose; FGMS = flash glucose monitoring system; NA = not applicable; SD = standard deviation.

## Table 31: Glucose Level Variability

| | Time 0 (SD) | | at 6 months (SD) | | P | Difference, % |
|---|---|---|---|---|---|---|
| | FGMS (n = 119) | CBG (n = 119) | FGMS (n = 119) | CBG (n = 119) | | |
| CV% | 43.0 (7.0) | 42.5 (6.6) | 37.6 (5.7) | 41.8 (6.8) | < 0.0001 | NA |

CBG = capillary blood glucose; CV = coefficient of variation; FGMS = flash glucose monitoring system; NA = not applicable; SD = standard deviation.

## Table 32: Study Details and Results from the RCT by Haak et al., 2017[13]

| Study | Population | Intervention | Measures |
|---|---|---|---|
| **Haak et al., 2017b (REPLACE)**<br><br>**Design**: RCT<br>Comparing FreeStyle Libre to capillary blood glucose testing<br><br>**Non-masked**<br><br>**Context**: 26 European diabetes centres<br><br>**Funded by the manufacturer** | **Patients**: adults with type 2 diabetes, A1C 7.5% to 12.0%, non-impaired awareness of hypoglycemia, insulin treatment for ≥ 6 months and on current insulin regimen ≥ 3 months<br><br>**Recruited**: n = 224<br><br>**Discontinued**:<br>Intervention arm: 10<br>Control arm: 13<br>Mean age: 59 years<br>BMI: 33<br>A1C: 8.7%<br><br>**FreeStyle Libre** | **Parallel group** 2:1<br><br>**Intervention**: FGMS<br><br>**Control**: CBG testing<br><br>**Duration of treatment**:<br>6 months | **Primary**: A1C at 6 months<br><br>**Secondary**:<br>Time spent in glycemic target<br><br>Time spent<br>< 3.9 mmol/L<br>< 3.1 mmol/L<br><br>Frequency of episodes<br>< 3.9 mmol/L<br>< 3.1 mmol/L<br><br>Time spent<br>> 10.0 mmol/L and<br>> 13.3 mmol/L |

| Study | Population | Intervention | Measures |
|---|---|---|---|
| | Time 0: n = 149<br>At 6 months: n = 139<br><br>**Control**<br>Time 0: n = 75<br>At 6 months: n = 62<br><br>**Exclusion criteria:**<br>Hypoglycemic unawareness; allergy to medical grade adhesives, pregnancy, taking oral steroids, myocardial infarction, CGM use, total daily dose of insulin: ≥ 1.75 u/kg | | Number of glucose measurements performed<br><br>System utilization<br><br>Change in treatment satisfaction |

A1C = glycated hemoglobin; BMI = body mas index; CBG = capillary blood glucose; CGM = continuous glucose monitoring; FGMS = flash glucose monitoring system; RCT: randomized clinical trial

## Table 33: A1C

| | Time 0 (SD) | | at 6 months (SD) | | P |
|---|---|---|---|---|---|
| | FGMS (n = 149) | CBG (n = 75) | FGMS (n = 149) | CBG (n = 75) | |
| A1C | 8.65 (1.01) | 8.75 (0.98) | 8.37 (0.83) | 8.34 (1.14) | 0.8222 |

A1C = glycated hemoglobin; CBG = capillary blood glucose; FGMS = flash glucose monitoring system; SD = standard deviation.

## Table 34: Glucose 3.9 mmol/L — 10.0 mmol/L over 24 hours

| | Time 0 (SD) | | at 6 months (SD) | | P | Difference, % |
|---|---|---|---|---|---|---|
| | FGMS (n = 149) | CBG (n = 75) | FGMS (n = 149) | CBG (n = 75) | | |
| Time (hours) | 13.9 (4.5) | 13.5 (5.2) | 13.6 (4.6) | 13.2 (4.9) | 0.7925 | 1.1 |

CBG = capillary blood glucose; FGMS = flash glucose monitoring system; SD = standard deviation.

## Table 35: Glucose < 3.9 mmol/L over 24 hours

| | Time 0 (SD) | | at 6 months (SD) | | P | Difference, % |
|---|---|---|---|---|---|---|
| | FGMS (n = 149) | CBG (n = 75) | FGMS (n = 149) | CBG (n = 75) | | |
| Time (hours) | 1.30 (1.78) | 1.08 (1.58) | 0.59 (0.82) | 0.99 (1.29) | 0.0006 | –43.1 |
| Events | 0.64 (0.63) | 0.63 (0.66) | 0.38 (0.45) | 0.53 (0.59) | 0.0164 | –27.7 |

CBG = capillary blood glucose; FGMS = flash glucose monitoring system; SD = standard deviation.

## Table 36: Glucose < 3.1 mmol/L over 24 hours

| | Time 0 (SD) | | at 6 months (SD) | | P | Difference, % |
|---|---|---|---|---|---|---|
| | FGMS (n = 149) | CBG (n = 75) | FGMS (n = 149) | CBG (n = 75) | | |
| Time (hours) | 0.59 (1.13) | 0.38 (0.83) | 0.19 (0.37) | 0.37 (0.69) | 0.0014 | –53.1 |
| Events | 0.34 (0.50) | 0.27 (0.44) | 0.14 (0.24) | 0.24 (0.36) | 0.0017 | –44.3 |
| Time, night (hours) | 0.27 (0.58) | 0.18 (0.35) | 0.09 (0.22) | 0.19 (0.40) | 0.0032 | –58.1 |
| Nocturnal events | 0.15 (0.23) | 0.13 (0.20) | 0.06 (0.13) | 0.13 (0.21) | 0.0012 | –53 |

CBG = capillary blood glucose; FGMS = flash glucose monitoring system; SD = standard deviation.

# Appendix 3: Budget Impact Analyses - Eligible Populations

## Table 37: Definition of Target Population and Determination of Market Size of the Eligible Populations for Ontario and Quebec (Year 1)

| ON[11] | | | QC[13] | | |
|---|---|---|---|---|---|
| **Target Population:** Patients with T1D and T2D requiring IIT[a]<br>**Subgroups:**<br>(i) T1D — IIT (unspecified); (n = 28,537)<br>(ii) T2D — IIT (via multiple daily insulin injections or CSII); (n = 61,263) | | | **Target population:** Patients with diabetes, aged 18 years and older, on insulin therapy<br>**Subgroups:**<br>(i) All individuals (T1D and T2D) on insulin therapy (n = 74,213)<br>(ii) T1D — IIT; (n = 10,597) ; (iii) T2D — IIT; (n = 33,300)<br>(iv) All individuals on IIT who required ≥ 8 daily test strips; (n = unspecified) | | |
| **Approach to derive population size for each subgroup** | | | | | |
| A2. Projected Ontario Population (2018), *n* | 14,000,100 | | A3. Quebec Population (2016), *n* | 8,164,361[b] | |
| B2. Projected prevalence of diabetes in Ontario (2016), *%* | 11.12 | | B3. Projected prevalence of diabetes in Quebec (2015/16), % | 7.8% | |
| C2. Projected Ontario population with diabetes, *n (A2 x B2)* | 1,557,256 | | C3. Projected Quebec population with diabetes (2015/16), *n* (A3 x B3) | 630,530 | |
| | | | **Subgroup (i): All individuals (T1D and T2D) on insulin therapy** | | |
| | | | D3. Projected population on insulin therapy using test strips, *n* | 74,213 | |
| | **Subgroup (i) and (ii): T1D and T2D on IIT[c]** | | | **Subgroup (ii) and (iii): T1D and T2D on IIT[c]** | |
| | **T1D on IIT** | **T2D on IIT** | | **T1D IIT** | **T2D IIT** |
| D2. %, by diabetes type | 6% | 94% | E3. %, by diabetes type | 24.1% | 75.9% |
| E2. Projected population by diabetes type, *n (C2 x D2)* | 93,435 | 1,463,821 | | | |
| F2. % treated with IIT[c] (NOTE: T2D only) | NA | 10% | F3. Population treated with multiple injections of insulin using test strips, *n* | 43,897 | |
| G2. Projected population requiring IIT *(E2 x F2)* | NA | 146,382 | G3. Projected population requiring IIT, *n* (*E3 X F3)* | **10,597** | **33,300** |
| H2. % Eligible for FGMS | 65% | 80% | | | |
| I2. Projected population suitable for FGMS, *n* (*G2* x *H2*) | 60,733 | 117,106 | | | |

| ON[11] | | | QC[13] | |
|---|---|---|---|---|
| 0 to 24 years of age, *n* | 16,702 | 1,757 | | |
| 25 to 64 years of age, *n* | 36,257 | 62,886 | | |
| ≥ 65 years of age, *n* | 7,774 | 52,463 | | |
| J2. Projected population covered by ODB program, *n (H2 x proportion of patients covered by ODB by age subgroup)*[d] | **28,537** | **61,263** | | |
| | | | **Subgroup (iv): All individuals on IIT who required ≥ 8 daily test strips** | |
| | | | I3. Projected population with IIT with ≥ 8 daily test strips, *n* | **NR** |

CSII = continuous subcutaneous insulin infusion; FGMS = flash glucose monitoring system; IIT = intensive insulin therapy; n = sample size; NR = not reported; ON = Ontario; QC = Quebec; T1D = Type 1 diabetes; T2D = Type 2 diabetes.

[a] Intensive insulin therapy in ON defined as multiple daily insulin injections or a CSII.

[b] Total population in 2016 reported by Statistics Canada.

[c] Patients require the injection of insulin to manage blood glucose.

[d] The percentage of patients covered by ODB differs by age group; it was estimated that for individuals with T1D, 27.5%, 59.7%, and 12.8% were in the age groups 0 to 24 years, 25 to 64 years, and 65 years and older, respectively. For individuals with T2D, an estimated 1.5% of individuals were 24 years or younger and approximately 44.8% were 65 years of age or older. Approximately 5.4% of individuals with T2D were between the ages 25 and 64 years (as calculated by CADTH).