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Glucose monitoring technologies for the management of insulin-dependent diabetes

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Acknowledgements

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1 Abbreviations

AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinology
AHRQ	Agency for Healthcare Research and Quality
CADTH	Canadian Agency for Drug and Technologies in Health
CASP	Critical Appraisal Skills Programme
CGM	Continuous glucose monitor
CL	Closed loop
CSII	Continuous subcutaneous insulin infusion
CTR	Control-to-range
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DHIP	Dual hormone artificial pancreas
DIC	Deviance information criterion
DKA	Diabetic ketoacidosis
dL	Deciliter
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EQ-5D	EuroQol-5D
ESRD	End-stage renal disease
EUnetHTA	European Network for Health Technology Assessment
FGM	Flash glucose monitor
FPG	Fasting plasma glucose
HAS	Haute Autorité de Santé
HbA1c	Glycated hemoglobin
HFS	Hypoglycemia Fear Survey
HQO	Health Quality Ontario
HR	Heart rate
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio

ISPED	International Society for Pediatric and Adolescent Diabetes
INESSS	Institut National d'Excellence en Santé et en Services Sociaux
MAS	Medical Advisory Secretariat
MDI	Multiple daily injections
mg	Milligram
MPC	Model predictive control algorithm
NICE	National Institute for Health Care Excellence (UK)
NIHR	National Institute of Health Research (UK)
OGTT	Oral glucose tolerance test
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
QOL	Quality of Life
RCT	Randomized Controlled Trial
rt-CGM	Real-time continuous glucose monitor
SAP	Sensor-augmented pump
SE	Standard error
SMBG	Self-monitored blood glucose
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TIR	Time in range
USD	United States Dollar

2 Executive Summary

This report presents the findings and conclusions of a provincial health technology assessment on the clinical effectiveness, patient perspectives, cost effectiveness, and the budget impact of using glucose monitors to help manage glucose levels in insulin-dependent patients with Type 1 or Type 2 diabetes. The technologies included in this review are continuous glucose monitors (CGMs), flash glucose monitors (FGMs) and hybrid closed loop insulin delivery systems.

The primary research questions were:

1. What is the clinical effectiveness of glucose monitors?
2. What are patients' perspectives and experiences with using glucose monitors?
3. What is the cost effectiveness and potential budget impact of using glucose monitors in comparison to current usual care (self-monitored blood glucose [SMBG]) to manage glucose levels?

Primary research questions:

1. **What is the clinical effectiveness of glucose monitors?**

Network meta-analyses were conducted on HbA1c, number of hypoglycemic events requiring assistance, and time-in-range), in adults with T1D and children with T1D. No significant differences between interventions were identified for outcomes of HbA1c or number of hypoglycemic events requiring assistance. Some significant differences between interventions in the outcome of time-in-range were identified in both adults and children with T1D. Glucose monitoring technologies appear to be similar in pregnant populations with T1D, and people with insulin dependent T2D.

2. **What are patients' perspectives and experiences with using glucose monitors?**

The biggest barrier for patients to use CGMs was cost. Alternatively, patients reported that the strongest enabler of using a CGM was having extended benefits that would cover the cost of the device. Patients found CGM devices to be relatively easy to use and integrated well into their daily life, allowing for more control and better planning for daily activities (e.g., diet, exercise, and travel).

3. **What is the cost effectiveness and potential budget impact of using glucose monitors in comparison to current usual care (self-monitored blood glucose) to manage glucose levels?**

Given that included technologies were found to have similar effectiveness, cost-effectiveness modelling is unlikely to increase current understanding of these technologies. In the budget impact analysis, three populations are considered: all people living in British Columbia with insulin dependent type 1 or type 2 diabetes, people with type 1 diabetes, and people with significant clinical need. Costs were predicted over three years for four implementation scenarios: 1) support varies by patient income; 2) support varies by glucose control; 3) support is limited to one specific technology; 4) support is limited to people with limited functional capacity. Depending on the population considered eligible for funding and the implementation scenario, costs to the province are predicted to range from $1.1 million to $3.5 billion. The predicted budget impact is sensitive to the size of the population considered, predicted market share of technologies, and the costs associated with each technology.

Background

Diabetes is a chronic metabolic disorder that interferes with the body's ability to produce or effectively use insulin. There are two main types of diabetes, type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D is an autoimmune disease that occurs when the immune system mistakenly attacks and destroys the beta cells of the pancreas, leading to little-to-no insulin production. Without adequate insulin to initiate glucose uptake (e.g., lowering blood sugar), blood glucose levels rise (e.g., hyperglycemia). The cause of T1D is generally unknown, though genetics and environmental factors (e.g., viruses) are thought to be triggers of the disease. T2D is a metabolic disorder. The cause may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance. Risk factors for developing T2D are genetics, age, ethnicity; and lifestyle factors such as poor diet, smoking, obesity, and sedentary behaviour. The prevalence of diabetes has been rising steadily over the past several decades, and it is estimated that around 10% of the Canadian population currently has diabetes. Diabetes-related health spending in Canada ranks seventh globally, costing 17 billion USD in 2015.

The complications of poorly controlled diabetes range from acute (e.g., seizure, fainting, ketoacidosis, blurred vision, headaches, and fatigue) to chronic (e.g., cardiovascular disease, eye damage, kidney damage, nerve damage, amputations), and in severe cases, can lead to death. In Canada, diabetes is the sixth leading cause for mortality, and the leading cause of blindness, end-stage renal disease, and non-traumatic amputation.

There is no cure for diabetes, but there are a number of ways to manage the disease. For people with T1D and some people with T2D, using a form of insulin delivery is a necessity. Multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) pump therapy are common forms of insulin delivery. To determine insulin use and dose to manage symptoms, blood sugar (glucose) must be monitored. Individuals who monitor their blood glucose frequently are better equipped to respond to dips and spikes in their blood glucose, helping to mitigate complications related to hyper- and hypoglycemia.

Common methods of monitoring blood glucose include: self-monitoring blood glucose (SMBG), continuous glucose monitoring systems (CGMs), and flash glucose monitors (FGM). Using SMBG, patients monitor their blood glucose by pricking their fingers with a lancet and delivering a drop of blood onto an enzyme-coated test strip. A meter reads the blood glucose level and displays the result for the patient to read. This process must be repeated several times a day and provides accurate, albeit intermittent, blood glucose readings. A CGM system consists of three parts: a thin needle-like sensor that is inserted in the abdomen or deltoid, in contact with interstitial fluid; a transmitter that sits overtop of the sensor; and a portable monitor which receives the signal and displays the results (with a minor lag time). Flash monitors use a sensor inserted into the skin, and an external transmitter (e.g., mobile phone). While not a complete substitute for capillary blood glucose tests (calibrating CGM or FGM with SMBG is still recommended with the exception of the Dexcom G6 CGM), CGMs do confer significant advantages over SMBG alone. Alarm features alert patients to deviations from recommended blood glucose levels (euglycemia), enabling them to take corrective action sooner resulting in improved metabolic control, and allow patients to view their glucose trends and time spent in and outside of the target glycemic range, known as "time in range" (TIR). TIR it is not clinically validated, though it is often used as a surrogate marker for glycemic control and clinical outcomes. This suggests the need to review the literature on the associations between TIR and clinical outcomes.

Methods

The following methodological approaches were used to gather and synthesize the available evidence:

I. Systematic review of the clinical validity of using time in range as a surrogate marker
II. Systematic review and grey literature review of health technology assessments
III. Systematic review on clinical effectiveness of continuous glucose monitors for the management of glucose levels in patients with insulin dependent diabetes (type 1 and type 2)
IV. Review of guidelines and best practice recommendations
V. Systematic review of patient perspectives literature
VI. Environmental scan across Canada

VII. Key informant interviews and patient focus groups
VIII. Implementation scenarios
IX. Budget impact analysis

Key Findings

In an effort to validate time in range (TIR) as a clinically meaningful outcome for diabetes management, a systematic review of clinical outcomes associated with TIR was conducted (Chapter 7). Two studies were identified for inclusion. One study explored the association between TIR and internalizing and externalizing behaviours, and concluded that higher percent time spent in range was associated with lower levels of externalizing behaviour. The second study explored the association between TIR and the risk for developing diabetic retinopathy and microalbuminuria in children and adults (age 13-39 years old). This study found that lower percent TIR was associated with higher risk of developing retinopathy and microalbuminuria. Given the lack of evidence, TIR should not be considered a validated surrogate marker for diabetes-related complications until more robust body literature on this topic exists.

A second review was conducted to synthesize health technology assessments (HTAs) on glucose monitoring technologies, including CGMs, FGMs, or sensor augmented pumps (SAP; continuous subcutaneous insulin infusion [CSII] + real-time-CGM [rt-CGM]) for people with insulin-dependent diabetes (Chapter 8). Ten HTAs were included for review. Seven HTAs examined CGMs (two of which also included SAPs and one included FGMs); the other three HTAs examined FGMs. In terms of clinical effectiveness, four HTAs favoured the use of CGM over SMBG; three determined that the evidence did not support the superiority of CGMs compared to SMBG; and three HTAs found that FGMs were superior to SMBG in some respects and similar in others. Three HTAs identified literature on the cost-effectiveness of CGMs. Four HTAs conducted their own cost analyses of glucose monitoring technologies. In all HTAs that conducted cost analyses, glucose monitors were unlikely to be the cost-effective option for any of the included comparators. Only two HTAs provided specific recommendations regarding the use of glucose monitors; one noted that the evidence supported the recommendation for CGMs to be used by children and adolescents over the age of eight; another noted that rt-CGM should not be offered routinely to adults with T1D, only to select groups of patients.

Current guidelines and best practice recommendations on the use of glucose monitoring technologies were synthesized to determine if differences in recommendations and guidelines exist between Canada and elsewhere (Chapter 9). Ten relevant guidelines were identified for the use of CGMs, SAPs, or FGMs (Canada, USA, UK, and Germany). The guidelines generally agreed that people at risk for severe hypoglycemia, and people not achieving their HbA1C goals may benefit the most from CGM and FGM technologies. With the exception of the Dexcom G6 CGM, non-adjunctive use of CGM is not recommended. Recommendations note that CGM should be used by patients willing to use the device more than 70% of the time. Children, especially those who cannot recognize or articulate symptoms of hypoglycemia, may benefit from CGMs. Individuals at low risk of severe hypoglycemia may benefit from FGMs.

A systematic review and a series of network meta-analyses were conducted on the clinical effectiveness of CGMs, FGMs, and hybrid insulin delivery systems for the management of insulin-dependent diabetes. Sixty-three studies of 70 sample populations were included in this review. The populations of interest were adults with T1D, children with T1D, adults with T2D that require insulin to manage their blood glucose, and pregnant women with T1D. Among the included studies, there was little overlap in the interventions described – resulting in sparse networks of evidence for network meta-analysis. Network meta-analysis was conducted on HbA1c, number of hypoglycemic events requiring assistance, and time-in-range (percent of time with blood glucose between 3.9-10.0mmol/L), in adults with T1D and children with T1D. No significant differences between interventions were identified for outcomes of HbA1c or number of hypoglycemic events requiring assistance. Although some significant differences between interventions in the outcome of time-in-range were identified in both adults and children with T1D, further study is required to connect this device evaluation metric to meaningful clinical outcomes. Other outcomes of interest were: number of diabetic ketoacidosis (DKA) events, DTSQ, HFS, and health-related quality of life. Few interventions resulted in any DKA events. Other outcomes were not reported with sufficient frequency for quantitative analysis, or meaningful comparisons. Little evidence was identified for T2D or T1D in a pregnant population, and no conclusions about efficacy could be drawn.

To synthesize the literature exploring the patient perspectives of glucose monitoring technologies, a systematic review was completed (Chapter 11). Patient perspectives offer valuable insight into how the technologies influence the experience of living with insulin-dependent diabetes. Patients found continuous monitoring to be an effective tool in managing their glucose levels, and this message was remarkably consistent across patient groups, countries, and study designs. Additional findings included improvement in sleep, a greater freedom when making life decisions and an improved ability to make informed life decisions such as vacations and exercise. Negative findings were primarily with technical issues such as calibration and trusting the technology.

With some background information on what is currently known about glucose monitoring (HTA review; clinical effectiveness review), what is currently being offered (guidelines/best practice recommendations review), and the lived experience of glucose monitoring (patient perspectives review), an environmental scan was conducted to determine the level of financial support offered to people living with insulin-dependent diabetes across Canada and elsewhere. In Canada, all jurisdictions have programs in place to provide full or partial funding of insulin pumps to qualifying patients with type 1 diabetes. Coverage for health-related expenses other than insulin pumps and pump supplies (e.g., blood glucose test strips) is provided through provincial drug programs. CGMs are provided for children and youth in Yukon, and FGMs are recommended to be provided to select patients in Quebec and Ontario; these recommendations have not been translated into policy yet. In international jurisdictions, insulin pump programs exist in the UK, Australia, and New Zealand. CGMs are less readily available for funding in these jurisdictions. Safety of insulin pumps was also a consideration. In recent years, insulin infusion pumps have been considered one of the top ten medical devices associated with medical complications and death. To address this, Health Canada plans to allow medical professionals to apply to conduct investigations into medical devices as early as 2019.

Building on what is known about the patient experience living and managing insulin-dependent diabetes, interviews with health care professionals (Chapter 13) and patient focus groups (Chapter 14) were conducted. The perspectives of health care professionals and patients were largely consistent. The biggest barrier to CGMs was cost. Alternatively, patients reported that the

strongest enabler of using a CGM was having extended benefits that would cover the cost of the device. Patients and clinicians found CGM devices to be relatively easy to use and integrated well into the patient's daily life, allowing for more control and better planning for daily activities (e.g., diet, exercise, and travel). Clinicians reported that CGMs lessened the frequency and severity of hypoglycemic events, and would be most beneficial for patients who have severe problems with hypoglycemia or patients who require considerable support from others to manage their diabetes (e.g., children, persons with disabilities, or people residing in assisted living).

Drawing on all the evidence in this report, several implementation options were developed for consideration (Chapter 16). Populations for which public funding could be provided are: 1) All people living with diabetes (T1D and T2D); 2) People living with T1D only; or, 3) People living with T1D or T2D where there is a clinical need for financial assistance. The current British Columbia PharmaCare program most closely aligns with the third population (financial need). Four implementation considerations could be applied across the three populations: 1) Support varies by patient income; 2) Support varies by patient's blood glucose control; 3) Access is limited to one specific technology; or, 4) Access is limited to people with limited functional capacity. The first implementation scenario (support varies by patient income) has the strongest support from the current evidence.

After completion of the clinical review, a cost-effectiveness model was not undertaken for a variety of reasons (Chapter 15). Both patients and the Ministry of Health consider cost in decision-making, therefore, a budget impact analysis was conducted to support the policy implementation scenarios (Chapter 17). This budget impact analysis considers four funding scenarios for the management of insulin dependent diabetes in British Columbia. Costs are predicted over a three-year time horizon. [redacted]. In scenario one funding is based on the patient's family income, like the Fair PharmaCare program. Costs to the province are predicted to range from $266 million over three years if income-based funding is provided to all patients with insulin dependent diabetes, to $1.1 million over three years if funding is provided to patients with significant difficulty managing their own diabetes. In scenario two, funding is provided to patients with glycated hemoglobin (HbA1c) greater than or equal to 7.0%. Costs to

the province range from $397 million over three years if funding is provided to all patients with insulin dependent diabetes and HbA1c ≥ 7.0%, to $1.7 million depending on the population funded. In scenario three, only one technology is funded by the province. If all patients with diabetes are eligible and all patients with diabetes select the most expensive technology considered, costs to the province could be as high as $15.7 billion. In scenario four, funding is limited to patients with limited functional capacity. Over three years, the predicted budget impact to the province is $15.6 million.

3 Purpose of this Health Technology Assessment

The purpose of this health technology assessment (HTA) is to synthesize the evidence on glucose monitoring technologies used by people who manage their diabetes with insulin. This report summarizes evidence of the current literature of clinical effectiveness, patient experience, the current context across Canada, cost-effectiveness and budget impact analysis. The evidence herein is then synthesized to develop possible implementation scenarios for consideration within the province.

4 Research Question and Research Objectives

The primary research questions are:

1. What is the prevalence and annual incidence of Type 1 and Type 2 diabetes in BC?
2. What are the direct/indirect costs to the health system associated with monitoring and measuring blood glucose levels in diabetic patients in BC?
3. How are blood glucose levels currently being monitored and measured in diabetic patients in BC (alternatives)?
4. Who would be indicated to use CGMs/ FGMs and hybrid closed loop insulin delivery systems as opposed to the alternatives? What would the eligibility criteria be if one is required? Are there ethical implications with setting an eligibility criteria?
5. What is the clinical effectiveness of CGMs/FGMs and hybrid closed loop insulin delivery systems? In comparison to the alternatives? Specifically, what is the clinical effectiveness of CGMs/FGMs and closed loop insulin delivery systems on time in target blood glucose range?
6. What is the clinical significance of time in target blood glucose range? Is time in target blood glucose range a validated measure?
7. Are CGMs/FGMs and hybrid closed loop insulin delivery systems currently publicly provided in other provinces? Other countries? Do these jurisdictions have an eligibility criteria and what is it? What are their clinical and practice guidelines surrounding CGMs/FGMs?

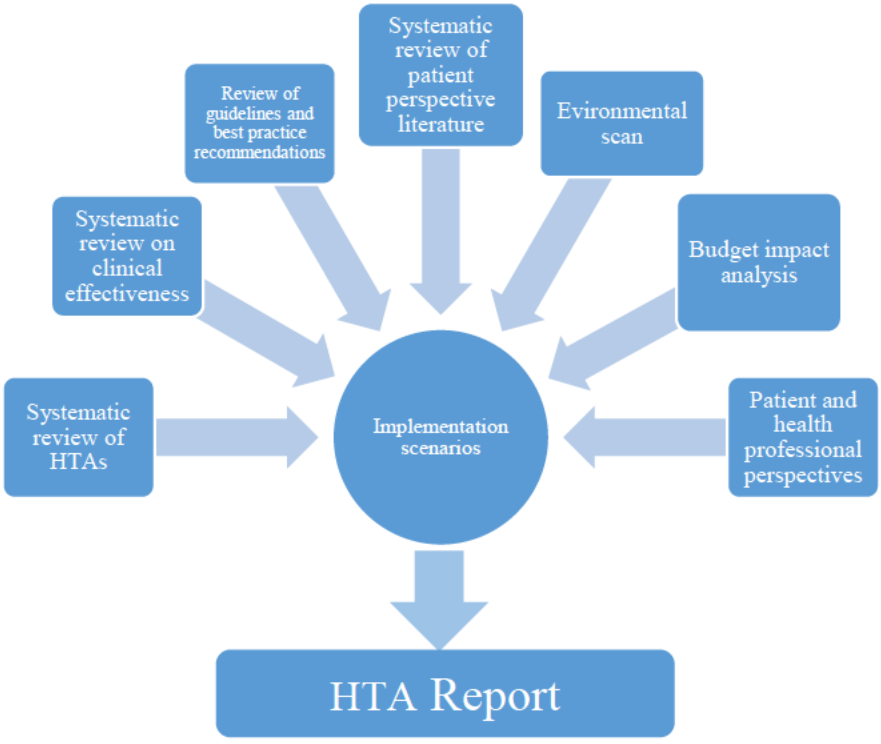
8. What is the cost-effectiveness and potential budget impact for publicly funding CGMs/FGMs and hybrid closed loop insulin delivery systems compared to alternatives?
9. What are the benefits/challenges to implementing public coverage for CGMs/FGMs and hybrid closed loop insulin delivery systems? What are the best practices for implementation?
10. What are the patient and clinician perspectives and experiences with monitoring and measuring blood glucose levels, and with CGMs/FGMs?
11. Would public coverage of CGMs/FGMs alter how diabetic care management is currently provided?
12. Are there other emerging technologies to monitor and measure blood glucose levels?

5 Overview of Approach

A variety of methodological approaches were used to gather and synthesize the available evidence in order to address the primary research questions. The following methodologies were used:

I. Systematic review of the clinical validity of using time in range as a surrogate marker
II. Systematic review and grey literature review of health technology assessments
III. Review of recent guidelines and best practice recommendations
IV. Systematic review of additional primary literature including only randomized controlled trials (RCTs) on clinical effectiveness of continuous glucose monitors
V. Systematic review of the patient perspective literature
VI. Jurisdictional scan across Canada, and internationally
VII. Key informant clinical interviews and patient focus groups
VIII. Implementation scenario development
IX. Budget impact analysis

Figure 5.1. Summary of Process



6 Background

6.1 Diabetes Overview

Diabetes is a chronic metabolic disorder that interferes with the body's ability to produce or effectively use insulin. It is a common condition in Canada, and is the sixth leading cause of death (behind cancer, heart disease, stroke, accidents, and chronic lower respiratory disease)[1]. The estimated prevalence of diabetes in 2015 was 3.4 million, or 9.3% of the population, and is expected to rise to 5 million or 12.1% of the population in Canada by 2025.[2] Contributing to this staggering projection is the prevalence of pre-diabetes (e.g., elevated blood glucose) in Canadian adults, which was estimated to be 5.7 million, or 22.1% of the population in 2015.[3] This HTA focuses on insulin-dependent diabetes, specifically people with Type 1 and some Type 2 who are insulin-dependent. Gestational diabetes is not included in this assessment.

6.1.1 Types of Diabetes

There are two main types of diabetes: Type 1 and Type 2. A third main type, gestational diabetes, can occur during pregnancy for some women. Other types of diabetes, e.g., cystic-fibrosis-related diabetes (CFRD), are uncommon.[4,5]

6.1.1.1 Type 1 Diabetes (T1D)

Type 1 diabetes (T1D) is a chronic, autoimmune disease that occurs when the immune system mistakenly attacks and destroys the beta cells of the pancreas. In a normal-functioning pancreas, the beta cells of the pancreas release the insulin hormone, which causes cells to take in glucose (sugar) to use as energy or store as fat; blood sugar levels decrease as a result. In T1D, the body can produce little to no insulin, due to the loss of beta cells, resulting in a build-up of sugar in the blood (hyperglycemia).[6-8] As a result, insulin therapy is required to manage blood glucose. The cause of T1D is still unknown, though scientists hypothesize that genetics and exposure to viruses and other environmental factors may trigger the disease.[9] Symptoms of T1D include: increased hunger, thirst, and urination; fatigue; vision problems; unexplained weight loss; decreased healing time from cuts/sores; and numbness and/or tingling in the hands or feet.[3,4]

Around 5-10% of people with diabetes have T1D.[10] T1D is often diagnosed in childhood and adolescence, however, diagnosis in adulthood is possible.[4] While T1D has historically been, and continues to be, the most common type of diabetes in children and youth, Type 2 diabetes is increasingly being diagnosed in youth[6,11].

6.1.1.2 Type 2 Diabetes (T2D)

Type 2 diabetes (T2D) is a metabolic disorder. It occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced.[4,5,11] The cause of T2D may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance. Around 90-95% of people with diabetes have T2D.[12] The prevalence of T2D has risen rapidly worldwide in the past three decades.[13] This rising epidemic can be attributed to a combination of factors, including genetic predisposition, and behavioural and environmental factors.[14] Notably, the increase in worldwide T2D prevalence mirrors the increase in the prevalence of obesity.[4] Obesity rates are increasing with over 60% of Canadian adults and 31.5% of children and adolescents being overweight or obese.[15,16] Symptoms of T2D are homogenous with T1D, however, unlike T1D symptoms that typically have a rapid onset, symptoms of T2D can develop slowly over time.[9] Many individuals with T2D display no symptoms, and may be unaware of the disease until they have been formally diagnosed.[7] The prevalence of undiagnosed T2D in the general Canadian population is estimated to be about 4%, which accounts for 20-40% of total diabetes cases.[17]

Modifiable risk factors for T2D include: overweight and obesity, physical inactivity or sedentary behaviour, dietary factors, smoking, previously identified glucose tolerance, abnormal lipids, hypertension, inflammation, and fetal undernutrition.[4,13] Non-modifiable risk factors include age, sex, ethnicity, family history of T2D, history of gestational diabetes, and polycystic ovary syndrome (PCOS).[13] Epidemiological studies have found that nearly 90% of cases of incident T2D can be attributed to lifestyle factors alone.[14]

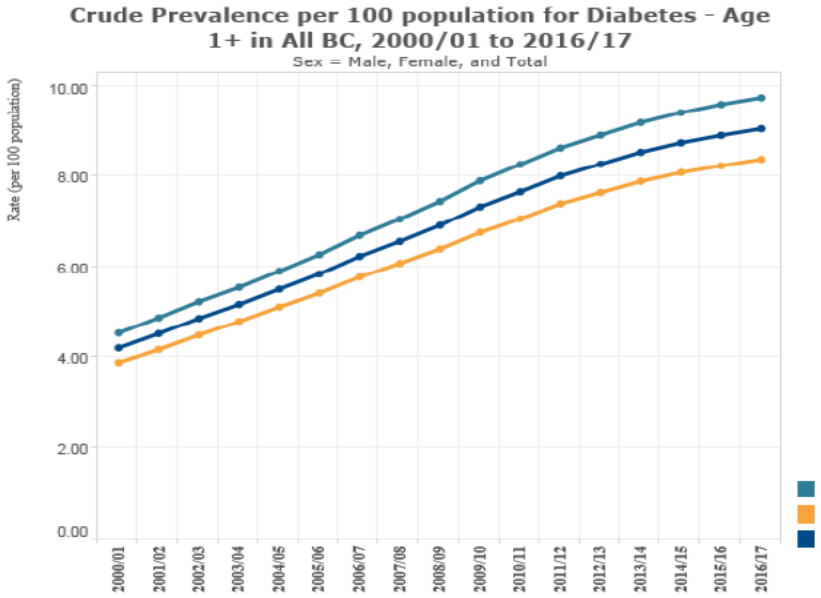
6.2 Prevalence of Diabetes

6.2.1 Overall Prevalence

The prevalence of diagnosed diabetes in British Columbia in 2000/01 was 171,127 or 4.21% of the population, rising to 445,436 in 2016/17, or 9.06% of the population[18]. The 2016/17 prevalence rate is similar to the Canadian estimate of 9.3% in 2015[3] and is predicted to rise to 12.1% of the population by 2025.

6.2.2 Prevalence by Male versus Female

The prevalence of diabetes has been steadily increasing over the previous two decades, with a consistently higher prevalence of diabetes in males versus females[18]. For instance, as seen in Figure 6.1, in 2017 the prevalence of diabetes in males was 9.74% versus 8.38% in females[18].



Footnotes

1. Chronic disease rates are calculated by BC Ministry of Health using the following data sources: Registration and Premium Billing (R&PB), HealthIdeas Fiscal Year Client Roster, Medical Service Plan (MSP) Physician Billing Data, PharmaNet Drug Dispensing History, and Hospital Discharge Abstract Database (DAD). Visualization is provided by the BC Observatory for Population and Public Health.

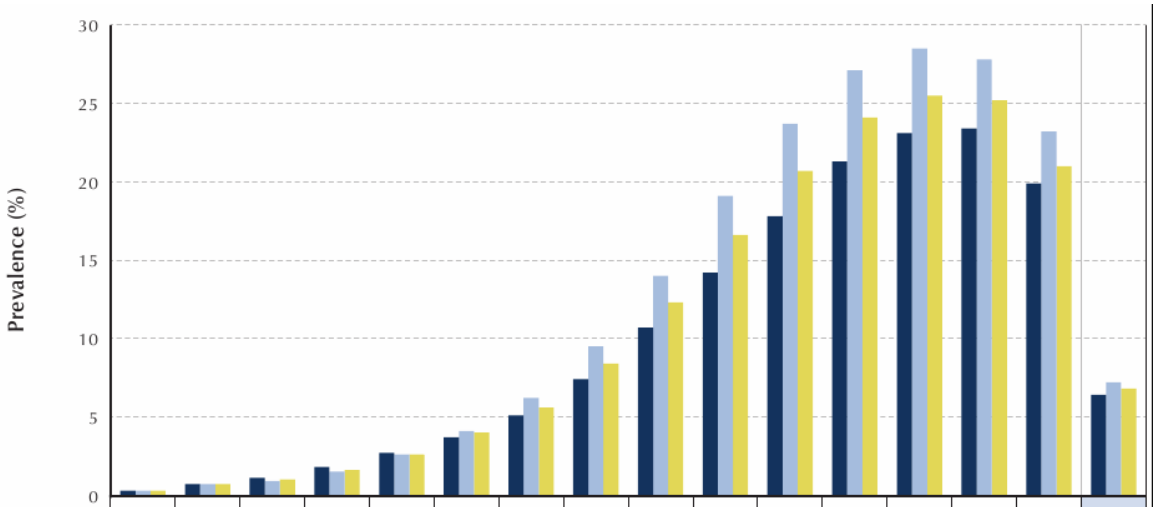
2. Age-standardized rates use the 2011 Canadian Standard Population weights.

3. Cases where sex is unknown are not presented due to small numbers, but remain in totals.

Figure 6.1 Crude Prevalence of Diabetes in British Columbia[1]

6.2.3 Prevalence by Age

The prevalence of diagnosed diabetes generally increases with age. Adults >40 years old, are at an elevated risk of developing T2D due to deterioration in the body's ability to produce and use insulin. Data from the Canadian Chronic Disease Surveillance System (2008/09) reported that adults between the ages of 75 to 79 had the highest prevalence of diabetes (Figure 6.2); however, more than 50% of the affected Canadian population is between 25-64 years old.



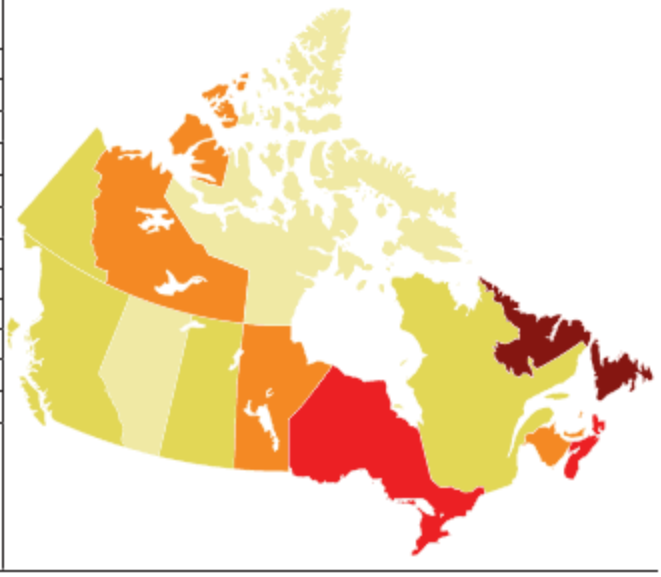
Age group (years)	1-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85	Canada
Females	0.3	0.7	1.1	1.8	2.7	3.7	5.1	7.4	10.7	14.2	17.8	21.3	23.1	23.4	19.9	**6.4**
Males	0.3	0.7	0.9	1.5	2.6	4.1	6.2	9.5	14.0	19.1	23.7	27.1	28.5	27.8	23.2	**7.2**
Total	0.3	0.7	1.0	1.6	2.6	4.0	5.6	8.4	12.3	16.6	20.7	24.1	25.5	25.2	21.0	**6.8**

Figure 6.2 Prevalence of diagnosed diabetes among individuals aged one year and older, by age group and sex, Canada, 2008/09[5]

6.2.4 Prevalence by Province/Territory

The prevalence of diabetes varies across Canada. Public Health Agency of Canada used 2008/09 data from the Canadian Chronic Disease Surveillance System to present Figure 6.3[19], with the data being age-standardized to the 1991 Canadian population. Newfoundland and Labrador, Nova Scotia and Ontario had the highest prevalence rate while Nunavut, Alberta and Quebec are ranked the lowest. BC at the age-standardized prevalence rate of 5.4% is similar to the rate of all of Canada at 5.6%[19].

	Age-standardized prevalence (%)
Newfoundland and Labrador	6.5
Prince Edward Island	5.6
Nova Scotia	6.1
New Brunswick	5.9
Quebec	5.1
Ontario	6.0
Manitoba	5.9
Saskatchewan	5.4
Alberta	4.9
British Columbia	5.4
Yukon	5.4
Northwest Territories	5.5
Nunavut	4.4



† Age-standardized to the 1991 Canadian population.

Figure 6.3 Age-standardized† prevalence of diagnosed diabetes among individuals aged one year and older, by province/territory, Canada, 2008/09[19]

6.3 Screening and Diagnosis

Individuals who have symptoms, or are at high-risk for developing diabetes, should be screened for the disease. Early diagnosis is important to disease management. The longer an individual lives with undiagnosed and untreated diabetes, the worse their health outcomes will be[17,20]. Screening strategies for T1D and T2D vary but are effective in preventing disease progression and reducing the risk of complications[20].

Since T1D is a chronic autoimmune disease and often develops in individuals who are genetically predisposed, patients with a family history of T1D or a positive screen for genetic markers should be screened immediately after presenting with an acute onset of symptoms[20]. Although no treatment exists for patients who are asymptomatic, screening can reduce risk of complications[17].

Screening for T2D is crucial as it can detect individuals who are in less severe states of dysglycemia (i.e., outside of the target blood glucose range). By screening for prediabetes and

providing effective intervention strategies, it can prevent the disease progression to T2D and therefore reducing the risk of diabetes complications[20].

6.4 Disease Management

There is no cure for diabetes. Health outcomes and complication mitigation relies on disease management practices. Changes to health behaviours, blood pressure control, lipid management, cardiovascular protection, and glycemic control with insulin or other drugs must be implemented. Technologies aimed at achieving recommended blood glucose, lipid and blood pressure targets include insulin-delivery devices and blood glucose monitoring devices[19].

6.4.1 Non-Pharmacological Management (Lifestyle)

Nutritional therapy helps maintain a healthy body weight and improves glycemic control. Consistency in meal consumption times and controlled intake of carbohydrates while following a long-term dietary pattern that best aligns with their values, preferences and treatment goals is crucial to disease management[19]. For individuals with prediabetes or recently diagnosed T2D, nutritional therapy leading to a 5-10% weight loss is an effective strategy in normalizing blood glucose levels[19]. The Diabetes Canada Clinical Practice Guidelines Expert Committee[19] recommends a number of dietary changes to decrease carbohydrate and sugar intake; and increase fiber, vegetable, healthy fat, and low-glycemic index food intake.

Besides changes to diet and nutrition therapy, physical activity and cardiorespiratory fitness are recommended to help patients improve glycemic control, decrease insulin resistance, improve lipid profile, blood pressure reduction and maintenance of weight loss[19]. The Diabetes Canada Clinical Practice Guidelines Expert Committee[19] suggest adopting the Canadian Physical Activity Guidelines of engaging in ≥150 minutes of moderate-vigorous physical activity per week[19], reducing sedentary behaviour, and using a step monitor to aid in monitoring activity[3].

6.4.2 Pharmacological Management

1.4.2.1 Insulin-delivery

Insulin is a hormone produced by the beta cells of the pancreatic islets, people with diabetes either can't produce insulin (T1D), or not enough of it (T2D), and/or they have insulin

resistance[21]. Insulin's role is to regulate the amount of glucose (sugar) in the blood, as too much can cause damage to organs, blood vessels, and nerves[21]. Insulin is also needed by cells to take glucose from the blood for energy[21].

Insulin therapy is initiated immediately once T1D is diagnosed as the body produces insufficient insulin to regulate blood glucose levels. Basal-bolus insulin therapy is usually used, consisting of a long- or intermediate-acting "basal" insulin that provides glucose control in the fasting state and between meals, and a rapid- or short-acting "bolus" insulin that controls the glycemic rise at meals. The selection of an insulin regimen is tailored to each individual's age, general health, treatment goals, lifestyle, diet, hypoglycemia awareness status, ability for self-management and adherence to treatment[22].

Insulin therapy may be delivered by injection or continuous subcutaneous insulin infusion (CSII) pump therapy. Both injections and pumps are considered standard of care for adults with T1D[22]. However, if individuals are not achieving optimal blood glucose through using insulin injections, CSII pump therapy may help. Whether due to medical indication or personal preference, candidates for CSII need to be screened to ensure that they have the motivation and capacity for frequent monitoring, plus attending follow-up visits with their healthcare team[22]. Limited research has found that use of CSII reduces HbA1c when compared to injection therapy. The use of CGMs to augment CSII has been shown to provide a substantial HbA1c benefit over injection therapy paired with self-monitoring of blood glucose[22].

Insulin may also be used to treat some patients with T2D. Insulin therapy increases risk of hypoglycemia (low blood sugar)[22,23], therefore individuals on insulin therapy need to monitor their blood glucose levels frequently. The need for regular glucose monitoring has resulted in the development of pumps that can pair easily with a glucose monitor (typically glucometers or CGMs), or that are integrated pump-monitor units.

6.4.2.2 *Glucose monitoring*

Testing blood glucose levels allows diabetic patients to detect and treat hypoglycemia and hyperglycemia. Patients who test often are better positioned to respond to drops or spikes in their

blood glucose level, as well as to understand the impact of their behaviours on their condition[24]. In particular, self-monitoring of blood glucose is important for patients undertaking intensive insulin therapy, as the risk of a hypoglycemic event increases as glycemic control tightens[22,23,25]. Patients who monitor their glucose levels frequently can act to avert severe hypoglycemic incidents associated with intensive insulin therapy[24]. There are various ways of monitoring glucose levels, including self-monitoring and the use of glucose monitor devices.

6.4.2.3 Self-monitoring Blood Glucose (SMBG)

Conventionally, patients monitor their blood glucose by pricking their fingers with a lancet and delivering a drop of blood onto an enzyme-coated test strip. A meter reads the blood glucose level, based on the electrical current that is generated by a reaction between the enzymes on the strip and the glucose in the blood sample,[26] and displays the result for the patient to read. This process must be repeated several times a day and provides accurate, albeit intermittent, blood glucose readings.[27] While the ideal number of tests per day varies between patients, performing three or more tests per day is associated with better glycemic control and reduced risk of hypoglycemia.[24]

6.4.2.4 Continuous Glucose Monitors

A continuous glucose monitor (CGM) consists of three parts: a thin needle-like sensor that is inserted in the abdomen or deltoid, in contact with interstitial fluid; a transmitter that sits overtop of the sensor; and a portable monitor which receives the signal and displays the results.[28] CGMs, like conventional monitors, most often use enzymes to detect glucose. In a CGM, the sensor is enzyme-coated, typically with glucose oxidase, and reacts with glucose present in the interstitial fluid. The reaction generates a weak electrical current, which is transmitted to the receiver, which calculates and displays the glucose concentration values.[29]

In February 2019, Health Canada approved the Dexcom G6® CGM System, which will eliminate the need for fingersticks.[30] However, for the majority of CGM devices on the market that do not completely obviate the need for fingersticks, CGMs still confer significant advantages over SMBG alone. Alarm features alert patients to deviations from euglycemia, enabling them to take corrective action sooner and possibly resulting in improved metabolic control.[31] CGMs also

allow patients to view their glucose trends, i.e., whether their glucose levels are rising or falling, and how fast.[29] This information can be used to evaluate the magnitude of metabolic changes "on-the-spot."

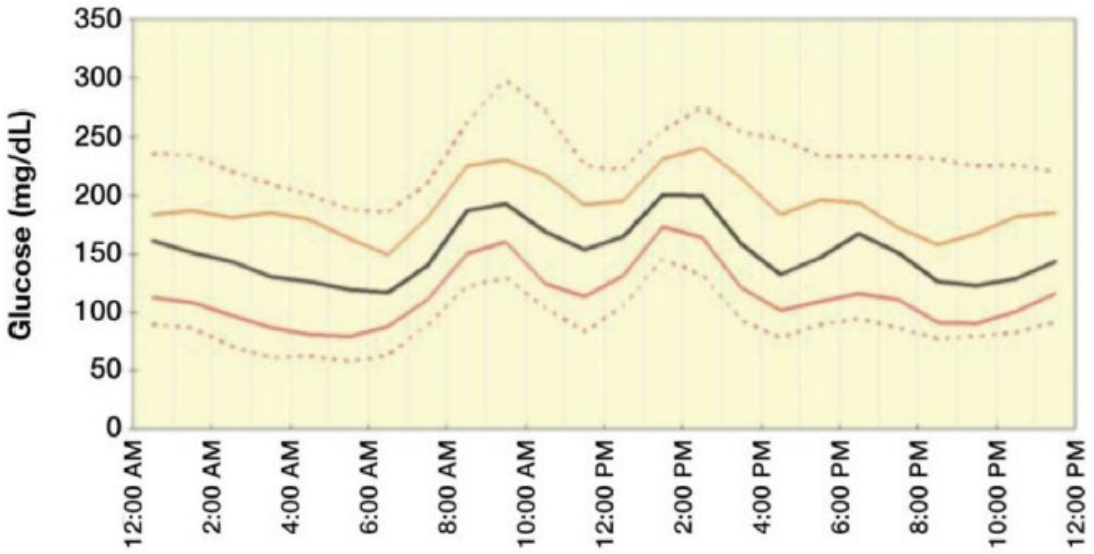


Figure 6.4. Example data chart from a CGM system for a hypothetical T1D patient[32]

6.4.2.5 Flash Glucose Monitors

A flash glucose monitor (Flash GM or FGM) is similar to a CGM as it uses a sensor implanted into the skin (often arm), however, the transmitter is a separate device that when placed over the sensor, provides the patient's current glucose level. A flash GM records glucose every 15 minutes, and only display readings when scanned, unlike a CGM which provides continuous readings[33].

6.4.2.6 Hybrid closed loop insulin delivery systems

A hybrid closed loop insulin delivery system combines a CGM, and insulin delivery device[34]. This system includes a sensor that is inserted under the skin, an insulin pump, and transmitter that collects data from the sensor and delivers it to the insulin pump. Insulin delivery can be manual or automatic. In an automatic system, insulin is delivered from the insulin pump in response to glucose readings from the CGM[34].

Table 6.1 Glucose Monitors (approved in Canada)

Monitor (Manufacturer)	Type	Features
FreeStyle Libre (Abbott)	Stand-alone (Flash GM)	Factory calibrated; no daily calibration required (however, Health Canada continues to recommend calibration with fingersticks); Flash monitor: pass the reader over the sensor (located on back of arm). Change sensor every 14 days.
G4 Platinum (Dexcom)	Stand-alone (CGM)	Built-in alarm system. Requires calibration every 12 hours with fingersticks. Change sensor every 7 days.
G5 Mobile (Dexcom)	Stand-alone (CGM)	Sends data and alerts to smartphone. Requires calibration every 12 hours with fingersticks. Change sensor every 7 days. Compatible with T:slim X2 (see last row of table).
G6 Mobile (Dexcom)	Stand-alone (CGM)	No finger sticks needed to make treatment decisions. Sends data and alerts to smartphone. Does not require calibration. Change sensor every 10 days. Compatible with T:slim X2. Can use acetaminophen.
MiniMed 530G (Medtronic)	Pump + monitor (Closed-Loop)	Alerts, and automatic control of certain insulin pump functions. Requires calibration with any conventional meter every 12 hours, but automatically acquires readings from compatible Contour Next meter for insulin dosing and calibration. Change sensor every 6 days.
MiniMed 630G (Medtronic)	Pump + monitor (Closed-Loop)	Alerts, and automatic control of certain insulin pump functions. Requires calibration with any conventional meter every 12 hours, but automatically acquires readings from compatible Contour Next 2.4 meter for calibration, insulin dosing, remote bolus delivery. Change sensor every 6 days.
MiniMed 670G (Medtronic)	Pump + monitor (Closed-Loop)	Alerts, and automatic control of certain insulin pump functions. AutoMode automatically adjusts basal insulin delivery based on glucose values and insulin delivery, but requires user to enter carb grams and confirm mealtime and correction bolus recommendations. Requires calibration

		with any conventional meter every 12 hours, but automatically acquires readings from compatible Contour Next 2.4 meter for calibration, insulin dosing, remote bolus delivery. Change sensor every 7 days.
MiniMed Paradigm Revel (Medtronic)	Pump + monitor (Closed-Loop)	Alerts, and automatic control of certain insulin pump functions. Requires calibration with any conventional meter every 12 hours, but automatically acquires readings from compatible Contour Next meter for insulin dosing and calibration. Change sensor every 6 days. Works with MiniMed Connect which links to smartphones.
T:slim X2 (Tandem)	Pump (hooks up with Dexcom G5 mobile sensor (Closed-Loop))	Operates as a pump, but integrates with the Dexcom G5 Mobile. No fingersticks required to confirm treatment decisions. Safety alarms. Calibration required every 12 hours. Change sensor every 7 days.

6.4.2.7 *Difficulties of Adequate Evidence Levels for Diabetes Technology*

The Diabetes Canada Guidelines note that studies using CSII pumps are limited.[22] The Endocrine Society guidelines also note that evidence on the efficacy of technologies is lacking: firstly, as FDA regulation is less rigorous for medical devices than pharmaceuticals, there is less demand for RCTs, hence less reliable data on the efficacy of new devices; secondly, it notes that the ongoing development of newer insulin analogs and advanced glucose monitoring and insulin delivery devices make comparisons between studies complex.[23] Finally, it also notes that the success of these devices and technologies is directly linked to the level to which individuals are educated, capable, and willing to use them[23]; as such it is important to match individuals to the best-suited technologies for their particular circumstances and preferences, as well as to ensure adults who use CSII and CGM receive education, training, and ongoing support to help achieve and maintain their individual glycemic objectives.[23] There is a rapid evolution of technologies that the literature cannot keep up with.

6.4.3 Glycemic Control

The focus of glycemic goals is on achieving target HbA1c levels and on minimizing symptomatic hyper- and hypoglycemia. Glycemic target recommendations are individualized based on the patient's age, duration of diabetes, risk of hypoglycemia, cardiovascular disease presence, and life expectancy (Figure 6.5)[35]. HbA1c is used as a surrogate marker for micro- and macrovascular outcomes such as risk for retinopathy, neuropathy, nephropathy, and cardiovascular disease[36].

Whereas HbA1c looks at glucose levels tested at static points in time, resulting in a blood glucose average over several months, time in range (TIR) captures the fluctuations in glucose levels continuously[37]. However, the association between maintaining blood glucose levels in the target range and improved health outcomes is lacking.

Although the clinical relevance of TIR has not yet been validated, researchers evaluating the precision and effectiveness of insulin delivery and glucose monitoring technologies continue to evaluate this outcome[37]. Most of these studies are of short duration and therefore challenging to validate TIR as being a long-term predictive outcome of health.

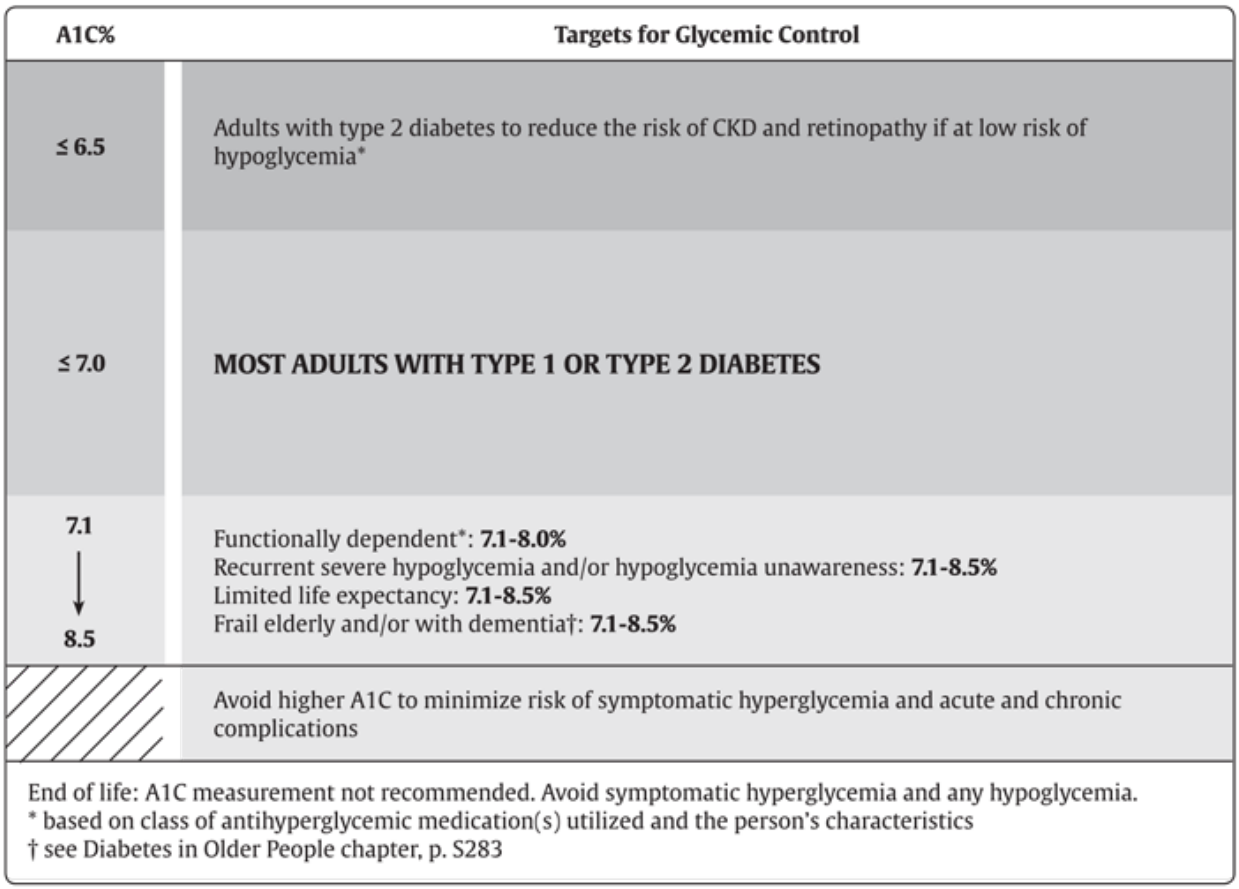


Figure 6.5 Recommendations for glycemic targets in adults[3]

6.4.4 Patient Perspectives on Management

Living with diabetes, and particularly so when on multiple daily injections of insulin, requires a lot of self-management[38]. Both the management of and the complications of diabetes, including hypoglycemia and the fear of 'hypos', has a large impact on people's lives and their quality of life[39]. This includes both the people with diabetes, and their families/caregivers[40]. Increasingly, people with diabetes are turning to technologies, for both insulin delivery and/or glucose monitoring, to help them in their diabetes management. Patients and their families/caregivers, understandably then, have a wealth of knowledge and experience on both managing diabetes and more recently also on using technologies to help them do this. Traditionally, this kind of knowledge and experience is not well captured through clinical effectiveness research, and most particularly through RCT's. Reviewing and/or conducting qualitative research on patient and family/caregiver experience is necessary, to increase understanding on what it's like to live with

diabetes, how the use of insulin delivery and/or glucose monitoring technologies can help with diabetes management, and what impact this can have on people's day-to-day quality of life.

6.5 Complications

Diabetes is the sixth leading cause of death in Canada leading to nearly 7,000 deaths (2.6%) in 2016[1]. Additionally, it is estimated that 1 of 10 deaths in Canada is attributable to diabetes-related complications. Diabetes and its complications are financially strenuous on the Canadian health care system due to increased use of health services, loss of productivity, and ongoing support needed to manage complications[2].

6.5.1 Physiological Complications

Many diabetes-related complications arise from chronic hyperglycemia. Hyperglycemia is the inability of the body to produce or effectively use insulin to reduce blood glucose levels, which can damage blood vessels over time, leading to serious microvascular complications affecting:

i) *Eyes*: Diabetes increases the risk of serious vision conditions such as cataracts and glaucoma. Damage to blood vessels in the retina (i.e., diabetic retinopathy) can lead to blindness, causing diabetes to become the leading cause of blindness[3].

ii) *Kidneys:* Damage to blood vessels in the kidney's filtering system is the leading cause of nephropathy and end-stage renal disease (ESRD)[3].

iii) *Nerves:* Excess glucose can also lead to nerve damage, in particular, in the feet and legs, leading to pain, numbness, and tingling[3,41]. Damage to nerves in the feet can lead to serious adverse outcomes – untreated sores or blisters on the feet can develop serious infections that may result in limb amputation, making diabetes the leading cause of non-traumatic amputation in Canadian adults[3]. Additionally, autonomic neuropathy (e.g., damage to nerves that control internal organs) can lead to serious problems for the vascular system (e.g., hypertension), digestive system (e.g., nausea, vomiting, diarrhea, and constipation), bladder, reproductive organs (e.g., erectile dysfunction), and sweat glands[41].

In addition to microvascular complications, macrovascular complications are also of concern. Cardiovascular disease (CVD) occurs two to four times more often in people with diabetes than people without diabetes[2], and people with diabetes are more likely to have a number of risk factors that increase the chances of heart disease or stroke such as hypertension and high cholesterol[42]. Furthermore, people with diabetes are more likely to develop heart disease at a younger age than people without diabetes[42].

Micro- and macrovascular complications develop over time. People with diabetes are also at risk for a number of acute complications that can arise due to poor glycemic control that can have rapid onset with serious consequences. Occurrences of hypo- and hyperglycemia can lead to acute symptoms such as fatigue, headache, blurred vision, anxiety, sweating,[19] and if left untreated long enough, complications such as seizure and loss of consciousness can occur[3]. Additionally, diabetic ketoacidosis (DKA) can occur if the body does not have enough insulin to lower blood glucose levels, resulting in hyperglycemia and ketosis. DKA is a serious medical emergency that if not treated immediately, can lead to death[43].

Properly managing blood sugar levels reduces the risk of developing the complications mentioned above. Yearly screening of diabetic patients for eye problems (retinopathy screening), nerve damage and circulation (foot examinations), cholesterol screening, blood pressure screening and kidney disease screening should be performed to prevent complications and prolong disease complications.

6.5.2 Psychological Effects

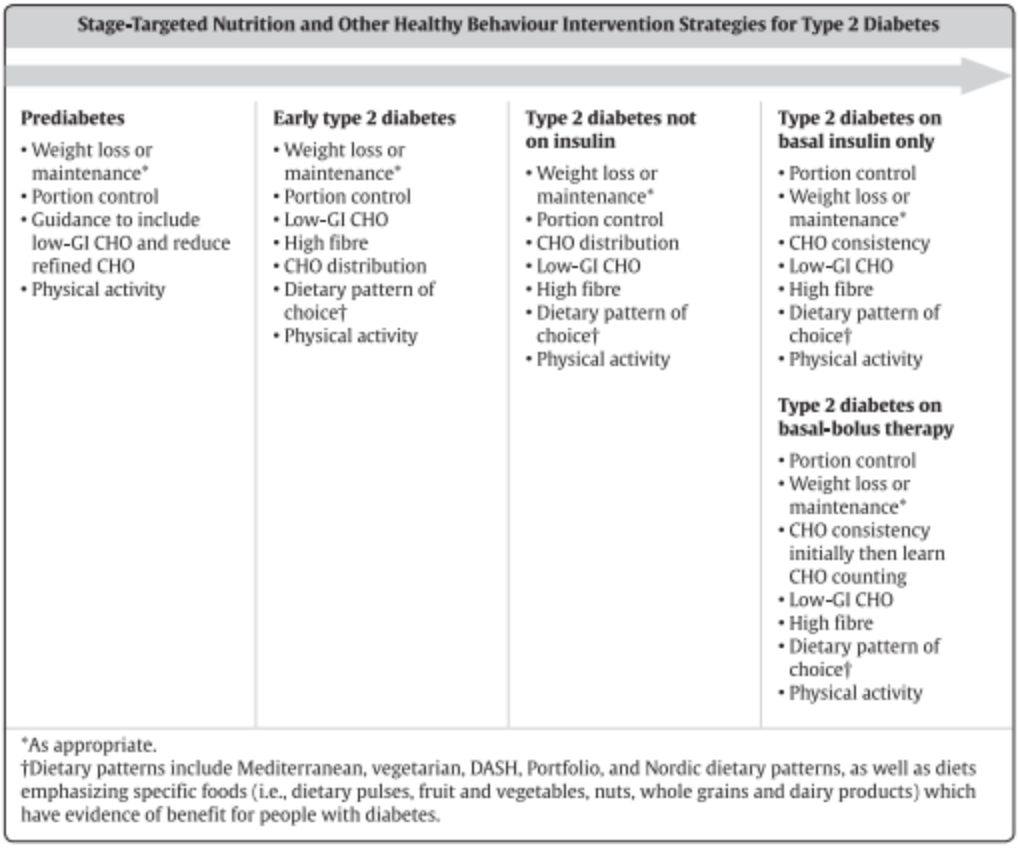
Psychological complications to quality of life and mental health are also a concern. It has been estimated that 30% of people with diabetes have clinically diagnosed depression[2]. Several psychological disorders are more prevalent amongst people with diabetes compared to the general population, including: schizophrenia spectrum disorder, anxiety and stress-related disorders, sleep disorders, and eating disorders[44]. People with diabetes can live in extreme fear of acute symptoms of the disease (e.g., severe hypoglycemic events), which can affect their day-to-day living, such as the ability to drive a car, travelling with insulin and glucose monitoring supplies, and the pain/discomfort of having to fingerprick multiple times per day.

6.6 Overall Costs of Diabetes in Canada

Canada's spending on diabetes-related health expenditure ranks as seventh globally, with a total of US$17 billion in 2015[2]. According to Bilandzic and Rosella's[45] diabetes incidence prediction model, the 10-year risk of Canadians developing diabetes is 9.98%, which accounts for 2,156,000 new cases between 2011/12 and 2021/22. The estimated total health care costs of just these new cases is $15.36 billion. The largest proportion of this health care costs is from acute hospitalizations ($6.64 billion) due to disease complications. The second largest at $3.37 billion is for physician costs, followed by prescription medication and assistive devices which account for $2.60 billion, followed by $1.05 billion in home care, non-physician care and long-term care. The remaining $1.71 billion is from other inpatient and outpatient clinic services[45].

6.7 Disease Prevention

The cause of T1D is still unknown; therefore, no preventative measures currently exist. However, the literature on the prevention of T2D is abundant. T2D can be prevented (or delayed in those with a strong genetic risk) through numerous strategies, including healthy behavior interventions (reducing overweight and obesity rates), introducing healthy dietary choices, and through pharmacotherapy. The Diabetes Canada Clinical Practice Guidelines Expert Committee recommended the following stage-targeted nutrition and other healthy behavior intervention strategies for T2D as seen in Figure 6.6 in their 2018 clinical practice guidelines[3]:



Footnote:

Abbreviations: CHO=carbohydrate, GI=glycemic index, NPH=neutral protamine Hagedorn

Figure 6.6 Stage-targeted nutrition and other healthy behavior strategies for people with T2D[3].

With Canada's diverse populations and certain ethnic populations being disproportionately affected by diabetes, health promotion and disease prevention strategies are important. Diabetes health education along with management strategies for those diagnosed should be culturally appropriate and tailored to high-risk populations.

Although maintaining a healthy lifestyle with a healthy body weight, healthy eating and physical activity is the primary goal in preventing T2D, an individual's ability to adopt this lifestyle is influenced by many factors including their socioeconomic status.

7 Clinical Validity of Time in Range: A Systematic Review

Summary

- A systematic review included two studies that examined the association between time in range and a clinical outcome in an outpatient, insulin-dependent population.
- One study explored the association between TIR and internalizing and externalizing behaviours, and concluded that higher % time spent in range was associated with lower levels of externalizing behaviour.
- The second study explored the association between TIR and the risk for developing diabetic retinopathy and microalbuminuria in children and adults (age 13-39 years old). This study found that lower % TIR was associated with higher risk of developing retinopathy, and microalbuminuria
- Given the lack of evidence, TIR should not be considered a validated surrogate marker for diabetes-related complications

7.1 Background

A surrogate marker can be considered a more easily measured outcome that represents the true clinical outcome of interest. Figure 7.1 demonstrates the expected validity of a surrogate marker[46]. With the increased reporting of time in range as a surrogate marker within clinical trials, it is important to understand its validity.

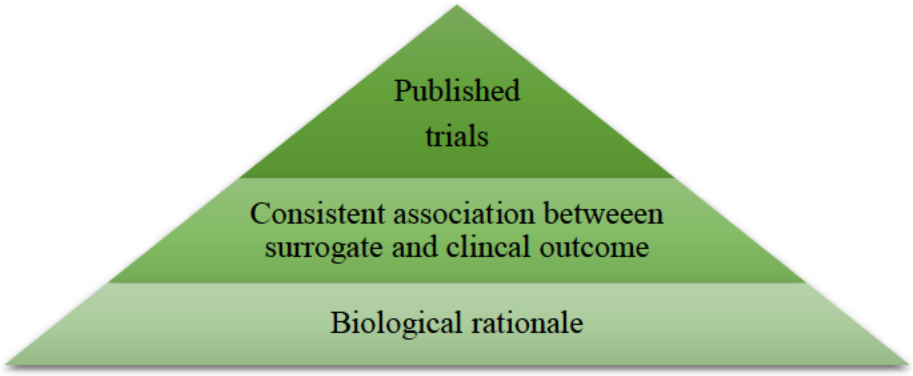


Figure 7.1 Hierarchy of evidence for validating surrogate markers as a useful tool for measuring clinical outcomes

7.2 Purpose

To assess the association between time in range (TIR) and clinical outcomes in people with diabetes.

7.3 Methods

7.3.1 Search Strategy

A systematic review was completed. Four databases (CINHAL, Cochrane Central, EMBASE, and MEDLINE) were searched from all-time to December 10, 2018. To identify relevant literature, terms used to describe diabetes (e.g., "type 1", "type 2", "diabetes", and "diabetes mellitus") or glucose monitoring (e.g., "blood glucose meters", "blood glucose monitor", and "blood glucose self monitor") were combined with terms describing TIR (e.g., "time in target", "euglycemia", "normal fasting glucose", and "normoglycemia"). Studies had to be in English or French. The full search strategy can be found in *Appendix B: Search Strategy for Systematic Review of TIR Clinical Validity.*

The abstracts retrieved were screened in duplicate by independent reviewers. Abstracts were assessed using the *a priori* inclusion and exclusion criteria (Table 7.1). Abstracts of articles that did not meet the inclusion criteria were excluded. Abstracts included by either reviewer proceeded to full-text review.

Table 7.1 Inclusion/Exclusion Criteria for TIR Clinical Effectiveness Systematic Review

Inclusion	**Exclusion**
Outpatient population	Inpatient population
Insulin dependent population	Non-insulin dependent population
Associates TIR with clinical, function, QoL outcomes	Does not associate TIR with clinical, functional, QoL outcomes
Any study design	
	Conference abstract, editorial, commentary

7.4 Results

The search identified 3669 studies; 1984 remained after duplicates were removed. After abstract screening, 14 studies were identified by either reviewer as meeting all inclusion criteria, and proceeded to full-text review. An additional 12 studies were removed during full-text review, resulting in two studies included in our analysis (Figure 7.2).

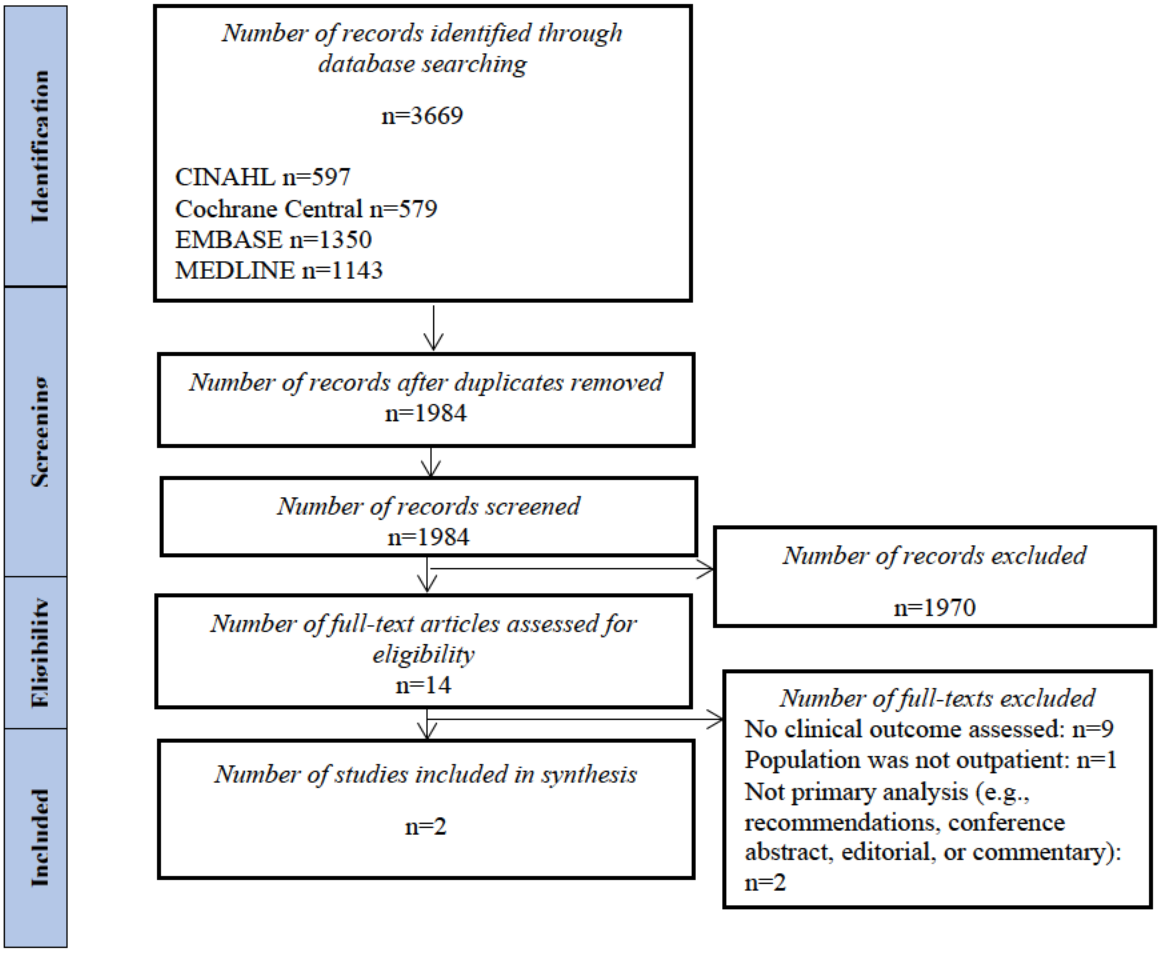


Figure 7.2 PRISMA Flowchart for Included Studies

Only two studies[47,48] explored the association between TIR and clinical outcomes in individuals with type 1 diabetes. The studies differ in both the population and the clinical outcomes studied (Table 7.2).

McDonnell and colleagues (2007)[47] explored the association between TIR and behaviour (externalizing and internalizing) in 42 children aged 5-10 years attending the Outpatient Clinic of the Royal Children's Hospital, Melbourne, Australia. To measure blood glucose levels, children

wore a continuous blood glucose monitor for 72 hours at two study time points (six months apart). Normal glycemic ranged was defined as between 4-12mmol/L. To measure externalizing behaviours (i.e., hyperactivity, aggression, and conduct scores), and internalizing behaviours (i.e., depression, anxiety, and somatization scores) parents completed the Behaviour Assessment System for children at the two study points.

The study found that TIR was associated with externalizing behaviours but not with internalizing behaviours. The higher the percentage of time that children's blood glucose levels were within 4-12 mmol/L, the lower the score of externalizing behaviours reported. The study also explored the association between the percentage of time in high glycemic (i.e., >12 mmol/L) and low glycemic (i.e., < 4 mmol/L) ranges and children's behaviour. No association was found between the percentage of time spent in the low glycemic range and children's behaviour. However, a higher percentage of time spent in high glycemic range was associated with higher score in externalizing behaviours.

Beck and colleagues (2019)[48] explored the association between TIR and the development of microalbuminuria, and the development and progression of diabetic retinopathy in individuals with type 1 diabetes aged 13-39 years. This was a secondary data analysis using data from the Diabetes Control and Complications Trial (DCCT) data set collected between 1983 and 1993. The main objective of Beck and colleagues' (2018)[48] study was the validation of TIR as outcome measure for clinical trials. The DCCT defined TIR as the percentage of the sample with blood glycemic range between 3.9-10 mmol/L (70-180 mg/L). The DCCT collected data on blood glucose concentrations during one day every three months. Participants provided seven fingerstick samples (pre and post meals and at bedtime) at each study point. Blood glucose concentrations were determined at a central laboratory. Retinopathy was assessed using gradings from fundus photographs taken every six months. Sustained progression of three or more steps from baseline at two or more consecutive visits indicated retinopathy progression. Microalbuminuria (i.e., album excretion rate (AER) >= 30g/24 h at two consecutive visits) was assessed every 12 months.

The study found a strong association between the percentage of time spent in blood glycemic range between 3.9-10 mmol/L and each of the outcomes measured. Lower TIR was associated with higher risk of developing retinopathy and with higher risk of developing microalbuminuria.

For each 10% lower TIR, the risk of developing retinopathy increased by 60%; and the risk of developing microalbuminuria increased by 40%.

Table 7.2 Summary TIR and Clinical Outcomes Literature

	Objective	Population	TIR definition	Outcome Measure	Results
McDonnell et al (2017)[47]	Association between TIR and children's behaviour	42 children aged 5-10 years attending the Outpatient Clinic of the Royal Children's Hospital, Melbourne, Australia	4-12 mmol/L	Externalizing and internalizing behaviour	-Higher % spent in TIR lower score externalizing behaviour -Higher % time in high glycemic range (>12 mmol/L) higher score externalizing behaviour
Beck et al (2019)[48]	-Association between TIR and development of retinopathy and development of microalbuminuria -Validation of TIR as outcome measure in clinical trials	Secondary data from 1,440 participants of the DCCT trial. Age 13-39 years.	3.9-10 mmo/L	-Development of retinopathy -Development of microalbuminuria	-Lower % time spent in TIR associated with higher risk of developing retinopathy and microalbuminuria

7.5 Conclusions

The literature in the association between TIR and clinical outcomes is very limited and it does not allow for comparisons across populations. If TIR is to be used as a quantifiable measure of diabetes complications and outcomes, future researchers may consider studying the association between TIR and complications of diabetes such as: symptomatic hypoglycemia and hyperglycemia, cardiovascular disease, eye disease, nephropathy, neuropathy, foot ulcers/amputations, stroke and general mortality[36,49]. Based on the literature to date, TIR should not be considered a validated surrogate.

8 Systematic Review of Health Technology Assessments on Glucose Monitoring Technologies

Summary

- Ten HTAs were included for review. Seven HTAs examined CGMs (two of which also included SAPs and one included FGMs); the other three HTAs examined FGMs.
- In terms of clinical effectiveness, four HTAs favoured the use of CGM over SMBG; three determined that the evidence did not support the superiority of CGMs compared to SMBG; and three HTAs found that FGMs was superior to SMBG in some aspects and similar in others.
- Four HTAs identified literature on the cost-effectiveness of CGMs. Four HTAs conducted their own cost analyses of glucose monitoring technologies. In all HTAs that conducted cost analyses, glucose monitors were unlikely to be the cost-effective option for any of the included comparators.
- Only two HTAs provided specific recommendations regarding the use of glucose monitors; one noted that the evidence supported the recommendation for CGMs to be used by children and adolescents over the age of eight; another noted that rt-CGM should not be offered routinely to adults with T1D, only to select groups of patients.

8.1 Purpose

To synthesize health technology assessments (HTAs) on glucose monitoring technologies, including continuous glucose monitors (CGMs), flash glucose monitors (FGMs), or sensor-augmented pumps (SAPs; continuous subcutaneous insulin infusion [CSII] + real-time-CGM) for patients with type 1 (T1) and type 2 diabetes mellitus (T2D).

8.2 Methods

8.2.1 Search Strategy

A systematic database search of HTAs was completed by searching the HTA Database from inception until April 10th, 2019. Terms aimed to capture the technologies of interest, such as "flash monitor," "continuous," "CGM," or "sensor augmented pump," were combined with the Boolean Operator "or." These searches were combined with terms to indicate blood glucose monitoring and diabetes such as "diabetes mellitus," "blood sugar," or "monitor." Terms were searched as text words in titles and abstracts or as subject headings (e.g. MeSH). The search

strategy was developed by a research librarian. The full search strategy is reported in *Appendix A: Search Strategy for Systematic Review of HTAs*

The systematic database search was supplemented by a grey literature search guided by the Canadian Agency for Drugs and Technologies in Health's (CADTH) "Grey Matters" document. Grey literature and the websites of known HTA organizations were searched using terms including "diabetes" and "glucose monitor."

8.2.2 Study Selection

Abstracts returned through the database search were screened in duplicate; all abstracts included at this stage by either reviewer proceeded to full-text review. Full-text publications were screened in duplicate. Any discrepancies between reviewers' inclusions were resolved through discussion between reviewers. Publications were excluded if they did not meet the inclusion criteria (Table 8.1), if full-text was not available, or if the study was not available in English or French. Publications were considered relevant if they included a systematic review of clinical effectiveness of any of the technologies of interest.

Table 8.1 Inclusion and Exclusion Criteria for HTA Review

Inclusion Criteria	Exclusion Criteria

• HTA or evidence review on glucose monitoring systems for insulin-dependent diabetes patients, including:
  ○ CGMs
  ○ FGMs
  ○ SAPs (CSII + rt-CGM)
• Adult or children population
• Insulin-dependent Type 1 or Type 2 patients
• English or French Language only
	• Not an HTA or evidence review
	• Not Type 1 or Type 2 diabetes
	• Not available in English or French
	• Full text not available

Abbreviations: CGM: continuous glucose monitor; FGM: flash glucose monitor; HTA: health technology assessment; SAP: sensor-augmented pump

8.2.3 Data Extraction

Data from the included HTAs were extracted in duplicate. Extracted outcomes included: study characteristics (author/date, country, study objectives, amount and type of evidence included), details on clinical effectiveness, cost-effectiveness and any *de novo* models included in each

HTA, and recommendations. Discrepancies between reviewers during data extraction were resolved through discussion.

8.3 Results

The database search identified 34 records. Two of the records were duplicates, resulting in 32 unique citations. After excluding 12 abstracts, 20 studies proceeded to full-text review. Ten additional HTAs were identified through grey literature searching and consultation with key stakeholders. Thus, a total of 30 studies were screened at the full-text stage (Figure 8.1). Twenty studies were excluded because they were either: not a full HTA that clearly conducted a systematic review of clinical effectiveness (n=12); not published in English or French (n=5); or not available as full-texts (n=3). A total of ten HTAs were included in the data set.

Four of the HTAs were from Canada,[50-52] two were from the UK,[53,54] one was from the US,[55] one was from Norway,[56] one was from France,[57] and one was from Europe.[58] A narrative synthesis of each HTA is provided below.

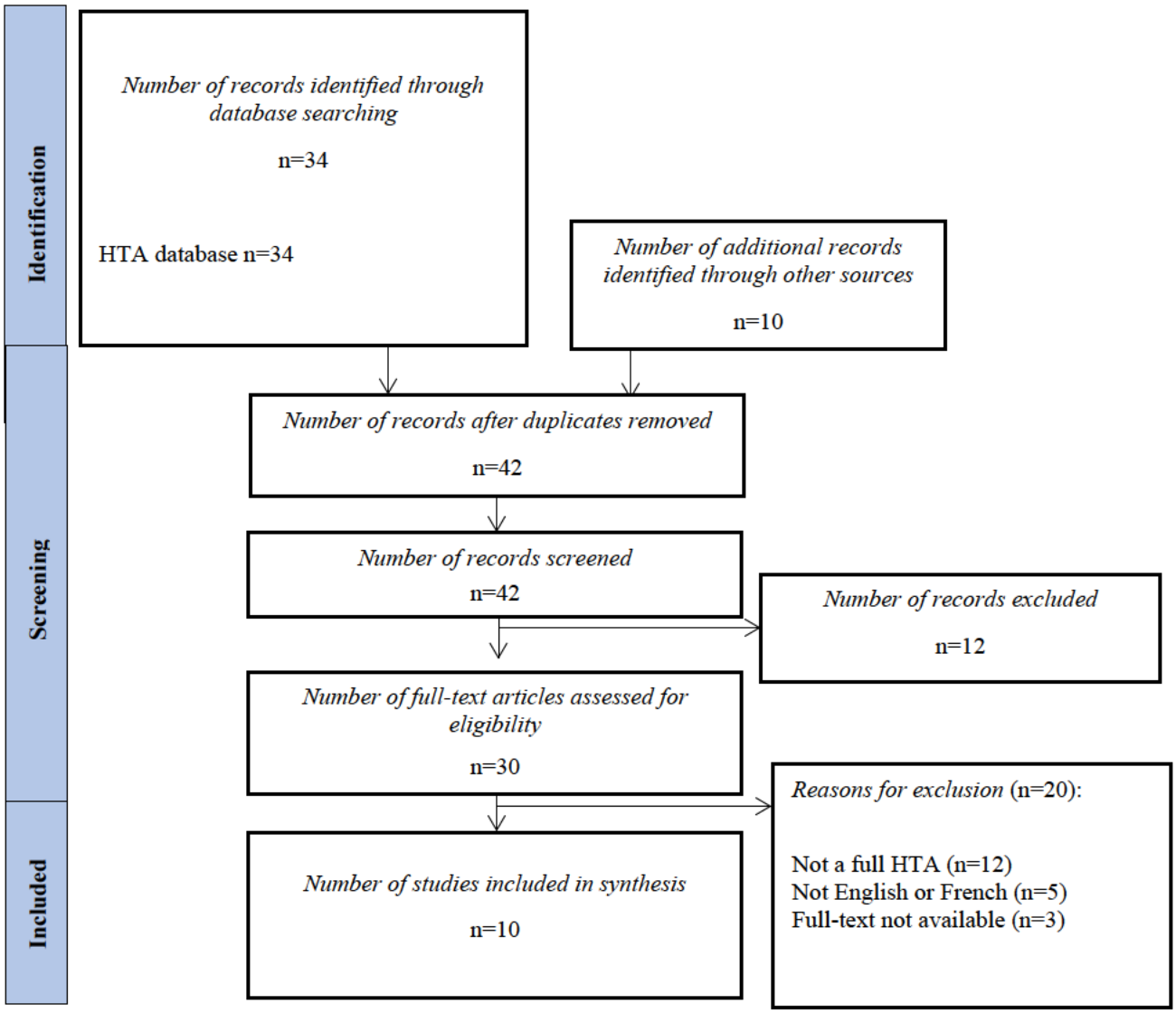


Figure 8.1 Study Inclusion Flow Chart

8.3.1 Health Quality Ontario (2019, 2018)

FGM for T1D or T2D (on MDI) (2019)

In 2019, Health Quality Ontario (HQO) in Canada conducted an HTA to examine the clinical benefit, cost-effectiveness, and patient experiences of FGM (Freestyle Libre) for patients with T1D or T2D who require intensive insulin therapy. Primary outcomes examined in the clinical effectiveness review were time spent in the target glucose range and hypoglycemia, hypoglycemia events, glucose variability, HbA1c values, severe hypoglycemic events, device-related adverse events, and quality of life outcomes; clinical databases were searched from January 2014 to April 2018. Primary outcomes examined in the cost-effectiveness review were costs and effects, incremental costs or cost of interventions, incremental effectiveness outcomes, incremental net benefit, and ICERs; economic databases were searched from January 2014 to April 2018. A primary economic evaluation was not conducted. This HTA is still undergoing stakeholder review; therefore, its findings should be interpreted with caution.[59]

The clinical effectiveness review in this HTA included six studies (2 RCTs, one separate RCT subgroup analysis, and three observational studies). Clinical findings suggest that FGM was more effective at SMBG at improving several glycemic outcomes (reducing glucose variability, as well as average time spent in target glucose range, time spent in hypoglycemia, and number of hypoglycemia events) in adults with T1D and T2D requiring intensive insulin therapy. The cost-effectiveness review identified two studies: one cost-utility analysis that was found to not be applicable to the Ontario health care system, and one cost analysis study from the UK that found that FGM reduced costs when SMBG was performed 10 times/day, but was more expensive when SMBG was performed 5.6 times/day. Budget impact analysis found that public funding of FGMs for these populations in Ontario would result in additional costs of $14.6 million and $38.6 million annually over the next 5 years. Adults with diabetes and parents of children with diabetes interviewed as part of the HTA reported having positive experiences with FGM with respect to helping them control their blood glucose levels, which resulted in physical, emotional, and social benefits; cost of FGM was noted as the largest barrier to its use.

CGM for T1D (2018)

In 2018, HQO in Canada conducted an HTA to examine the clinical benefit, cost-effectiveness, and patient experiences of CGMs (Medtronic or Dexcom) vs. usual care (SMBG) for management of T1D.[51] Primary outcomes examined in the clinical effectiveness review were time-related glucose variability, hypoglycemia, HbA1c levels, and user satisfaction; clinical databases were searched from January 2010 to January 2017. Primary outcome examined in the cost-effectiveness review was costs; economic databases were searched between January 2010 and January 2017. A Markov model of CGM vs. SMBG complications in patients with T1D was adapted from the literature.

The clinical effectiveness review in this HTA included 20 studies (16 RCTs and four observational studies). Clinical findings suggest that CGM was more effective than SMBG for managing T1D in terms of time spent in target glucose range and severe hypoglycemic events. Economic evidence from the literature suggests that CGM was more effective but also more costly. Primary economic evaluation conducted in a Canadian context found that CGM was not more cost-effective vs. SMBG at common willing-to-pay thresholds, and that there was considerable uncertainty about value for money (ICERs ranged from $592,206/QALY gained to $1,108,812/QALY gained). Adults with diabetes and parents of children with diabetes interviewed as part of the HTA reported that CGMs provided important social, emotional, medical, and safety benefits in management of T1D, particularly in children.

8.3.2 Institut National d'Excellence en Santé et en Services Sociaux (2018)

Institut National d'Excellence en Santé et en Services Sociaux (INESSS) in Canada conducted an HTA to examine whether Freestyle Libre (FGM) should be reimbursed for adults with T1D and T2D who have a minimum of two years' experience in diabetes self-management.[52] Primary outcomes examined in the clinical review were HbA1c, hypoglycemia, safety, treatment satisfaction, and QoL. Primary outcomes examined in the economic review were costs, QALY,

and utility/disutility. Clinical and economic databases were searched between 2014 and January 2018.

Although several studies were identified, two RCTs formed the basis of the decision in the INESSS HTA. In these studies, FGM led to a significant reduction in the number and duration of daytime and nighttime hypoglycemic events in patients with T1D and T2D (who have poor blood glucose control and are undergoing insulin treatment), but no difference in severe hypoglycemic events. FGM also led to an increase in time spent in the normal glycemic range in T1D but not T2D patients; and no improvement in HbA1c in T2D. QoL improvements were noted only with respect to treatment satisfaction. Economic evidence on the incremental value of FGM vs. SMBG was uncertain. INESSS' cost analyses suggested that FGM is not a cost-efficient option. Physicians and patients interviewed as part of this HTA noted that pricking one's finger less frequently to measure blood glucose levels can improve the quality of life in patients with diabetes.

8.3.3 European Network for Health Technology Assessment (2018)

The European Network for Health Technology Assessment (EUnetHTA) HTA was conducted in 2018 in Europe to examine the effectiveness and safety of rt-CGM (several models) and FGM (FreeStyle Libre) as personal, standalone systems in patients with insulin-dependent diabetes.[58] The primary outcome examined was HbA1c; clinical databases were searched in March 2018. A cost-effectiveness review was not conducted.

The EUnetHTA found 12 RCTs on the use of rt-CGM and FGMs compared with SMBG; three non-RCTs on safety were identified. rt-CGM led to a statistically significant reduction in HbA1c levels compared with SMBG in the majority of studies with MDI patients and two studies with MDI and CSII patients; both the rt-CGM and FGM devices were associated with reduction in hypo- and hyperglycemia outcomes and improved satisfaction in patients with type 1 or type 2 diabetes mellitus, compared with SMBG. Adults, children, and parents of children with T1D interviewed as part of this HTA reported having very positive experiences with rt-CGM and FGM devices; notable benefits included emotional and social impact, better quality of life, changes to sleeping patterns, independence, and better control and normal life. Patients stressed

the importance of education and noted concerns around the high cost and unavailability of these devices in some countries.

8.3.4 Norwegian Institute of Public Health (2017)

In 2017, Norwegian Institute of Public Health (NIPH) in Norway conducted an HTA to assess the clinical effectiveness, cost effectiveness and safety of the Freestyle Libre (FGM) for patients with T1D and T2D.[56] Primary outcomes examined in the clinical review were HbA1c, hypoglycemia or hyperglycemia (day, night time, and episodes), QoL, patient/treatment satisfaction, pain, and adverse events; databases were searched from inception to January 2017. An economic review of the literature was not conducted. Cost-effectiveness estimates were provided by the manufacturer using the IMS Core Diabetes model.

Two RCTs were identified as part of the review. Clinical findings from the limited literature suggest that FreeStyle Libre increases treatment satisfaction, reduces some hypo-and hyperglycemic measures, and has similar adverse events as SMBG, without differences in other outcomes including HbA1c and QoL. NIPH considered the results of the manufacturer-submitted cost-effectiveness analysis to be not reliable. NIPH concluded that because FreeStyle Libre does not seem to provide a higher efficacy or fewer adverse events or increased QoL for insulin treated patients than other SMBG devices, it makes it difficult to support the lower costs associated with FreeStyle Libre. NIPH noted that additional clinical trials are ongoing and that the results of this assessment will likely change when new evidence becomes available.

8.3.5 National Institute for Health Research (2016)

In 2016, the National Institute for Health Research (NIHR) in the UK conducted an HTA on MiniMed Paradigm Veo (SAP) and the Vibe and G4 Platinum (CGM) for the management of T1D in adults and children.[53] The devices were compared to MDI or CSII, both either with SMBG or CGM. Primary outcomes examined in the clinical effectiveness review were HbA1c levels, frequency of hyperglycemic events and number of hyperglycemic episodes, frequency of (nocturnal) hypoglycemic evens and number of hypoglycemic episodes, and DKA; clinical databases were searched from inception to September 2014. Primary outcome examined in the

cost-effectiveness review was costs; economic databases were searched from inception to September 2014. The IMS Core diabetes model was used in the economic analysis.[60]

The NIHR HTA included nine studies assessing glucose monitors. Clinical findings suggest that MiniMed Paradigm Veo system reduces hypoglycemic events in adults more than other treatments, without any differences in other outcomes, including changes in HbA1c levels. The evidence also favoured CSII+CGM over MDI+SMBG with respect to HbA1c levels and QoL. However, the evidence base was poor and was based on studies of low quality that often consisted of single studies comparing treatments in a specific population at a specific follow-up time. Cost-effectiveness analyses suggest that MDI+SMBG is likely the most cost-effective option given the current threshold of £30,000 per QALY gained, whereas CSII+CGM dominates and extendedly dominates integrated CSII + CGM systems and MiniMed Paradigm Veo, respectively.

8.3.6 National Institute for Health and Care Excellence (2015)

In 2015, National Institute for Health and Care Excellence (NICE) in the UK published an update to a guideline on adult T1D. The guideline was based on clinical and economic systematic review components to examine whether rt-CGM (several models) is more effective than SMBG for optimum diabetic control, and whether continuous or intermittent rt-monitoring is more effective.[54] Primary outcomes in the clinical review were HbA1c, hypoglycemia, QOL, adverse events, and adherence; clinical databases were searched in August 2014. Primary economic outcomes were costs; economic databases were searched from inception to August 2014, and select clinical databases were searched between 2009 and August 2014. The IMS Core diabetes model was used in the economic analysis.

Nine studies (three RCTs) were found that examined rt-CGM vs. SMBG. Clinical evidence suggested no clinical difference between rt-CGM and SMBG for hypoglycemic episodes per day, severe hypoglycemia, adverse events, or QOL; and a clinically important reduction in HbA1c with rt-CGM, compared to SMBG. Review of the economic literature suggested that CGM was not cost effective compared with SMBG in people with T1D (ICERs: £29,029 per QALY gained and £63,828 per QALY gained). In economic modelling, SMBG (8 times a day)

was dominant (less costly and more effective) to CGM in people with T1D. NICE did not recommend offering rt-CGM routinely to adults with T1D, with the exception of adult patients with T1D who are willing to commit to using it ≥70% of the time and calibrate as needed and who meet any of the following criteria despite optimal use of insulin therapy and conventional SMBG:

- >1 episode a year of severe hypoglycemia with no obviously preventable precipitating cause;
- complete loss of awareness of hypoglycemia;
- frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities;
- extreme fear of hypoglycemia;
- hyperglycemia (HbA1c level ≥75 mmol/mol [9%]) that persists despite testing ≥10 times a day; continue rt-CGM only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of ≥27 mmol/mol (2.5%).

8.3.7 Agency for Healthcare Research and Quality (2012)

The Agency for Healthcare Research and Quality (AHRQ) in the United States conducted an HTA on rt-CGMs (several models) and SAPs in 2012 to examine the efficacy in patients with diabetes mellitus who are receiving intensive insulin therapy (multiple daily injections [MDI] or continuous subcutaneous insulin infusion [CSII]).[55] Primary outcomes examined in the clinical review were HbA1c, rates of hypoglycemia, rates of hyperglycemia, and weight gain; clinical databases were searched from inception to July 2011. A cost-effectiveness review was not conducted.

The AHRQ HTA found nine RCTs for the rt-CGM vs. SMBG comparison and four RCTs vs. MDI/SMBG comparison. In the rt-CGM vs. SMBG comparison, rt-CGM was superior to SMBG in lowering HbA1c in non-pregnant individuals with T1D without affecting the risk of severe hypoglycemia, particularly in people who are compliant with wearing the device. In the SAP vs. MDI/SMBG comparison, SAPs were superior to MDI/SMBG in lowering HbA1c in non-pregnant individuals with T1D; evidence on severe hypoglycemia or QoL was insufficient to draw definitive conclusions. Results from the rt-CGM vs. SMBG comparison support the clinical

practice recommendations suggesting rt-CGM use in children and adolescents over the age of 8 years.

8.3.8 Medical Advisory Secretariat (2011)

In 2011, the Medical Advisory Secretariat (MAS) in Canada conducted an HTA on clinical and cost-effectiveness of CGMs+SMBG (several models) vs. SMBG alone in the management of diabetes.[50] Primary outcomes examined in the clinical effectiveness review were change in HbA1c, frequency or duration of hypo-or hyperglycemic episodes or euglycemia, and adverse effects; clinical databases were searched between January 2002 and September 2010. Primary outcomes examined in the cost-effectiveness review were costs and consequences of CGMs; economic databases were searched in March 2011.

Findings from the two large RCTs identified as part of the MAS HTA suggest that CGM+SMBG is not more effective than SMBG alone in reduction of HbA1c using insulin infusion pumps for T1D. Similarly, findings suggest that CGM+SMBG is not more effective than SMBG alone in reduction of hypoglycemic or severe hyperglycemic events using insulin infusion pumps for T1D No cost-effectiveness studies that met the inclusion criteria were identified.

8.3.9 Haute Autorité de Santé (2006)

A 2006 HTA of the efficacy and safety of CGM (several models) vs. SMBG in patients with insulin-dependent diabetes mellitus published by the Haute Autorité de Santé (HAS) in France was located as part of the systematic HTA search.[57] Details of the findings of the HAS HTA are reported in Table 8.2; however, it should be noted that the HTA would have assessed evidence on older versions of CGMs that may currently exist on the market.

Table 8.2 Study Characteristics of Included Health Technology Assessments

Organization, Country, Year	Technology	Recommendations/ Conclusions
HQO, 2019, Canada [DRAFT – interpret with caution][59]	FGM [Freestyle Libre] vs. SMBG	• FGM was more effective at SMBG at improving several glycemic outcomes (reducing glucose variability, as well as average time spent in target glucose range, time spent in hypoglycemia, and number of hypoglycemia events) in adults with T1D and T2D requiring intensive insulin therapy. • Public funding of FGMs for these populations in Ontario was estimated to result in additional costs of $14.6 million and $38.6 million annually over the next 5 years. • Adults with diabetes and parents of children with diabetes interviewed as part of the HTA reported having positive experiences with FGM with respect to helping them control their blood glucose levels, which resulted in physical, emotional, and social benefits; cost of FGM was noted as the largest barrier to its use.
Health Quality Ontario (HQO), 2018, Canada[51]	CGM [Medtronic or Dexcom], standalone or integrated SAPs vs. usual care (SMBG)	• CGM was more effective than SMBG for managing T1D in terms of time spent in target glucose range and severe hypoglycemic events. • Economic evidence was mixed. All studies indicated CGM was more effective but also more costly. • Primary economic evaluation (conducted for Canadian context) found that CGM interventions were not cost-effective vs. SMBG at common willing-to-pay thresholds; ICERs ranged from $592,206/QALY gained to $1,108,812/QALY gained. • Adults with diabetes and parents of children with diabetes interviewed as part of the HTA reported that CGMs provided important social, emotional, medical, and safety benefits in management of T1D, particularly in children.
Institut National d'Excellence en Santé et en Services Sociaux (INESSS), 2018, Canada[52]	FGM [Freestyle Libre] vs. SMBG	• No improvement in HbA1c in the FGM group after 6 months in patients with T2D who have poor blood glucose control and are undergoing insulin treatment. • Number and duration of daytime and nighttime hypoglycemic events were significantly reduced in the FGM group in T1D and T2D; no differences were observed with respect to severe hypoglycemic events. Time spent in normal range was increased in T1D but not T2D. QoL improvements were noted only with respect to treatment satisfaction. • Economic evidence on the incremental value of FGM vs. SMBG was uncertain. INESSS cost analyses suggest that FGM is not a cost-efficient option.

Organization, Country, Year	Technology	Recommendations/ Conclusions
		• Physicians and patients interviewed as part of this HTA noted that pricking one's finger less frequently to measure blood glucose levels can improve the quality of life in patients with diabetes.
European Network for Health Technology Assessment (EUnetHTA), 2018, European Union[58]	rt-CGM [several models] and FGM [Freestyle Libre], vs. SMBG	• rt-CGM led to a statistically significant reduction in HbA1c levels compared with SMBG in the majority of studies on MDI patients, and two studies on MDI and CSII patients. • No difference was identified in the only and small head-to-head study comparing rt-CGM to FGM. • Both rt-CGM and FGM devices were associated with reduction in hypo- and hyperglycemia outcomes and improved satisfaction in patients with T1D or T2D, compared with SMBG. • Adults, children, and parents of children with T1D interviewed as part of this HTA reported having very positive experiences with rt-CGM and FGM devices; notable benefits included emotional and social impact, better quality of life, changes to sleeping patterns, independence, and better control and normal life. Patients stressed the importance of education and noted concerns around the high cost and unavailability of these devices in some countries.
Norwegian Institute of Public Health, 2017 (NIPH; Folkehelseinstituttet), Norway[56]	FGM [Freestyle Libre]	• Limited clinical efficacy evidence suggests that FreeStyle Libre increases treatment satisfaction, reduces some hypo-and hyperglycemic measures, and has similar adverse events as SMBG, without differences in other outcomes including HbA1C and QoL, in patients with T1D and T2D. • NIPH considered the results of the manufacturer-submitted cost-effectiveness analysis to be not reliable. • FreeStyle Libre does not seem to provide a higher efficacy or fewer adverse events or increased QoL for insulin treated patients than other SMBG devices, which makes it difficult to support the lower costs associated with FreeStyle Libre.
National Institute for Health Research (NIHR), 2016, UK[53]	SAP [MiniMed Paradigm Veo system and Vibe and G4 Platinum CGM system], vs. MDI+SMBG, CSII+SMBG	• Limited evidence suggests MiniMed Paradigm Veo system reduces hypoglycemic events in comparison with other treatments, with no difference in other outcomes, including HbA1c, in T1D. • The evidence favoured CSII+CGM over MDI+SMBG with respect to HbA1c levels and QOL.

Organization, Country, Year	Technology	Recommendations/ Conclusions
		• MDI+SMBG is most likely to be cost-effective at the threshold of £30,000 per QALY gained where CSII+CGM systems and MiniMed Paradigm Veo are dominated and extendedly dominated, respectively, by stand-alone CSII+CGM.
National Institute for Health and Care Excellence (NICE), 2015, UK[54]	rt-CGM [several models] vs SMBG	• No clinical difference between rt-CGM and SMBG for hypoglycemic episodes per day, severe hypoglycemia, adverse events, or QOL (physical health, mental health, hypoglycemia fear score, problem areas in diabetes, and total score). • No clinically important reduction in HbA1c for rt-CGM vs. SMBG. • Economic evidence in the literature found that CGM was not cost effective compared with SMBG in people with T1D (ICERs: £29,029 per QALY gained and £63,828 per QALY gained in two studies). • The NICE model found that people with type 1 diabetes, SMBG (8 times a day) was dominant (less costly and more effective) compared with CGM. • Do not routinely offer rt-CGM to adults with T1D, with the exception of select patients who are willing to calibrate the CGM as needed and meet any of the following criteria despite optimal insulin therapy and SMBG: o >1 episode a year of severe hypoglycemia with no obviously preventable precipitating cause; o complete loss of awareness of hypoglycemia; o frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities; o extreme fear of hypoglycemia; o hyperglycemia (HbA1c level ≥75 mmol/mol [9%]) that persists despite testing ≥10 times a day; continue rt-CGM only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of ≥27 mmol/mol (2.5%).
Agency for Healthcare Research and Quality (AHRQ), 2012, United States[55]	rt-CGM [several models] vs. SMBG; SAP vs. MDI/SMBG	• rt-CGM is superior to SMBG in lowering HbA1c, without affecting the risk of severe hypoglycemia, in non-pregnant individuals with T1D, particularly when compliance is high. • SAPs are superior to MDI+SMBG in lowering HbA1c. • Results from the rt-CGM vs. SMBG comparison support the clinical practice recommendations suggesting rt-CGM use in children and adolescents over the age of 8 years.

Organization, Country, Year	Technology	Recommendations/ Conclusions
Medical Advisory Secretariat (MAS), 2011, Canada[50]	CGM+SMBG [several models], vs SMBG alone	• CGM+SMBG is not more effective than SMBG alone in reduction of HbA1c using insulin infusion pumps for T1D. • CGM+SMBG is not more effective than SMBG alone in reduction of hypoglycemic or severe hyperglycemic events using insulin infusion pumps for T1D.
Haute Autorité de Santé (HAS), 2006, France[57]	CGM [several models] vs. SMBG	• RCTs do not show superiority of CGMs compared to SMBG in terms of metabolic control (HbA1c) in patients with insulin-dependent diabetes. • The evidence for the usefulness of CGMs in preventing excessive glycemic variability was stronger, especially for detection of nocturnal hypoglycemia, dawn phenomena, etc. • There is insufficient evidence to make a recommendation on the use of CGMs for treatment decisions vs. SMBG.

8.4 Conclusion

Ten HTAs of glucose monitors (including CGMs and FGMs) were included in this systematic review. All of the included HTAs evaluated clinical effectiveness. The findings were mixed with respect to the use of glucose monitors instead of SMBG: four HTAs favoured the use of CGM over SMBG; three determined that the evidence did not support the superiority of CGMs compared to SMBG; and three HTAs found that FGM was superior to SMBG with respect to some measures but not others.

Four HTAs identified literature on the cost-effectiveness of CGMs. One of these found that the evidence was mixed and determined that CGM was more effective but also more costly than SMBG. The other three determined that CGM was not more cost-effective than SMBG. Four HTAs conducted their own cost analyses of glucose monitoring technologies: one used a Markov model,[51] two used the IMS Core Diabetes Model,[53,54] and one conducted a cost minimization study.[52] In all HTAs that conducted cost analyses, glucose monitors were unlikely to be the cost-effective option for any of the examined comparators.

Only two HTAs provided specific recommendations regarding the use of glucose monitors. The US HTA noted that the evidence supported the recommendation that CGMs be used by children and adolescents over the age of eight.[55] One UK HTA noted that rt-CGM should not be offered routinely to adults with T1D, only to select groups of patients.[54]

9 Review of Guidelines and Best Practice Recommendations

Summary:

- Ten relevant guidelines were identified for the use of CGMs, SAPs, or FGMs.
- The guidelines generally agreed that people at risk for severe hypoglycemia, and people not achieving their HbA1c goals may benefit the most from CGM technologies.
- Use of CGM for blood glucose management without adjunctive SMBG is not recommended.
- Increased use of CGM correlates with better outcomes; CGM should be used by patients willing to use the device more than 70% of the time.
- Anyone who cannot recognize or articulate symptoms of hypoglycemia, including children, may benefit from CGM.

9.1 Purpose

To synthesize current guidelines and best practice recommendations on the use of continuous glucose monitoring systems (CGMs) by people with type 1 and type 2 insulin-dependent diabetes.

9.2 Methods

A grey literature search was conducted. CADTH's *Grey Matters* guide was used to locate agencies issuing guidelines. Searches were conducted on the websites of these agencies for guidelines related to continuous glucose monitoring specifically and diabetes treatment technologies generally. Websites of diabetes organizations such as Diabetes Canada and Diabetes UK were searched for guidelines related to diabetes technologies generally, and continuous glucose monitoring technologies in particular. Websites of health agencies in Canada, the United States, the United Kingdom, Australia, New Zealand, and Europe were searched for guidelines related to diabetes. A review of the guidelines was conducted to eliminate those guidelines that covered diabetes treatment but did not mention continuous glucose monitoring.

9.3 Results

Ten unique guidelines were identified as relevant[24,61-69]. They were published between 2015 and 2019, in Canada[24,66], the United States[61,68,69], the United Kingdom[62-65], and Germany[67]. The guidelines are summarized in Table 9.1.

Two guidelines were published in Canada, one by Health Quality Ontario (HQO)[66] and the other by Diabetes Canada[24]. The HQO document, published in 2017, recommends public funding of CGM devices for patients with type 1 diabetes willing to use the device most of the time. This recommendation is specifically for 1) patients who have had severe hypoglycemia without an obvious cause, despite optimized insulin therapy and SMBG, or 2) patients without the ability to recognize or communicate symptoms of hypoglycemia[66]. The Diabetes Canada document, published in 2018, is one chapter of a comprehensive guideline. The chapter addresses monitoring of glycemic control. This guideline recommends the use of CGM for people with type 1 diabetes who have not achieved their target HbA1c level. FGM is recommended for anyone with diabetes to reduce time spent in hypoglycemic ranges. The guideline also notes that CGM may not be appropriate for non-adjunctive use (use without SMBG testing), and that wearing the device more often improves outcomes[24].

Three guidelines were published by the UK's National Institute for Health and Care Excellence (NICE) [62-64]. Two were published in 2015, both as comprehensive guidelines for diabetes care[62,63]. One of these 2015 guidelines addresses type 1 and type 2 diabetes in children[63], while the other addresses type 1 diabetes in adults[62]. The pediatric guideline recommends the use of CGM with alarms for children at risk of hypoglycemia, for example children who cannot recognize or communicate symptoms of hypoglycemia, and the use of intermittent or retrospective CGM to optimize care for children not meeting their HbA1c goals[63]. For adults, NICE recommends the use of CGM in adults able to use the device upwards of 70% of the time, and who have a history of severe hypoglycemia, hypoglycemia unawareness, extreme fear of hypoglycemia, or high HbA1c (≥9%) despite 10-point SMBG testing[62]. These guidelines are largely similar to the more recent Canadian guidelines from 2017 and 2018, which also emphasize patients at risk of severe hypoglycemia or patients with high HbA1c not improving despite optimized insulin therapy.

The third NICE guideline specifically addresses two SAP systems: the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system[64]. The MiniMed Paradigm Veo system is recommended for people with type 1 diabetes who continue to suffer episodes of severe hypoglycemia, despite optimized insulin therapy with CSII. Patients must also agree to wear the system more than 70% of the time, and use of the system should be supervised by a trained and experienced care team. The guideline determines that the Vibe and G4 PLATINUM CGM lacks sufficient evidence to recommend it[64]. The Canadian guidelines do not address SAPs specifically, but are similar in requiring patients to use the devices most of the time, and focusing on patients at risk of hypoglycemia.

Another guideline from the UK, published by Diabetes UK in 2017, addresses the use of FGM[65]. This guideline recommends that FGM be made available to patients with all types of diabetes undergoing intensive insulin therapy. FGM may also be useful in the short-term to help patients and carers establish optimal personalized diabetes treatment. FGM should not be used by patients at risk of severe hypoglycemia; these patients should employ CGM. Funding for FGM should be provided to patients actively working toward or consistently achieving their glycemic control targets. This guideline also emphasizes education for patients and providers in the use of FGM[65].

Three guidelines were published in the United States[61,68,69]. The first guideline was published in 2015 by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE). AACE/ACE recommend that CGM be used adjunctive to SMBG by patients with type 1 or type 2 patients on basal-bolus insulin therapy, and by patients with hypoglycemia unawareness. The guideline recommends that the device be used as much as possible, since increased use correlates with better outcomes[61].

In 2018, the Endocrine Society updated its 2011 guideline for the use of CGM in children[70] and its 2016 guideline for the use of CGM and CSII in adults[71] (published in the United States). The updated guideline recommends the use of CGM by patients willing to use the device on a nearly daily basis, with particular emphasis on patients not achieving their HbA1c goals. This guideline also mentions that increased device usage corresponds with better outcomes[68].

The most recent guideline was published in United States in 2019[69]. This guideline recommends use of CGM by patients looking to improve their glycemic control, especially in combination with intensive insulin therapy. Additionally, people at risk of hypoglycemia (for example, those with hypoglycemia unawareness) and pregnant women may derive particular benefit from CGM. FGM, while not a replacement for CGM, may be useful for patients who require frequent SMBG tests. This guideline also recommends continued education, training and support for CGM users, and emphasizes the correlation between frequent CGM use and improved outcomes[69]. The three American guidelines correspond well with Canadian guidelines: those at high risk of hypoglycemia benefit the most from CGM, and the more the device is used the better.

The International Society for Pediatric and Adolescent Diabetes (ISPAD), based in Germany, published a guideline in 2018 which recommends CGM for young people with diabetes[67]. Real-time CGM may be particularly beneficial for patients who cannot recognize or express symptoms of hypoglycemia. CGM and FGM should be complemented by regular SMBG testing. The data from CGMs may be useful for developing and optimizing treatment plans. CGM is more effective when combined with CSII[67]. Though neither Canadian guidelines specifically addresses a pediatric population, the Canadian guidelines also mention patients who cannot recognize or articulate hypoglycemia symptoms, the correlation between increased use and better outcomes, and the importance of adjunctive SMBG testing.

Table 9.1 Guidelines for the use of CGMs

Organization, year, country	Title	Objective	Recommended population	Other recommendations	Funding
American Association of Clinical Endocrinologists, American College of Endocrinology, 2015, United States[61]	Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan- 2015	To provide guidance on the creation of comprehensive care plans for patients with diabetes	• Patients with type 1 and type 2 diabetes receiving basal-bolus therapy • Even patients not taking insulin may benefit from CGM, but more research is required • Patients with hypoglycemia unawareness	• Use the device as often as possible • Use in conjunction with SMBG	• Not disclosed
National Institute for Health and Care Excellence, 2015, United Kingdom[62,63]	"Diabetes (type 1 and type 2) in children and young people: diagnosis and management" "Type 1 diabetes in adults: diagnosis and management"	To provide comprehensive guidance on diabetes care for type 1 adults and type 1 and 2 children	• Offer real-time CGM with alarms for children with type 1 diabetes who have frequent episodes of severe hypoglycemia, hypoglycemia unawareness with adverse effects, or the inability to recognize or communicate symptoms of hypoglycemia • Intermittent real-time or retrospective CGM may help children who have hyperglycemia despite optimized insulin therapy • Do not offer real-time CGM to all adults with type 1 diabetes • Offer real-time CGM to adults willing to use the device at least 70% of the time, calibrate the device, and who have more than one episode of severe hypoglycemia with no preventable cause, complete hypoglycemia unawareness,	• Adults with type 1 diabetes using real-time CGM should use flexible insulin therapy with MDI or CSII • Real-time CGM should be administered by a centre with expertise, as part of an optimization strategy	• Not disclosed

Organization, year, country	Title	Objective	Recommended population	Other recommendations	Funding
			frequent asymptomatic hypoglycemia, extreme fear of hypoglycemia, HbA1c of 9% or more despite 10 SMBG tests per day		
National Institute for Health and Care Excellence, 2016, United Kingdom[64]	Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system)	To provide guidance regarding to use of two specific SAPs	• The MiniMed Paradigm Veo should be used for people with type 1 diabetes only if they have episodes of severe hypoglycemia despite optimized insulin therapy with CSII • Use of the MiniMed Paradigm Veo should be supervised by a trained multidisciplinary team experience in CSII and CGM for managing type 1 diabetes • The MiniMed Paradigm Veo should only be used if the patient or carer agrees to sensor use at least 70% of the time, understands and can use the system, and agrees to a structured education on diet, lifestyle, and counselling	• The MiniMed Paradigm Veo should be used if the company arranges for collection, analysis, and publication of data on the use of the system • Set appropriate targets, and only continue to use the system if there is a decrease in hypoglycemic episodes • There is insufficient evidence for the widespread routine use of the Vibe and G4 Platinum CGM system • Patients using these technologies for other indications or reasons should be allowed to continue to use them until a plan can be made with their healthcare providers	• Not disclosed
Diabetes UK, 2017, United Kingdom[65]	Diabetes UK Consensus Guideline for Flash Glucose Monitoring	To provide recommendations regarding which patients benefit	• Should be available to any adult or child with type 1 diabetes, and to people with other types of diabetes when they are	• FGM should be funded for patients who demonstrate progress towards targets, and	• Not disclosed

Organization, year, country	Title	Objective	Recommended population	Other recommendations	Funding
		from FGM, how care providers can optimize use of FGM, and communicate considerations for funders	undergoing intensive insulin therapy • Short-term use by healthcare professionals may help to inform personalized treatment, or for those with frequent hypo- or hyperglycemia • FGM should not be used for those with severe hypoglycemia unawareness – CGM is appropriate for these patients (patients with mild or recent unawareness may use FGM to regain awareness) • Should not be used by patients who qualify for CGM	active management of their illness (assessed at least annually) • Structured education for patients, as recommended by NICE • Education for providers on interpretation of glucose information	
Health Quality Ontario, 2017, Canada[66]	Continuous Monitoring of Glucose for Type 1 Diabetes	To provide a recommendation on funding for CGM	• Recommends public funding for CGM in patients with type 1 diabetes willing to use CGM most of the time, and who have severe hypoglycemia without obvious precipitant despite optimized insulin therapy and use of SMBG, and/or people who cannot recognize or communication symptoms of hypoglycemia	• None	• Not disclosed
Endocrine Society, 2018, United States[68] (update of previous guidelines from	Advances in Glucose Monitoring and Automated Insulin Delivery: Supplement to Endocrine Society Clinical Practice Guidelines	To update recommendations made in 2016 for use of CSII and CGM in adults, and recommendations made in 2011 for	• Real-time CGM is recommended for adults with type 1 diabetes (especially those with above-target HbA1c levels) who are willing to use the device daily or near-daily	• More frequent wear of real-time CGM corresponds to best benefits • Some CGMs may be approved for non-adjunctive use (no	• Funded by the Endocrine Society

Organization, year, country	Title	Objective	Recommended population	Other recommendations	Funding
2016[71] and 2011[70])		use of CGM in children	• People with type 2 diabetes willing and able to use the device may benefit from intermittent short term use to optimize care	SMBG); consult FDA approvals	
Diabetes Canada, 2018, Canada[24]	Monitoring Glycemic Control	To provide guidance on monitoring and improvement of glycemic control	• People with type 1 diabetes not achieving their target HbA1c to improve glycemic control and reduce duration of hypoglycemia • FGM may be offered to decrease time spent in hypoglycemia	• CGM should not replace SMBG; follow manufacturer recommendations • The more time wearing CGM, the more improvement noted in outcomes	• Not disclosed
International Society for Pediatric and Adolescent Diabetes, 2018, Germany[67]	ISPAD Clinical Practice Consensus Guidelines 2018: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes	To provide guidance on setting and achieving glycemic control goals in children, adolescents, and young people	• CGM should be available to children, adolescents, and young adults with diabetes • Real-time CGM may especially benefit children who cannot articulate hypo- or hyperglycemic symptoms or those with hypoglycemia unawareness	• Regular SMBG should be used with or without CGM or FGM • FGM cannot completely replace SMBG • Periodic download and review of CGM data can inform treatment adjustments • CGM is more effective with CSII, particularly combined in the form of an SAP	• Not disclosed
American Diabetes Association, 2019, USA[69]	Diabetes Technology: Standards of Medical Care in Diabetes-2019	"…to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate care."	• For children, adolescents, and adults to improve glycemic control • In conjunction with intensive insulin therapy, real-time CGM is useful to improve HbA1c • Real-time CGM may be particularly useful in people with	• Accompany CGM prescription with education, training and support • Real-time CGM should be used daily or nearly daily	• Not disclosed

Organization, year, country	Title	Objective	Recommended population	Other recommendations	Funding
			hypoglycemia unawareness or frequent hypoglycemia; those at high risk of hypoglycemia may also benefit from SAP with low-glucose suspend features • Real-time CGM may improve HbA1c and neonatal outcomes in pregnant women with type 1 diabetes • FGM may be useful for adults requiring frequent testing	• For those who have successfully used CGM, continued access should be ensured through third-party payers	

Abbreviations: FGM = Flash Glucose Monitor; CGM = Continuous Glucose Monitor; SMBG = Self Monitored Blood Glucose; SAP = Sensor Augmented Pump; CSII = Continuous Subcutaneous Insulin Infusion

9.4 Conclusions

Guidelines generally agree that patients at high risk for severe hypoglycemia benefit from use of CGM[61-63,66,67,69], that increased use of CGM results in better outcomes[24,61,63,68,69], and that use of CGM should ideally be adjunctive to regular SMBG testing[61,67,68]. Children may also benefit from CGM technologies. The recent 2018 ISPED guideline recommends CGM for all pediatric diabetes patients[67], while the 2015 NICE guideline recommends CGM in children at risk for hypoglycemia[63]. People with diabetes struggling to achieve theirHbA1c goals may benefit from CGM[24,62,63,68,69], though some guidelines indicate that short-term use of CGM may be sufficient to optimize a care routine for these patients[24,63]. Guidelines also recommend educating patients and carers on the use of CGMs or FGMs, and diabetes care generally [62,63,65,69].

Those guidelines that specifically address FGM emphasize its limits as well as its benefits[24,65,69]. FGM should not replace CGM in populations at risk for severe hypoglycemia[65].

The guideline that addressed SAPs specifically shared many recommendations with guidelines about CGM, including recommending SAPs to people vulnerable to hypoglycemia, willing to use the device more than 70% of the time, and undergo structured education[64]. This guideline is of limited applicability, since most of its recommendations only addresses one specific device.

People with type 1 diabetes may benefit more from CGM technologies than people with type 2 diabetes. However, intensive insulin therapy in both people with type 1 and type 2 diabetes increases risk of hypoglycemia. Thus, intensive insulin therapy in type 2 patients may provide reason to prescribe CGM, and people with type 2 diabetes may benefit from short-term use of CGM to optimize their routines [61,68,69].

10 Systematic Review of Clinical Effectiveness

Summary

- 63 studies of 70 sample populations – 36 for adults (age >18 years) with type 1 diabetes, 26 for children (age <18 years) with type 1 diabetes, 4 for adults with type 2 diabetes, and 4 in pregnant women with diabetes were included in the final data set.
- Among the included studies, there was little overlap in the interventions described – resulting in sparse networks of evidence for network meta-analysis.
- Network meta-analysis was conducted on HbA1c, number of hypoglycemic events requiring assistance, and time-in-range (percent of time with blood glucose between 3.9-10 mmol/L), in adults with type 1 diabetes and children with type 1 diabetes. There is no significant difference between interventions for HbA1c or number of hypoglycemic events requiring assistance.
- Some significant differences in time-in-range were identified in both adults and children with type 1 diabetes. However, it is unknown if, and how, this surrogate outcome translates into meaningful clinical outcomes.
- Other outcomes of interest were: number of diabetic ketoacidosis events, DTSQ, HFS, and health-related quality of life. DKA events were rare, occurring no more than three times in a given study. Nearly all of the interventions resulting in a DKA event were SMBG or CGM. Other outcomes were not reported with sufficient frequency for quantitative analysis or meaningful comparisons.
- Little evidence was identified for type 2 diabetes or type 1 diabetes in a pregnant population, and no conclusions about efficacy could be drawn.

10.1 Purpose

To assess clinical effectiveness of continuous glucose monitors (CGMs), flash glucose monitors (FGMs), and hybrid insulin delivery systems for the management of insulin-dependent diabetes.

10.2 Methods

10.2.1 Search Strategy

A systematic review of the quantitative literature was completed. MEDLINE, EMBASE, Cochrane Central, and CINAHL were searched from January 1, 2003 until December 31, 2018. We chose 2003 as it corresponded with a significant change in the clinical guidelines on the diagnosis and management of type 1 diabetes. Terms capturing the technology of interest (e.g. "blood glucose self-monitoring," "automated delivery" and "closed loop") were searched in combination with terms such as "type 1" and "type 2" and "diabetes mellitus" to ensure the search addressed the correct population – which was patients with insulin dependent-diabetes in

the outpatient setting. Interventions of interest included CGMs, FGMs, and hybrid insulin delivery systems such as a closed-loop CGM and insulin pump, or the dual hormone artificial pancreas. The search was limited to randomized controlled trials. Results were filtered to exclude non-human studies and studies not peer reviewed (e.g. opinion, letter to editor or conference abstracts). The full search strategy can be found in *Appendix C: Search Strategy for Systematic Review of Clinical Effectiveness*.

The abstracts retrieved were screened in duplicate by independent reviewers. Abstracts of articles that clearly did not meet the inclusion criteria were excluded. Abstracts included by either reviewer proceeded to full-text review. Full-text were assessed independently in duplicate using the inclusion and exclusion criteria listed in Table 10.1, which were developed prior to conducting the search. Any disagreement between reviewers at the full-text assessment stage was resolved through discussion, until a consensus was met. If required, a third reviewer was consulted.

Table 10.1 Inclusion and Exclusion Criteria for Systematic Review of Clinical Effectiveness

Inclusion Criteria	Exclusion Criteria

• Insulin-dependent Type 1 or Type 2 diabetes
• Adult or children population
• RCT study design
• Assesses glucose monitoring,
  o Sensor augmented pumps (SAPs)
  o Continuous glucose monitors (CGM)
  o Flash glucose monitors (FGMs)
  o Closed loops, open loops, hybrid loops
  o Artificial pancreas
  o Algorithms for insulin delivery in SAPs
• Reports glycated hemoglobin, time-in-range, number of hypoglycemic events requiring assistance, diabetic ketoacidosis, EuroQol 5D, hypoglycemia fear survey overall score, or diabetes treatment satisfaction questionnaire overall score
• English or French Language only
	• Hospital inpatient population
	• Diabetes not pre-existing at pregnancy (i.e. gestational diabetes)
	• Evaluates a non-CGM related technology using CGM data (e.g. compares effects of two insulin types, using CGM as a data source)
	• Does not assess glucose monitoring technology
	• Education program
	• Outcome of interest not reported
	• Not an RCT
	• Animal studies

Data from the final included studies were extracted by one reviewer using a standard data extraction form and was verified independently by a second reviewer. Extracted data included the study design, follow-up period, washout period if applicable, number of patients, intervention – with details about glucose monitoring method(s), insulin delivery, algorithm for insulin and/or glucagon delivery, if applicable, and estimates of effect. Intervention descriptions were heterogeneous, with similar interventions containing CGM and CSII being described as "open-loop," "sensory augmented pump," or "CGM with insulin pump." To enhance overlap between interventions and connectivity of networks, all of these interventions were classified based on presence of CGM and CSII.

Quality of included studies was assessed using the Cochrane Risk of Bias Tool 2.0[1]. With this tool, each randomized controlled trial is assessed for risk of bias in five domains: randomization, deviation, missing outcome data, measurement, reported results[1]. Each study was assessed as either "low risk," "high risk," or "some concerns" related to risk of bias in each of these domains, and an overall category. Where appropriate, the risk of bias tool specific to crossover studies was used.

10.2.2 Outcomes

Initially, outcomes available in the literature were categorized as functional, clinical, and patient reported outcomes (Figure 10.1). Given the breadth of available data in the published literature, outcomes were prioritized to select a feasible number of outcomes that meaningfully impacted clinical and patient-experience. The final list of outcomes were selected by an Expert Advisory Group of 3 clinicians and 3 patient partners in collaboration with the research team. The outcomes were selected based on the impact of the outcome on clinical care, disease management, a patient's daily life, to represent a range of outcomes and the frequency of report within the published literature. Outcomes of interest included in the analysis were: glycated hemoglobin (HbA1c), time-in-range (TIR), number of hypoglycemic events requiring assistance, diabetic ketoacidosis (DKA), EuroQol-5D (EQ-5D), hypoglycemia fear survey (HFS) overall score, the diabetes treatment satisfaction questionnaire (DTSQ) overall score, and the Pediatric Quality of Life Inventory (PedsQL). Network meta-analysis was conducted on HbA1c (%), time-

in-range (percent of time spent in range of 3.9-10 mmol/L), and the number of hypoglycemic events requiring assistance (hazard). Other outcomes were narratively synthesized.

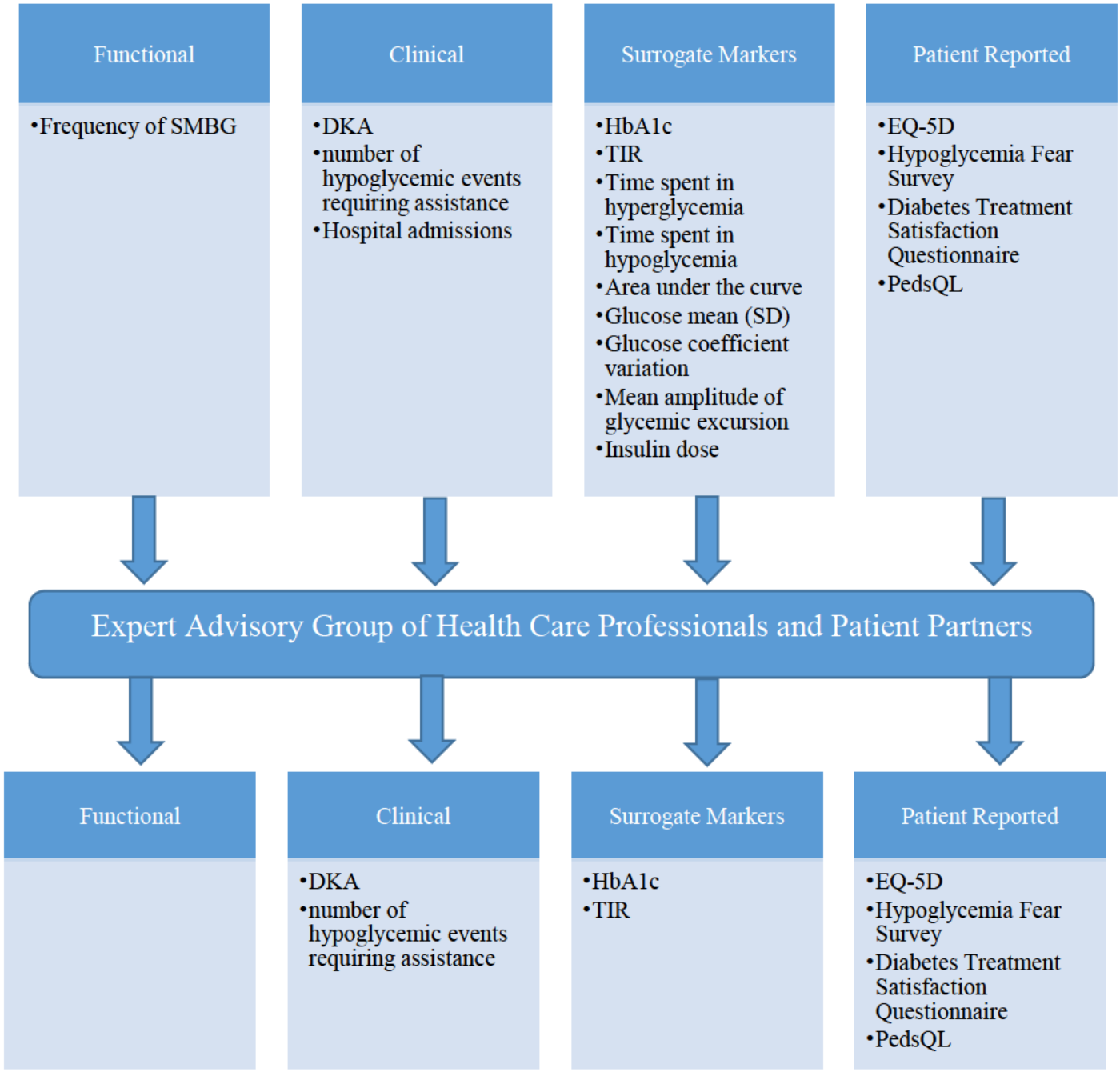


Figure 10.1 Flowchart of Outcome Selection Process

10.2.2.1 HbA1c

HbA1c provides information about blood glucose over the course of the previous 120 days (the average lifespan of red blood cells). It is a convenient test as it requires no fasting, and can be determined from a single blood sample[72]. HbA1c has become a commonly used tool for diagnosing and managing diabetes[3]. The healthy reference range for HbA1c in adults is <6.0%[3]. HbA1c value ≥6.5% is the clinical designation for diabetes for adults, and it is recommended that adults with diabetes maintain an HbA1c level below 7.0%[73,74]. The recommendations for children and adolescents (<18 years old) with diabetes is ≤7.5%[3]. Elevated levels of HbA1c have been identified as a risk factor for micro- and macrovascular complications (e.g., retinopathy, neuropathy, heart disease, and stroke)[73]. A difference in HbA1c of 0.5% between successive patient samples is accepted as significant change in glycemic control[75,76].

10.2.2.2 Time in Range (TIR)

TIR is used as a surrogate marker for glycemic control, and is typically reported as percent of time, or minutes per day spent in the target range. The fasting/pre-meal blood glucose target range for people with diabetes (≥6 years old) is 3.9 to 10.0 mmol/L (70-180 mg/dL)[37]. The range for young children >6 years old is 6.0 to 10.0 mmol/L[77]. For women with type 1 or type 2 diabetes who are pregnant, the recommended range for fasted/pre-meal blood glucose is <5.3 mmol/L[77]. TIR is easily captured using CGMs, however, it is not yet a validated measure of glycemic control (see Chapter 7).

10.2.2.3 Hypoglycemic events requiring assistance

Hypoglycemic events requiring assistance is an important indicator of a technology's ability to provide understandable and actionable information about glucose monitoring; and in the case of hybrid insulin delivery systems, to deliver the appropriate dose of insulin. Although frequently reported as the number of events below a specific glucose threshold, such as 3.9mmol/L[78], this lacks information about the symptoms that can accompany hypoglycemia; and for some technologies, such as the dual-hormone artificial pancreas, the ability to recover from hypoglycemia is an important metric.

Frequency of severe hypoglycemia (i.e., hypoglycemic events requiring assistance) is associated with lower quality of life, increased fear of hypoglycemia, and poor glycemic control[3]. It is also associate with mild intellectual impairment, permanent neurological dysfunction, major micro-

and macro-vascular events, and possible fatal outcomes[3,79]. A clinically important improvement in hypoglycemic control is determined by a reduction of 30% or more in the frequency of reported hypoglycemic events (plasma glucose 3.9 mmol/L [<70 mg/dl]), with or without symptoms. For severe hypoglycemia, a 10-20% reduction in the number of events may be considered meaningful[78].

10.2.2.4 Diabetic Ketoacidosis (DKA)

DKA is a serious diabetic complication associated with hyperglycemia, ketonemia, and acidosis that has serious consequences and can lead to diabetic coma, cerebral edema, acute respiratory distress, thromboembolism, and death[80]. DKA is the leading cause of morbidity and mortality[81] in children with diabetes. DKA is more common in type 1 diabetes than in type 2. It is a result of lack of insulin[82]. DKA can be prevented at early stages of diabetes by public awareness and education about early diabetes symptoms, and immediate assessment of ketonemia and acidosis in newly diagnosed diabetes cases. In established diabetes cases, DKA can be reduced with availability of support services, behavioural intervention, education[3], and frequent self-monitoring of blood glucose level and appropriate insulin adjustments[83].

10.2.2.5 EQ-5D

The EQ-5D measures self-reported health-related quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and pain/depression[84]. There are two versions of this tool for use in adults, one with five levels of severity and one with three levels of severity[84] – ranging from no impairment to severely impaired in that specific domain. Participant responses are converted to a utility value anchored at one, or no health problems in each domain, and zero, indicating death[85]. Scoring algorithms used to convert EQ-5D responses to utility are based on the relative preferences for each health state. Health states resulting in utility of less than zero indicate a health state where death would be preferable[86]. In a review examining the minimum clinically important differences in EQ-5D scores, absolute values were specific to the diagnosis; and no diabetes-specific value was reported[87]. However, the lowest minimum clinically important difference identified for any diagnosis was 0.03[87].

10.2.2.6 Hypoglycemic Fear Survey (HFS)

The HFS is a validated instrument commonly used to measure fear of hypoglycemia in individuals with diabetes and their relatives. The HFS is composed of two subscales: behavioral

(i.e., actions carried out to avoid hypoglycemia) and worry (i.e., anxiety provoking) subscales. Higher scores indicate higher fears of hypoglycemia[88]. Elevated fear of hypoglycemia has been associated with suboptimal glucose control and higher risk of complications, and lower quality of life[89]. To our knowledge, the minimum clinically importance difference of the HFS has not been calculated.

10.2.2.7 Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The DTSQ is a validated measure of satisfaction with diabetes-specific treatment using six items: satisfaction with current treatment, convenience, flexibility, satisfaction with own understanding of diabetes, likelihood of continuing with diabetic treatment, and likelihood of recommending current treatment. The total score is 36 with higher score indicating higher satisfaction with treatment. The DTSQ also contains two questions that allow determining the burden from hyper and hypoglycemia. These two questions do not form part of the total score[90]. The DTSQ provides an indication of self-efficacy and treatment adherence, which is important for achieving stable glycemic control and reducing risk of diabetic complications[91]. The minimum clinically important difference for the DTSQ is unknown[90].

10.2.2.8 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL is a validated measure of children's (2-18 years of age) and parent's perception of health-related quality of life (QOL) in children with chronic conditions[92]. There is a generic version of the scale and condition specific modules including one for diabetes. The generic scale measures QOL in four dimensions: physical functioning, emotional functioning, social functioning, and school functioning. The diabetes module measures QOL based on diabetes symptoms, treatment barriers, treatment adherence, worry and communication. Higher scores indicate higher quality of life[93]. A study on youth with type 1 and type 2 diabetes identified minimum clinically important differences scores for the generic (type 1: parent 4.88; child 4.72. type 2: parent 6.27; child: 5.41), and the diabetes (type 1: parent 4.54; child 5.27. type 2: parent 6.06; child: 5.96)[94].

10.2.3 Analysis

Bayesian network meta-analysis was conducted with WinBUGS 1.4[95], using Markov-chain Monte Carlo methods. WinBUGS code used in this network meta-analysis was adapted from

Dias et al., 2018[96], and is provided in the appendices (Appendix 2-4). WinBUGS is the only publicly available software with the flexibility required to accommodate multi-arm trials, and both trial- and arm-specific outcomes. Network diagrams were generated with the "pcnetmeta"[97] package for R statistical software[98]. Primary outcomes of network meta-analysis are the relative estimates of treatment effect, and median rank of each treatment. Adults (age greater than 18) and children were meta-analyzed separately, to reduce heterogeneity. In studies that presented stratified outcomes for both adults and children, these populations were considered as separate trials and included in the appropriate network meta-analysis. Uninformative prior distributions were assigned to treatment effects and the between-trial standard deviation for random effects models. HbA1c and time-in-range are both continuous outcomes – for which a normal likelihood and identity link was used. For hypoglycemic events requiring assistance, it was assumed that events are independent, and hazard is constant over the follow-up period - the Poisson likelihood with log link was used.

Convergence of three chains was assessed through examination of plots of history, kernel density, and the Brooks-Gelman-Rubin statistic, and comparison of Monte Carlo error to standard deviation of relative estimates of effect. Both fixed effects and random effects models were fitted to extracted data. Deviance information criteria (DIC) and posterior mean residual deviance were assessed to select the model that fits the data best for each outcome. For all analyses, burn-in simulations were run until converge of posterior distributions of relative treatment effects was achieved. Where loops of evidence were encountered, consistency was assessed using the Bucher method which compares direct and indirect evidence[99]. To identify studies contributing to a model's lack of fit, leverage plots were generated. In the leverage plot, leverage, or contribution to the effective number of parameters, is plotted against the posterior mean residual deviance for each data point[96]. In sensitivity analysis, studies contributing greater than three to the total deviance information criterion (DIC) were removed and estimates of effect were compared to the base case analysis. Leverage plots are included in the appendices.

10.3 Results

Five thousand and seventy-five abstracts were identified; 3,030 remained after duplicates were removed (Figure 10.2). Two-hundred and seventy-seven abstracts continued to the full-text

review stage, of which 212 were excluded. The final dataset included in this review included 65 studies. Study characteristics for included studies can be found in *Appendix F Clinical Effectiveness Supplementary Material*.

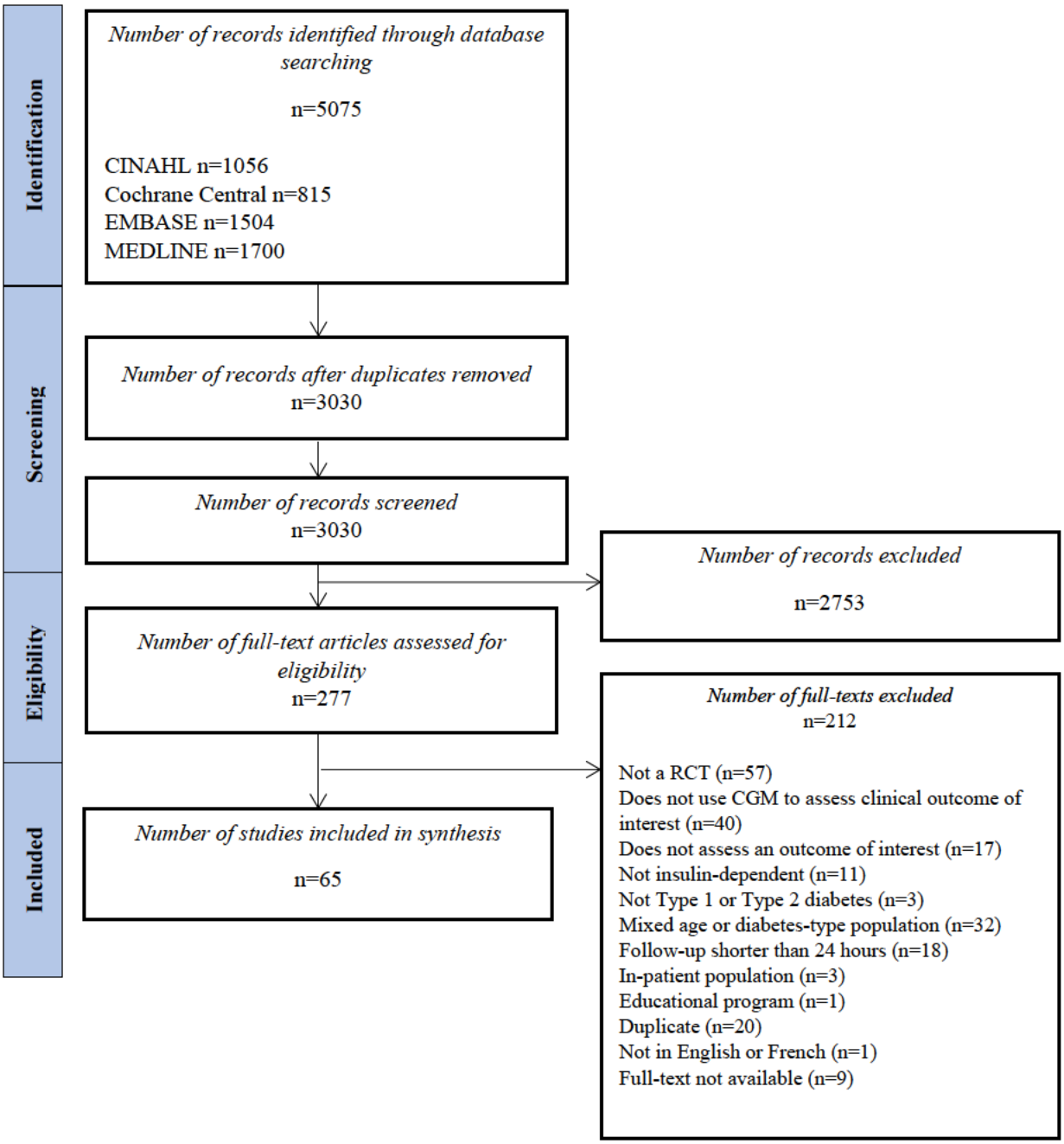


Figure 10.2 PRISMA Flowchart for Included Studies

Within the 65 included studies, a number of publications reported outcomes stratified by age (adult or children), type of diabetes (type 1 or type 2), or method of insulin delivery. Adults were defined by age, and included studies with ages greater than 18. Children were defined as individuals of age less than 18 years. To maximize the amount of data considered and prevent loss of power, stratified outcomes were included as separate samples in network meta-analysis. This resulted in 72 samples with unique data. A breakdown of the categories of included studies can be found in Figure 10.3. Of the 72 samples included, 42 included adult patients with type 1 diabetes, four included adults with type 2 diabetes, and 26 included pediatric patients with type 1 diabetes. Of the 42 samples examining an adult population with type 1 diabetes, four studies focused on a population of pregnant patients, and 38 focused on the general population. Study characteristics of the included studies can be found in *Appendix F Clinical Effectiveness Supplementary Material.*

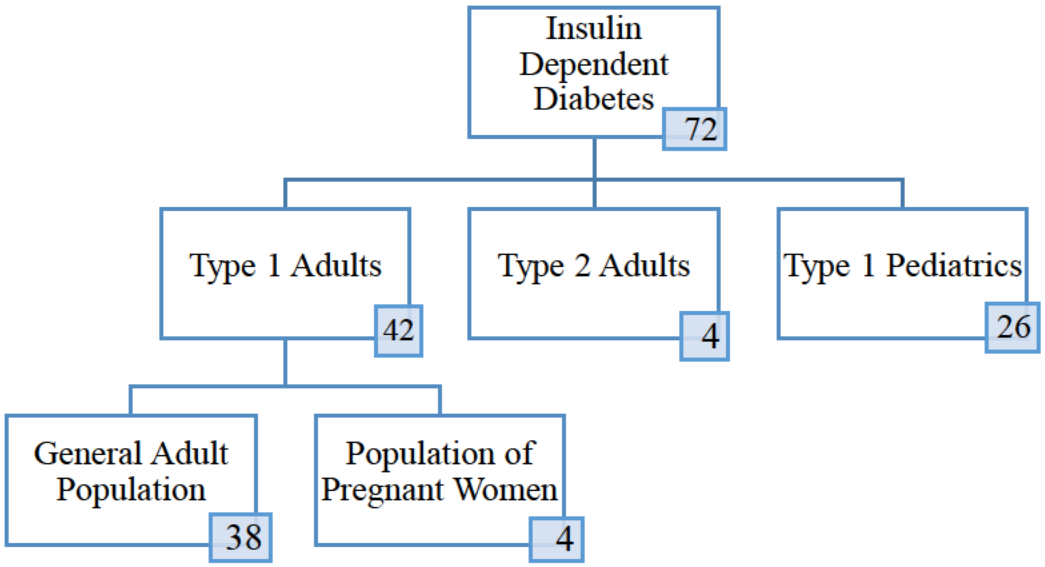


Figure 10.3 Breakdown of populations in clinical effectiveness review (number of studies are presented in the blue boxes). Some studies reported more than one population (e.g., stratified analysis of adults and children with type 1 diabetes).

10.3.1 Adult Type 1 Diabetes

Just over half (52.7%, n=38) of the included samples were non-pregnant adult populations (Figure 10.3). Table 10.2 presents a summary of studies and the reported outcomes. The most reported outcome was TIR (n=23), followed by hypoglycemic events requiring assistance

(n=20), and HbA1c (n=20). Two studies[100,101] explored only Patient Reported Outcomes Measures (PROMs); 26 studies reported only on clinical outcomes; and 10 studies reported on both clinical and PROMs.

Table 10.2 Outcomes reported in studies of adults with T1D

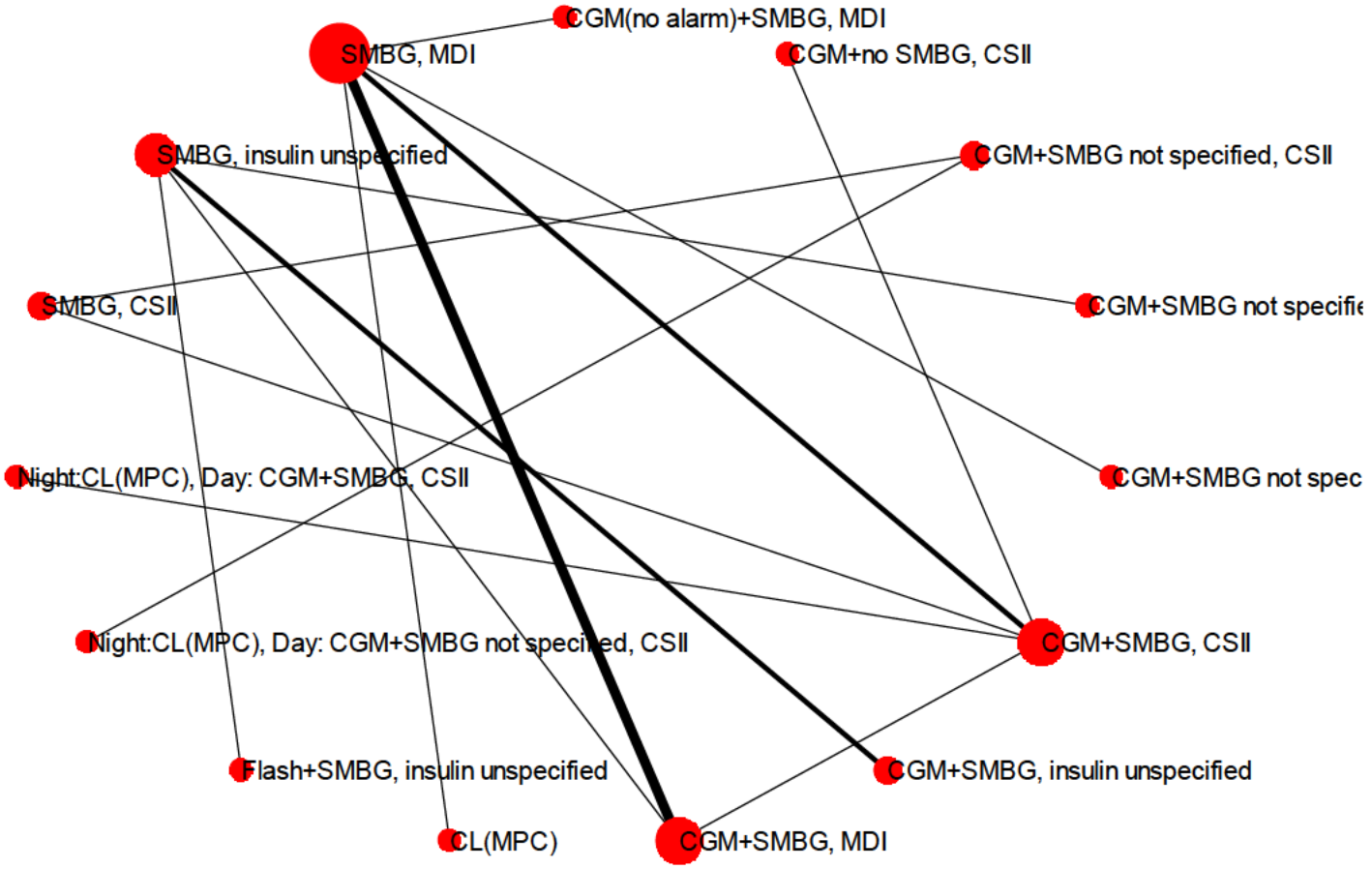
First Author (Year)	HbA1c	TIR	Hypos[a]	DKA	EQ-5D	HFS	DTSQ
Ajjan (2016)[102]	■						■
Aleppo (2017)[103]	■	■	■	■		■	■
Bally (2017)[104]		■	■	■			
Beck (2010)[100]						■	
Beck (2017)[105]	■		■	■			
Beck (2017)[106]	■		■	■			
Bergenstal (2010)[107]	■		■	■			
Blauw (2016)[108]		■		■			
Bolinder (2016)[109]	■	■	■	■		■	■
Breton (2014)[110]		■					
Breton (2018)[111]		■					
Brown (2017)[112]		■	■	■			
Brown (2015)[113]		■	■	■			
El-Khatib (2017)[114]		■					
Feig (2017)[115]	■		■	■		■	
Forlenza (2017)[116]		■	■				
Haidar (2017)[117]		■					
Heinemann (2018)[118]	■	■	■		■	■	
Hermanns (2014)[119]		■					
Hommel (2014)[101]							■
JDRF (2008)[120]	■		■	■			
Kovatchev (2014)[121]		■					
Kropff (2015)[122]	■	■	■	■			
Langeland (2012)[123]	■						■
Leelarathna (2014)[124]		■					
Leelarathna (2013)[125]	■						
Lind (2017)[126]	■		■	■		■	■
Little (2014)[127]	■	■		■		■	■
Peyrot (2009)[128]	■		■	■			
Polonsky (2017)[129]					■		
Reddy (2015)[130]		■					
Reddy (2018)[131]	■	■	■			■	
Russell (2015)[132]		■	■				
Sequeira (2013)[133]	■						
Thabit (2014)[134]	■	■					
Thabit (2015)[135]	■	■	■	■			
Tumminia (2015)[136]	■		■	■			
Van Beers (2016)[137]	■	■	■	■	■	■	
Total	**21**	**23**	**20**	**18**	**3**	**9**	**7**

Footnote:
[a]Hypoglycemic events requiring assistance
Abbreviations: HbA1c = glycated hemoglobin; TIR = Time in Range; DK = diabetic Ketoacidosis; HFS = Hypoglycemia Fear Survey; DTSQ = Diabetes Treatment Satisfaction Questionnaire

10.3.1.1 Glycated Hemoglobin (HbA1c)

Included within the network meta-analysis of HbA1c in adults with type 1 diabetes were 20 studies, and 15 treatments (Figure 10.4). One study that presented HbA1c included treatments that did not connect to the network of evidence; this study compared Flash, MDI to CGM+no SMBG, MDI, and found no evidence of a difference in this outcome[131]. A second study comparing SMBG with MDI; to CGM+SMBG not specified with MDI; and presented no measure of spread, and was therefore excluded from network meta-analysis[133]. This study also identified no statistically significant reductions in HbA1c[133]. The random effects model was considered as the base case (*Appendix E: WinBUGS Codes for Network Clinical Effectiveness Meta-analysis*). In this model, there were 31 data points, which is similar to the posterior mean residual deviance of the random effects model, and suggests adequate fit. In addition, the lower posterior mean residual deviance suggest this model is the best fit to the data. Finally, deviance information criterion of the random effects model is less than that of the fixed effects model, which also supports selection of the random effects model *Appendix F Clinical Effectiveness Supplementary Material*.

Forty-thousand burn-in iterations were required to reach convergence – which was assessed through examination of plots of history, kernel density, and plots of the Brooks-Gelman-Rubin statistic, and comparison of Monte Carlo error to standard deviation of relative estimates of effect. Model outcomes were recorded following 80,000 additional iterations, also with three chains.



SMBG=self-monitoring of blood glucose; MDI=multiple daily injections; CGM=continuous glucose meter; CSII=continuous subcutaneous insulin infusion; CL=closed-loop; MPC=model predictive control algorithm

Figure 10.4 Network diagram for HbA1c in adults with type 1 diabetes

As seen in Figure 10.4, there were few studies assessing each intervention. The most common comparison identified was between SMBG with MDI, and CGM+SMBG, with MDI. Only one loop of evidence was encountered in this network diagram, between SMBG with MDI, CGM+SMBG with CSII, and CGM+SMBG with MDI. Within this single loop of evidence, inconsistency was assessed with the Bucher method[99]. No evidence of inconsistency was found (p=0.48).

Median rank and 95% credible interval for each treatment are shown in Table 10.3, with lower ranks indicating greater probability of being the most effective treatment for reducing HbA1c. No treatment has median rank of 1, and 8 treatments have a 95% credible interval spanning from rank 1 to 15. Median estimate of effect for each treatment relative to all other treatments are present in Figure 10.5. Within the included studies, no statistically significant differences were identified between the different treatments. For each pairwise comparison, the 95% credible interval included the null value.

For example, intervention one or SMBG, MDI has median rank of 10, meaning it is the 10th most likely to be effective. There is 95% probability that the rank of this intervention falls between ranks 5 and 14 (Table 10.3). Compared to CGM (no alarm) + SMBG, MDI; SMBG, MDI is likely to result in HbA1c decrease of 0.3% with a 95% credible range from a decrease of 2.1% to an increase of 1.5% in HbA1c (Figure 10.5). Outcomes presented in the step diagram are calculated as the predicted effect of the intervention indicated by the row, minus the predicted effect for the intervention indicated by the column.

Table 10.3. Median rank of each treatment for lowering HbA1c in adults with type 1 diabetes.

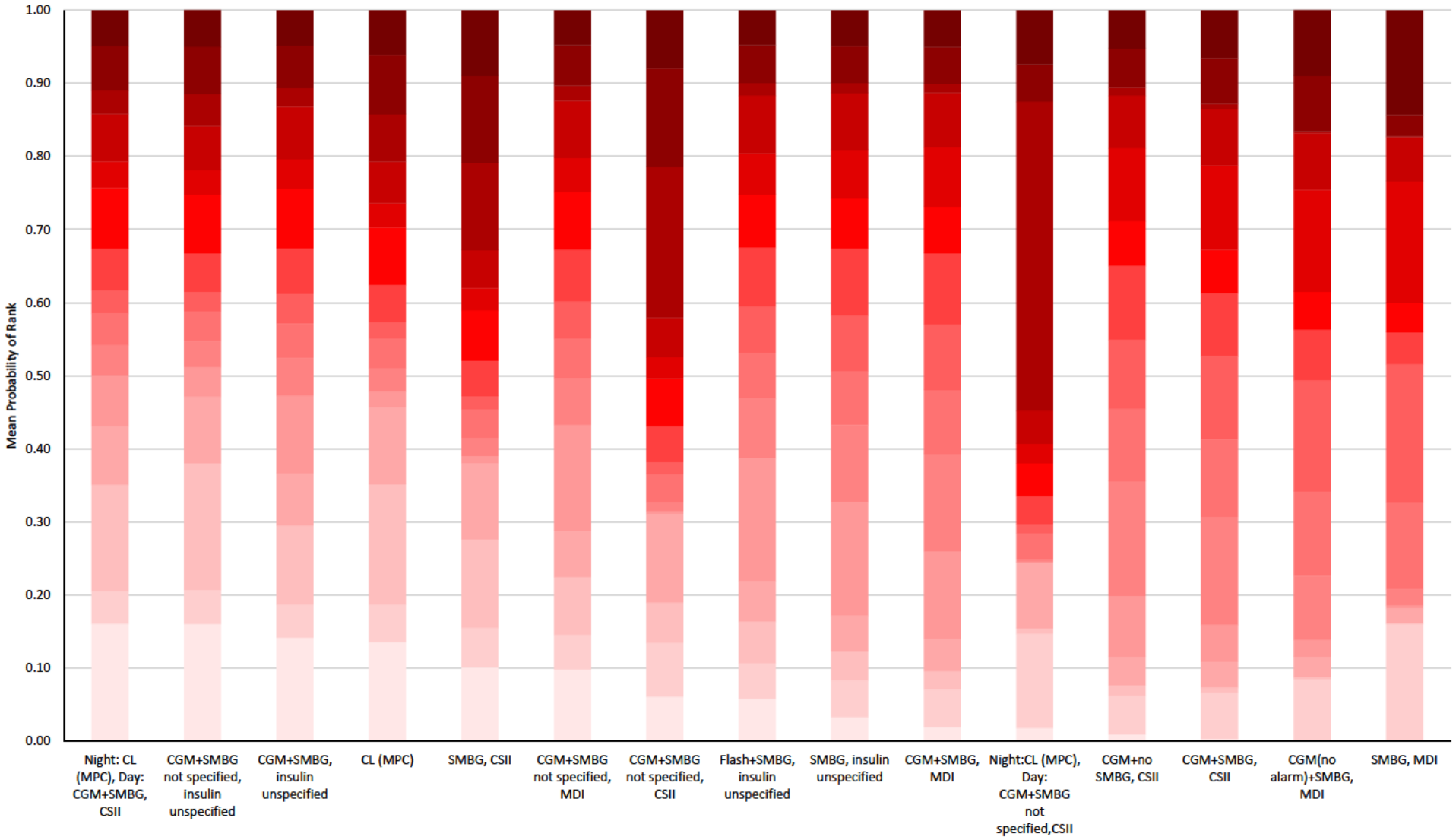
Treatment	Median Rank	95% Credible Interval
SMBG, MDI	10	5 to 14
CGM(no alarm)+SMBG, MDI	7	1 to 15
CGM+SMBG, CSII	11	5 to 14
CGM+no SMBG, CSII	11	2 to 15
CGM+SMBG, MDI	7	2 to 12
SMBG, insulin reported together	5	2 to 13
Flash+SMBG, insulin reported together	5	1 to 15
CGM+SMBG not specified, MDI	4	1 to 14
CGM+SMBG, insulin reported together	7	1 to 15
Night: CL (model predictive control), Day: CGM+SMBG, CSII	9	1 to 15
CGM+SMBG not specified, insulin reported together	4	1 to 15
CL (model predictive control algorithm)	7	1 to 15
SMBG, CSII	14	5 to 15
CGM+SMBG not specified, CSII	10	1 to 15
Night:CL (model predictive control algorithm), Day: CGM+SMBG not specified, CSII	8	1 to 15

1													
-0 3 (-2 1 to 1 5)	2												
0 03 (-0 73 to 0 67)	0 32 (-1 63 to 2 22)	3											
0 03 (-1 34 to 1 27)	0 33 (-1 93 to 2 49)	0 (-1 11 to 1 1)	4										
-0 33 (-0 88 to 0 17)	-0 03 (-1 91 to 1 83)	-0 36 (-1 08 to 0 44)	-0 37 (-1 65 to 1 02)	5									
-0 51 (-1 76 to 0 71)	-0 21 (-2 39 to 1 95)	-0 54 (-1 84 to 0 86)	-0 54 (-2 22 to 1 24)	-0 18 (-1 29 to 0 95)	6								
-0 51 (-2 18 to 1 12)	-0 21 (-2 63 to 2 19)	-0 54 (-2 23 to 1 24)	-0 54 (-2 54 to 1 55)	-0 18 (-1 74 to 1 39)	0 (-1 1 to 1 09)	7							
-0 67 (-1 81 to 0 47)	-0 37 (-2 49 to 1 75)	-0 7 (-1 96 to 0 7)	-0 7 (-2 37 to 1 1)	-0 33 (-1 57 to 0 93)	-0 16 (-1 83 to 1 52)	-0 16 (-2 14 to 1 86)	8						
-0 37 (-1 86 to 1 1)	-0 07 (-2 39 to 2 24)	-0 4 (-1 92 to 1 23)	-0 4 (-2 26 to 1 57)	-0 04 (-1 41 to 1 35)	0 14 (-0 66 to 0 95)	0 14 (-1 2 to 1 51)	0 3 (-1 57 to 2 16)	9					
-0 17 (-1 55 to 1 07)	0 12 (-2 12 to 2 29)	-0 2 (-1 31 to 0 91)	-0 2 (-1 76 to 1 36)	0 16 (-1 22 to 1 46)	0 34 (-1 46 to 2 03)	0 34 (-1 75 to 2 34)	0 5 (-1 3 to 2 18)	0 2 (-1 78 to 2 07)	10				
-0 61 (-2 27 to 1 04)	-0 31 (-2 74 to 2 11)	-0 64 (-2 32 to 1 16)	-0 64 (-2 64 to 1 46)	-0 28 (-1 83 to 1 31)	-0 1 (-1 19 to 1 01)	-0 1 (-1 64 to 1 45)	0 06 (-1 96 to 2 06)	-0 24 (-1 6 to 1 12)	-0 44 (-2 43 to 1 67)	11			
-0 3 (-1 48 to 0 87)	0 01 (-2 15 to 2 14)	-0 33 (-1 63 to 1 09)	-0 33 (-2 02 to 1 47)	0 03 (-1 23 to 1 33)	0 21 (-1 48 to 1 92)	0 21 (-1 8 to 2 24)	0 37 (-1 27 to 2)	0 07 (-1 8 to 1 96)	-0 13 (-1 82 to 1 69)	0 31 (-1 7 to 2 34)	12		
0 55 (-0 84 to 1 81)	0 84 (-1 42 to 3 02)	0 52 (-0 6 to 1 64)	0 52 (-1 05 to 2 09)	0 88 (-0 51 to 2 19)	1 06 (-0 74 to 2 76)	1 06 (-1 05 to 3 09)	1 22 (-0 59 to 2 9)	0 92 (-1 07 to 2 8)	0 72 (-0 85 to 2 3)	1 16 (-0 97 to 3 18)	0 85 (-0 98 to 2 55)	13	
-0 07 (-1 92 to 1 67)	0 23 (-2 34 to 2 73)	-0 09 (-1 73 to 1 55)	-0 1 (-2 07 to 1 89)	0 27 (-1 59 to 2 05)	0 44 (-1 73 to 2 55)	0 45 (-2 to 2 82)	0 6 (-1 57 to 2 67)	0 3 (-2 04 to 2 55)	0 11 (-1 87 to 2 09)	0 55 (-1 9 to 2 9)	0 24 (-1 97 to 2 31)	-0 61 (-1 82 to 0 6)	14
-0 27 (-2 46 to 1 82)	0 03 (-2 8 to 2 78)	-0 29 (-2 3 to 1 72)	-0 29 (-2 59 to 2 01)	0 07 (-2 12 to 2 19)	0 24 (-2 23 to 2 64)	0 25 (-2 46 to 2 88)	0 4 (-2 07 to 2 77)	0 1 (-2 49 to 2 63)	-0 09 (-2 39 to 2 21)	0 34 (-2 36 to 2 98)	0 03 (-2 44 to 2 41)	-0 81 (-2 48 to 0 86)	-0 2 (-1 37 to 0 96)

Treatment Number	Treatment Description
1	SMBG, MDI
2	CGM (no alarm) + SMBG, MDI
3	CGM + SMBG, CSII
4	CGM + no SMBG, CSII
5	CGM + SMBG, MDI
6	SMBG, insulin unspecified
7	Flash + SMBG, insulin unspecified
8	CGM + SMBG not specified, MDI
9	CGM + SMBG, insulin unspecified
10	Night: CL (MPC); Day: CGM + SMBG, CSII
11	CGM + SMBG unspecified, insulin unspecified
12	CL (MPC)
13	SMBG, CSII
14	CGM + SMBG unspecified, CSII
15	Night: CL (MPC); Day: CGM + SMBG unspecified, CSII

Figure 10.5. Step diagram for all treatment comparisons for HbA1c in adults with type 1 diabetes. Outcomes presented as median (95% credible interval).

The mean probability of each treatment occupying each rank is presented in Figure 10.6. Lighter colours indicate lower rank and greater probability of efficacy. This figure should be interpreted by relative colour. For example, the interventions on the left side of the figure appear to be lighter than the interventions appearing on the right side of the figure. This indicates a greater probability of lower rank. One intervention, “Night: CL(MPC), Day: CGM+SMBG not specified, CSII” stands out as being darker than the neighbouring interventions, and therefore has a greater probability of higher rank. The mean probability that any treatment was likely to be the best was less than 0.20. The mean probability that CGM+SMBG not specified, MDI was likely to be the best was 0.19, followed by CGM+SMBG not specified, insulin unspecified was 0.17. No studies contributed greater than three to the model’s deviance information criterion, and therefore no sensitivity analysis was conducted for this outcome.



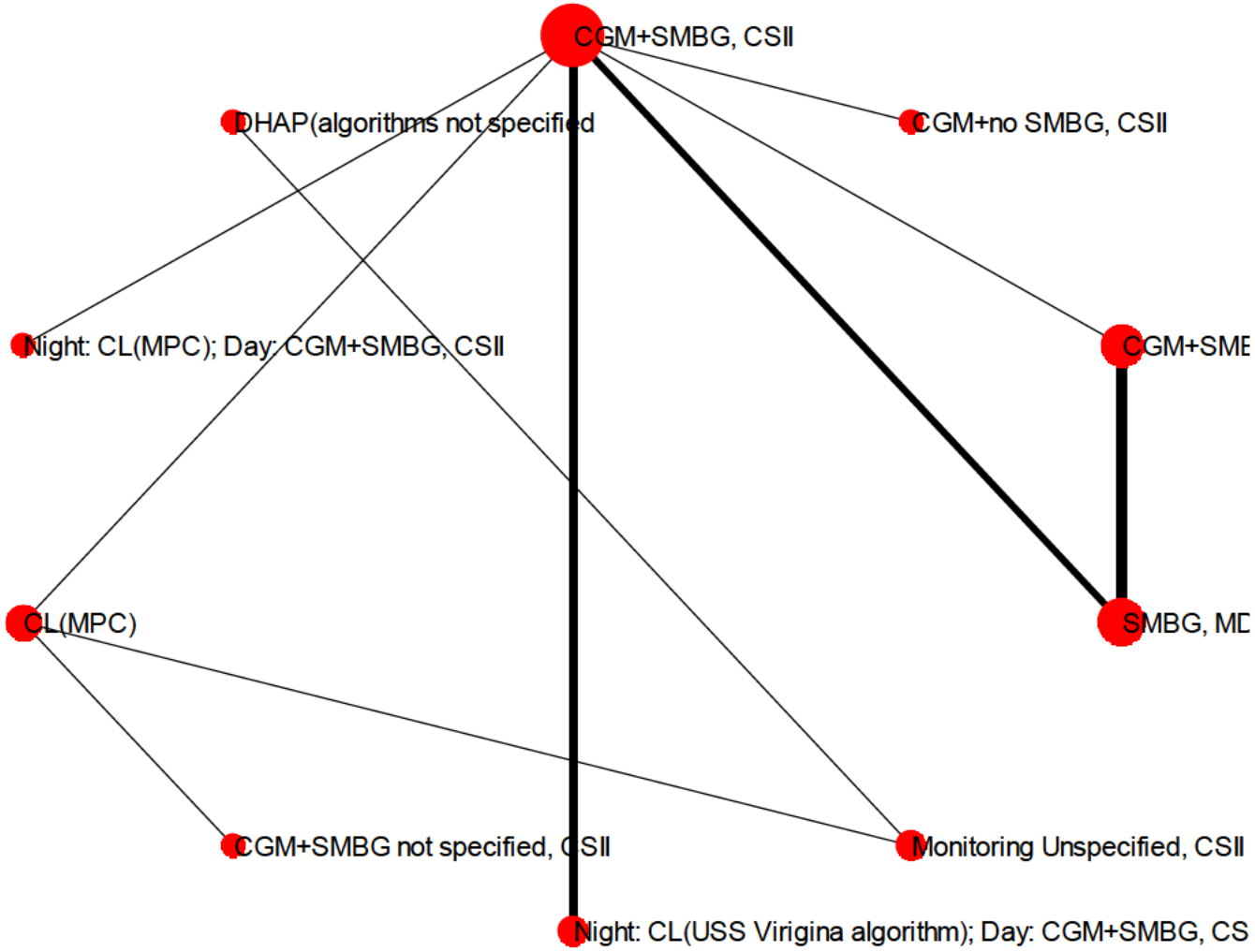
*CL=closed loop; MPC=model predictive control algorithm; CGM=continuous glucose monitor; SMBG=self-monitoring of blood glucose

Figure 10.6. Mean probability of rank, by treatment. Lighter colour indicates lower rank and greater probability of efficacy.

10.3.1.2 Hypoglycemic Events Requiring Assistance

The number of hypoglycemic events requiring assistance in adults with type 1 diabetes was presented in 14 studies including 10 treatments (Figure 10.7). There were seven additional studies that presented this outcome, however, the treatments in these studies did not connect to the primary network[109,115,131,136-139]. Interventions in these studies were: 1) SMBG, insulin unspecified; 2) Flash+SMBG, insulin unspecified; 3) CGM+SMBG not specified, insulin unspecified; 4) Night: CL(proportional integral derivative algorithm), Day: CGM+SMBG, CSII(LGS); 5) CGM+SMBG, CSII(LGS); 6) Flash, MDI; and 7) CGM+no SMBG, MDI.

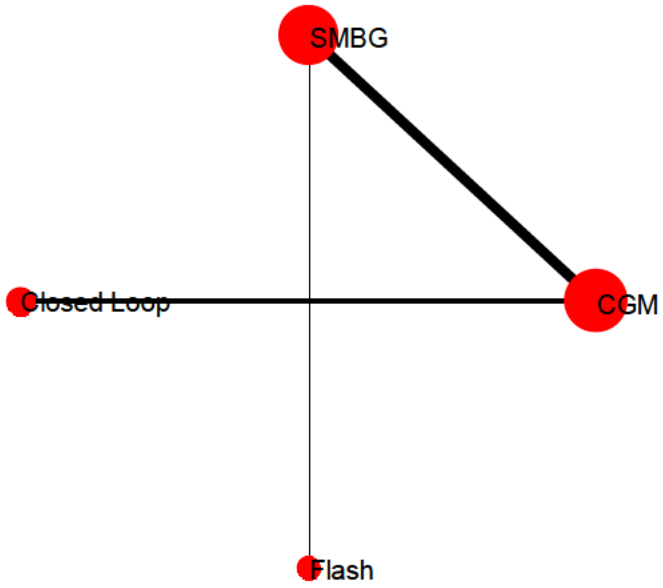
In the base case network depicted in Figure 10.7, convergence was not reached at 250,000 iterations with three chains for either the fixed effects or the random effects model. Therefore, treatments were simplified (Figure 10.8). No hypoglycemic events requiring assistance were observed in studies that included closed-loop treatment at night and continuous glucose monitor during the day. To encourage convergence of the model, these four studies[112,113,122,139] were excluded from the simplified treatment model.



*CGM=continuous glucose monitoring; SMBG=self-monitoring of blood glucose; CSII=continuous subcutaneous insulin infusion; MDI=multiple daily injections; CL=closed loop; MPC=model predictive control algorithm, DHAP=dual hormone artificial pancreas

Figure 10.7. Hypoglycemic events requiring assistance in adults with type 1 diabetes network diagram

The random effects model fits the data better, as evidenced by the lower posterior mean residual deviance. For the random effects model, the posterior mean residual deviance was close to the observed number of data points 24, suggesting adequate fit. The posterior mean residual deviance of the fixed effects model was greater than 24, which suggests a lack of fit. The lower DIC associated with the random effects model also supports selection of the random effects model (*Appendix E: WinBUGS Codes for Network Clinical Effectiveness Meta-analysis)*. Sixty-thousand burn-in iterations were required to reach convergence – which was assessed through examination of plots of history, kernel density, and plots of the Brooks-Gelman-Rubin statistic, and comparison of Monte Carlo error to standard deviation of relative estimates of effect. Model outcomes were recorded following 120,000 additional iterations, also with three chains.



*SMBG=self-monitoring of blood glucose; CGM=continuous glucose monitor

Figure 10.8. Simplified network diagram for number of hypoglycemic events requiring assistance in adults with type 1 diabetes.

The simplified evidence network includes 12 studies, and four treatments. The most numerous comparisons in this simplified network were SMBG versus CGM, which appeared in nine studies. There was one study examining a flash glucometer. There are no loops of evidence in this network – therefore assessment for consistency was not possible.

Median rank and 95% credible interval for each treatment are shown in Table 10.4 with lower ranks indicating greater probability of being the most effective treatment for reducing the number of hypoglycemic events requiring assistance. No treatment has median rank of one, and three out of four treatments have a 95% credible interval spanning from rank one to four.

SMBG has median rank of two, and 95% probability that the rank falls between one and four (Table 10.4), Compared to SMBG, CGM is predicted to have relative hazard of 0.8 for hypoglycemic events requiring assistance, with 95% probability of falling between 0.4 to 2.1. Because the 95% credible interval includes the null value of one, this comparison is not statistically significant. The step diagram should be interpreted as the hazard of the outcome of the intervention indicated by the row, relative to the intervention indicated by the column.

Table 10.4. Median rank of each treatment for preventing hypoglycemic events requiring assistance in adults with type 1 diabetes.

Treatment	Median Rank	95% Credible Interval
SMBG	2	1 to 4
CGM	3	1 to 4
Flash	3	2 to 4
Closed Loop	2	1 to 4

Median hazard ratio for each treatment relative to all other treatments is presented in Figure 10.9. No statistically significant differences were identified between treatments. For all pairwise comparisons, the 95% credible interval included the null value of one.

SMBG			
0.8 0.4 to 2.1	CGM		
0.5 0.0 to 6.5	0.5 0.0 to 8.4	Flash	
0.8 0.0 to 63.8	1.0 0.0 to 67.7	1.9 0.0 to 349.9	CL

*SMBG=self-monitoring of blood glucose; CGM=continuous glucose monitor; Flash=flash glucometer; CL=closed loop

Figure 10.9. Step diagram for all treatment comparisons for relative hazard of hypoglycemic events requiring assistance. Outcomes presented as median (95% credible interval).

Mean probability of each treatment occupying each rank is presented in Figure 10.10. Lighter colours indicate lower rank and greater probability of efficacy. In this figure, Flash has much more of the lighter colours than the other treatments, suggesting that this intervention is the most likely to be effective, and therefore have lower rank. The mean probability that Flash is the most effective treatment is 0.50, followed by the closed loop at 0.34. The probability that SMBG was most likely to be effective was 0.05.

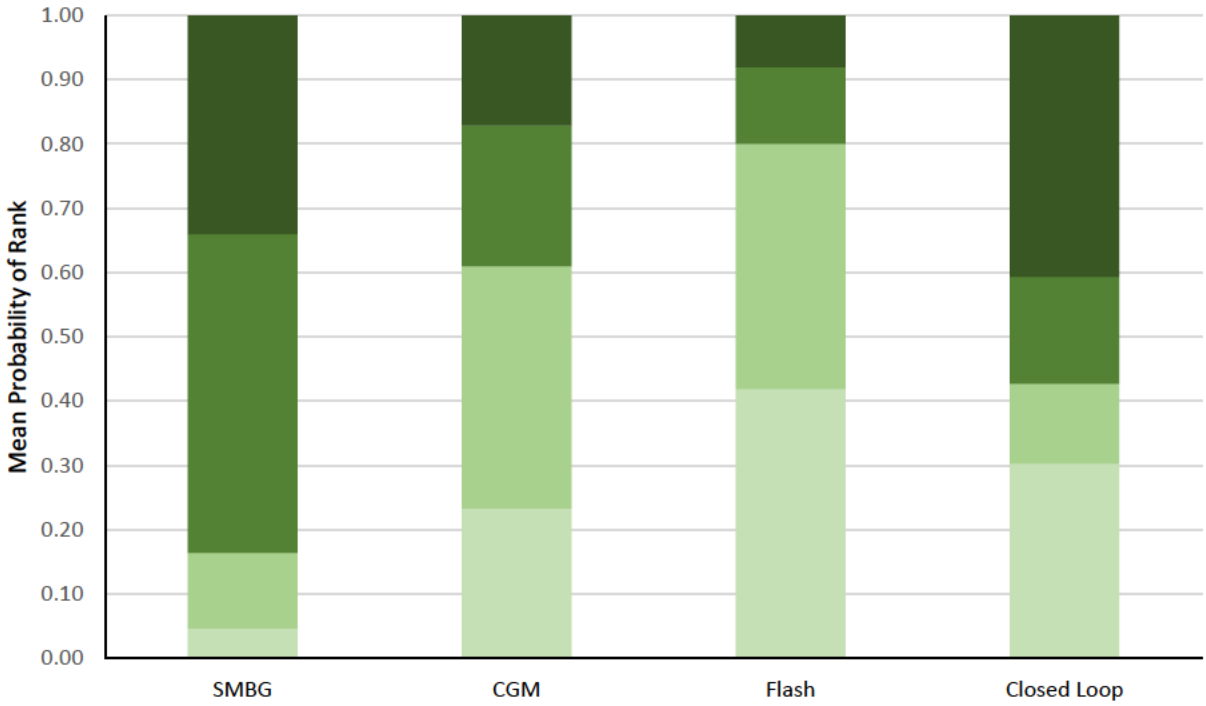


Figure 10.10. Mean probability of rank, by treatment. Lighter colour indicates lower rank and greater probability of efficacy.

One study by Peyrot & Rubin[128] contributed more than three to the model's deviance information criterion (*Appendix F Clinical Effectiveness Supplementary Material*). This study compared SMBG, MDI to CGM+SMBG, CSII over 16 weeks in a parallel arm RCT[128]. In sensitivity analysis, this study was excluded from the random effects network meta-analysis. Although relative magnitude of estimates of effect were slightly different, no statistically significant differences in effect were identified between comparators (*Appendix F Clinical Effectiveness Supplementary Material*).

10.3.1.3 Time-in-Range for Blood Glucose 3.9 to 10.0 mmol/L

Twenty-three studies describing 20 treatments were included in the network meta-analysis of time-in-range for adults with type 1 diabetes (Figure 10.11). Four studies[131,140-142] described interventions not encountered elsewhere in the network and were therefore excluded from network meta-analysis. The interventions in these studies were: 1) DHAP(Insulin: fading memory proportion-derivative algorithm, Glucagon: algorithm not specified)[140]; 2) CL(modified fading memory proportion-derivative algorithm)[140]; 3) CL(modified fading memory proportion-

derivative algorithm with PLGS)[140]; 4) current care[140]; 5) DHAP(Insulin: MPC, Glucagon: proportional derivative)[141]; 6) DHAP(Insulin: MPC, Glucagon: proportional derivative algorithm) with adaptive meal-priming insulin boluses[141]; 7) SMBG with continuous intraperitoneal insulin infusion[142]; 8) CGM+SMBG and continuous intraperitoneal insulin infusion[142]; 9) Flash, MDI[131]; and 10) CGM+ no SMBG, MDI[131]. Results of studies excluded from network meta-analysis of time-in-range are in Table 10.5. Because no studies comparing these interventions to the rest of the evidence network were identified, no comparisons between these studies and the other evidence were made.

Among the studies included in network meta-analysis, the most frequent comparators are between: SMBG, MDI versus CGM+SMBG, MDI; and SMBG, insulin unspecified versus CGM+SMBG, insulin unspecified. Both comparisons occur in three studies. Both the fixed effects and random effects models were similar in terms of posterior mean residual, posterior mean deviance, effective number of parameters, and deviance information criteria. Effects of interventions are also similar between models; therefore, the fixed effects model is preferred for ease of interpretation (*Appendix F Clinical Effectiveness Supplementary Material*). Seventy-thousand burn-in iterations were required to reach convergence, which was assessed through examination of plots of history, kernel density, and plots of the Brooks-Gelman-Rubin statistic, and comparison of Monte Carlo error to standard deviation of relative estimates of effect. Model outcomes were recorded following 140,000 additional iterations, also with three chains. Only one loop of evidence was identified, however, this loop of evidence occurs within a single study[117]. Because inconsistency cannot occur within a single study, and no other loops of evidence were identified, no assessment of inconsistency was conducted. No studies were identified as contributing greater than three to the model's deviance information criterion (*Appendix F Clinical Effectiveness Supplementary Material*).

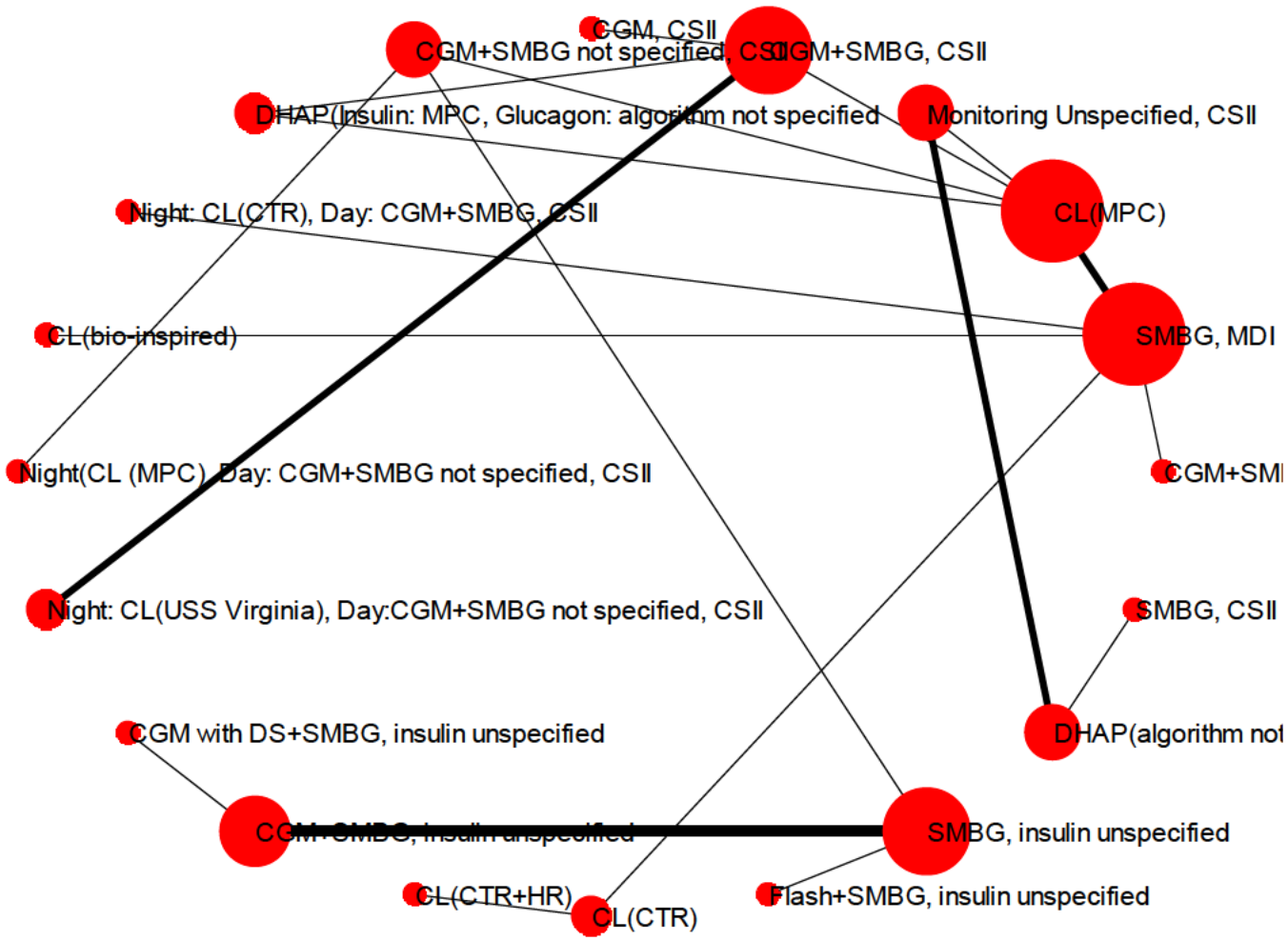


Figure 10.11. Network diagram for time-in-range in adults with type 1 diabetes.

Table 10.5. Percent of time-in-range 3.9-10.0 mmol/L blood glucose in trials not included in network meta-analysis.

First Author, Year	Design	Follow-Up (weeks if not otherwise specified)	Treatment 1 Number of Participants (n)	Percent Time-in-Range 3.9-10.0 mmol/L (mean ± SE)	Treatment 2 Number of Participants (n)	Percent Time-in-Range 3.9-10.0 mmol/L (mean ± SE)
Castle, 2018[140]	Crossover (7- to 45-day washout)	4 days	Current Care (n=20)	63.1 ± 3.9	Dual hormone closed loop (modified fading memory proportion-derivative algorithm for insulin, glucagon delivery algorithm not specified) (n=20)	72.0 ± 2.4
			Closed loop (modified fading memory proportion-derivative insulin delivery algorithm) (n=20)	74.3 ± 1.8	Predictive low glucose suspend closed loop (modified fading memory proportion-derivative insulin delivery algorithm) (n=20)	65.2 ± 3.0
El-Khatib, 2014[141]	Parallel Arm	48 hours	Dual hormone artificial pancreas (model predictive control algorithm for insulin delivery, proportional derivative algorithm for glucagon) (n=6)	70.0 ± 3.7	Dual hormone artificial pancreas (model predictive control algorithm for insulin delivery, proportional derivative algorithm for glucagon) with adaptive meal-priming insulin boluses (n=6)	80.0 ± 2.5
Logtenberg, 2009[142]	Crossover (1-week washout)	6 days	Self-monitoring of blood glucose with continuous intraperitoneal insulin infusion (n=12)	63.7 ± 3.9	Continuous glucose monitoring with self-monitoring of blood glucose and continuous intraperitoneal insulin infusion	65.2 ± 4.0
Reddy, 2018[131]	Parallel Arm	8 weeks	Flash monitoring of blood glucose with multiple daily injections of insulin (n=20)	59.5 ± 2.0	Continuous glucose monitoring without self-monitoring of blood glucose for treatment decisions, and multiple daily injections of insulin (n=19)	62.6 ± 3.5

Median rank and 95% credible interval for each treatment are shown in Table 10.6, with lower ranks indicating greater probability of being the most effective treatment for increasing percent of time spent with blood glucose between 3.9 and 10.0 mmol/L. The dual hormone artificial pancreas with unspecified algorithms for insulin delivery and glucagon delivery had a median rank of 1, and the closed-loop with bio-inspired insulin delivery algorithm had a median rank of 20.

DHAP(algorithm not specified) had median rank of one, with 95% probability of rank between one and three (Table 10.6), indicating that this intervention is likely to be more effective for time-in-range than interventions with higher median rank, such as the CL(bio-inspired algorithm) intervention, with median rank of 20, and 95% probability of rank between 11 and 20.

Table 10.6. Median rank of each treatment for increasing time-in-range for blood glucose 3.9-10.0 mmol/L in adults with type 1 diabetes.

Treatment	Median Rank	95% Credible Interval
CGM+no SMBG, CSII	11	5 to 19
CGM+SMBG, CSII	8	4 to 16
Monitoring unspecified, CSII	13	8 to 18
CL (MPC algorithm)	4	2 to 7
SMBG, MDI	13	8 to 18
CGM+SMBG, MDI	12	6 to 18
SMBG, CSII	10	2 to 20
DHAP (algorithm not specified)	1	1 to 3
SMBG, insulin unspecified	18	13 to 20
Flash+SMBG, insulin unspecified	13	8 to 18
CL (CTR algorithm)	17	7 to 20
CL (CTR + HR)	11	1 to 20
CGM+SMBG, insulin unspecified	17	9 to 20
CGM with decision support	14	3 to 20
Night: CL (USS Virginia algorithm), Day: CGM+SMBG, CSII	4	1 to 10
Night: CL (MPC algorithm), Day: CGM+SMBG not specified, CSII	4	1 to 9
CL (bio-inspired algorithm)	20	11 to 20
Night: CL (CTR algorithm), Day: CGM+SMBG, CSII	9	3 to 17
Dual Hormone Artificial Pancreas (Insulin: MPC algorithm; Glucagon: algorithm not specified)	3	1 to 7
CGM+SMBG not specified, CSII	9	5 to 14

Among the included studies, few statistically significant differences in time-in-range were identified and are bolded and red in Figure 10.12. Differences in time-in-range were calculated by the predicted effect of the row treatment minus the column treatment. For example, CGM, CSII is likely to result in 2.0% (95% CrI: -1.2 to 5.2) more time-in-range than CGM+no SMBG, CSII. Because the 95% credible interval crosses the null value of zero for this comparison, the difference in time-in-range between these two interventions is not statistically significant.

1																		
2 (-1 2 to 5 3)	2																	
-2 4 (-12 to 7 5)	-4 5 (-13 5 to 4 9)	3																
8 2 (-0 6 to 17 3)	6 2 (-2 to 14 6)	**10.6 (6.8 to 14.4)**	4															
-2 3 (-12 4 to 8 2)	-4 3 (-14 to 5 6)	0 1 (-6 4 to 6 6)	**-10.5 (-15.7 to - 5.3)**	5														
-1 5 (-12 7 to 10)	-3 5 (-14 3 to 7 5)	0 9 (-7 2 to 9)	**-9.7 (-16.8 to - 2.5)**	0 8 (-4 to 5 7)	6													
0 1 (-17 3 to 17 9)	-1 9 (-19 to 15 5)	2 6 (-11 9 to 17 1)	-8 1 (-23 to 7)	2 5 (-13 3 to 18 4)	1 7 (-14 9 to 18 3)	7												
15.4 (4.9 to 26.1)	**13.4 (3.4 to 23.6)**	**17.8 (13.8 to 21.9)**	**7.2 (1.6 to 12.8)**	**17.7 (10 to 25.3)**	**16.9 (7.8 to 26)**	**15.3 (1.2 to 29.1)**	8											
-7 8 (-18 3 to 3)	-9 8 (-19 8 to 0 5)	-5 4 (-12 3 to 1 6)	**-16 (-21.7 to - 10.2)**	-5 5 (-13 3 to 2 4)	-6 3 (-15 5 to 2 9)	-7 9 (-24 1 to 8)	**-23.2 (-31.2 to - 15.1)**	9										
-2 8 (-13 7 to 8 5)	-4 8 (-15 2 to 5 9)	-0 4 (-7 9 to 7 3)	**-11 (-17.5 to - 4.4)**	-0 5 (-8 9 to 8)	-1 3 (-11 to 8 5)	-2 9 (-19 4 to 13 4)	**-18.2 (-26.8 to - 9.5)**	**5 (1.9 to 8.1)**	10									
-6 7 (-21 4 to 8 2)	-8 7 (-23 to 5 9)	-4 3 (-16 8 to 8 4)	**-14.9 (-26.8 to - 2.9)**	-4 4 (-15 1 to 6 5)	-5 2 (-17 to 6 7)	-6 8 (-25 9 to 12 4)	**-22.1 (-35.2 to - 8.8)**	1 1 (-12 3 to 14 6)	-3 9 (-17 6 to 9 9)	11								
-0 5 (-19 1 to 18 1)	-2 5 (-20 9 to 15 9)	1 9 (-14 9 to 18 9)	-8 7 (-25 2 to 7 9)	1 8 (-13 8 to 17 5)	1 (-15 4 to 17 4)	-0 7 (-22 9 to 21 7)	-15 9 (-33 3 to 1 5)	7 3 (-10 3 to 24 9)	2 3 (-15 5 to 20 1)	6 2 (-5 2 to 17 6)	12							
-6 2 (-19 to 6 7)	-8 3 (-20 6 to 4 3)	-3 8 (-13 9 to 6 3)	**-14.4 (-23.8 to - 5.1)**	-3 9 (-14 6 to 6 8)	-4 8 (-16 5 to 7)	-6 4 (-24 2 to 11 3)	**-21.7 (-32.5 to - 10.7)**	1 5 (-5 8 to 8 9)	-3 5 (-11 4 to 4 5)	0 4 (-14 9 to 15 6)	-5 7 (-24 8 to 13 3)	13						
-3 1 (-19 to 12 8)	-5 1 (-20 7 to 10 5)	-0 7 (-14 4 to 13 1)	-11 3 (-24 5 to 1 9)	-0 8 (-15 to 13 5)	-1 6 (-16 6 to 13 5)	-3 2 (-23 4 to 16 6)	**-18.5 (-32.9 to - 4.2)**	4 7 (-7 3 to 16 6)	-0 4 (-12 6 to 12)	3 5 (-14 5 to 21 4)	-2 6 (-23 9 to 18 5)	3 1 (-6 3 to 12 5)	14					
9.3 (3.7 to 14.9)	**7.2 (2.7 to 11.8)**	**11.7 (1.3 to 21.8)**	1 1 (-8 6 to 10 5)	**11.6 (0.7 to 22.2)**	10 7 (-1 1 to 22 5)	9 1 (-8 9 to 26 8)	-6 2 (-17 3 to 4 8)	**17 (5.8 to 28)**	**12 (0.4 to 23.4)**	**15.9 (0.7 to 31)**	9 7 (-9 1 to 28 7)	**15.5 (2.2 to 28.7)**	12 4 (-3 9 to 28 5)	15				
8 1 (-3 2 to 19 6)	6 1 (-4 8 to 17 1)	**10.5 (2.4 to 18.6)**	-0 1 (-7 2 to 7)	**10.4 (1.5 to 19.3)**	9 6 (-0 5 to 19 7)	8 (-8 8 to 24 5)	-7 3 (-16 4 to 1 8)	**15.9 (9.7 to 22.1)**	**10.9 (4 to 17.8)**	**14.8 (0.7 to 28.7)**	8 6 (-9 5 to 26 6)	**14.3 (4.7 to 23.9)**	11 2 (-2 2 to 24 6)	-1 2 (-12 9 to 10 8)	16			
-13 3 (-29 2 to 2 6)	-15 4 (-30 9 to 0 2)	-10 9 (-24 7 to 2 8)	**-21.5 (-34.8 to - 8.4)**	-11 (-23 2 to 1 1)	-11 9 (-25 to 1 2)	-13 5 (-33 5 to 6 4)	**-28.8 (-43.1 to - 14.5)**	-5 6 (-20 to 8 8)	-10 6 (-25 4 to 4 1)	-6 7 (-22 9 to 9 5)	-12 9 (-32 8 to 6 9)	-7 1 (-23 3 to 9)	-10 2 (-28 9 to 8 4)	-22 6 (-38 8 to - 6 4)	**-21.4 (-36.5 to - 6.4)**	17		
2 (-10 7 to 15)	0 (-12 4 to 12 6)	4 4 (-5 7 to 14 6)	-6 2 (-15 5 to 3 2)	4 3 (-3 4 to 12 1)	3 5 (-5 6 to 12 7)	1 9 (-15 8 to 19 5)	**-13.4 (-24.3 to - 2.5)**	9 8 (-1 2 to 20 8)	4 8 (-6 6 to 16 2)	8 7 (-4 6 to 22)	2 5 (-15 to 20)	8 3 (-5 to 21 5)	5 2 (-11 1 to 21 3)	-7 2 (-20 4 to 6 2)	-6 1 (-17 9 to 5 7)	**15.4 (1 to 29.8)**	18	
10.7 (1.5 to 20.1)	**8.7 (0.1 to 17.5)**	**13.1 (5.3 to 21)**	2 5 (-4 3 to 9 4)	**13.1 (4.4 to 21.6)**	**12.2 (2.3 to 22.1)**	10 6 (-6 to 27)	-4 7 (-13 5 to 4 1)	**18.5 (9.5 to 27.5)**	**13.5 (4 to 23)**	**17.4 (3.6 to 31.1)**	11 2 (-6 6 to 29)	**17 (5.4 to 28.5)**	13 8 (-1 to 28 7)	1 5 (-8 3 to 11 4)	2 6 (-7 3 to 12 5)	**24.1 (9.2 to 39)**	8 7 (-2 9 to 20 2)	19
1 8 (-8 1 to 12 1)	-0 2 (-9 7 to 9 5)	4 2 (-1 9 to 10 4)	**-6.4 (-11.2 to - 1.6)**	4 1 (-3 to 11 3)	3 3 (-5 3 to 11 9)	1 7 (-14 2 to 17 3)	**-13.6 (-20.9 to - 6.2)**	**9.6 (6.4 to 12.8)**	**4.6 (0.1 to 9)**	8 5 (-4 6 to 21 4)	2 3 (-14 9 to 19 5)	**8.1 (0.1 to 16)**	4 9 (-7 4 to 17 2)	-7 4 (-17 9 to 3 3)	**-6.3 (-11.6 to - 1)**	**15.2 (1.2 to 29.3)**	-0 2 (-10 7 to 10 3)	**-8.9 (-17.3 to - 0.5)**	20

Treatment Number	Treatment Description
1	CGM+no SMBG, CSII
2	CGM + SMBG, CSII
3	Unspecified monitoring, CSII
4	CL (MPC)
5	SMBG, MDI
6	CGM + SMBG, MDI
7	SMBG, CSII
8	DHAP (algorithms unspecified)
9	SMBG, insulin unspecified
10	Flash + SMBG, insulin unspecified
11	CL (CTR)
12	CL (CTR + HR)
13	CGM + SMBG, insulin unspecified
14	CGM (DS) + SMBG, insulin unspecified
15	Night: CL (USS Virginia); Day: CGM + SMBG, CSII
16	Night: CL (MPC); Day: CGM + SMBG not specified, CSII
17	CL (bio-inspired algorithm)
18	Night: CL (CTR); Day: CGM + SMBG, CSII
19	DHAP (Insulin: MPC, Glucagon: algorithm unspecified)
20	CGM + SMBG not specified, CSII

Figure 10.12. Step diagram for all treatment comparisons for relative percent of time-in-range of blood glucose 3.9-10.0 mmol/L. Outcomes presented as median (95% credible interval) on natural scale. Red, bolded outcomes indicate comparisons where the difference is statistically significant.

Interventions frequently resulting in significant increases in time in range were the: CL(MPC); both DHAP interventions; the Night: CL(USS Virginia), Day: CGM+SMBG, CSII; and the Night: CL(MPC), Day: CGM+SMBG not specified, CSII. Interventions frequently resulting in less time-in-range than its comparators were: SMBG, MDI; and Flash+SMBG, insulin unspecified. Most comparisons between interventions were not statistically significant.

Mean probability of each treatment occupying each rank is presented in Figure 10.13. Lighter colours indicate lower rank and greater probability of efficacy. The interventions in the center of the figure appear to be generally lighter coloured than the interventions appearing on the left and right sides of the figure. This indicates a greater probability of lower rank. The mean probability that the DHAP(algorithms not specified) has the greatest efficacy measured in percent of time-in-range for blood glucose between 3.9-10.0 mmol/L is 0.70. In Figure 10.13, the DHAP(algorithms not specified) has a larger proportion of the bar shaded by the lightest colour on the figure, indicating that the probability of efficacy with this intervention is greater than the comparators.

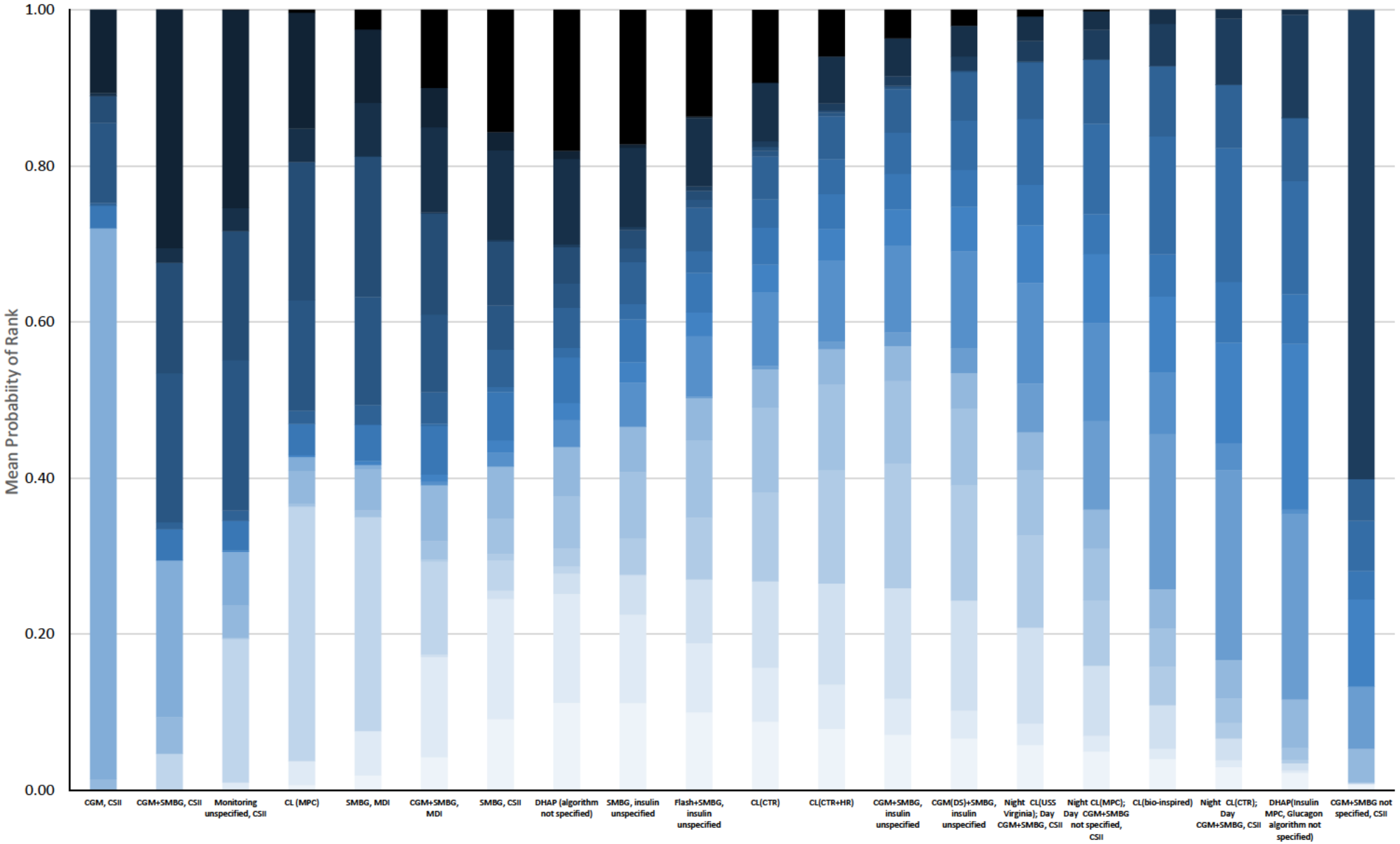


Figure 10.13. Mean probability of rank, by treatment. Lighter colour indicates lower rank and greater probability of efficacy.

10.3.1.4 Diabetic Ketoacidosis Events

The outcome of diabetic ketoacidosis (DKA) events was presented in 16 studies (Figure 10.14). There were no DKA events observed in 11 studies. No more than three DKA events were observed in a single trial. Significant variation in follow-up time and number of participants inhibit comparability of these findings. It is not clear whether differences in number of DKA events were due to interventions, or differences in sample size and follow-up.

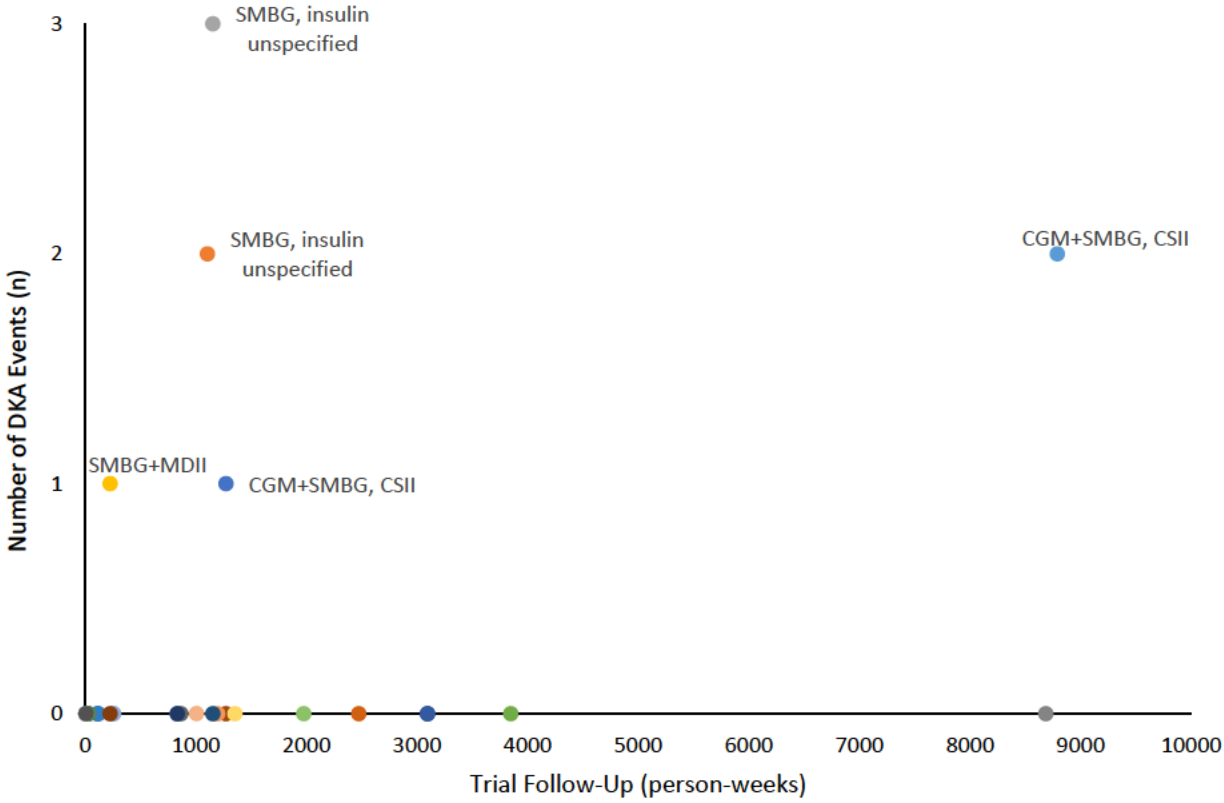


Figure 10.14. Number of diabetic ketoacidosis events observed in each trial, by length of trial follow-up in person-weeks.

10.3.1.5 EuroQol-5D (EQ-5D)

Three studies presented outcomes measured with the EQ-5D tool. Only one study specifies whether the five-question or three-question version of the tool was used – the study by Polonsky et al.[129] used the EQ-5D-5L. All three studies presenting EQ-5D outcomes compared self-monitoring of blood glucose to continuous glucose monitoring strategies. No statistically significant differences in utility measured with the EQ-5D were identified in the included studies (Table 10.7).

Table 10.7 Mean difference between treatments measured with EQ-5D

First Author, Year	Treatment One	Treatment Two	EQ-5D Mean Difference Between Treatments[a]
Heinemann (2018)[118]	SMBG, MDI	CGM+SMBG, MDI	0.03 increase with CGM+SMBG, MDI compared to SMB, MDI
Polonsky (2017)[129]	SMBG, MDI	CGM+SMBG, MDI	-0.78 decrease CGM+SMBG, MDI compared to SMB, MDI
Van Beers (2016)[137]	SMBG, insulin unspecified	CGM, insulin unspecified	Data not shown

[a]Calculated as treatment two minus treatment one

10.3.1.6 Hypoglycemia Fear Survey Overall Score (HFS)

Overall scores by for the HFS tool were presented in seven studies at the end of trial follow-up (Figure 10.15). Higher scores indicate greater fear of hypoglycemia with this tool[143]. Although multiple studies compare similar interventions, there is variation in terms of the effect size for each intervention. Visually, no intervention stands out as superior to the other interventions in terms of the HFS overall score.

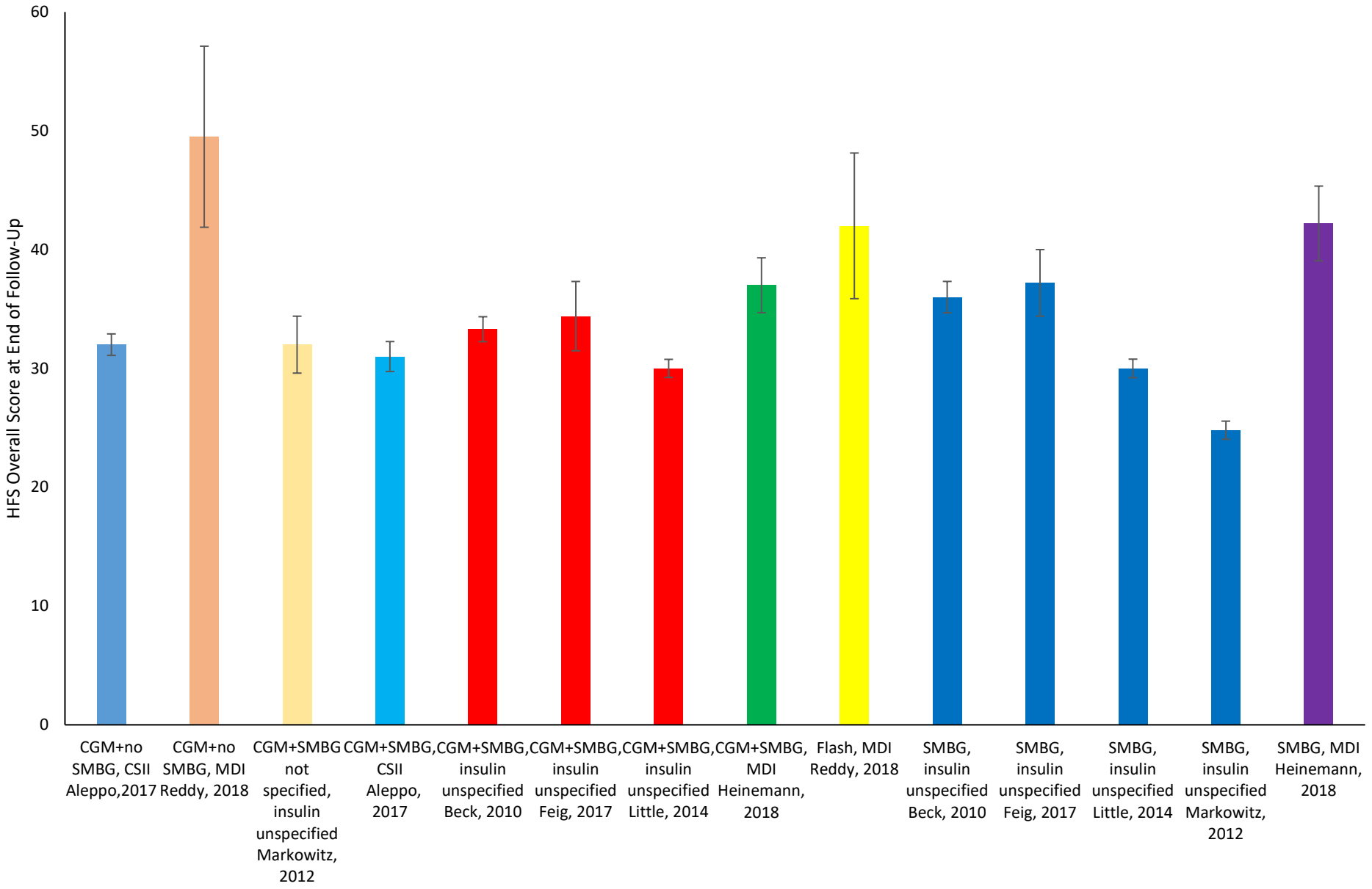


Figure 10.15 Hypoglycemia fear survey overall score by intervention. Different colours indicate different interventions. Bars represent mean score and error bars represent standard error.

10.3.1.7 Diabetes Treatment Satisfaction Questionnaire (DTSQ)

DTSQ outcomes were presented in seven studies, as a mixture of differences between interventions, and overall scores associated with interventions. The highest possible score for treatment satisfaction measured with the DTSQ is 36[91]. Higher score means higher satisfaction with diabetes treatment. Mean differences between the treatments in each study, calculated as treatment two minus treatment one, are presented in Table 10.8. Measures of spread were not presented in each study – therefore no measure of spread was included here. No consistent direction of effect was identified for treatments present in more than one study.

Table 10.8 Mean difference between treatments, measured with DTSQ

First Author, Year	Treatment One	Treatment Two	DTSQ Mean Difference Between Treatments[a]
Aleppo, 2017[103]	CGM + no SMBG, CSII	SMBG + CGM, CSII	0.00
Hommel, 2014[101]	SMBG, CSII	CGM + SMBG, CSII	1.16
Bolinder, 2016[109]	SMBG, insulin unspecified	Flash + SMBG, insulin unspecified	-0.24
Ajjan, 2016[102]	SMBG, MDI	CGM, MDI	1.08
Lind, 2017[126]	SMBG, MDI	CGM + SMBG, MDI	3.76
Langeland, 2012[123]	SMBG, insulin unspecified	CGM + SMBG, insulin unspecified	-1.81
Little, 2014[127]	SMBG, insulin unspecified	CGM + SMBG, insulin unspecified	0.00

[a]Calculated as treatment two minus treatment one

10.3.1.8 Quality Assessment

Of the 38 included studies for adult Type 1 diabetes summarized below in Table 10.9, 18 were considered to be at a moderate risk for bias due to randomization largely due to not reporting allocation concealment methods.

With respect to bias from deviation, 12 studies were given a moderate risk of bias rating largely due to participants and/or caregivers and trial personnel being aware of participants' assigned intervention during the trial. One study was rated as high risk due to not having sufficient time for any carry-over effects to have disappeared before outcome assessment in the second period[110].

Bias from missing outcome data was present in three studies, which were given a moderate risk of bias rating due to imbalances in missing data between groups and substantial drop-out rates that would have underpowered the study based on the study authors' power calculations. Two studies were rated as high risk due to outcome data not available for all, or nearly all participants that were randomized, proportions of missing outcome data were not similar across intervention groups and there was no evidence that results were robust to the presence of missing outcome data.

Bias from measurement was high in six studies due to studies using subjective self-report outcome measures as their primary outcomes, which may have been biased due to lack of blinding.

Nearly all studies were considered to be at low risk for bias in reported results. Twelve studies were deemed to have low overall risk of bias, 17 studies were deemed to have moderate overall risk of bias, and 9 studies were deemed to have high overall risk of bias.

Table 10.9 Risk of Bias for Included Studies for Adult Type 1 Diabetes

First Author (Year)	Bias from Randomiz-ation	Bias from Deviation	Bias from Missing Outcome Data	Bias from Measurement	Bias in Reported Results	Overall Risk of Bias
Ajjan (2016)[102]	low risk	low risk	high risk	low risk	low risk	high risk
Aleppo (2017)[103]	some concern	some concern	low risk	low risk	low risk	some concern
Bally (2017)[104]	low risk	low risk	low risk	low risk	low risk	low risk
Beck (2010)[100]	low risk	some concern	low risk	high risk	low risk	high risk
Beck (2017)[105]	low risk	low risk	low risk	low risk	low risk	low risk
Beck (2017)[106]	low risk	low risk	low risk	low risk	low risk	low risk
Bergenstal (2010)[107]	some concern	some concern	low risk	low risk	low risk	some concern
Blauw (2016)[108]	some concern	low risk	some concern	low risk	low risk	some concern
Bolinder (2016)[109]	some concern	low risk	low risk	low risk	low risk	some concern
Breton (2014)[110]	some concern	high risk	low risk	low risk	low risk	high risk
Breton (2018)[111]	some concern	low risk	low risk	low risk	low risk	some concern
Brown (2017)[112]	some concern	low risk	low risk	low risk	low risk	some concern
Brown (2015)[113]	some concern	low risk	low risk	low risk	low risk	some concern
El-Khatib (2017)[114]	low risk	low risk	low risk	low risk	low risk	low risk
Feig (2017)[115]	low risk	low risk	low risk	low risk	low risk	low risk
Forlenza (2017)[116]	some concern	low risk	low risk	low risk	low risk	some concern
Haidar (2017)[117]	some concern	some concern	low risk	low risk	low risk	some concern
Heinemann (2018)[118]	some concern	some concern	low risk	low risk	low risk	some concern
Hermanns (2014)[119]	some concern	some concern	low risk	low risk	low risk	some concern
Hommel (2014)[101]	low risk	low risk	low risk	high risk	low risk	high risk
JDRF (2008)[120]	low risk	some concern	low risk	low risk	low risk	some concern
Kovatchev (2014)[121]	some concern	some concern	low risk	low risk	low risk	some concern

First Author (Year)	Bias from Randomiz-ation	Bias from Deviation	Bias from Missing Outcome Data	Bias from Measurem ent	Bias in Reported Results	Overall Risk of Bias
Kropff (2015)[122]	low risk	low risk	low risk	low risk	low risk	low risk
Langeland (2012)[123]	low risk	low risk	low risk	low risk	low risk	low risk
Leelarathna (2014)[124]	some concern	some concern	low risk	low risk	low risk	some concern
Leelarathna (2013)[125]	some concern	some concern	low risk	high risk	low risk	high risk
Lind (2017)[126]	low risk	low risk	high risk	high risk	low risk	high risk
Little (2014)[127]	low risk	some concern	low risk	high risk	low risk	high risk
Peyrot (2009)[128]	some concern	some concern	low risk	high risk	low risk	high risk
Polonsky (2017)[129]	some concern	low risk	low risk	low risk	low risk	some concern
Reddy (2015)[130]	low risk	low risk	low risk	low risk	low risk	low risk
Reddy (2018)[131]	low risk	some concern	low risk	low risk	low risk	some concern
Russell (2015)[132]	low risk	low risk	low risk	low risk	low risk	low risk
Sequeira (2013)[133]	some concern	high risk	some concern	some concerns	high risk	high risk
Thabit (2014)[134]	low risk	low risk	low risk	low risk	low risk	low risk
Thabit (2015)[135]	low risk	low risk	low risk	low risk	low risk	low risk
Tumminia (2015)[136]	low risk	low risk	some concern	low risk	low risk	some concern
Van Beers (2016)[137]	low risk	low risk	low risk	low risk	low risk	low risk

10.3.2 Pediatric Type 1 Diabetes

Of the 70 unique samples, 37% (n=26) studied pediatric populations. Hypos requiring assistance was reported most often (n=12), followed by TIR (n=10), and HbA1c (n=8) (Table 10.10). None of the studies explored satisfaction with diabetes treatment. Four studies explored only patient reported outcomes using either the HFS (n=1), or the PedsQL (n=3); 18 studies reported only on clinical outcomes; and two studies reported both clinical outcomes and patient reported outcomes (both of them explored only fear of hypoglycemia using the HFS).

Table 10.10 List of outcomes for studies on pediatric populations with T1D

First Author (Year)	HbA1c	TIR	Hypos[a]	DKA	HFS	DTSQ	PedsQL
DirecNet (2005)[144]	■		■				
Abraham (2018)[145]	■			■	■		■
Barnard (2014)[39]							■
Battelino (2017)[146]			■	■			
Beck (2010)[100]							■
Bergenstal (2010)[107]	■		■	■			
Breton (2017)[147]		■					
Chase (2003)[148]					■		
DeBoer (2017)[149]		■	■				
DeBoer (2017)[150]		■					
Elleri (2013)[151]		■					
Elleri (2015)[152]		■					
Hommel (2014)[101]							■
Hovorka (2014)[153]		■					
JDRF (2008)[120]	■		■	■			
Kordonouri (2010)[154]	■						
Lagarde (2006)[155]	■		■				
Ly (2011)[156]	■						
Mauras (2012)[157]	■		■	■	■		
Piona (2018)[158]		■	■	■			
Russell (2015)[132]		■	■				
Russell (2016)[159]		■	■				
Sharifi (2016)[139]			■	■			
Tauschmann (2016)[160]		■					
Thabit (2015)[135]			■				
Wysocki (2006)[161]							■
Total	**8**	**10**	**12**	**7**	**3**	**0**	**5**

Footnote:
[a]Hypoglycemic events requiring assistance
Abbreviations: HbA1c = glycated hemoglobin; TIR = Time in Range; DK = diabetic Ketoacidosis; HFS = Hypoglycemia Fear Survey; DTSQ = Diabetes Treatment Satisfaction Questionnaire; PedsQL= Pediatric Quality of Life Inventory

10.3.2.1 HbA1c

Included within the network meta-analysis of HbA1c in children with type 1 diabetes were eight studies, and seven treatments (Figure 10.16). All studies that presented HbA1c in a pediatric population were connected to the network of evidence, therefore no studies were excluded from analysis. The random effects model fits the data better, as evidenced by the lower posterior mean residual deviance. For the random effects model, the posterior mean residual deviance is close to the observed number of data points 18, suggesting adequate fit. The posterior mean residual deviance of the fixed effects model is greater than 18, which suggests a lack of fit. The difference in DIC between the two models is less than three, and therefore is not meaningful. It is noted that the median estimates of effect are similar between the two models. Here, the random effects model was considered as the base-case analysis (*Appendix F Clinical Effectiveness Supplementary Material).* Eighty-thousand burn-in iterations were required to reach convergence – which was assessed through examination of plots of history, kernel density, and plots of the Brooks-Gelman-Rubin statistic, and comparison of Monte Carlo error to standard deviation of relative estimates of effect. Model outcomes were recorded following 160,000 additional iterations, also with three chains.

The most frequent interventions compared within a study were: SMBG, insulin unspecified; and CGM+SMBG, insulin unspecified. This comparison was present in two studies. Because there are no loops of evidence in this network, assessment for inconsistency was not possible (Figure 10.16). No study contributed greater than three to the model's deviance information criterion *(Appendix F Clinical Effectiveness Supplementary Material).*

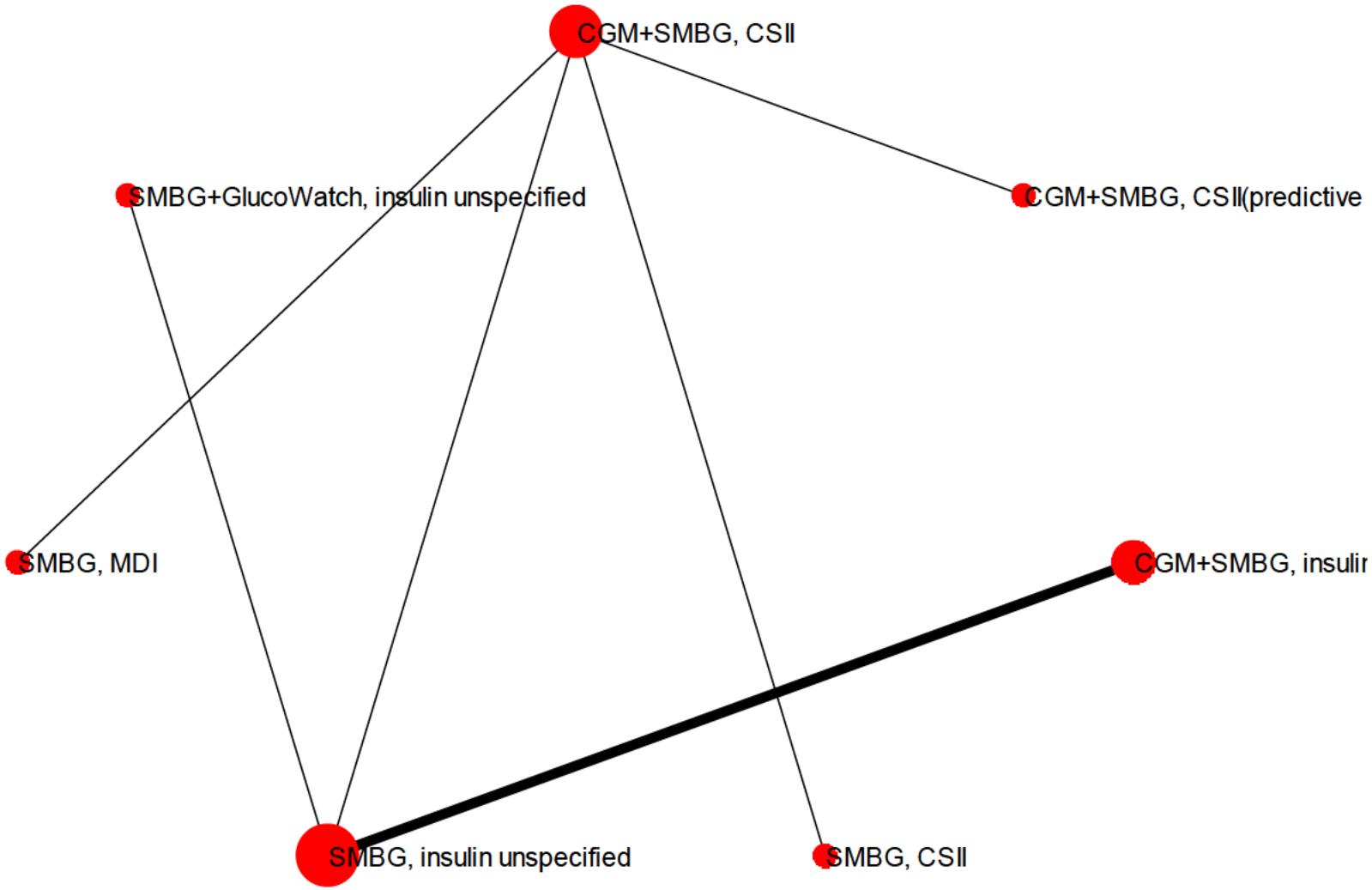


Figure 10.16. Network diagram for HbA1c in children with type 1 diabetes

Median rank and 95% credible interval for each treatment are shown in Table 10.11, with lower ranks indicating greater probability of being the most effective treatment for reducing HbA1c. No treatment has the median rank of one, and no treatment has the median rank of seven. All but one of the 95% credible intervals include all possible ranks. For example, the median rank of SMBG, CSII was three, with 95% credible interval indicating that there is 95% probability that the rank falls between one and seven.

Table 10.11. Median rank of each treatment for lowering HbA1c in children with type 1 diabetes.

Treatment	Median Rank	95% Credible Interval
SMBG, insulin unspecified	4	1 to 7
CGM+SMBG, insulin unspecified	4	1 to 7
CGM+SMBG, CSII	4	1 to 6
SMBG+GlucoWatch, insulin unspecified	4	1 to 7
CGM+SMBG, CSII (predictive low glucose suspend)	4	1 to 7
SMBG, MDI	6	1 to 7
SMBG, CSII	3	1 to 7

Median estimates of effect for each treatment relative to all other treatments are presented in Figure 10.17. Within the included studies, no statistically significant differences were identified between the different treatments. For each pairwise comparison, the 95% credible interval included the null value. Compared to CGM+SMBG, insulin unspecified; SMBG, insulin unspecified is likely to result in a difference in HbA1c of 0.0%. Outcomes presented in the step diagram are calculated as the predicted effect of the intervention indicated by the row, minus the predicted effect for the intervention indicated by the column.

SMBG, insulin unspecified						
0.0 (-1.6 to 1.6)	CGM+SMBG, insulin unspecified					
0.0 (-2.8 to 2.8)	0.0 (-3.2 to 3.3)	CGM+SMBG, CSII				
0.1 (-2.7 to 2.9)	0.1 (-3.1 to 3.4)	0.1 (-3.9 to 4.1)	GlucoWatch+SMBG, insulin unspecified			
0.1 (-3.9 to 4.1)	0.1 (-4.2 to 4.4)	0.1 (-2.7 to 2.9)	0.0 (-4.9 to 4.9)	CGM+SMBG, CSII (LGS)		
0.6 (-3.4 to 4.6)	0.6 (-3.7 to 5)	0.6 (-2.2 to 3.4)	0.5 (-4.4 to 5.4)	0.5 (-3.4 to 4.5)	SMBG, MDI	
-0.1 (-4.1 to 3.9)	-0.1 (-4.4 to 4.3)	-0.1 (-2.9 to 2.7)	-0.2 (-5.1 to 4.7)	-0.2 (-4.2 to 3.8)	-0.7 (-4.7 to 3.3)	SMBG, CSII

Figure 10.17. Step diagram for all treatment comparisons for HbA1c in children with type 1 diabetes. Outcomes presented as median (95% credible interval) on natural scale.

The mean probability of each treatment occupying each rank is presented in Figure 10.18. Lighter colours indicate lower rank and greater probability of efficacy. In this case, each intervention has similar proportions of each colour, and reflects the uncertainty present in this comparison. The intervention with the greatest probability of being the most effective is SMBG, CSII with continuous subcutaneous insulin infusion, at 0.31. The intervention with the lowest probability of being the most effective in terms of HbA1c is self-monitoring of blood glucose with multiple daily injections of insulin, at 0.06. Although Figure 10.18 appears to contradict the probability that SMBG, CSII is the most effective intervention, this is not the case. Looking at all interventions relative to SMBG, insulin unspecified, the 95% credible interval for SMBG, CSII goes to a lower value than any other; and SMBG, CSII has the lowest estimate of effect. With such small differences between interventions, slight differences in posterior distributions of estimates of effect will affect the rank of the outcome.

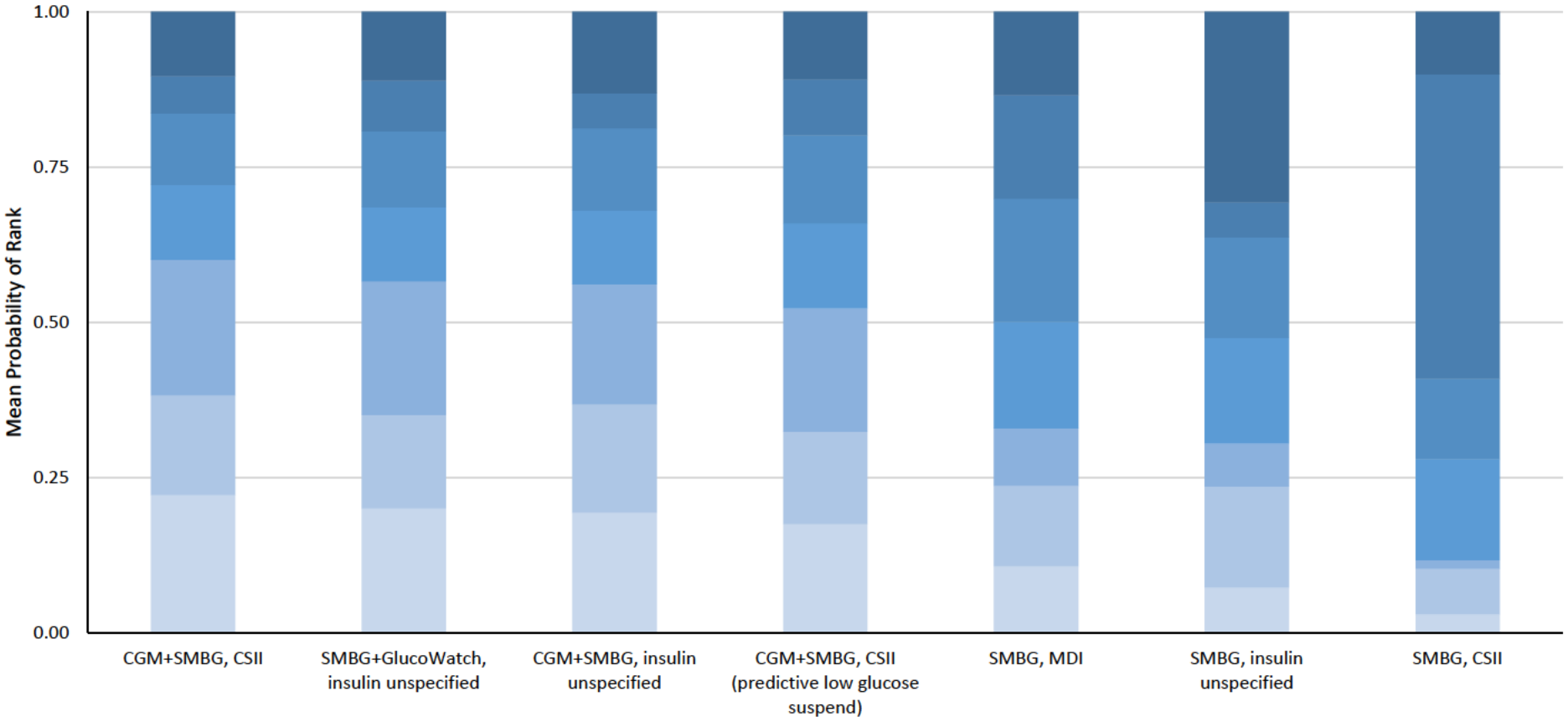


Figure 10.18. Mean probability of rank, by treatment. Lighter colour indicates lower rank and greater probability of efficacy.

10.3.2.2 Hypoglycemic Events Requiring Assistance

The number of hypoglycemic events requiring assistance in children with type 1 diabetes was presented in seven studies, with seven treatments (Figure 10.19). There were five additional studies that presented this outcome, however, the treatments in these studies did not connect to the primary network[139,149,158,159,162]. Interventions in these studies were: 1) CGM+SMBG not specified, CSII; 2) CL(CTR); 3) SMBG, CSII; 4) Flash+SMBG, CSII; 5) DHAP(algorithms unspecified); 6) Monitoring not specified, CSII; 7) Night: CL(proportional integral derivative algorithm), Day: CGM+SMBG not specified, CSII(LGS); and 8) CGM+SMBG not specified, CSII(LGS).

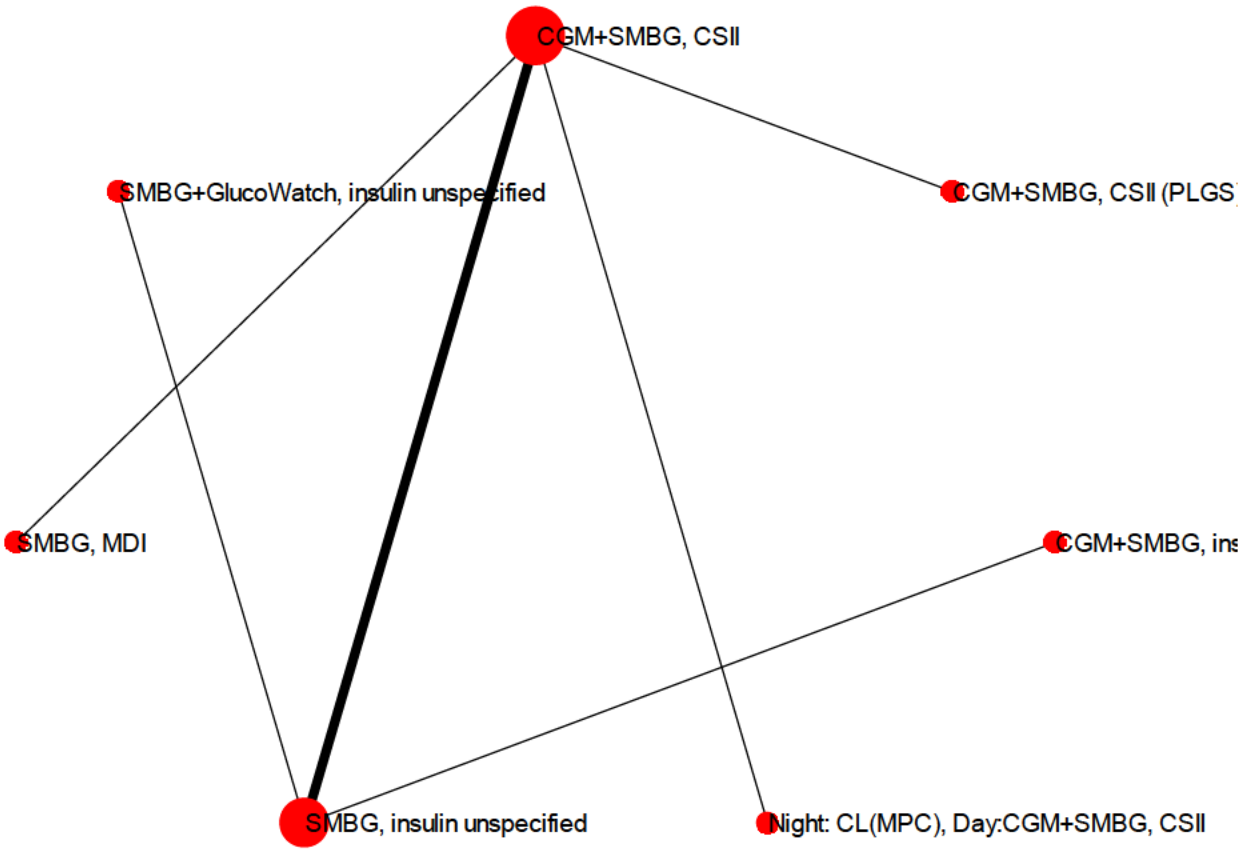


Figure 10.19. Hypoglycemic events requiring assistance in children with type 1 diabetes network diagram.

In the base case network depicted in Figure 10.19, convergence was not reached at 250,000 iterations with three chains for either the fixed effects of the random effects model. Therefore,

treatments were simplified (Figure 10.20). Treatments informed only by zero event studies or that would compare the same treatment to itself were excluded from this simplified network to encourage convergence[135,139,146,149,158,159]. This simplified network included five studies and three treatments.

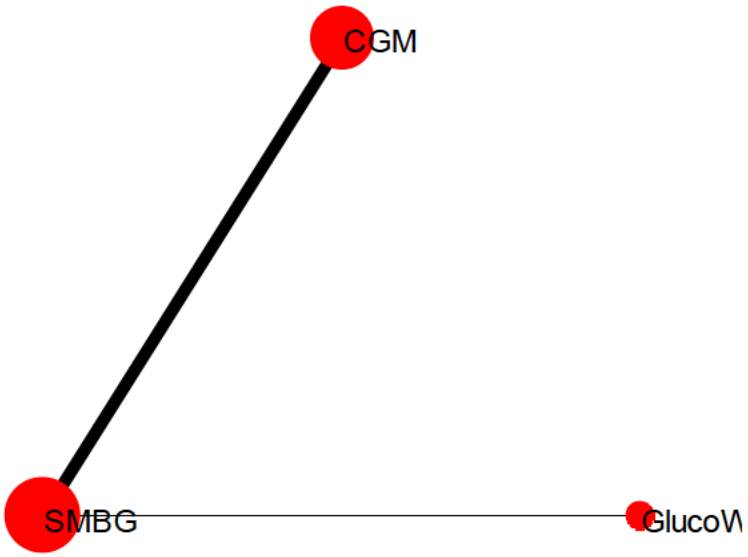


Figure 10.20. Hypoglycemic events requiring assistance in children with type 1 diabetes network diagram for simplified treatments

The posterior mean residual deviance, posterior mean deviance, effective number of parameters, and deviance information criterion were similar between the fixed and random effects model. The median estimates of effect were also similar between models; therefore, the fixed effects model is preferred for ease of interpretation *(Appendix F Clinical Effectiveness Supplementary Material)*. One-hundred and eighty-thousand burn-in iterations were required to reach convergence – which was assessed through examination of plots of history, kernel density, and plots of the Brooks-Gelman-Rubin statistic, and comparison of Monte Carlo error to standard deviation of relative estimates of effect. Model outcomes were recorded following 360,000 additional iterations, also with three chains. No studies were identified as contributing greater than three to the model's deviance information criterion.

Median rank and 95% credible interval for each treatment are shown in Table 10.12, with lower ranks indicating greater probability of being the most effective treatment for reducing the

number of hypoglycemic events requiring assistance. The CGM had median rank of one, and the GlucoWatch had median rank of three. Credible intervals for all interventions indicate 95% probability that the rank falls between one and three.

Table 10.12. Median rank of each treatment for preventing hypoglycemic events requiring assistance in children with type 1 diabetes.

Treatment	Median Rank	95% Credible Interval
SMBG	2	1 to 3
Glucowatch	3	1 to 3
CGM	1	1 to 3

No statistically significant differences were identified between treatments. For all pairwise comparisons, the 95% credible interval included the null value of one.

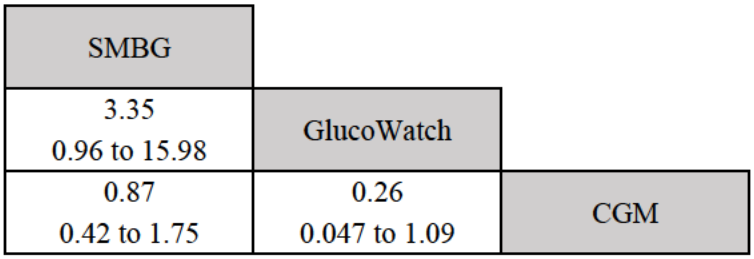


Figure 10.21. Step diagram for all treatment comparisons of relative hazard of hypoglycemic events requiring assistance. Outcomes presented as median (95% credible interval).

Mean probability of each treatment occupying each rank is presented in Figure 10.22. Lighter colours indicate lower rank and greater probability of efficacy. The mean probability that the continuous glucose monitor is the most effective is 0.65, and the mean probability that the GlucoWatch is the most effective is 0.02.

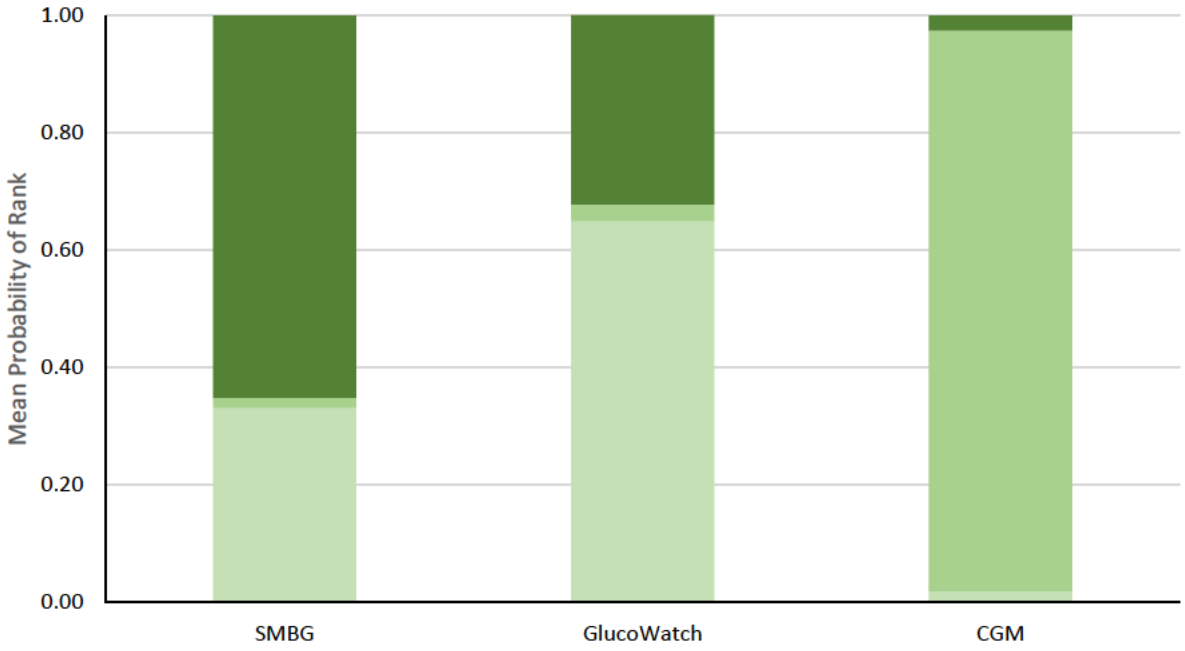


Figure 10.22. Mean probability of rank, by treatment. Lighter colour indicates lower rank and greater probability of efficacy.

10.3.2.3 Time-in-Range for Blood Glucose 3.9-10.0mmol/L

Eight studies describing nine treatments were included in the network meta-analysis of time-in-range for children with type 1 diabetes (Figure 10.23). Three studies[141,159,162] described interventions not encountered elsewhere in the network and were therefore excluded from network meta-analysis. The interventions in these studies were: 1) dual hormone artificial pancreas with model predictive control algorithm for insulin delivery and proportional-derivative algorithm for glucagon delivery; 2) dual hormone artificial pancreas with model predictive control algorithm for insulin and proportional-derivative algorithm for glucagon delivery, with adaptive meal priming boluses; 3) monitoring not specified with continuous subcutaneous insulin infusion; and 4) dual hormone artificial pancreas with control algorithms unspecified. Results of studies excluded from network meta-analysis of time-in-range are included in Table 10.13. Because no studies comparing these interventions to the rest of the evidence network were identified, no comparisons between these three studies and the other evidence were made.

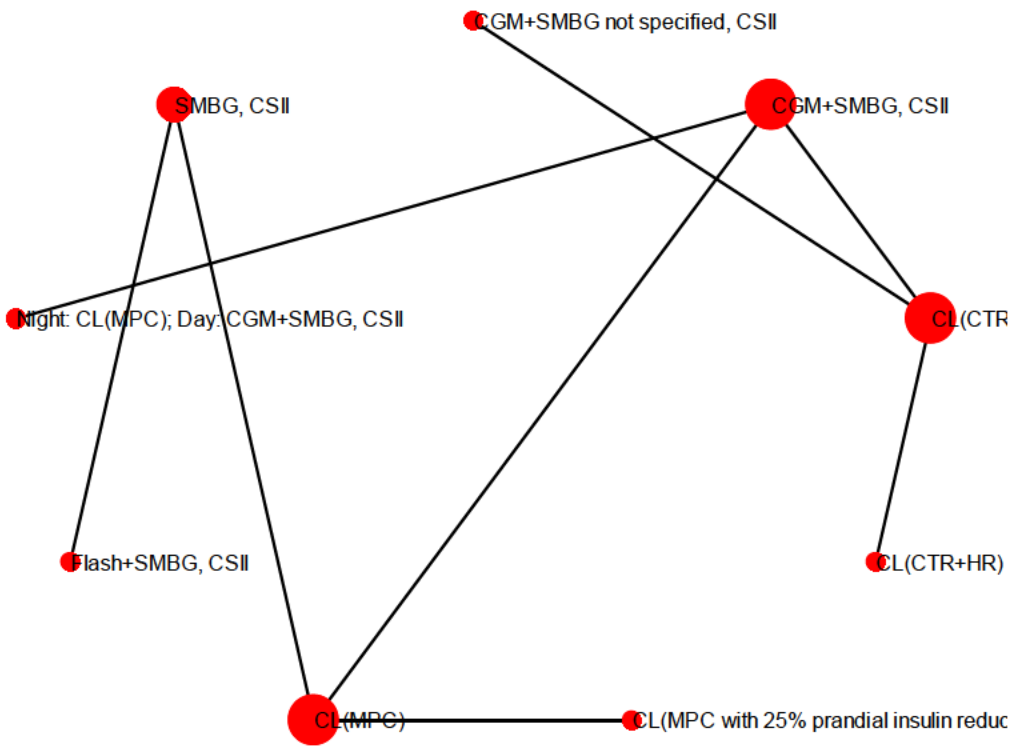


Figure 10.23. Network diagram for time-in-range in children with type 1 diabetes.

Table 10.13. Percent of time-in-range 3.9-10.0 mmol/L blood glucose in trials not included in network meta-analysis.

First Author, Year	Design	Follow-Up (weeks if not otherwise specified)	Treatment 1 Number of Participants (n)	Percent Time-in-Range 3.9-10.0 mmol/L (mean ± SE)	Treatment 2 Number of Participants (n)	Percent Time-in-Range 3.9-10.0 mmol/L (mean ± SE)
El-Khatib, 2014[141]	Parallel Arm	48 hours	Dual hormone artificial pancreas (model predictive control algorithm for insulin delivery, proportional derivative algorithm for glucagon) (n=6)	60.0 ± 1.6	Dual hormone artificial pancreas (model predictive control algorithm for insulin delivery, proportional derivative algorithm for glucagon) with adaptive meal-priming insulin boluses (n=6)	68.0 ± 3.3
Russell, 2014[162]	Crossover (2-day washout)	5 days	Monitoring not specified, continuous subcutaneous insulin infusion (n=32)	64.5 ± 2.5	Dual hormone artificial pancreas with control algorithms unspecified (n=32)	75.9 ± 1.4
Russell, 2016[159]	Crossover (3-day washout)	5 days	Monitoring not specified, continuous subcutaneous insulin infusion (n=19)	57.6 ± 3.2	Dual hormone artificial pancreas with control algorithms unspecified (n=19)	80.6 ± 1.7

There was no more than one study making each comparison in this network. Fixed effects and random effects models were similar in terms of posterior mean residual, posterior mean deviance, effective number of parameters, and deviance information criteria. Effects of interventions were also similar between models; therefore, the fixed effects model is preferred for ease of interpretation. No loops of evidence were identified, therefore no assessment for consistency was possible. No studies contributed greater than three to the model's deviance information criterion *(Appendix F Clinical Effectiveness Supplementary Material)*.

Median rank and 95% credible interval for each treatment are shown in Table 10.14, with lower ranks indicating greater probability for being the most effective treatment for increasing percent of time spent with blood glucose between 3.9 and 10.0 mmol/L. The closed loop with model predictive control algorithm for insulin delivery had median rank of one. The continuous glucose monitor with self-monitoring of blood glucose not specified and continuous subcutaneous insulin infusion had median rank of nine. There were no interventions whose 95% credible interval spanned from one to nine.

Table 10.14. Median rank of each treatment for increasing time-in-range for blood glucose 3.9-10.0 mmol/L in children with type 1 diabetes.

Treatment	Median Rank	95% Credible Interval
CGM + SMBG, CSII	6	4 to 8
CL(CTR)	4	2 to 7
CGM+SMBG unspecified, CSII	9	7 to 9
CL(CTR+HR)	3	1 to 7
SMBG, CSII	8	3 to 9
CL (MPC)	1	1 to 4
CL(MPC) with 25% prandial insulin reduction	2	1 to 7
Night: CL (MPC); Day: CGM + SMBG, CSII	3	1 to 7
Flash + SMBG, CSII	8	3 to 9

Among the included studies, few statistically significant differences in time-in-range were identified and are bolded and red in Figure 10.24. Relative treatment differences in time-in-range were calculated by the predicted effect of the row treatment minus the column treatment.

Continuous glucose monitoring with self-monitoring of blood glucose not specified and continuous subcutaneous insulin infusion was frequently less effective than its comparators – only two comparisons with this technology were not significant. The closed loop with model predictive control algorithm for insulin delivery was superior to four other comparators. No significant differences were identified that were not related to the two treatments previously listed for time-in-range in children with type 1 diabetes.

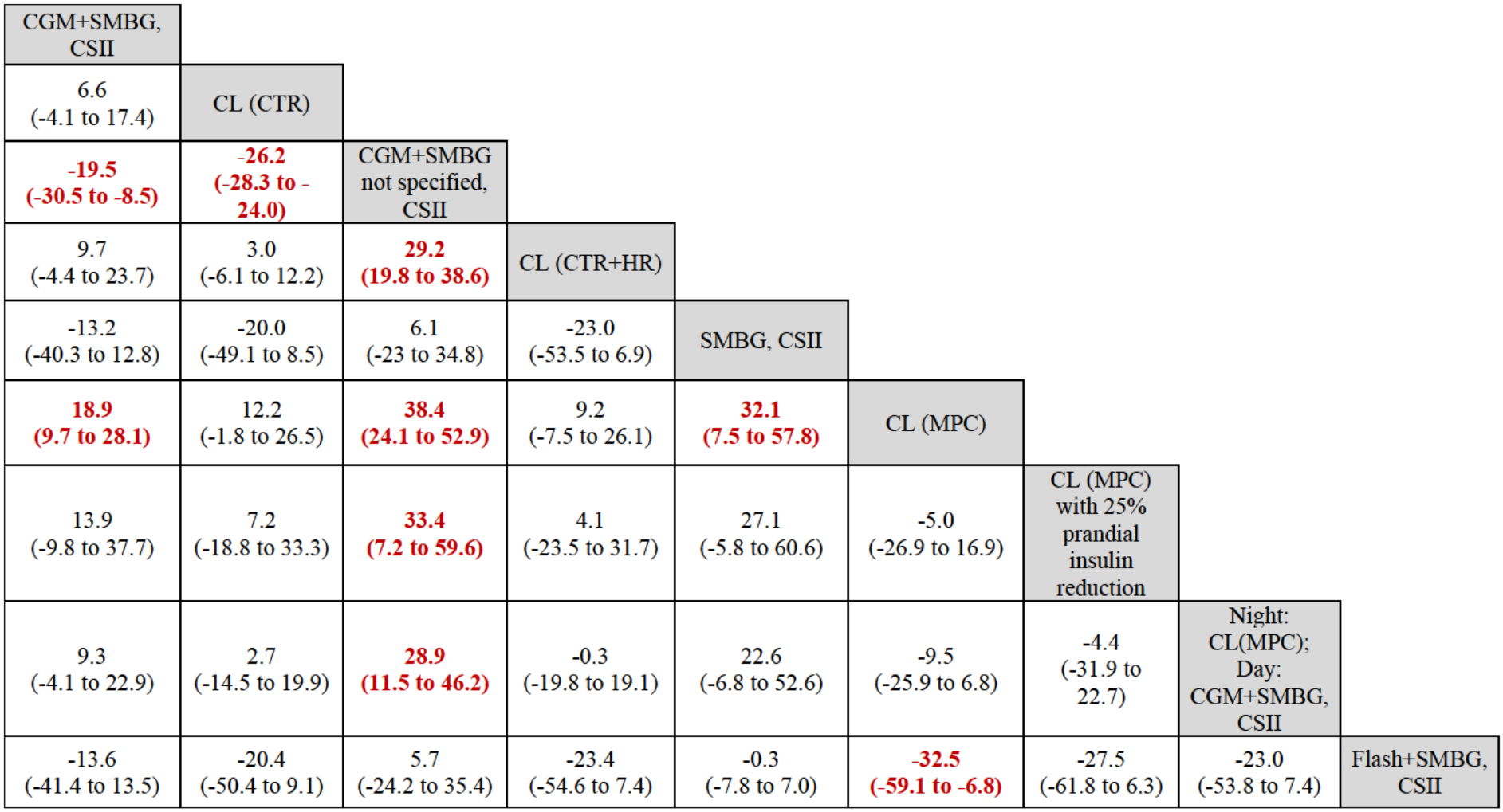


Figure 10.24. Step diagram for all treatment comparisons for relative percent of time-in-range of blood glucose 3.9-10.0 mmol/L. Outcomes presented as median (95% credible interval) on natural scale.

Mean probability of each treatment occupying each rank is presented in Figure 10.25. Lighter colours indicate lower rank and greater probability of efficacy. The mean probability that the closed loop with model predictive control algorithm for insulin delivery is best is 0.51, which is followed closely by the closed loop with model predictive control algorithm and 25% prandial insulin reduction at 0.30. The probability that continuous glucose monitoring with self-monitoring of blood glucose and continuous subcutaneous insulin infusion is best, or continuous glucose monitoring with self-monitoring of blood glucose not specified and continuous subcutaneous insulin infusion is best, is zero.

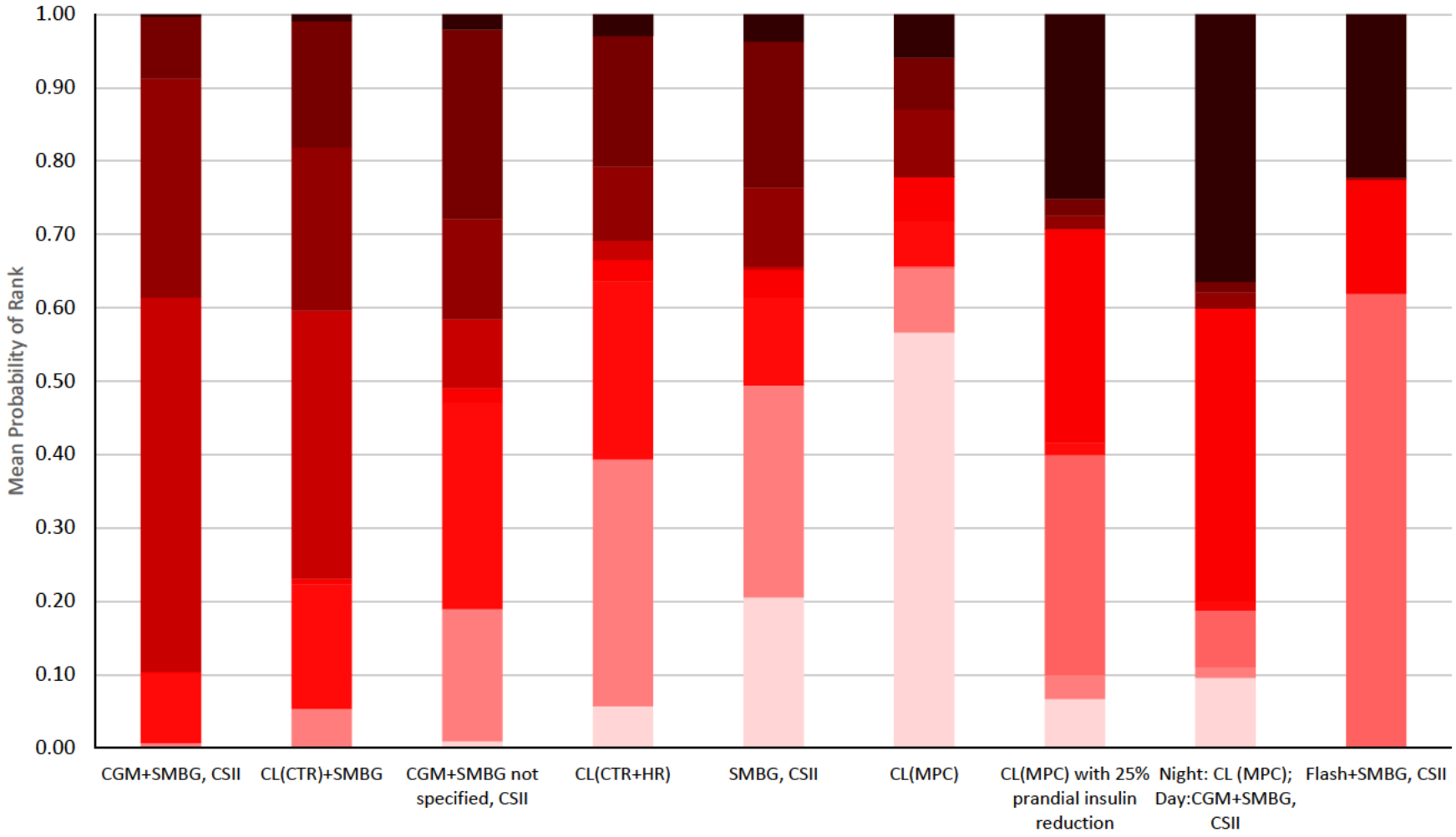


Figure 10.25. Mean probability of rank, by treatment. Lighter colour indicates lower rank and greater probability of efficacy.

10.3.2.4 Diabetic Ketoacidosis Events

The outcome of diabetic ketoacidosis events was presented in seven studies (Figure 10.26). There were no diabetic ketoacidosis events observed in four studies. No more than two diabetic ketoacidosis events were observed in a single trial.

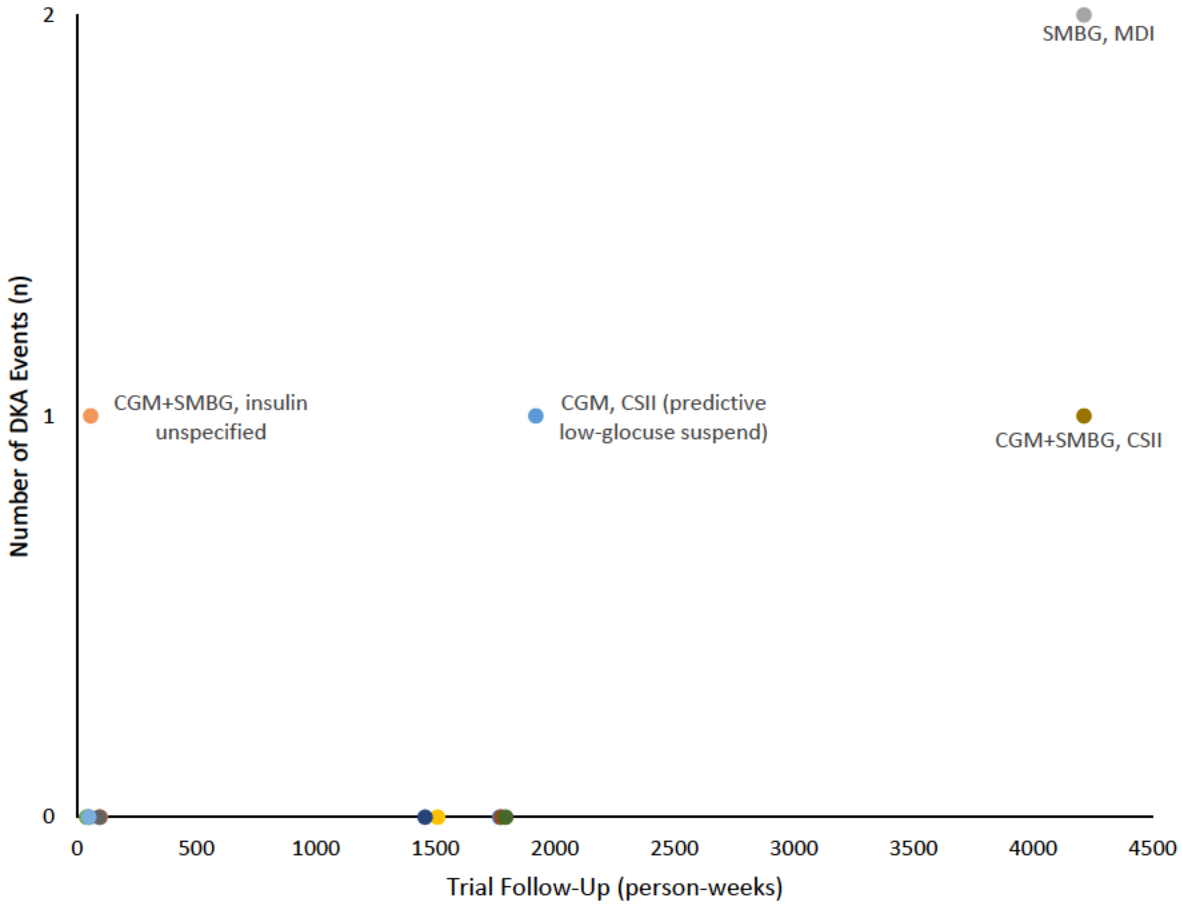


Figure 10.26. Number of diabetic ketoacidosis events observed in each trial, by length of trial follow-up in person-weeks.

10.3.2.5 PedsQL

Health related quality of life in pediatric type 1 diabetes studies was measured with the generic PedsQL only in one study[101], with the diabetes-specific PedsQL only in two studies[145,163], and with both versions in one study[164]. All included studies presented the PedsQL scores from questionnaires filled out by the child. The study by Hommel et al.[101] compares self-monitoring of blood glucose with continuous subcutaneous insulin infusion, to continuous glucose monitoring and self-monitoring of blood glucose with continuous subcutaneous insulin infusion, and finds

the mean difference due to continuous glucose monitoring to be -0.31 (SE:0.84). All other trials provide treatment-level outcomes, with no clear differences between interventions (Figure 10.27). The study by Abraham et al.[145] compared continuous glucose monitoring with self-monitoring of blood glucose and continuous subcutaneous insulin infusion, to continuous glucose monitoring with self-monitoring of blood glucose and continuous subcutaneous insulin infusion with predictive low-glucose suspend, and stratified PedsQL scores by age group.

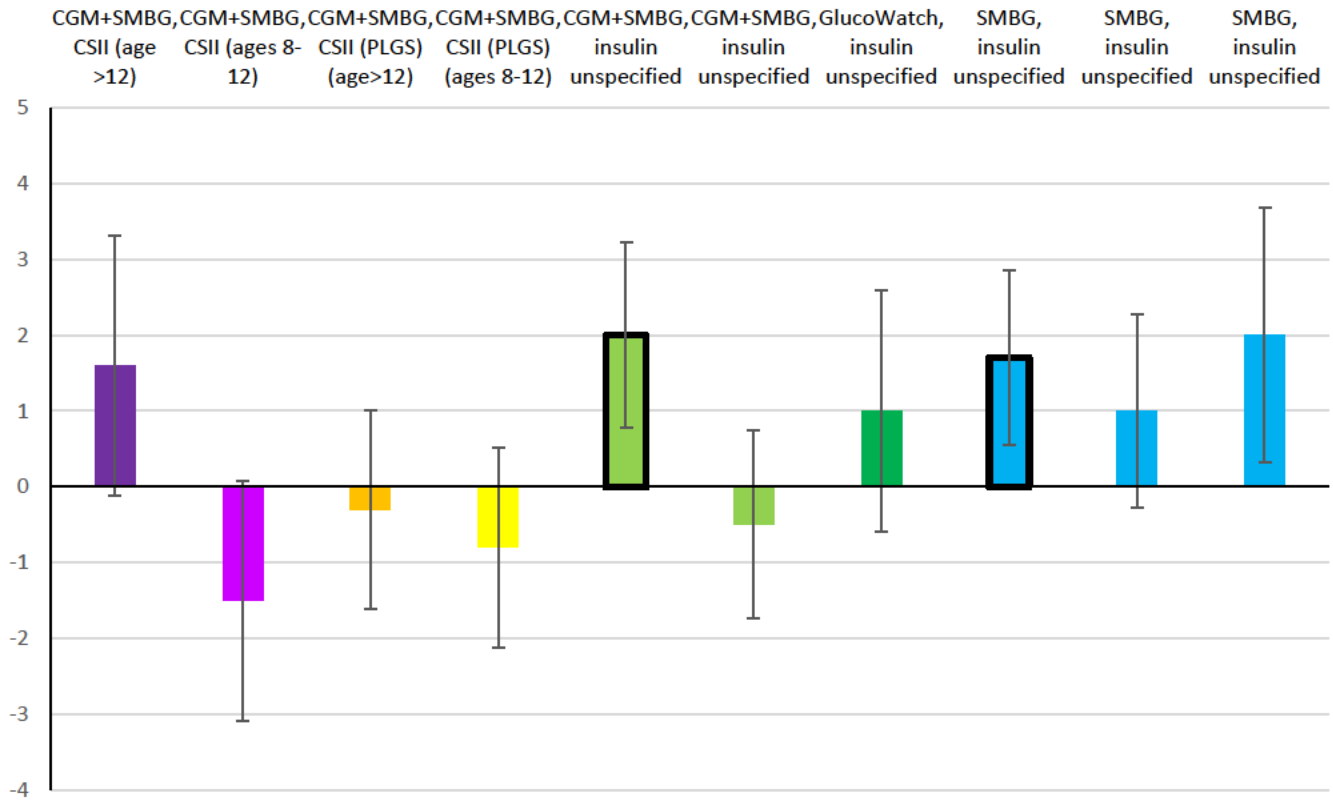


Figure 10.27. Mean effect of intervention on PedsQL outcomes. Different coloured bars represent different treatments, and black outline to bar indicates measurement of PedsQL with generic scale. Lack of black outline to bar indicates measurement of PedsQL with diabetes-specific tool. Error bars represent standard error.

10.3.2.6 Hypoglycemia Fear Survey Overall Score

The hypoglycemia fear survey overall score was reported in four studies[127,145,165,166]. Higher scores indicate greater fear of hypoglycemia with this tool[143]. Very little overlap was observed in the interventions included within these studies – the only intervention present in more than one study was self-monitoring of blood glucose with insulin unspecified, which was present in two

studies[165,166]. Visually, no intervention stands out as superior to the other interventions in terms of the HFS overall score (Figure 10.28).

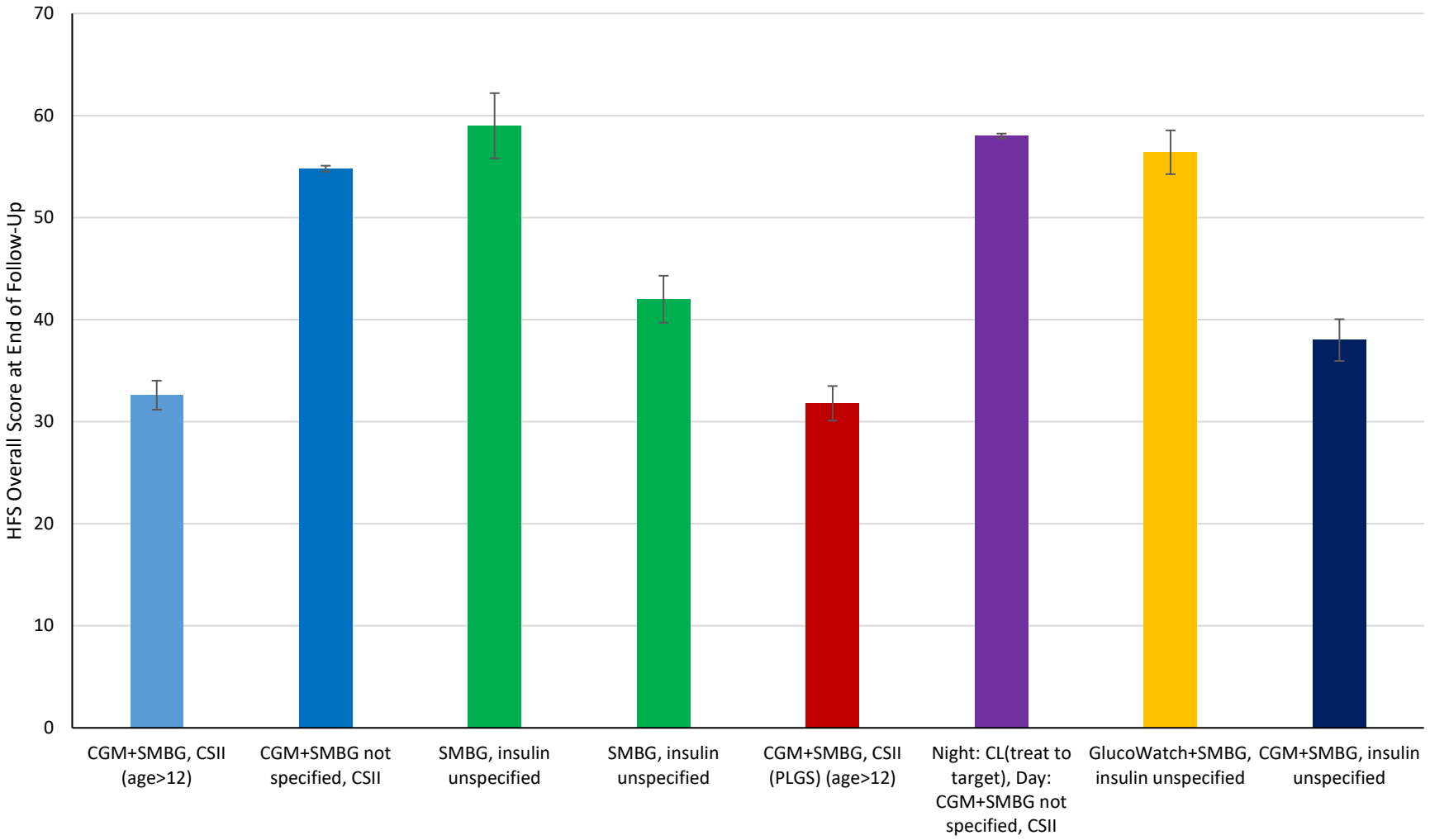


Figure 10.28. Hypoglycemia fear survey overall score by intervention. Different colours indicate different interventions. Bars represent mean score and error bars represent standard error.

10.3.2.7 Diabetes Treatment Satisfaction Questionnaire (DTSQ)

DTSQ outcomes were not reported in any included studies for a pediatric population with type 1 diabetes.

10.3.2.8 Quality Assessment

Of the 26 included studies for pediatric Type 1 diabetes presented in Table 10.15, 17 were considered to be at a moderate risk for bias due to randomization largely due to not reporting allocation concealment methods. One study was considered to be high risk due to unclear reporting of randomization methods and baseline imbalance between study groups[158].

With respect to bias from deviation, 14 studies were given a moderate risk of bias rating largely due to participants and/or caregivers and trial personnel being aware of participants' assigned intervention during the trial.

Bias from missing outcome data was present in three studies, which were given a high risk of bias rating due to imbalances in missing data between groups and substantial drop-out rates that would have underpowered the study based on the study authors' power calculations. One study was rated as high risk due to outcome data not available for all, or nearly all participants that were randomized, proportions of missing outcome data were not similar across intervention groups and there was no evidence that results were robust to the presence of missing outcome data.

Bias from measurement was high in four studies due to studies using subjective self-report outcome measures as their primary outcomes, which may have been biased due to lack of blinding.

Lastly, all studies were considered to be at low risk for bias in reported results. Six studies were deemed to have low overall risk of bias, 15 studies were deemed to have moderate overall risk of bias, 5 studies were deemed to have high overall risk of bias.

Table 10.15 Risk of Bias for Included Studies for Pediatric Type 1 Diabetes

First Author (Year)	Bias from Randomization	Bias from Deviation	Bias from Missing Outcome Data	Bias from Measurement	Bias in Reported Results	Overall Risk of Bias
DirecNet (2005)[144]	some concern	some concern	low risk	low risk	low risk	some concern
Abraham (2018)[145]	low risk	some concern	low risk	low risk	low risk	some concern
Barnard (2014)[39]	some concern	low risk	low risk	high risk	low risk	high risk
Battelino (2017)[146]	some concern	some concern	low risk	low risk	low risk	some concern
Beck (2010)[100]	low risk	some concern	low risk	high risk	low risk	high risk
Bergenstal (2010)[107]	some concern	some concern	low risk	low risk	low risk	some concern
Breton (2017)[147]	some concern	some concern	some concern	low risk	low risk	some concern
Chase (2003)[148]	some concern	some concern	some concern	low risk	low risk	some concern
DeBoer (2017)[149]	some concern	low risk	low risk	low risk	low risk	some concern
DeBoer (2017)[150]	some concern	low risk	low risk	low risk	low risk	some concern
Elleri (2013)[151]	low risk	low risk	low risk	low risk	low risk	low risk
Elleri (2015)[152]	some concern	low risk	low risk	low risk	low risk	some concern
Hommel (2014)[101]	low risk	low risk	low risk	high risk	low risk	high risk
Hovorka (2014)[153]	low risk	low risk	low risk	low risk	low risk	low risk
JDRF (2008)[120]	low risk	some concern	low risk	low risk	low risk	some concern
Kordonouri (2010)[154]	some concern	some concern	low risk	low risk	low risk	some concern
Lagarde (2006)[155]	some concern	some concern	low risk	low risk	low risk	some concern
Ly (2011)[156]	some concern	some concern	some concern	low risk	low risk	some concern
Mauras (2012)[157]	low risk	some concern	low risk	low risk	low risk	some concern
Piona (2018)[158]	high risk	low risk	high risk	low risk	low risk	high risk
Russell (2015)[132]	low risk	low risk	low risk	low risk	low risk	low risk
Russell (2016)[159]	low risk	low risk	low risk	low risk	low risk	low risk

First Author (Year)	Bias from Randomization	Bias from Deviation	Bias from Missing Outcome Data	Bias from Measurement	Bias in Reported Results	Overall Risk of Bias
Sharifi (2016)[139]	some concern	some concern	low risk	high risk	low risk	high risk
Tauschmann (2016)[160]	low risk	low risk	low risk	low risk	low risk	low risk
Thabit (2015)[135]	low risk	low risk	low risk	low risk	low risk	low risk
Wysocki (2006)[161]	low risk	some concern	low risk	low risk	low risk	some concern

10.3.3 Pregnant Population

Four studies included a sample of pregnant women with type 1 diabetes[115,167-169]. Outcomes reported within these studies included HbA1c (n=2), TIR (n=3), hypoglycemic events requiring assistance (n=3), DKA (n=1), and HFS (n=2) (Table 10.16). None of the studies explored either quality of life or satisfaction with diabetes treatment. One study explored only patient reported outcomes using the hypoglycemia fear survey. Two of the studies reported only on clinical outcomes; and one study reported on both clinical outcomes and patient reported outcomes.

Table 10.16 List of outcomes reported in studies of pregnant women with T1D

First Author (Year)	HbA1c	TIR	Hypos[a]	DKA	EQ-5D	HFS	DTSQ
Farrington (2017)[170]							
Feig (2017)[115]							
Stewart (2018)[168]							
Stewart (2016)[167]							
Total	**2**	**3**	**3**	**1**	**0**	**2**	**0**

Footnote:
[a]Hypoglycemic events requiring assistance
Abbreviations: HbA1c = glycated hemoglobin; TIR = Time in Range; DKA = diabetic Ketoacidosis; HFS = Hypoglycemia Fear Survey; DTSQ = Diabetes Treatment Satisfaction Questionnaire

10.3.3.1 HbA1c

Two studies reported mean changes in HbA1c (%) from baseline to the end of follow-up for four difference interventions[115,168] (Figure 10.29). Mean improvements in HbA1c were similar for all interventions. The largest change in HbA1c from baseline was reported for the CGM and SMBG

with unspecified insulin with an improvement of 0.54%. The closed-loop intervention reported the most modest improvement of 0.2%.

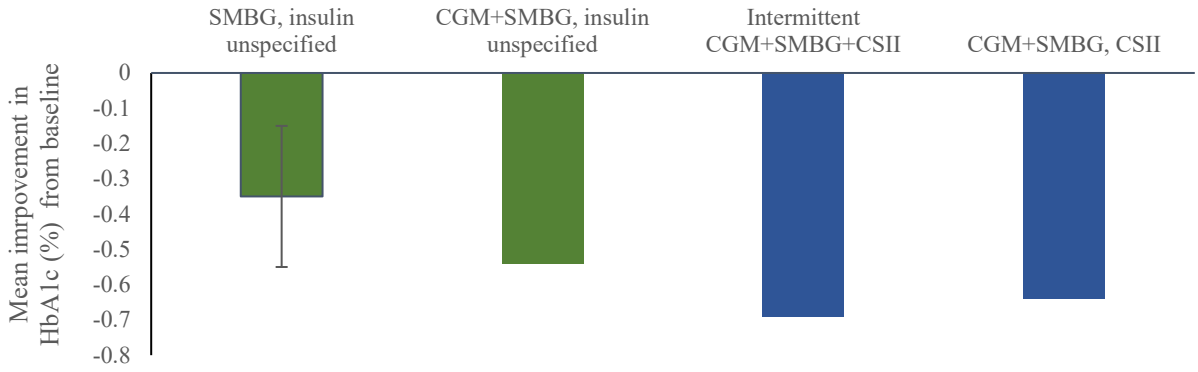


Figure 10.29. Mean improvements in HbA1c from baseline in samples of pregnant women with type 1 diabetes. Bars represent standard error.

10.3.3.2 Time in Range for Blood Glucose 3.5 to 7.8 mmol/L

Time in range (3.5 to 7.8 mmol/L) was reported in three studies[115,167,168] (Figure 10.30). Percent spent in the target blood glucose range was similar across all interventions, and ranged from 56.8 to 68.0%.

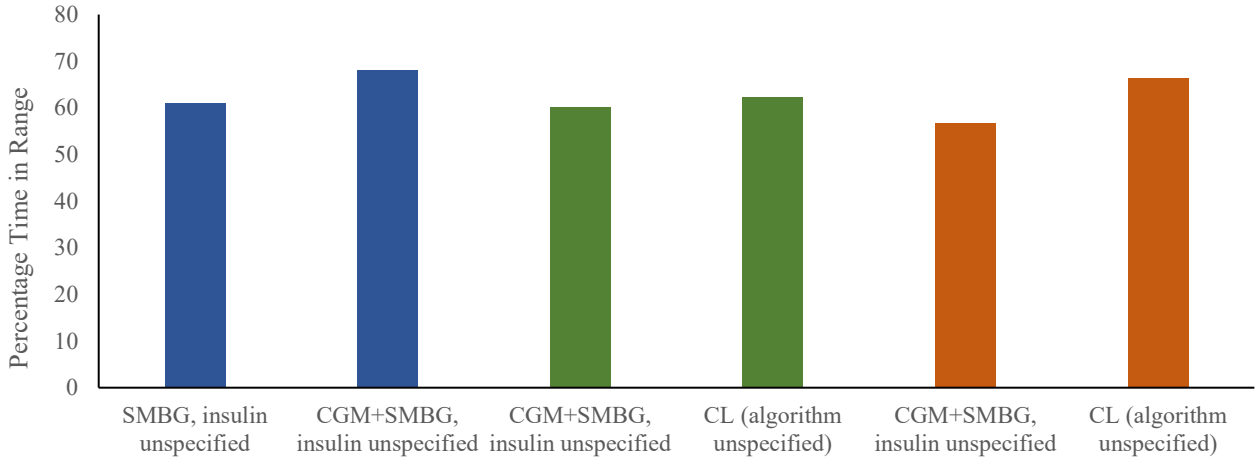


Figure 10.30. Percentage of time spent in range from baseline in samples of pregnant women with type 1 diabetes.

10.3.3.3 Hypoglycemic Events Requiring Assistance

Three studies reported the number of hypoglycemic events requiring assistance[115,167,168]. In two studies, no hypoglycemic events requiring assistance were reported. Feig et al.[115] reported similar numbers of events between interventions (11 in SMBG group versus 12 events in CGM+SMBG group).

10.3.3.4 Diabetic Ketoacidosis and Hypoglycemia Fear Survey

One study reported two occurrences of DKA in both interventions (SMBG and SMBG+CGM)[115]. Overall scores of the HFS were reported in two studies. Farrington et al.[170] reported a mean difference of 0.3 points favouring an intervention comprised of nighttime CL(model predictive control algorithm), and daytime CGM+SMBG, CSII versus the control group (CGM+SMBG, CSII). Feig et al.[115] reported a difference of 2.1 points on the overall HFS favouring SMBG over CGM+SMBG.

10.3.3.5 Quality Assessment

Of the four included studies for pregnant adult Type 1 diabetes as presented in Table 10.17

all were deemed low risk for bias from randomization, bias from deviation, bias from missing outcome data and bias in reported results.

Bias from measurement was high in one study due to studies using subjective self-report outcome measures as their primary outcomes, which may have been biased due to lack of blinding. Because of this, the one study was deemed to have high overall risk of bias. The other three studies were deemed to have low overall risk of bias.

Table 10.17 Risk of Bias for Included Studies for pregnant adult Type 1 diabetes

First Author (Year)	Bias from Randomization	Bias from Deviation	Bias from Missing Outcome Data	Bias from Measurement	Bias in Reported Results	Overall Risk of Bias
Farrington (2017)[170]	low risk	low risk	low risk	high risk	low risk	high risk
Feig (2017)[115]	low risk	low risk	low risk	low risk	low risk	low risk
Stewart (2018)[168]	low risk	low risk	low risk	low risk	low risk	low risk
Stewart (2016)[167]	low risk	low risk	low risk	low risk	low risk	low risk

10.3.4 Adult Type 2 Diabetes

Four studies were included that reported the outcomes of interest in an adult population with type 2 diabetes[102,171-173] (Table 10.18). None of the studies explored fear of hypoglycemia (HFS). One study explored only patient reported outcomes. One study reported only on clinical outcomes; while, two of the studies reported on both clinical and patient reported outcomes.

Table 10.18 List of outcomes reported in studies on adults with T2D

First Author (Year)	HbA1c	TIR	Hypos[a]	DKA	EQ-5D	HFS	DTSQ
Ajjan (2016)[102]							
Beck (2017)[174]							
Tang (2014)[175]							
Tildesley (2013)[176]							
Total	**3**	**0**	**1**	**1**	**1**	**0**	**2**

Footnote:
[a]Hypoglycemic events requiring assistance
Abbreviations: HbA1c = glycated hemoglobin; TIR = Time in Range; DK = diabetic Ketoacidosis; HFS = Hypoglycemia Fear Survey; DTSQ = Diabetes Treatment Satisfaction Questionnaire

In three studies that reported HbA1c, there were five different interventions. Two studies presented treatment specific effects of interventions, and one study presented the mean difference between treatments (Figure 10.31). In the study that presented the mean difference

between treatments, the difference was calculated as the effect of intervention two minus intervention one. No intervention stands out as clearly superior.

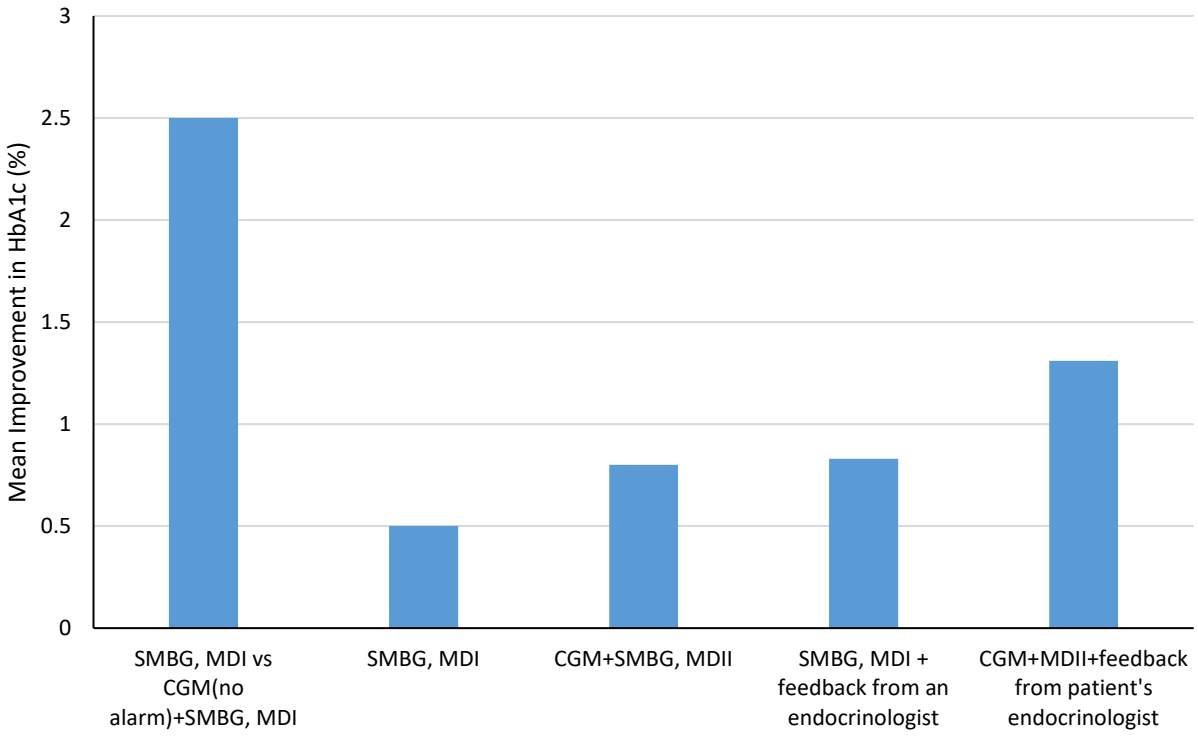


Figure 10.31. Mean improvements in HbA1c (%) in adults with type 2 diabetes.

Percent of time-in-range (blood glucose between 3.9-10.0 mmol/L), and overall score with the hypoglycemia fear survey was not reported in any included studies. In one study comparing self-monitoring of blood glucose with multiple daily injections of insulin, to continuous glucose monitoring with self-monitoring of blood glucose and multiple daily injections of insulin, no hypoglycemic events requiring assistance or diabetic ketoacidosis events were observed over 24 weeks of follow-up – with 79 participants randomized to each arm[171]. The same study by Beck et al.[171] was the only included study to report EQ-5D outcomes. The mean effect of either intervention in this study, measured with the EQ-5D, was zero (SE: 0.02).

Two studies reported overall treatment satisfaction measured with the Diabetes Treatment Satisfaction Questionnaire[102,172]. The study by Ajjan et al.[102] compared self-monitoring of blood glucose with multiple daily insulin injections, to continuous glucose monitoring (without alarms)

with self-monitoring of blood glucose and multiple daily injections, and found a mean difference of -0.13. The study by Tang et al.[172] compared self-monitoring of blood glucose with multiple daily insulin injections and an internet application for reporting and monitoring blood glucose, to continuous glucose monitoring with multiple daily insulin injections and endocrinologist feedback, and found a mean difference of -8.61. Both mean differences were calculated as the effect of treatment two, minus the effect of treatment one.

10.3.4.1 Quality Assessment

Of the four included studies for adult Type 2 diabetes as presented in Table 10.19, one was considered to be at a moderate risk for bias due to randomization largely due to not reporting allocation concealment methods.

With respect to bias from deviation, two studies were given a moderate risk of bias rating largely due to participants and/or caregivers and trial personnel being aware of participants' assigned intervention during the trial.

Bias from missing outcome data for three studies were rated as high risk due to outcome data not available for all, or nearly all participants that were randomized, proportions of missing outcome data were not similar across intervention groups and there was no evidence that results were robust to the presence of missing outcome data.

Bias from measurement was high in one study due to studies using subjective self-report outcome measures as their primary outcomes, which may have been biased due to lack of blinding.

Lastly, all studies were considered to be at low risk for bias in reported results. One study was deemed to have low overall risk of bias, and three studies were deemed to have high overall risk of bias.

Table 10.19 Risk of Bias for Included Studies for Adult Type 2 Diabetes

First Author (Year)	Bias from Randomization	Bias from Deviation	Bias from Missing Outcome Data	Bias from Measurement	Bias in Reported Results	Overall Risk of Bias
Ajjan (2016)[102]	low risk	low risk	high risk	low risk	low risk	high risk
Beck (2017)[174]	low risk	low risk	low risk	low risk	low risk	low risk
Tang (2014)[175]	low risk	some concern	high risk	high risk	low risk	high risk
Tildesley (2013)[176]	some concern	some concern	high risk	low risk	low risk	high risk

10.4 Conclusions

This systematic review and network meta-analysis included a robust body of evidence that examined the effects of a variety of treatments on six key diabetes outcomes: HbA1c, number of hypoglycemic events requiring assistance, percent of time-in-range, number of diabetic ketoacidosis events, hypoglycemia fear survey overall score, health related quality of life, and the diabetes treatment satisfaction questionnaire. The majority of evidence studied interventions for adults or children with type 1 diabetes. Little evidence for type 2 diabetes or pregnant patients with type 1 diabetes was included. Network meta-analysis was conducted on the outcomes of HbA1c, number of hypoglycemic events requiring assistance, and percent of time-in-range (blood glucose between 3.9-10.0 mmol/L); in adults with type 1 diabetes and children with type 1 diabetes.

For both children and adult type 1 diabetic populations, no significant differences in HbA1c or number of hypoglycemic events requiring assistance were identified in the network meta-analysis. In terms of time-in-range, interventions such as the closed loop or dual-hormone artificial pancreas appeared to increase the time spent in the optimal glucose range. However, these effects were specific to the type of intervention – including control algorithms for insulin delivery and glucagon (if applicable). When ranked by probability of efficacy in terms of each outcome, significant uncertainty remains.

In the four studies that were included for adults with type 2 diabetes, there were a total of seven distinct interventions. Only one intervention was encountered in more than one study. This severely inhibits comparisons between interventions in this population. The outcomes of interest were infrequently reported, further reducing the ability to compare outcomes. A similar situation was encountered in pregnant adults with type 1 diabetes.

Study quality was heterogeneous. More than half of included studies were deemed to have "some concerns" related to risk of bias. Frequently, this was due to a lack of blinding – study participants and study personnel were frequently aware of the intervention that they were randomized to. However, there was only one study in which this was the only category deemed to not be of "low risk" of bias. The remainder of studies were approximately evenly split between "low risk" and "high risk" of bias.

The evidence included in network meta-analysis was sparse, and included few studies examining effects of the same interventions. To answer the decision question, interventions needed to be described in significant detail – including the glucose monitoring strategy, whether or not self-monitoring of blood glucose was also used, insulin delivery technologies, and algorithms underlying hormone delivery in hybrid glucose monitoring and insulin delivery technologies. This results in increasing "links" between evidence to make indirect treatment comparisons, and wide credible intervals for the relative estimates of effect.

Sparse networks of evidence also inhibit the ability to assess for consistency. Both inconsistency and heterogeneity are related to the assumption that treatments are exchangeable between trials, and are the result of imbalances in effect modifiers in direct and indirect evidence[96]. The only network for which a loop of evidence was identified was HbA1c in adults with type 1 diabetes. To limit exposure to risk of inconsistency, populations of patients with type 1 diabetes were separated from patients with type 2 diabetes, and adults were separated from children. However, this stratification of the population was balanced with broader inclusion criteria increasing the number of interventions and connectivity of networks.

Network meta-analysis of hypoglycemic events requiring assistance was complicated by numerous zero-event studies, in which no events were observed during trial follow-up. For both adult and children with type 1 diabetes, convergence of models could not be reached with interventions specified in the same detail as for HbA1c and time-in-range. This could be because included studies were not powered for this outcome, or due to the efficacy of the interventions included. Dias et al.[96] suggests that when many zero-event studies are present, strategies to encourage convergence include specification of a more informative prior distribution for the between-study variance, or as a last resort, putting a random effects model on the trial-specific baselines. Given that the randomized controlled trial is at the top of the hierarchy of evidence, it is unlikely that additional high quality evidence to support the choice of an informative prior distribution exists, and approximately matches the decision problem. Before treatments were simplified, most interventions had zero events observed. Placing a random effects model on the trial-specific baselines would have contributed to uncertainty in relative estimates of effect, and was deemed unlikely to assist in decision-making if convergence had been reached.

In spite of these limitations, findings related to HbA1c and number of hypoglycemic events requiring assistance agree with each other. Interventions included in these network meta-analyses are unlikely to result in significant differences in adults or children with type 1 diabetes. In terms of time-in-range, there were statistically significant differences in estimates of effect. Although time-in-range is an excellent metric for distinguishing interventions, this outcome has not yet been validated as contributing to meaningful differences in clinical outcomes. Time-in-range has been connected to HbA1c by Kaufman et al.[177] and Vigersky & McMahon[178]. However, HbA1c has been connected to long-term diabetes complications, and has been identified as an independent risk factor for coronary heart disease and stroke in patients with and without diabetes[73]. Many of the same studies that reported time-in-range in this review also reported HbA1c. Given that no significant differences in HbA1c were identified between interventions, differences in time-in-range between outcomes should be interpreted cautiously – at least until long-term data links time-in-range to meaningful outcomes.

Overall, this systematic review and network meta-analysis suggests that interventions are equivalent in terms of HbA1c and number of hypoglycemic events requiring assistance. It is

advised that differences in time-in-range due to included interventions are interpreted cautiously. Future research connecting time-in-range to meaningful clinical outcomes in the long-term would enhance confidence in clinical decision-making based on time-in-range findings.

11 Systematic Review of Patient and Family Experiences with Continuous Glucose Monitoring

Summary:

- Patients found continuous monitoring to be an effective tool in managing their glucose levels. This message is remarkably consistency across patient groups, countries and study design.
- Additional findings included improvement in sleep, a greater freedom when making life decisions and an improved ability to make informed life decisions such as vacations and exercise.
- Negative findings were primarily with technical issues such as calibration, and trusting the technology.
- There is a period of learning and adjustment required for patients to optimize the integration of this technology into their diabetes management routine and their life, and to learn to trust the technology.

11.1 Purpose

The purpose of this systematic review of qualitative research was to understand the experience of insulin dependent individuals using continuous glucose monitoring (CGM) technology to help manage their diabetes.

11.2 Methods

11.2.1 Search Strategy

A systematic review on patient and family/caregiver perspectives was completed. MEDLINE, EMBASE, and CINAHL were searched from January 1, 2003 until December 31, 2018. We chose 2003 as it corresponded with a significant change in the clinical guidelines on the diagnosis and management of type 1 diabetes. Terms capturing the service (e.g. blood glucose self-monitoring, automated delivery and closed loop) were combined to include only qualitative studies by using terms such as “qualitative research,” “focus groups,” and “grounded theory.” Results were filtered to exclude non-human studies and studies not peer reviewed (e.g. opinion, letter to editor or conference abstracts). The full search strategy can be found in *Appendix D: Search Strategy for Systematic Review of Patient Perspectives*.

11.2.2 Study Selection

The abstracts retrieved were screened in duplicate by independent reviewers. Records were screened and advanced to full-text review if they were: qualitative study designs that described insulin dependent patients of all ages, and/or family caregivers', perspectives on and/or experiences with using glucose monitoring technologies. Abstracts were excluded if they did not meet the above inclusion criteria, or if they: did not report results from the patient, family or caregiver perspective; presented primarily quantitative data; did not focus on glucose monitoring; or if the study looked only at education or software systems to support monitoring. Abstracts included by either reviewer proceeded to full-text review; consensus was not required. This abstract screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after the first screen proceeded to full-text review, which was also completed in duplicate. The following inclusion and exclusion criteria (Table 11.1) were used to assess eligibility in full-text review. Discrepancies in included studies were resolved through discussion between the two reviewers. Systematic reviews were hand-searched to ensure that all relevant articles were included.

Table 11.1 Inclusion and Exclusion Criteria for Systematic Review of Patient Experiences with Glucose Monitoring Technologies.

Inclusion Criteria	Exclusion Criteria
• Patient, family/caregiver perspective • Qualitative study design (i.e., interviews, focus groups) • Technologies: CGM closed loop systems, open loop systems, artificial pancreas, insulin infusion system with a glucose monitor • Any age (general population, Adults, Children) • Insulin dependent Type I or Type II • Limited to: patient outcomes, patient experience, patient satisfaction, optimizing self-management, adherence and fear of hypoglycemia	• No reported patient perspectives • Not human • Does not focus on glucose monitoring (e.g. pumps without glucose monitors, finger prick) • Gestational Diabetes • Education and software • Not qualitative study design (e.g., survey) • Letter, opinion • Conference abstracts

11.2.3 Data Analysis

A narrative synthesis approach was used to identify and understand the key findings from the included studies. This approach is commonly used to synthesize heterogeneous literature[179], including qualitative studies. In the first stage of this narrative synthesis, independent reviewers extracted the overarching themes presented by each study in order to identify themes most frequently discussed within the included studies. Any discrepancies in the themes identified by the two reviewers were resolved through consensus. Using these overarching themes as a framework, sub-themes and more detailed description were subsequently extracted from each study. Relationships between themes were explored. During data extraction, information about the publication such as journal, study design, participant selection, participant inclusion and exclusion criteria, participant characteristics, and findings were also extracted in duplicate from each included study.

11.2.4 Quality Assessment

Included studies were assessed for quality using the Critical Appraisal Skills Programme (CASP) checklist for qualitative literature[180]. This checklist is comprised of ten questions, each assessing areas of potential bias, such as: was a clear objective stated, was the recruitment strategy appropriate, and was data analysis rigorous[180]. Each question is answered with "yes," "no," or "can't tell"[180]. Studies were then assigned to low, medium and high quality (less than 3 "yes"; medium 4-7 "yes" and high 8 "yes" or greater). Studies were not excluded based on quality.

11.3 Findings

Six hundred and thirty-three abstracts were identified; four hundred and forty-six after duplicates were removed (Figure 11.1). During abstract review, 39 abstracts were selected by the reviewers and continued to full-text review. Sixteen studies were included after full-text review. Twenty-three studies were excluded for the following reasons: not qualitative literature (n=6), no continuous monitoring (n=9), not clear if insulin dependent (n=3), not insulin dependent (n=2), at risk population (n=1), gestational diabetes (n=1), and not primary research (n=1). Of the included studies, five were conducted in the United States of America[181-185], four in the United Kingdom[39,186-188], two in Canada[189,190] and Germany[38,40] and one in each of the following locations: Australia[191], Denmark[192] and Amsterdam[193].

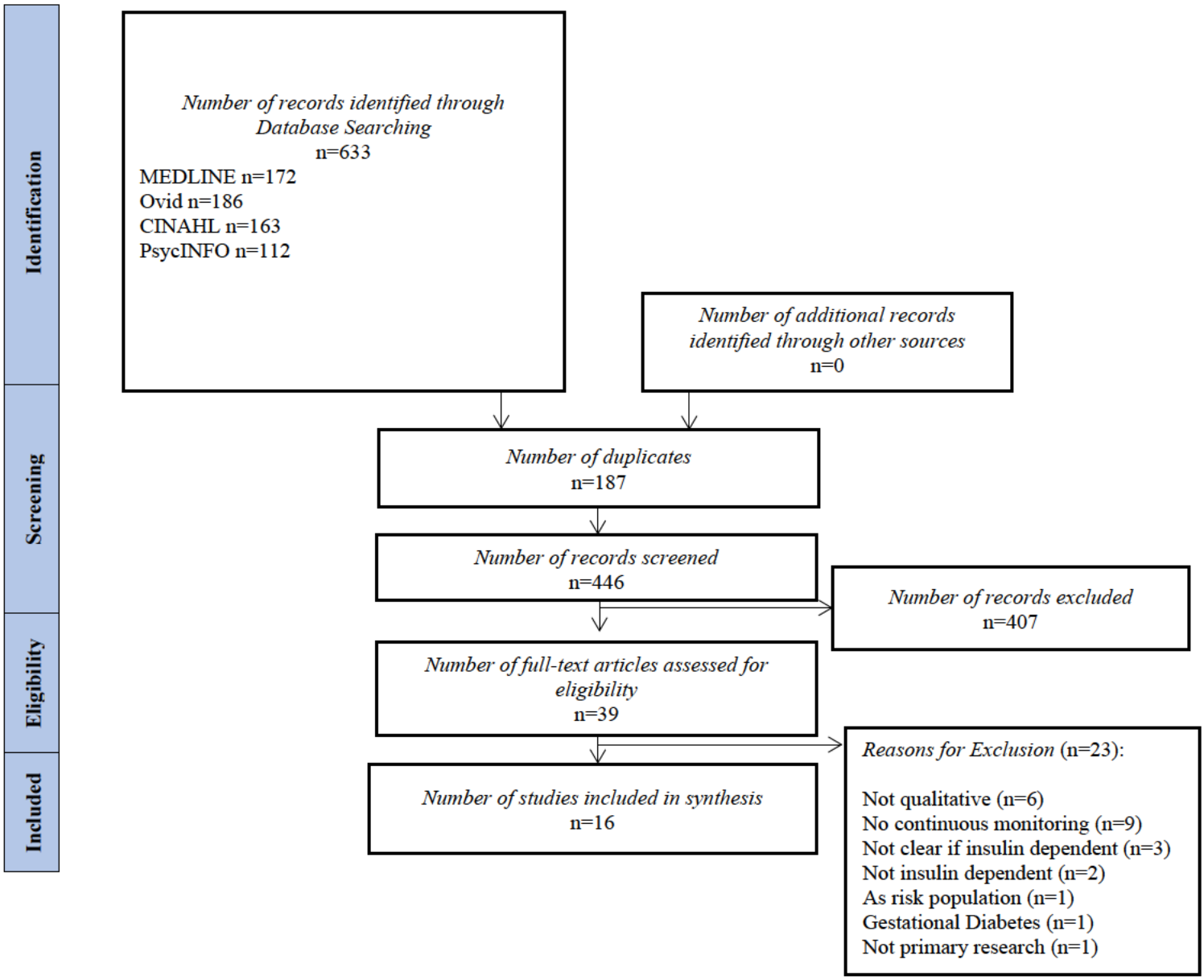


Figure 11.1 Inclusion flow-chart for patient perspectives review

11.3.1 Quality Assessment

Broadly, the studies were of medium to high quality. The objectives of studies were clear and the methodologies were appropriate. The areas where quality were most clear, based on the CASP checklist, were related to Questions 6, 7 and 8. Question 6, asks "Has the relationship between researcher and participants been adequately considered?"[180] with a focus on researcher bias influencing results (Figure 11.2). Only two of the included studies reported any information on the relationship between researcher and participant, the remaining studies were unclear. Question 7, which asked "Have ethical issues been taken into consideration?" was poorly reported in all but 2 studies. Question 8, which asked "Was the data analysis sufficiently rigorous?" was poorly reported in all but five studies.

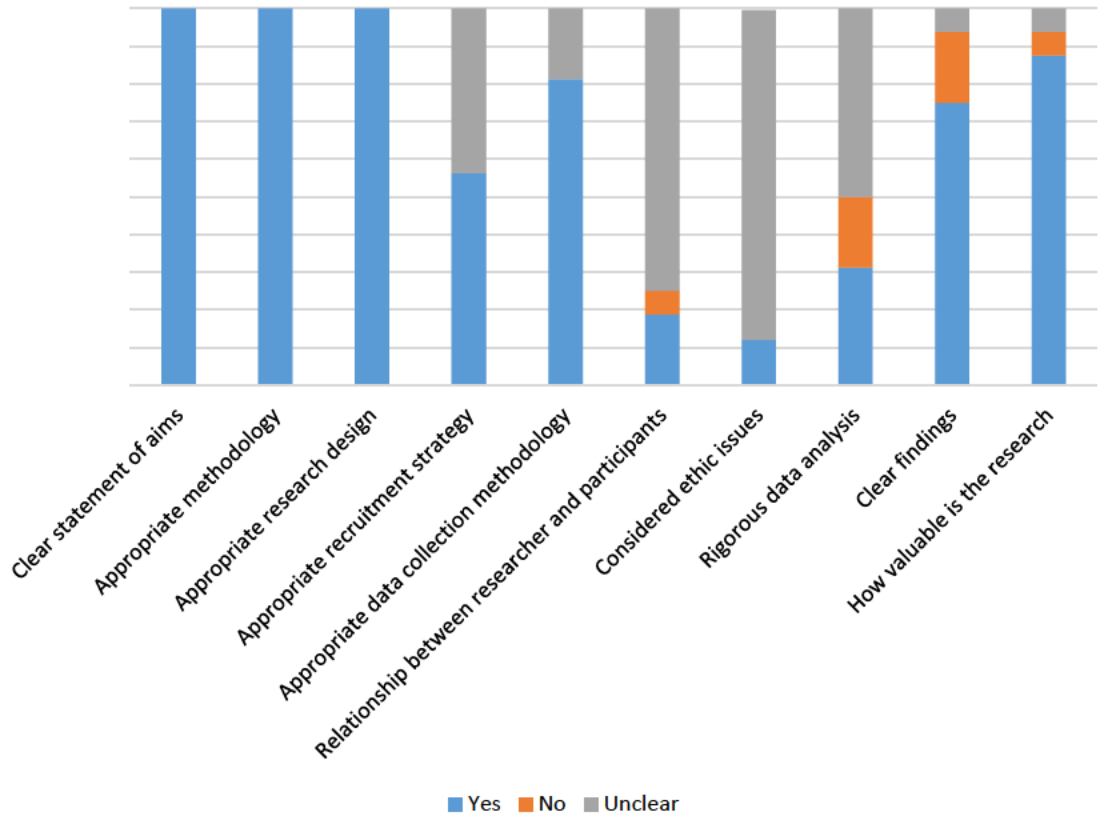


Figure 11.2 Quality Assessment of Included Studies using Critical Appraisal Skills Programme (CASP) Checklist

11.3.2 High level summary of findings

The findings of the systematic review with respect to patient and family members' experiences with and perspectives on continuous glucose monitoring are summarized in *Appendix G: Study Characteristics for Systematic Review of Patient Perspectives*. All of these studies used interviews and/or focus groups as their data collection strategy. Ten of these 16 studies included adults living with diabetes, six included children and/or adolescents living with diabetes, and six included parents of these children. One study included physicians and parents. Eight of these studies looked at both continuous glucose monitoring being used with pumps in either open or closed loop systems, and eight looked at continuous glucose monitoring alone. In five of the 16 studies, the study participants had experience with the new technology for a limited period of time (i.e., a month or less).

11.3.3 Thematic Analysis

Three overarching themes emerged through the analysis of findings from the 16 included studies: 1) experience with the equipment; 2) experience using the CGM technology to manage diabetes; and 3) how using CGM technology affects living with diabetes.

11.3.3.1 Experience with the Equipment

Experience with the equipment itself is a dominant theme that emerged through this body of research, in part because many of the studies were exploring people's experience with CGM and insulin pump technology over a short period of time; some for only a few days or weeks. Key sub-themes here include: adapting to and learning to use the technology, physical comfort related to inserting and wearing the technology, and other aspects of the technology itself (e.g., calibrating the device, alarms).

Adaption to the technology occurred over several phases, with most patients eventually adjusting to their new reality[190]. Some patients struggled initially with the diagnosis and when coupled with learning how to operate the glucose monitor found it initially overwhelming[189]. For some parents and adolescents, it was a struggle to balance living with the demands of using the technology to help manage their disease[190]. The timing of the introduction of the technology was described by some parents as an issue for their child.

> "It was very frustrating for her, being woken up at night by different alarms, trying to figure out what those alarms were, trying to figure out whether they were alarms that could be ignored or alarms that needed to be attended to, played a very big part in the overwhelmingness of this technology... It was all added pressure on her. And I know today that the timing was just really bad because there was just too much else that she was dealing with..."[190, p. 259]

In order to use the monitoring technology, patients were often required to insert sensors. Some parents expressed concern and frustration with sensor insertion and had challenges developing a regular calibration routine[40]. Sensor insertion was described by some as painful[40,189,190,193]. Some patients felt the sensor was outdated with respect to the overall design and were annoyed when the results proved to be inaccurate[193]. Patients described challenges inserting or removing the sensor and finding the right spot on their bodies[188]. When asked about the comfort of the sensor itself, some patients and parents felt it was a possible cause of skin problems. Contributing factors to skin sensitivity were: the adhesive glue, the hard material used to make the sensor, and having to wear it for long periods of time[192].

> "Like any technology it's one more added thing. It's one more thing he has to insert, so now he has two things connected to him. It's one more thing we have to buy. It's one more thing we have to trust to help us manage his diabetes. It's one more thing to talk about. It's one more thing to troubleshoot. It's just one more thing that you have to learn to incorporate into everything else that goes on in a family from the time you wake up in the morning to showers, to catching the bus, little things that people do every day without having to add this to it. So, it's added to discussion in the family, to management of his diabetes."[190, p. 259]

Participants reported technical issues, transmission problems and sensor inaccuracies as 'tolerant experiences' since patient believed, overall, the technology had the potential to significantly improve their diabetes management and their quality of life[188]. Some patients and parents experienced stress, such as when the alarm sounded at inconvenient times[190]. Patients commented on the lack of training and shared a sense of frustration as they learned how best to incorporate the various features of the machine[184]. Despite some of the challenges described here, many parents felt continuous glucose monitoring was a necessary tool to assist in managing their children's diabetes (especially for younger children)[189].

11.3.3.2 Experience Using Continuous Glucose Monitoring to Manage Diabetes

A second theme identified is the overall experience of using continuous glucose monitoring to manage diabetes. Two sub-themes emerged here, with the most dominant theme being the many benefits of using CGM. Benefits described by people include: improved perceived blood glucose control[181,183,189,193], reduced anxiety[182], improved knowledge and understanding of diabetes[188,189], increased confidence in managing their diabetes[189], and improved collaboration and relationships with family[38,182].

The second sub-theme relates to the initial hassles of establishing a routine around the CGM and learning to trust the equipment[185,189]. Having large amounts of available data readily available was seen positively, with many patients and family members describing how this helped with their overall understanding and knowledge of blood sugar levels and diabetes[188,189].

> "For [my son], I'm making adjustments, sometimes on a daily basis, based on what his blood sugar is doing. For me, having [continuous glucose monitoring], honestly, I couldn't do it without it, because I'm able to get that data reporting just by plugging it in, I can see what the trends are, and I can make adjustments on the fly so easily."[189, p. 95]

Parents reported they felt more confident and more competent in managing their children's diabetes[188]. The information provided through continuous glucose monitoring also enabled individuals to prevent hypoglycemic events[188]. Patients who previously had difficulty controlling some aspects of their diabetes, such as hypoglycemia incidents, found they had reduced incidents with CGM[193].

> "I don't have any sense of a hypo coming, it was just there instantly and it was done. [. . .] I had an accident with a scooter [. . .] that was a sort of eye-opener to me."[193, p. 1472]

Many patients felt that continuous monitoring enhanced partnerships (between parents and children or adolescents, between patients and their spouses)[181]; for example, the more visible nature of the technology encouraged interest and desire to discuss diabetes and increased collaboration between couples planning and managing pregnancy[182]. The better understanding of the factors influencing glucose levels provided by CGM allowed for better control and the ability of individuals to effectively collaborate with parents/spouses around diabetes management.

Some described the relationships between parents and children improving as a result of increased transparency[183].

Some patients described experiencing some initial hassles establishing a routine but over time felt the monitor became part of their daily lives. Some indicated their adaption to the technology was quick, while for others (especially parents) it was a long and winding road. The biggest hurdle for many parents was the difficulty in developing a regular routine.

In one study[191] individuals described some concerns with the accuracy of the system, being able to trust the technology, and having to relinquishing personal control of diabetes management to a machine. In this study, patients were interviewed after using CGM for four days, and even within this short period of time patients build up their trust in the system[191]. This initial lack of trust seems to be common concern, especially in the early adjustment period, but if and when this lack of trust subsides is not known[38,185,193]. Patients expressed a sense of comfort and reassurance with having their blood glucose continually monitored[188,193]. Initially, parents were concerned about allowing their children to control their own illness out of fear of the monitor not working[189]. During the night, parents would often wake up to check on their child's blood glucose level. The fear of a hypoglycemic event often meant parents had issues getting a good night's sleep.

Parents expressed a desire to have more options and control over the machine and functionality. When asked about the artificial pancreas, parents felt it was important to have control over insulin setting and the ability to change settings should be limited to certain people.

> "I absolutely want a passcode to change settings. 100%. I don't want somebody to change the carb ratio; that needs to be me or the doctor."[184]

11.3.3.3 How using the continuous glucose monitoring technology affects living with diabetes

The third theme is about how using the CGM technology affects living with diabetes. Three connected sub-themes were identified: confidence and reassurance, social benefits, and ability to live a more normal life.

People described the monitor providing a sense of confidence and reassurance[182,189]. Having this kind of control over their diabetes gave people a sense of freedom and allowed them to not think as often about diabetes control.

> "I can only be positive and in two sentences: I was in the middle of a diabetes-burnout and I am now sure of myself and that is what it brought me. This study I think is called 'IN CONTROL', well that's it."[193, p. 1473]

Many patients commented on their improved sleep as a result of using the monitor and this quality of rest helped them feel better and more energetic[188].

Patients expressed a number of social benefits including the ability to discretely check their glucose levels[38,189]. Working patients describe that fewer interruptions allowed them to have increased concentration and ability to work more efficiently[38]. Children and young adolescents shared that games and school activities were interrupted less as a result of the monitor[183]. Patients also expressed emotional benefits such as being able to manage their illness without fear. Patients described medical and safety benefits, viewing the monitor as a tool that kept then away from hospitals. Patients living on their own felt a sense of increased comfort[189]. The monitor was a constant reminder of the importance of self-care activities such as checking glucose levels.

> "I just didn't want to give [the system up after the study]… I don't think it is a cure for diabetes by any means, but for me, 28 years of never having a second of a break from this disease state. . . I'd rather spend time thinking about my children and being with my children or planning a date for my husband."[183, pg. 228]

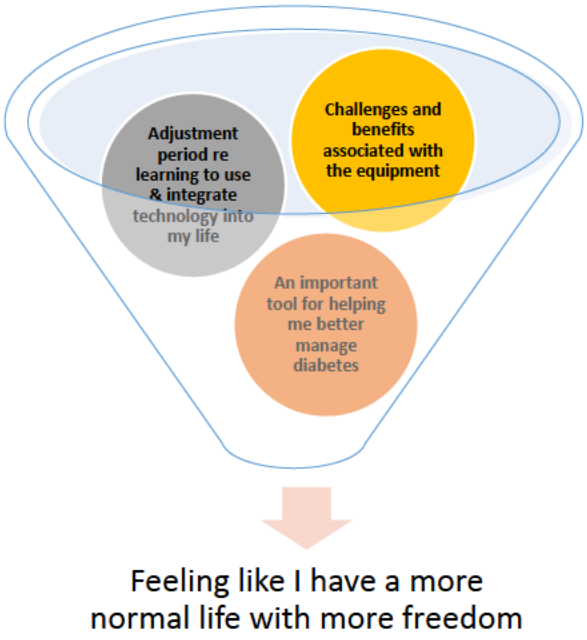


Figure 11.3 Overall patient experiences with continuous glucose monitoring

11.4 Discussion

The 16 included studies are remarkably consistent across patient groups, countries and study design. Patients found continuous monitoring to be an effective tool in helping them to manage their diabetes. Additional findings included a noticeable improvement in sleep, a greater freedom when making life decisions and an improved ability to make informed life decisions about such things as vacations and exercise. Negative findings were primarily with the monitor itself and often with the alarms, technical issues related to the calibration, and learning to understand and trust the overall technology.

Many of the participants in these studies noted that a period of learning and adjustment is required in order to optimally integrate the use of this new technology into their diabetes management routines and their lives. In about a third of the studies, patients and their families had been using the equipment for less than a month, and sometimes for less than a week, meaning that they would still be in this adjustment period. Continuous glucose monitoring is a tool that most, but not all patients found helpful in managing their diabetes. Additional research as to why people choose to use continuous glucose monitoring and their overall experience with the technology should be undertaken.

One systematic review of patient perspectives was identified[194]. This review focused on the experience of caring for children with type 1 diabetes and included nine studies, five of which are included in our review. The other four studies were not included as they did not meet our inclusion and exclusion criteria. All included papers were published between 2009 and 2016, search dates for this review were March/April 2017 and searched databases, including: PubMed, PsychINFO, CINAHL, Web of Science and EMBASE. Despite these differences, there were similarities between the findings of this review and to this work.

This review has limitations. First, the search strategy may have missed studies. It was designed in collaboration with a librarian to be broad and inclusive; however, given the consistency in findings across the 22 studies, it is unlikely that any missed studies would contribute new information. Thus, we feel this body of literature represents saturation. Secondly, there may be subgroups of patients with diabetes that are not meaningful reflected in this literature. For example, groups of different income status or ethnicity are not specifically represented in this literature. The findings of this review may not be generalizable beyond the broad label of patients with type 1 or type 2 insulin-dependent diabetes. Finally, in half of the studies a continuous glucose monitor was being used along with an insulin pump, and sometimes the monitor was part of a closed-loop system. This made it challenging to disentangle experiences with the continuous glucose monitor and with the insulin pump; this was particularly difficult in closed-loop systems.

11.5 Conclusion

The literature identified in this review can be described as robust and consistent. The themes reported in each study are echoed across the patient groups; this body of literature is likely to represent saturation. Patients found continuous monitoring to be an effective tool in managing their glucose levels. Additional findings included a noticeable improvement in sleep, a greater freedom when making life decisions and an improved ability to make informed life decisions such as vacations and exercise. Negative findings were primarily with the monitor itself, specifically with the alarms, the size of the monitor, technical issues such as calibration and understanding and trusting the overall technology.

12 Environmental Scan of Diabetes Supplies Coverage across Canada and International Jurisdictions

Summary:

- All Canadian jurisdictions have programs in place to provide insulin pumps to qualifying patients with type 1 diabetes: full coverage for pumps is available to qualifying patients in nine jurisdictions, and patient co-pay is required in four jurisdictions.
- Insulin pumps available through these programs are predominantly Omnipod's Insulet and Medtronic's MiniMed.
- Coverage for health-related expenses other than insulin pumps and pump supplies (e.g., blood glucose test strips) is provided through provincial drug programs.
- CGMs are provided for children and youth in Yukon, and flash GMs are recommended to be provided to select patients in Quebec and Ontario; these recommendations have not been translated into policy yet.
- Insulin pump programs exist in some international jurisdictions including the UK, Australia, and NZ. CGMs are less readily available for funding in these jurisdictions
- In recent years, insulin infusion pumps have been considered one of the top ten medical devices associated with medical complications and death
- In 2019 Health Canada plans to allow medical professionals to apply to conduct investigations into medical devices

12.1 Purpose

An environmental scan was conducted to determine the public availability and coverage of diabetes supplies across Canada, in selected international jurisdictions and emerging safety issues. These programs include insulin pumps, pump supplies such as Pods, infusion sets/kits, pump reservoirs/cartridges, and other non-pump diabetes supplies including blood glucose test strips, urine test strips, lancets, syringes, and skin preparation swabs. Information was also sought regarding the publicly available coverage towards the costs of these supplies.

12.2 Method

Grey literature and provincial government websites were searched to identify programs and initiatives that provide coverage for diabetes supplies across Canadian jurisdictions. Where information was not available online, provincial diabetes centres were contacted by phone or email to determine the availability of information.

12.3 Findings

12.3.1 Coverage across Canada

12.3.1.1 Insulin pump programs

All provinces and territories have programs in place to provide some degree of coverage for general diabetes supplies (e.g., blood glucose test strips). Jurisdictional programs specifically geared towards providing either full or partial coverage of the costs of insulin pumps and pump supplies (e.g., Insulin Pump Therapy program in Alberta) are typically available to patients with type 1 diabetes only. Jurisdictions differ with respect to whether they have specific pump programs and whether they provide coverage of insulin pumps and supplies to individuals of all ages or children and youth only (Table 12.1).

12.3.1.2 Programs providing full coverage of insulin pumps

Alberta, British Columbia, Ontario, Nunavut, and the Northwest Territories have programs in place that provide a free insulin pump and pump supplies to patients of all ages with type 1 diabetes. Manitoba, Newfoundland and Labrador, Saskatchewan, and Quebec have provincial programs that provide free insulin pumps to children and youth only. Unlike the pump programs in Newfoundland and Labrador and Quebec, Manitoba's and Saskatchewan's pump program do not cover pump supplies; however, coverage of pump supplies is available through Manitoba's PharmaCare and Saskatchewan's Drug Plan programs, respectively. Insulin pumps available through these programs can typically be replaced for free every 4–5 years.

12.3.1.3 Programs providing partial coverage of insulin pumps

The Yukon provides partial coverage of insulin pumps and supplies for patients of all ages, with a patient co-pay of a maximum of $250 per person or $500 per family. Insulin pump programs in New Brunswick, Nova Scotia, and Prince Edward Island provide only partial coverage of insulin pumps and supplies to youth with type 1 diabetes; the extent of the coverage depends on family size and income.

12.3.1.4 Coverage of non-pump diabetes supplies

Non-pump diabetes supplies include blood glucose test strips, urine test strips, lancets, syringes, or needles and are typically covered through the provincial drug programs.

12.3.1.5 Flash glucose monitors, continuous glucose monitors (CGM), and CGM-integrated insulin pumps

Freestyle Libre is the only flash glucose monitor (FGM) approved by Health Canada[195]. It is not publicly funded anywhere in Canada; however, coverage may be available through private insurers, depending on the plan. FGMs have been recently recommended for funding in Ontario by Health Quality Ontario (HQO) and in Quebec by Institut national d'excellence en sante et services sociaux (INESSS), suggesting that coverage in those provinces may be available soon[52,196]. Notably, in July 2018, INESSS recommended that the FGM FreeStyle Libre (Abbott) be supplied to patients aged 18 years and older who have at least two years of experience in self-management of their diabetes and who meet the following three criteria: receiving intensive insulin therapy; have experienced problems of frequent or severe hypoglycemia; and need to self-monitor blood glucose at least eight times a day[52]. The INESSS recommendation to list the FGM on the provincial Regime d'assurance medicaments plan was contingent upon the following conditions: the initial application is authorized for three months, in order to assess the capacity of the patients to use the glucose monitor and wear the sensor; if the patient demonstrates optimal use of the monitor (at least 70% of the time) then requests for further treatment will be authorized for a maximum of 12 months. The HQO recommendation appears to be in development, but draft recommendations include public funding of FGMs for "people with type 1 diabetes who experience recurrent hypoglycemia despite frequent self-monitoring of blood glucose and efforts to optimize insulin management" and "people with type 2 diabetes requiring intensive insulin therapy (multiple daily injections of insulin or continuous subcutaneous insulin infusion) who experience recurrent hypoglycemia despite frequent self-monitoring of blood glucose and efforts to optimize insulin management."[197]

Continuous glucose monitors (CGMs) are currently not covered in Canada through provincial healthcare plans[198]; however, coverage may be available through private insurers, depending on the plan and provider. Yukon is the only jurisdiction that is currently helping to cover the cost of CGMs for all youth with type 1 diabetes under 19 years of age and for some young adults aged 19-25 years, as part of a two-year ongoing program funded through the Territorial Health Investment Fund[199]. Lastly, in October 2018, Health Canada approved a CGM-integrated insulin pump, the t:slim X2 (Tandem)[200,201], which is now covered in Ontario, Manitoba, and Saskatchewan.

12.3.2 In-depth look: Coverage in British Columbia

12.3.2.1 Insulin Pumps

In British Columbia, individuals eligible for insulin pump coverage are covered under Fair PharmaCare, Plan C (BC Income Assistance), Plan F (At Home Program), or Plan W (First Nations Health Benefits), and have: T1D or other insulin-dependent diabetes, confirmation by endocrinologist/diabetes physician specialist that they meet medical criteria, and have received Special Authority coverage approval[202]. Currently, Omnipod Insulin Management System (Insulet) is the only pump that is 100% covered by PharmaCare. In exceptional circumstances where this device is clinically unsuitable for an individual as determined by an endocrinologist/diabetes physician specialist, coverage may be provided for a MiniMed Insulin Pump System (Medtronic). Coverage of the MiniMed pump is dependent on the individuals PharmaCare plan.

12.3.2.2 Diabetes Supplies

12.3.2.2.1 Blood Glucose Test Strips

Similar to the insulin pumps, PharmaCare covers blood glucose test strips if an individual is covered under Fair PharmaCare, Plan C, Plan F, or Plan W[203]. Coverage for blood glucose test strips is dependent on the patient's diabetes treatment. The most significant coverage is for individuals managing their diabetes with insulin, who have an annual quantity limit of 3,000 test strips. For individuals managing their diabetes with anti-diabetes medications with a high risk of hypoglycemia, the annual quantity limit is 400 test strips. For individuals on anti-diabetes medication with low risk of hypoglycemia, and individuals managing their diabetes through diet/lifestyle, the annual quantity limit is 200 test strips.

12.3.2.2.2 Needles and Syringes

PharmaCare covers needles and syringes to people with insulin-dependent diabetes covered under Fair PharmaCare, and Plan C, F, and W. The dispensing fee for needles is not covered by PharmaCare[203].

12.3.2.2.3 Insulin

Insulin is covered if the individual is covered under Fair PharmaCare and Plans B (Residential Care), C, F, P (BC Palliative Care Drug Plan), and W. Dispensing fee for insulin is not covered[203].

12.3.2.2.4 Other Supplies

Lancets, blood and urine ketone strips, and alcohol swabs are covered for individuals who are covered under Plan W (First Nations Health Benefits) only[203].

12.3.3 International Programs

12.3.3.1 Australia

12.3.3.1.1 Insulin Pump Program

The Australian Government's Insulin Pump Program provides full coverage to low income families with children (≤18 years old) with type 1 diabetes[204]. To qualify for coverage, the family must meet an income eligibility, not be covered under any other program (e.g., private insurer), and the patient must meet clinical eligibility (e.g., benefit from transition to, or continued use, of insulin pump therapy; patient or caregiver willingness to check blood glucose levels four times per day, and demonstrated competence at injecting insulin). There is a fixed number of pumps available per fiscal year, therefore not every family that meets criteria for coverage is provided with a pump in the given fiscal year[204].

12.3.3.1.2 CGM Coverage

CGMs are fully subsidized for eligible individuals through the National Diabetes Services Scheme (NDSS)[205]. Eligibility criteria is determined by an authorized health professional. Patients eligible for CGM subsidies include: people under 21 years old with type 1 diabetes, or a similar condition requiring insulin; people ≥21 years old who have valid need for CGM (e.g., will benefit from CGM and is committed to actively participating in diabetes management plan)[206]; or women with type 1 diabetes who are actively planning pregnancy, pregnant, or immediately post-pregnancy. Coverage for individuals who do not qualify for one of the above criteria are assessed on a case-by-case basis to determine if subsidies can be provided.

12.3.3.1.3 Other Supplies

Other diabetes supplies such as blood glucose testing strips, urine testing strips, insulin pump consumables, and CGM products can be purchased through the NDSS at a subsidized cost[207]. Eligibility criteria exists for each of these supplies. For example, insulin pump consumables are subsidized for eligible people with type 1 diabetes or gestational diabetes, whereas blood glucose testing strips are subsidized for people with non-insulin dependent type 2 diabetes.

12.3.3.2 New Zealand

12.3.3.2.1 Insulin Pump Program

Funding for insulin pumps and consumables may be provided by PHARMAC if the patient meets one of the following Special Authority criteria: type 1 diabetes, permanent neonatal diabetes, cystic fibrosis diabetes, undergone a pancreatectomy[208]. Furthermore, there are four additional categories through which individuals may be considered for funding: severe unexplained hypoglycemia, inability to reduce HbA1c, or has previously used an insulin pump before September 1st, 2012[208].

12.3.3.2.2 Diabetes Meters and Test Strips

PHARMAC has a sole supply arrangement with Pharmaco (NZ) Limited to supply the only subsidized diabetes meters and test strips in NZ[209,210]. Funded meters include blood glucose (not continuous) and blood ketones meters. Products are available to individuals who meet the criteria listed in the section above (11.5.2.1). Continuous glucose monitors are not currently funded or subsidized in NZ[209].

12.3.3.3 United Kingdom

12.3.3.3.1 Insulin Pump Program

The National Health Service (NHS) may fund insulin pumps for individuals that meet the National Institute for Health and Care Excellence (NICE) guidelines of: frequent hypo- or hyperglycemic events without warning, or an HbA1c of ≥69 mmol/mol despite efforts to reduce and manage blood glucose levels[211]. NICE recommends the use of SAP (MiniMed Paradigm Veo system) for people with type 1 diabetes if they have disabling hypoglycemic events despite using CSII, and the patient or their caregiver agrees to use the sensor 70% of the time, is confident in using the device, and agrees to participate in an education program on diet, lifestyle, and counselling[212].

12.3.3.3.2 CGMs

CGMs are recommended by NICE for funding through the NHS if the individual is struggling with hypoglycemia or have hypoglycemic events without warning, have severe fear of hypoglycemia, or are unable to manage HbA1c despite testing blood sugar several times per day[213,214]. Coverage through the NHS varies throughout England[213], and qualification guidelines are not publicly available from the NHS website[213].

Table 12.1: Provincial Programs for Providing Insulin Pumps and Diabetes Supplies

Region	Pumps and supplies covered?	Youth or adults?	Free or co-pay?	Which devices?	Specific Pump Programs?	Provincial Program(s) for General Diabetes Supplies?
AB[215,216]	1 pump/5 yrs, plus supplies	All ages (T1)	Free to patients	• Insulet (Omnipod) • Medtronic (MiniMed)	**Insulin Pump Therapy (IPT):** provides coverage for pumps and pump supplies to T1 diabetes patients; program delivered at 10 Diabetes Insulin Pump Clinics in Alberta **Pump supplies covered**: infusion sets, cartridges/reservoirs, serters, skin preparation (dressings, skin adhesives and adhesive removers), blood glucose test strips, blood ketone test strips and test meter, lancets, syringes/Pen tip needles	**Diabetic Supply Coverage** (provided to patients registered with one of Alberta's supplementary health benefit plans): $600 per year for supplies, including blood glucose test strips, urine test strips, lancets, syringes, needles
BC[202,203,217]	1 pump/5 yrs, plus pump supplies	All ages (T1)	Omnipod is free MiniMed is free to Plans C, F, W (co-pay for others)	• Insulet (Omnipod) • Medtronic (MiniMed)	No stand-alone Pumps Program; pumps supplied within **PharmaCare** coverage; first choice device is Omnipod; for special cases, exceptional coverage for MiniMed may be provided if advised by the patient's endocrinologist/diabetes physician **Pump supplies covered:** pods, infusion sets/kits, and pump reservoirs/cartridges	Diabetes supplies covered under **Fair PharmaCare, Plans C, F or W**: blood glucose test strips and needles/syringes; insulin covered through Fair PharmaCare, Plans, B, C, F, P, and W **Plan W** also covers**:** lancets, blood and urine test strips, and alcohol swabs
MB[218]	Pump only	Until 18 yrs (T1)	Free to patients	-	**Pediatric Insulin Pump Program**: covers the cost of pumps for individuals aged 17 years and under **Pump supplies covered**: under the PharmaCare program	Pump supplies and other diabetes supplies covered through **PharmaCare:** insulin, oral agents, blood glucose test strips, ketone test strips, pump supplies (infusion sets, cannulae, cartridges), needles, lancets, and syringes

Region	Pumps and supplies covered?	Youth or adults?	Free or co-pay?	Which devices?	Specific Pump Programs?	Provincial Program(s) for General Diabetes Supplies?
NB[219-221]	1 pump/5 yrs; plus supplies	Until 25 yrs (T1)	Patients co-pay portion of costs	• Insulet (Omnipod) • Medtronic (MiniMed 630G or Paradigm Veo)	**New Brunswick Insulin Pump Program (IPP):** covers the cost of pumps and supplies for individuals aged 25 years and under; co-pay is assessed based on family size and income **Pump supplies covered:** infusion sets. cartridges/reservoirs, blood glucose meter, and serters	**New Brunswick Prescription Drug Program:** provides financial assistance for diabetes supplies not covered by IPP (e.g., insulin, blood glucose strips)
NL[222-224]	1 pump/4 yrs, plus supplies	Until 25 yrs (T1)	Free to patients	-	**Adult Insulin Pump Program:** covers the cost of pumps and supplies for individuals aged 18-24 years **Pump supplies covered:** infusion sets and reservoirs NB. Although a source indicates that the NL regional health authorities may supply individuals under the age of 18 with insulin pumps, details regarding this program were not available.	**Newfoundland and Labrador Prescription Drug Program (NLPDP):** provides financial assistance for diabetes supplies including insulin, oral medications, blood glucose test strips, and lancets
NS[225-227]	1 pump/5 yrs, plus pump supplies	Until 25 yrs (T1)	Patients co-pay portion of costs	• Insulet • Medtronic • Animas	**Nova Scotia Insulin Pump Program:** covers the cost of pumps and supplies for individuals aged 25 years and under; co-pay is assessed based on family size and income **Pump supplies covered**: insertion sets, cartridges/reservoirs, tape, skin preparation	**Family PharmaCare Program:** helps to cover the costs of insulin, oral agents, blood glucose test strips, urine ketone test strips, and lancets
ON[228-231]	1 pump/5 yrs, plus $2,400/yr for supplies	All ages (T1)	Free to patients	• Insulet (Omnipod) • Medtronic (MiniMed 630G, 670G, Paradigm	No stand-alone Pumps Program; **Assistive Devices Program** for T1 diabetes patients covers 100% of the price of an insulin pump and	**Ontario Monitoring for Health Program:** assists with costs for blood glucose meters, lancets and test strips for insulin-dependent

Region	Pumps and supplies covered?	Youth or adults?	Free or co-pay?	Which devices?	Specific Pump Programs?	Provincial Program(s) for General Diabetes Supplies?
				Veo 554 or Paradigm Veo 754) • Tandem (T:Slim)	provides a yearly grant to help cover pump supplies **Pump supplies covered:** $2,400 annual grant for pump supplies, such as infusion sets and cannulas, (excludes non-pump supplies, such as insulin and glucose strips)	diabetes and gestational diabetes; does not cover insulin, oral medications, pen needles, or other diabetes supplies Other plans **(e.g. Ontario Drug Benefit Plan, Trillium Drug Plan)** are in place to assist with costs of other diabetes supplies, including insulin, oral medications, and blood glucose testing strips
QC[52,232,233]	1 pump/4 yrs, plus $4,000/yr for supplies	Under 18 yrs (T1)	Free to patients	• Insulet (Omnipod) • Medtronic (MiniMed 630, Paradigm Veo) • Animas (OneTouch Ping) • Roche (Accu-Check Combo)	**Insulin Pump Access Program**: Provides a maximum refund of $6,300 per pump plus an annual maximum refund for pump supplies **Pump supplies covered**: maximum refund of $4,000 per year for pump supplies (e.g., reservoirs, catheters)	**Régime public d'assurance medicaments** administered through the Régie de l'assurance maladie (RAMQ) includes coverage for: glucose test strips, ketone strips, and syringes/pen needles Freestyle Libre (FGM) is provided to qualifying patients
PEI[234-236]	1 pump/5 yrs, plus pump supplies	Until 19 yrs (T1)	Patients co-pay portion of costs	• Medtronic (MiniMed Paradigm Veo) • Animas (Vibe, OneTouch Ping)	**Insulin Pump Program**: covers the cost of the pump and supplies for individuals aged 19 years and under; co-pay is assessed based on household income and private medical insurance (up to 90% maximum coverage) **Pump supplies covered**: infusion sets, reservoirs, site inserts, skin adhesive wipes, dressings	**Diabetes Drug Program**: covers a portion of the cost of approved medications and supplies (e.g., insulin products, oral agents, blood strips, and urine-testing materials) **Provincial PharmaCare Program:** covers costs of prescription medications and medical supplies, such as insulin and blood glucose test strips
SK[237-239]	1 pump/5 yrs, plus supplies	Until 25 yrs (T1)	Free to patients (up to $6,300)	Any patient-selected pump supplier and pump model	**Saskatchewan Insulin Pump Program (**through **Saskatchewan Aids to Independent Living [SAIL] Program).**	**Saskatchewan Drug Plan**: covers insulin, oral agents, blood glucose test strips, ketone test strips, needles, syringes, lancets and swabs

Region	Pumps and supplies covered?	Youth or adults?	Free or co-pay?	Which devices?	Specific Pump Programs?	Provincial Program(s) for General Diabetes Supplies?
					Pump supplies covered (as regular benefits through the **Saskatchewan Drug Plan)**: infusion sets, insertion devices, cartridges/reservoirs, IV Prep and Skin Prep wipes	
NWT[240-243]	Pump and supplies	All ages	Free to patients	-	No stand-alone Pumps Program; pumps may be provided on a case-by-case basis through the **Extended Health Benefits for Specified Disease Conditions Program, Metis Health Benefits Program,** and **Non-Insured Health Benefits (NIHB) Program** **Pump supplies covered:** the **Extended Health Benefits for Specified Disease Conditions Program, Metis Health Benefits Program,** and **NIHB Program** provide partial coverage for pump supplies	**Extended Health Benefits for Specified Disease Conditions Program, Metis Health Benefits Program,** and **NIHB Program**: provide coverage for diabetes supplies including insulin and blood glucose test strips
YT[244-247]	Pumps and supplies	All ages	Deductibles ($250 per person; $500 maximum per family)	-	No stand-alone Pumps Program; **Chronic Disease Program** provides pump and supplies (with special approval) to individuals with diabetes; deductible may be waived in cases of hardship; social assistance is available based on eligibility **Territorial Health Investment Fund** provides coverage for CGMs to individuals aged 18 and under	**Yukon Health Care Insurance Plan**: provides coverage (through the **Chronic Disease Program**) for diabetes supplies including insulin, blood glucose test strips, ketone strips, lancets, monitors/meters, syringes/pen needles **NIHB Program**: provides supplementary coverage to individuals with First Nations and Inuit status
NU[247-249]	Pumps and supplies	All ages	Free to patients	-	No stand-alone Pumps Program; pumps are provided through the **Extended Health Benefits for**	**Extended Health Benefits for Specified Disease Conditions Program** and **NIHB Program:** provide coverage for insulin, oral

Region	Pumps and supplies covered?	Youth or adults?	Free or co-pay?	Which devices?	Specific Pump Programs?	Provincial Program(s) for General Diabetes Supplies?
					Specified Disease Conditions Program and **NIHB Program** **Pump supplies covered:** the **Extended Health Benefits for Specified Disease Conditions Program** and **NIHB Program** provide coverage for insulin pump supplies	agents, lancets, blood glucose test strips, ketone test strips, syringes/pen needles, and monitors/meters

12.3.4 Safety of insulin pumps

On November 29, 2018, the Canadian Minister of Health published a statement in response to "recent reports of serious issues Canadians have been facing with implanted medical devices." The Minister of Health directed Health Canada to implement an Action Plan to intensify the pre-market approval process, increase post-market surveillance, and enhance the transparency of approval and surveillance[250]. In December 2018, Health Canada published an Action Plan to address these three priorities. To address the Minister's first priority, strengthening the pre-market approval process, starting in early 2019 Health Canada plans to allow medical professionals to apply to conduct investigations into medical devices (where before only manufacturers are able to do so). Health Canada will also review its evidence requirements for approval of high-risk medical devices.

To address the Minister's second priority of robust post-market surveillance, *Vanessa's Law* will require Canadian hospitals to report medical device complications. Health Canada will also expand the Canadian Medical Devices Sentinel Network. *Vanessa's Law* will also obligate manufacturers to provide more information to Health Canada, such as notifying Health Canada of regulatory actions taken by foreign regulatory agencies, and it will allow Health Canada to require manufacturers to undertake additional studies on devices. The *Regulatory Review of the Drugs and Devices initiative* will propose a framework to increase the use of real world evidence to evaluate devices throughout their market lifespans. More inspectors, more frequent inspections, onsite inspections of foreign manufacturers, and rigorous investigations will also support post-market surveillance[251].

To improve transparency, Health Canada will begin to release the evidence upon which it bases its approvals. In 2019, Health Canada will publish summaries of its decisions for class III devices (where before only class IV device reports were published). A searchable database will be launched to allow Canadians to access device incident reports, and Health Canada's inspection results and regulatory actions[251].

13 Key Informant Interviews

Summary

- Ten healthcare professionals with expertise and interest in diabetes and/or continuous/flash glucose monitoring technology participated in in-depth telephone interviews
- A sub-group of patients for whom continuous glucose monitors (CGMs) would specifically benefit are patients with severe problems with hypoglycemia, and children and others requiring considerable support from others to manage their diabetes
- The biggest barrier to CGMs is the cost
- Most patients find the technology easy to use, and are able to use the information to make adjustments to their insulin, diet and activity
- CGMs benefit patients by improving quality of life, decreasing the frequency and severity of hypoglycemic events, improvement in AIC level and time spent in the target blood glucose range
- Benefits to the health care system by using CGMs include fewer ambulance calls and ER visits, decreases in longer terms complications from diabetes, and decreased healthcare costs
- Some considerations for eligibility criteria for publicly funded CGMs are to use the same eligibility criteria currently used for PharmaCare funding of diabetes supplies (e.g., test strips)
- Priority population for CGM coverage include people experiencing severe episodes of hypoglycemia and/or with hypoglycemia unawareness, and people requiring others to support their diabetes management.

13.1 Purpose

To understand the BC experience with glucose monitoring, including current practices and options for monitoring and measuring blood glucose, the effectiveness of these option, any challenges experienced, and possibilities for the future.

13.2 Methods

Telephone interviews were conducted with a purposive sample of health care professionals. A snowball sampling approach was taken; health professionals who agreed to be interviewed were asked to identify other potential participants for this study. An effort was made to speak with individuals who: had expertise in supporting patients living with insulin-dependent diabetes (Type 1 or Type 2); had some interest or experience with flash or continuous glucose monitors; and/or understood how care in BC was currently being provided to people living with diabetes.

A semi-structured interview guide was developed to support the interview process. This guide included questions on the current state of glucose monitoring in BC and how this has been evolving; where glucose monitors fit in the patient care pathway, experience with the effectiveness of glucose monitors, the challenges patients experience obtaining and then using glucose monitors, the establishment of eligibility criteria for publicly funded glucose monitors, and how public coverage of glucose monitors might affect how diabetic care is provided. The guide evolved over the course of the interviews, as questions were refined to reflect what had been learned through the previous interview(s). All interviews were conducted by an experienced qualitative researcher, audiotaped with the consent of the interview participants, and detailed notes were taken. The data were qualitatively analyzed, informed by the constant comparative analysis method, to develop a picture of the BC context and to identify key themes related to the policy questions being posed.

13.3 Findings

13.3.1 Participants

Telephone interviews were conducted, in February and March 2019, with ten BC-based health care professionals with an interest in and/or expertise in diabetes and glucose monitoring; six endocrinologists, one diabetes nurse educator, one school resource nurse, one family physician, and one pharmacist with policy expertise. Seven of the interview participants were based in the lower mainland (i.e., four in the Vancouver Coastal and three in the Fraser Health Authority catchment areas), one was based in Victoria (Vancouver Island Health Authority), one was based in Kelowna (Interior Health Authority) and one was a provincial government employee.

These health professionals had a range of experience with continuous and flash glucose monitors, with some having a lot of experience working with and supporting their patients to use the information generated by the monitors, and some were earlier in their learning curve. One of the endocrinologists had established a multi-disciplinary clinic that used a case management approach to patient care, where nurse and physician case managers work with patients to actively coach them with the goal of better management to improve outcomes. Two of these healthcare professionals also had personal experience with diabetes and glucose monitors. The interviews ranged in length from 33 to 55 minutes.

13.3.2 Monitoring blood glucose and the use of monitors

BC healthcare professionals explained the recent history and evolution of blood glucose testing as follows. Traditionally patients have monitored their blood glucose by doing testing with finger pokes, and the majority of patients still use this method. The use of continuous glucose monitors has occurred in waves. Initially the patient group most commonly using glucose monitors were those people with insulin pumps who wanted to also use a CGM. As this technology has been refined and improved, more patients became interested in giving this a try and particularly those people who were struggling with controlling their blood sugar levels, and/or were having severe problems with hypoglycemia. More recently, with the newer pumps coming onto the market with insulin algorithms involved that rely on the information from the CGM, health professionals are seeing more people again paying out of pocket for access to this technology. This will likely continue to increase with the introduction of the hybrid closed loop pump systems just coming onto the market now.

Another big change in the past year and a half, with the flash glucose monitor now approved for use in Canada, is that health professionals are seeing an increasing number of patients without pumps using flash monitors. As one person stated: *"There are just tons and tons of people in transition".* The most common continuous glucose monitors being used by these health professionals' patients are those produced by Dexcom, and the flash monitor used is the Abbott produced Freestyle Libre. With respect to hybrid loop insulin delivery systems, some very informed patients, primarily those who have lived with Type 1 diabetes for many years and are actively involved in support groups, are using self-developed systems already; the Medtronic 670G pump is just starting to be used by some patients.

13.3.3 Where blood glucose monitors fit in the patient care pathway

Patients are becoming increasingly aware of glucose monitoring technology, and will come into an endocrinology appointment asking about it. The advertising of the Freestyle Libre over the past year has very much increased public awareness of this technology as an option for people living with diabetes. All of the healthcare professionals interviewed believe that every patient with diabetes using insulin, particularly those on multiple daily injections, could benefit from using a continuous or flash glucose monitor to manage their diabetes. To use short acting insulin safely, and to achieve good control, usually requires 6-10 tests (finger pokes) a day. The

logistical challenges are massive, and it is also expensive. In addition, anyone who is not able to test themselves, but who would be willing to visit a diabetes education centre or healthcare professional and get help with their data (e.g., frail elderly who are living alone), and patients with Type 2 diabetes who may not be on insulin, but are on Sulphonylurea (medications that lower blood glucose rapidly and therefore increases the risk of hypoglycemia) could benefit from having a flash glucose monitor.

Both the Dexcom CGM and the Freestyle Libre (flash) provide reliable trending information. Patients may still need to use finger pokes to confirm reading accuracy 1-2X/day. The main difference between the two, is that with the CGM the data is being pushed to the patient including in the form of alarms when their blood glucose falls outside of a pre-set range, and to others who may be supporting a patient to manage their diabetes (e.g., parents). With flash, the patients need to pull the data by swiping a reader over the sensor. The sub-groups of patients for which the CGM is particularly helpful are those who have problems with severe hypoglycemia events and/or hypoglycemia unawareness and those who require support to manage their diabetes (e.g., children, people with cognitive challenges). One endocrinologist estimated that about 25% of her patient population has a history of severe hypo event and/or hypoglycemia unawareness, noting that the longer a patient lives with diabetes, the less likely they are to recognize lows. She stated:

> *So, very often patients will say, "I used to, when I had a low, I used to get super shaky and sweaty and now I just, my thinking isn't as clear as it used to be so I don't recognize it as well." And I guess my concern about that and patients will often say this, they'll say, "During the day, I'm confident I can catch my lows but not at night time," which makes sense. If your only warning is cognitive dysfunction, how are you going to recognize that when you're sleeping?"*

Although healthcare professionals believe that all patients with diabetes could benefit from using these glucose monitors, and particularly patients on insulin, they may not raise this option with all their patients with the major reason stated being the potential cost of the technology to the patient. If patients are on limited incomes, and/or have no extended health coverage, the cost of the flash and particularly the continuous glucose monitors can be prohibitive. A few endocrinologists noted that the first question they ask patients is if they have extended health

benefits, and if yes asks them to find out if their plan covers flash and/or continuous glucose monitors. One endocrinologist described feeling very uncomfortable discussing this option with patients whom she knew would not be able to afford it, even if she felt they would benefit.

A number of healthcare professionals commented that they found the flash monitor to be particularly valuable for people as a learning tool when they initially start on multiple daily insulin injections; as it helps them learn how to better manage their blood sugar levels from the start. A few healthcare professionals described providing loaner flash monitors to patients for 2-4 weeks, and then using the data collected in their work with patients to help them plan their insulin delivery, diet, activity, etc.

13.3.4 Challenges

From the perspective of the clinicians interviewed, the greatest challenge patients experience with respect to obtaining and using glucose monitors is the cost. As noted previously, some healthcare professionals are reluctant to discuss this technology as an option for patients if they believe the cost will be a major barrier. More extended health plans are beginning to cover this technology. Flash monitors may be covered by more plans that the continuous monitors, in part because they are less costly.

It is not an easy process to get coverage, however. Most plans seem to require an endocrinologist to say that the patient requires this technology to manage their diabetes before it will be covered. If patients do not have an endocrinologist, then getting a referral to and appointment with an endocrinologist can be a barrier to access as well. Also, patients often have to do a lot of advocacy themselves with their health plans to get the coverage. Endocrinologists also described completing a lot of forms, and advocacy, to get their patients' access to technology (both pumps and glucose monitors) not covered by PharmaCare.

Some endocrinologists expressed deep frustration at not being able to get flash monitors funded for patients they feel would benefit. One endocrinologist described how they had been unsuccessful in their efforts to get PharmaCare to cover flash monitors for patients who were already eligible for coverage for 3000 test strips a year, even after explaining the costs of monitoring blood glucose using a flash monitor would be less costly than using eight test strips a day.

Learning to insert the sensors usually involves a short learning curve; what takes longer is learning how to optimally use the data to make adjustments to insulin, diet, etc. in order to better control blood glucose. This is discussed in more depth below.

13.3.5 Supporting patients to learn how to use glucose monitors

Learning to use the technology was not felt to be a major challenge for most patients. The technology was described as easy to learn to use, even by patients who may be illiterate and/or do not speak English. Being able to see the blood glucose level immediately and quickly, along with the trend arrows, is incredibly helpful. Many health professionals felt that this new glucose monitoring technology was easier for patient to use and understand than the data obtained from finger poke testing.

One endocrinologist, for example, described his patient population - prior to flash or continuous monitors - as follows: 20% are highly motivated patients, usually of higher socio-economic status who learn quickly how to monitor and manage their blood glucose levels; 50% learn this more slowly but with a lot of support and coaching; and 30% just never get it, even if they can afford both the test strips and fast-acting insulin. They go on to describe how the use of continuous and flash monitors has transformed their work, referring to this as "disruptive technology". The 50% of the 'slow learners' now get it instantly; that is, they go home and record their blood sugar for two weeks and they come back and say they now get it (i.e., they understand what influences their blood glucose levels and are able to adjust their insulin, eating and activity to better control their blood glucose). Of the 30% who just never were able to get it, many now get it.

Others may be reluctant to do much adjusting of insulin on their own based on the data they are receiving, but are happy to use the monitor and to provide case managers or diabetes educators with the data and have them help them with the adjustments. Most patients apparently experience few problems adapting to the technology and/or having problems with the equipment. Rarely, a patient's anxiety can increase with the additional amount of data they are getting, but this usually decreases over time as they get used to the technology and learn how to understand and use the data.

These healthcare professionals provide a range of support to their patients to help them optimize the use of their glucose monitors. Some health professionals have considerable experience with

the technology, and invite their patients to send their uploaded monitor computer files to them before, during and/or even between appointments so that they can actively use the information to discuss recommended adjustments to their insulin regime, as well as other aspects of their daily life. Some healthcare professionals noted that they had patients, who were early adopters of the technology, teaching them about it and how they were using the data to make adjustments to their insulin, their diets, etc.

Health care professionals spoke about both the pros and cons of this new technology, with respect to how it is influencing how they work with patients, with the pros far outweighing the cons. The major pro is the quality of the information now available to both the patient and their healthcare professionals, which increases understanding of what is happening with the patient's blood glucose level at many points in time through both the day and night, as well as what is influencing these changes. Many used the same analogy: "driving a car with your eyes closed" to describe what it is like to adjust insulin delivery and manage blood glucose with only a few blood glucose readings during the day, which is often the most people can manage when using finger pokes. The ability to actually see what is happening over time, as a result of the trend data provided by these monitors, was described as incredibly useful. Now when sitting down with patients, health professionals have the information they require to help patients make needed adjustments. One endocrinologist described how she frequently had to book extra follow-up appointments with patients struggling to control their blood sugar, when they simply didn't bring in enough data from their finger poke testing for her to provide any useful advice about how to adjust their insulin. These specialist appointments are costly to the system, and to the patient with respect to their time. She concluded by stating: "*We as physicians can only be helpful if we have data to work with."*

A potential con of this new technology is the amount of information which they generate, which can take more time for healthcare professionals to review in the context of a typical appointment time. The time this requires does diminish as professionals become used to working with patients who use this technology, but it can still be seen as a burden. Ultimately, as healthcare professionals support their patients to use this data the patients become more able to do a lot of this work on their own. As a result of this, patients may need to visit their endocrinologist or

diabetes educator less often, freeing up time for other patients who may require more help. It does take more time up front, however, for healthcare professionals to provide this support.

A diabetes educator described how it was changing the way they were doing their work, for example:

> *Patients can share data with us from home, so they don't even need to come into clinic; we can provide feedback this way instead of the traditional 1-1 clinic visit. Younger clients, in particular, really like this. People can also always call between appointments. to troubleshoot…So it is changing the way we are doing our work.*

The family physician interviewed felt that the flash technology would be very easy for most family physicians to use and understand, helping them to better able to support their patients achieve better control over their blood glucose levels.

13.3.6 Experience with the effectiveness of glucose monitors

The experience of these healthcare professionals, then, is that glucose monitors are a valuable tool to help patients better manage their diabetes. A number of healthcare professionals described having patients struggle for years to get blood sugars under control, and just using a flash monitor, even for just a few weeks if that is all that was possible for a particular patient, has made a huge difference. Their patients' partners describe what a difference it makes for them in supporting this partner, in that they can easily simply scan their partner's arm, if they wake in the night and notice they seem a bit sweaty, for example. It makes a big difference for children in schools, as they no longer need to be pulled out of class or other activities to get their fingers poked. This is discussed in more depth later.

The healthcare professionals described seeing improvements in the percentage of time patients spend in their target blood glucose range, HbA1c levels, and the number of serious hypoglycemia events. Patients are now able to understand what their blood sugars are at, and what is influencing it. They avoid hypoglycemia, which is a huge positive for safety and theirHbA1c's get better. In one health authority, they have seen a decrease in the number of ambulance calls and ER visits for serious hypoglycemia events.

A number of endocrinologists commented on the weakness ofHbA1c as a measure of blood glucose control, describing it as really just a surrogate for overall control, in that it averages out

the lows and highs over time. For this reason, time-in-range is the primary outcome measure used by a large diabetic clinic in the lower mainland that is supporting many patients to optimize the use of a flash monitor. As the time-in-range improves, they see the AIC improving as well. One academic endocrinologist stated:

> *"I don't have the studies to prove [that blood glucose variability contributes to long term complications] but we know that hypoglycemia induces stress hormone release. So, when I think about what those additional stress mediators do for micro vascular and macro vascular complications even though I don't have clinical trial data to back that up. Mechanistically it makes sense that the two HbA1cs, one achieved with little variability and one with crazy variability are different… And from a patient's lifestyle perspective, they hate being on that roller coaster."*

These healthcare professionals also spoke about the big difference it makes in their patients' quality of life, with many saying that their patients describe it as "life-changing". Healthcare professionals described the relief their patients experience from having to do finger pokes far less frequently, and the decrease in anxiety related to the fear of hypoglycemia events. As one endocrinologist said:

> *Hypoglycemia has a huge negative impact on quality of life… in part because of the psychological stress associated with it. Some patients find it difficult to sleep become they are so afraid of having another severe 'hypo'. Research shows that some patients rate this fear as absolutely terror.*

They went on to say that there is research showing the new integrated close loop system (Medtronic 670G) does increase time in range.

Finally, many hoped that having patients come in with their blood-stained log books would soon be a thing of the past. They felt that the long-term benefits of the use of this glucose monitoring technology would be most pronounced as a result of decreased complications from diabetes. This in turn would result in a decrease in hospital stays, and overall savings to the healthcare system.

13.3.7 Diabetes care in BC

Family physicians support many patients living with diabetes and may be the only healthcare professional supporting patients with Type 2 diabetes. Currently, the majority of

endocrinologists in BC are located in the lower mainland and on Vancouver Island, meaning that access to endocrinologists may be difficult for patients living outside these areas. There is one endocrinologist in the Interior Health Authority. In outlying areas, people with Type 1 or poorly controlled Type 2 diabetes are usually supported by internists who take an interest in diabetes, as well as by diabetes education centres.

Generally, people with diabetes who have highly variable blood glucose levels, who experience severe episodes of hypoglycemia, and/or are beginning to develop diabetes-related complications are more likely to get referred to an endocrinologist. Who gets referred to an endocrinologist was described as highly variable, however, with many factors contributing to this variability, including family physician preferences, location in the province, and type of diabetes (i.e., Type 1 vs Type 2).

Each health authority operates diabetes education centres, and where there are endocrinologists, they would be attached to these centres. In most health authorities, getting access to these centres requires a referral from a physician. Vancouver Island Health Authority centres are apparently accessible to patients without a referral, a model described as preferable by one medical leader/endocrinologist. The one diabetes educator interviewed noted that they had recently tightened up their eligibility criteria, meaning that only people living with Type 1 diabetes, or people with Type 2 experiencing some challenges with blood glucose control and/or severe hypoglycemia could access this support.

According to a medical leader in one health authority, there is active planning underway to try and provide better support in primary care for patients living with uncomplex Type 2 diabetes, leaving the diabetes education centres more time for more complex patients, including supporting patients to optimize the use of their insulin delivery and/or glucose monitoring technology. There are many certified educators working at the diabetes education centres, including certified pump trainers, but the *"manpower is stretched."* Currently, if a small diabetes education centre doesn't have the expertise to support a patient with a pump and CGM, they would be referred to a centre that does have this expertise.

A number of suggestions were made with respect to how to build capacity in the BC healthcare system to support patients to optimize the use of this new technology. These include:

- Having diabetes educators working in primary care offices to support family physicians provide better support to patients with their diabetes management;
- Providing more resources for diabetes education centres, so they can hire more staff and provide more training for their staff on these new technologies and how to support patients to optimize its use;
- Working with manufacturers to increase training and support for both health professionals and patients, and to improve the ease of downloading and reviewing the data; and,
- The introduction of some kind of new fee item to the medical plan for reading and interpreting and providing advice regarding monitoring data, as it does take time and expertise to optimally support patients to use this technology.

The way that this new glucose monitoring and insulin delivery technology is currently being distributed in B.C. is limiting community pharmacists' ability to be involved and support these patients using the technologies; many of whom apparently would like to be involved in the care of these patients. They aren't able to access the products to provide it, meaning they don't have access to training from the vendors so are not able to problem-solve with patients.

BC has guidelines for diabetes care[35]. One of the interview participants involved in the development of these guidelines noted that they are targeted at primary care physicians and are based on the Diabetes Canada guidelines.

13.3.8 Support in schools for children with diabetes

There is a provincial school care plan for children with diabetes[252]. Nurses go into schools and train educational assistants or teachers how to support children to manage their diabetes. They are trained to check blood glucose levels and give insulin, including how to use the technology (i.e., pumps, continuous glucose monitors). The ability to be able to incorporate the use of continuous glucose monitors in these care plans was introduced recently (September 2018). They are only able to support the use of Dexcom 5 continuous glucose monitors, currently, as it's the only one approved for use in a pediatric population by Health Canada. So they are unable to support the use of the Medtronic CGM or the Freestyle Libre flash monitor. Many children are currently using these, but because these monitors cannot be supported through the provincial care plan, when these children are at school the blood glucose testing needs to be done using finger

pokes. Endocrinologists are supporting these children and their families to use these tools, so when the school says they cannot use them, it can create some contention between the school, the physician and the child and family, making this far from ideal.

Overall, the experience with continuous glucose monitors has been very positive for children. It is far less disruptive, as the child does not need to be removed from the classroom, the gym or the middle of a concert to wash their hands and have their finger poked. As one healthcare professional said: *The children are so much happier, as they don't feel as different from all the other kids…one more step to normalizing it [diabetes].* They are also seeing less cellulitis, and less building up of scar tissue, in children's finger tips. The trending information provided by a glucose monitor also helps school staff to better understand how different foods are affecting a child's blood glucose.

13.3.9 Coverage of glucose monitors

Public funding for glucose monitors is likely to increase the number of people who use this technology, as the cost of the technology is the major current deterrent to its use. What will also change, however, is the type of people who have access to this technology. Currently people with no extended health coverage for this technology, and particularly those living on limited incomes, are not able to afford it. This population of people would now have the choice of trying this technology. Given that using this technology may provide even greater benefit to those patients currently struggling to better understand and to better manage their diabetes, this was described by some as an important ethical consideration. As one endocrinologist said: *"it's often the people who desperately need it who just can't afford it."*

Most healthcare professionals commented on the importance of considering the differences between flash and CGM when establishing eligibility criteria. As one endocrinologist said: *I think it's a big mistake that Flash got lumped together with CGM, instead of viewing it as a tool to support blood glucose monitoring. The patient is still monitoring their own blood glucose; they are just using different tools to do so.* They went on to say that flash monitors should be treated more like testing strips, meaning that there should not be limitations around who can prescribe them.

Retaining patient choice regarding how they want to monitor their blood glucose was also described by many as an important consideration. Specific suggestions made with respect to eligibility criteria include:

- Use the same eligibility criteria currently used for PharmaCare funding of test strips (i.e., funding for 3000 strips/yrs. for patients on multiple daily injections of insulin) to support the use of any kind of glucose monitoring the patient chooses (i.e., finger pokes, flash, continuous) up to a maximum of the same cost as the test strips ($3000/yr.);
- For people experiencing severe episodes of hypoglycemia and/or with hypoglycemia unawareness and people requiring others to support their diabetes management (e.g., children, adults with some cognitive impairment), allow for additional funding to support the use of CGMs [which are more expensive than flash monitoring systems].

With respect to the integration of glucose monitoring technology with pumps, health professionals felt that continuous glucose or flash monitoring optimizes the benefit of a pump making it difficult to talk about one without the other. As one endocrinologist noted:

> *"Type 1 diabetes is the most dynamic disease in the world…It's always changing. Your insulin requirements are always changing. Your blood sugars are always changing so to set somebody up on a pump and reassess them a year later and assume that everything is fine is ridiculous."*

One endocrinologist working in a diabetes and pregnancy clinic believes that glucose monitoring will be of huge benefit for women with gestational diabetes, as currently they are being asked to finger poke six times/day. This can be very challenging, so they are looking forward to when flash monitors are approved for use during pregnancy. Women are already using them but need to pay out-of-pocket.

In addition, the integration of a pump with a CGM is required to have a low glucose suspend feature, and as one endocrinologist who works with many patients on pumps said: *And it's that low glucose suspend feature that I think is the critical piece that's actually saves lives. Many healthcare professionals recommended that everyone in BC currently eligible for a pump be eligible for a continuous glucose monitor.* They also made it clear that there is no use providing

funding for the Medtronic 670G pump, unless they also providing funding for the CGM component. As one endocrinologist stated:

> *"I think 670G is going to be so game changing, I'd love to see every Type 1 who wants to be on a pump on 670G…So, anybody who is wanting 670G who the physician thinks is an appropriate pump candidate should have access to a sensor otherwise there's no point of giving them that device… It can't do its job without the critical component of CGM."*

Finally, there should be consideration given to supporting patients already using a particular technology to continue to use it. As one healthcare professional said:

> *I do think there was a bit of a mis-step on the pump coverage…should have grandfathered in people who were also using a particular technology. It's a pretty hard thing to trust a machine that is a life-saving technology. Once patients have developed confidence in a machine, it can be hard to develop trust in another machine.*

13.4 Conclusion

Healthcare professionals believe that all patients living with Type 1 diabetes, or Type 2 diabetics who require insulin, and particularly multiple daily injections, or are on Sulphonylurea (i.e., medications that lower blood glucose rapidly and therefore increase the risk of hypoglycemia) to manage their diabetes could benefit from some form of continuous or flash glucose monitoring. A sub-group of patients for whom continuous glucose monitors specifically are of particular value are people with lots of problems with hypoglycemia, and children and others requiring support from others to manage their diabetes.

According to the healthcare professionals, the major barrier or challenge for patients trying to access these glucose monitors is cost, with this being even more of a barrier for continuous glucose monitors as they are more costly. A related challenge is the work that patients may need to go to get this technology covered under their extended healthcare plan, should they have one. Most patients find the technology easy to use and the information easy to understand, once they have a little experience with it and/or get some help from others.

Both patients and healthcare professionals describe the difference it makes to their health and their lives, as well as the healthcare system. Improved outcomes outlined include:

- Improvement in quality of life, including freedom and flexibility;
- Decrease in frequency & severity of hypoglycemic events, as resulting ambulance calls and ER visits;
- Improvement in AIC levels;
- Improvement of time in range; and,
- Decrease in longer terms complications from diabetes & healthcare costs.

Finally, healthcare professionals were asked about considerations with respect to public support of flash and continuous glucose monitors. One recommendation made by many, as a starting point, is to use the same eligibility criteria currently used for PharmaCare funding of test strips to support the use of any kind of glucose monitoring the patient chooses (i.e., finger pokes, flash, continuous) up to a certain maximum amount. This maximum amount could be set at the same amount as currently provided by test strips. For people experiencing severe episodes of hypoglycemia and/or with hypoglycemia unawareness and people requiring others to support their diabetes management, additional funding should be allowed to support the use of continuous glucose monitors.

14 Patient Interviews and Focus Groups

Summary

- Twenty-seven people living with insulin-dependent diabetes participated in a focus group or interview
- The greatest barrier to using a glucose monitors is the cost of the technology, with many participants sharing strategies they used to keep the costs down
- Having access to extended health benefits through their work was the strongest enabler for using a glucose monitor, although some people experienced challenges in getting their insurer to cover the technology
- All the participants had been able to integrate these glucose monitors quite easily into their routine diabetes management strategies, and expressed relief at no longer having to use finger pokes as the only way to determine their blood sugar levels
- Most importantly, participants described the CGM or flash technology as providing the type of information necessary to make decisions to better control their diabetes and making a positive difference in their quality of life

14.1 Purpose

Understanding the patient experience with using CGM to help manage their diabetes is an important component of this HTA. A systematic review of the qualitative research on patient perspectives was conducted to understand the experience of insulin dependent individuals using continuous glucose monitoring (CGM) technology to help manage their diabetes. As a result of this evidence synthesis, some significant gaps were identified in the literature. Specifically, the patient perspective with respect to why people choose to use CGM, how they use CGM, the barriers to use and how using CGM affects quality of life were not well explored.

The purpose of this study was to explore and describe the lived experience of people using insulin and continuous glucose monitoring (CGM) or flash to help manage their Type 1 or Type 2 diabetes.

14.2 Methods

A combination of focus groups and interviews were used to speak with patients living with insulin-dependent diabetes about their experiences with, and perspectives on, using continuous or flash glucose monitoring technology to help manage their diabetes. The University of Calgary

HTA Unit worked with Diabetes Canada, a diabetes expert panel, patient partners, and personal networks to reach out to patients who were using or had considered using a continuous or flash glucose monitor[1]. This study was approved by the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary (REB18-1996). A semi-structured focus group and interview guide was developed to support the process. This guide included questions on: what led participants to consider or try these technologies; barriers or challenges they might have experienced in obtaining these devices; the experience with the health system in providing education and support; their experience using the technology to help manage their diabetes; and, their perceived difference in quality of life. The guide evolved over the course of the interviews, as questions were refined to reflect what had been learned through the previous interview(s). All interviews were conducted by an experienced qualitative researcher, audiotaped with the consent of the interview participants, and detailed notes were taken. We continued to collect data until we reached saturation[253]. The data were qualitatively analyzed using a modified constant comparative analysis to identify key themes across the interview and focus groups[254]. A meeting was held on April 4, 2019 with our expert panel of patient partners. Together, we reviewed the findings and asked our patient partners to provide their thoughts on what might be missing, areas that stood out for them, and their comments on the findings overall.

14.3 Findings

14.3.1 Participants

Focus groups and interviews were conducted with people living with insulin dependent diabetes in February and March 2019. A 2-hour focus groups was held in Vancouver. The focus group was facilitated by two qualitative researchers trained in qualitative methods; additional members of the research team attended to observe and take detailed notes. In addition, 16 individuals participated in individual interviews, nine from Alberta and seven from British Columbia. The interviews ranged in length from 20 to 120 minutes.

Of the participants who filled out the pre-survey questions (n=25), 12 of the participants were male and 12 were female, one individual did not disclose their sex at birth. Most participants

[1] Throughout this section, the term ‘glucose monitor’ is used to refer to both continuous and flash glucose monitoring technology.

were between the ages of 50-69 (n=13) followed by 30-49 years of age (n=7). 3 participants were between the ages of 18-29, and 2 participants were 70+. Most participants in this study were well educated (n=20) having some form of post-secondary education. Three participants indicated they had completed high school and one indicated they had completed grade 10. Most live in a major urban center (n=14) or a smaller city (n=7) such as Lethbridge or Prince George. Five of the seven BC interview participants lived in the lower mainland, one lived on Vancouver Island, and one lived in the North.

Eighteen of the participants are living with Type 1 diabetes and six with Type 2. One individual indicated they had been diagnosed with both Type 1 and 2 diabetes. The majority of participants have had their diabetes for more than 20 years (n=14) followed by individuals who have had their diabetes between 11-20 years (n=4). The majority of participants (n=12) have used either flash or CGM for 1-2 years with five participants using the technology for less than a year. Most participants delivered their insulin using a pump (n=14) followed by injection (n=8).

14.3.2 Finding out about and trying the technology

The focus group and interview participants found out about glucose monitors in a number of different ways, including: being told about them by a health professional, usually an endocrinologist or a diabetes educator; hearing about them through a Facebook or support group; seeing an advertisement on TV or online; and learning about them at a diabetes trade show or conference. Flash monitors were more commonly heard about through advertisements, and continuous glucose monitors through Type 1 diabetes and/or insulin pump support groups, including online groups.

> "It [the flash monitor] sure beats finger sticks! There was a commercial on TV and then I went to a diabetes awareness day at the University in November. A doctor did a demo where he tested his blood before and after (his blood glucose was the same of course, being non-diabetic). I picked up some brochures at the event and did some more research when I got home – I was curious! Then I just decided, I would try one. I wasn't sure if it was covered but I thought I would go for it."

Some participants referred to incentives offered by the manufactures and coming up for a renewal option as part of the pump program as the reason for trying the technology.

> "My original pump wasn't eligible to use CGM. When it came up to renewal, I switched pumps and the new model was eligible (added later: when Animas discontinued the pump, I transitioned to Medtronic, and Medtronic offered free sensors as incentive to try CGM)."

The focus group and interview participants articulated a number of reasons for trying a glucose monitor, with the most commonly described ones being experiencing problems with and/or fear of hypoglycemia, a large variation in their blood glucose levels and higher than desired HbA1c levels. They were interested in a simpler, less painful method for checking their blood glucose levels; wanting to be able to check their blood glucose levels more frequently and be able to get information about their blood glucose over time, including knowing what was happening while they were sleeping.

Participants emphasized the daily burden and stress of managing this disease. People with diabetes have to regularly monitor their blood glucose levels and make necessary adjustments depending on the results of these glucose levels. Many participants stated that one of the most painful components to managing their diabetes results from having to prick their finger multiple times per day; both the pricking itself and the ensuing tenderness.

> "Lancing hurts you know! Sometimes you don't get enough blood, or the strip doesn't work, and you have to lance again."

A few individuals cite the need to test frequently or the desire for more information and to be able to understand what was happening with their blood glucose levels and the desire to know what was going on inside them.

> "My doctor even said that I test a lot. CGM was very attractive to me because I could see my blood sugar levels at any time. I can just look on my phone and get a reading."

Wanting to exercise or participate in life activities exacerbated this feeling and ultimately resulted in these participants trying the technology.

> "I do a lot of swimming and had difficulty managing my blood sugars during swims. I found a system that worked well for me, I could manage my diabetes and continue swimming. I was using a DEXCOM CGM and a tubeless OmniPod. I had to switch back to Medtronic because of the expense and I am not really pleased... not needing tubes was a new sense of freedom! This was an incredible freedom and I didn't worry anymore about things like getting dressed or about finding things at the bottom of the pool. Being tethered again is a real pain…"

Another participant described not knowing why her blood glucose levels were high, even after doing everything she was told to do, she was worried what the long-term impact on her and her family might be if she didn't get her diabetes under control.

> "Before I got my CGM I always had a hard time getting control of my diabetes. I got myHbA1c reading of 9.2 back and I looked at my husband and said, if I was eating a Mars bars every other day this would explain it [the highHbA1c level]. I wouldn't question it [theHbA1c level] but I can't explain it [myHbA1c level] ... we need to invest the $10,000 and get a CGM."

There are many situations in the context of living one's life, where testing blood glucose using finger pokes is challenging; such as, while: in meetings, driving, doing manual labour, working outside, in the gym, cycling, running and skiing. One individual, for example, described the difficulty trying to lance dry or cracked fingers when working outside, in the oil sands on a cold Alberta day, as the primary reason for compelling him to try a glucose monitor.

> "I am in the field working with high levels of Hydrochloric acid, pricking my finger [to test my blood] would put me in too much risk so I never check my sugars unless I feel like crap."

14.3.3 Barriers or challenges to using the technologies

Participants were asked about their perceptions of the existing barriers or challenges related to obtaining and using a monitor. Participants consistently reported that by far the greatest barrier was cost.

> "You are told that the best thing you can do is to keep your blood sugar under control, but then nobody will pay for it."

> "I tried the CGM for the first time about a year ago. It was about the same time the Free Style Libre was announced. I looked at CGM's but nothing was covered. So once the Free Style came into play it was a lot cheaper so I went with that."
>
> "With everybody, the cost is prohibitive, but I would skip a vacation or eat cat food before I skip this."

A number of participants described not wanting the costs they were incurring for this technology to help them manage their diabetes to negatively affect their families.

> "But if I was in a position where I felt my husband was suffering because I was spending all our money on test strips, I would reluctantly go back to finger pricking. But I think I would have much worse results, I think I would be much more prone to lows." (FG2)
>
> "The huge cost sort of really stopped me, I would've been on one right away but, frankly, the trouble with being a diabetic is you always feel you're bankrupting your family... but when the Libre came in and I knew that I could get it covered by the school board, it was like a no brainer" (FG2)

Participants shared the compromises they made in order to afford the technology. A number report not using their monitors all the time, but rather in a limited, targeted way to minimize costs. Some use it for a period of time to get data they can then share with their physician or diabetes educator. Others when they want to monitor their blood glucose more closely for a period of time, because they are making some changes to their insulin regime, their diet and/or their activity level.

> "I use it for a full month prior to seeing [my Endocrinologist] so that I can share the data with him. He looks at the graphs or the specific readings and we have found that I really spike after meals. [Interviewer asks why do you only use the device for the month prior to your visit?] I pay out of my own pocket, I am from a diabetic family, so we are used to having to do this, but I have issues with the sensors. I am clumsy, if I bump into something, even if it isn't even really hard, [the sensors] pop off and go flying across the room. They are $90 so when this happens after only a few days it gets to be pricey. I

> can’t justify the cost to use it all the time because the sensors just pop off. If I could get the full 2 weeks out of the sensor it might not be so bad. I have even tried different locations on my body.”

Others choose those times where it is more difficult to measure their blood glucose with finger pokes to wear a sensor for a couple of weeks, such as: when going backcountry skiing; long bike, motorcycle or car trips; and travelling.

> “The reason I'm using the Libre only some of the time is because of the cost, it's all out of pocket and I feel if I can use it 50% of the time I can afford that, but to use it 100%, that's $2,400 a year… I wouldn't go in the back country now without it… I've had some serious lows in the back country… I've had one for three weeks over the Christmas holidays…And now, I've been off it for a few weeks, and I really miss it, that's the hard part.” (FG2)

Other participants tried to decrease the costs by extending the life of their sensors and/or transmitters beyond the time recommended by the manufacturer. They spoke about the information that is readily available online about how to do this. Many people had good success with this, noting that they were able to determine, when the sensor was no longer reading accurately. Some did not have success, however.

> “You can fool it. You can just pretend you have changed it and reset it. I have found that I get issues. I could get 10 days but then I get weird alarms or it’s not accurate. Some people have good success, but not me.”

> “There are these groups in the US, apparently there is an app you can download, and people have shared how to do make the sensors and transmitters last longer. These groups are huge in the US, normally you can get 3 months out of the transmitter but there are a whole bunch of people who have been able to extend the lifespan of the transmitters to 6 months.”

Some participants shared their creativity in getting the sensors to stick and adhere for as long as possible, with many people getting ideas about things to try from Facebook groups, and/or from the manufacturer.

> "I use patch, there are smaller and larger options, but I put the sensor over that. We use glue as well. So, what I do is I clean it [the sensor], put the glue on it [the sensor] and then cover it [the sensor] with patch. It may last more than 2 weeks, I know when it is done [because the sensor] curls. The triceps is the best spot, I switch every two weeks."

A number of participants wondered why the government is willing to provide funding for some diabetes technology and supplies, but yet not others; for example, why insulin pumps and blood testing strips are funded but not glucose monitors. They also expressed concern that they would no longer be able to afford to use a monitor if they lost or had to change jobs, or when they retired.

> "I don't really understand it. Finger pricks adds up. It is about a $1 for each strip. The Insulin Pump Program indicates that the Alberta average is 6 finger pokes a day. That is about $2,200 per year. The sensors are about $2,300 per year. Even if they only covered the same amount, it would be better!"

> "I am over 70. I started working as a part time diabetic counsellor. I really enjoy it and provides me with benefits. If I wasn't working, I would have to have to go back to finger pricking."

Some participants also revealed challenges with getting information about whether they were covered by their insurance, and then getting the necessary paperwork completed to be eligible to get a glucose monitor covered.

> "Getting started and set up was the hardest thing I have ever had to do! Getting approved and covered through my insurance company was an issue. The experience was so annoying I stopped using it [the monitor] for about a month."

> "I phoned my insurance provider prior to the purchase of my insulin pump to find out what my coverage entitled me to receive through my benefits. I was informed that I could receive $2,500 towards the purchase of the pump itself, which could be billed directly to the insurance company through the supplying company. I was also informed that all supplies connected to the pump fell under the category of "diabetic supplies", for which I am covered for up to $2,500 per calendar year. I asked specifically about each of the parts that I would need for using the specific pump that I was considering purchasing: the infusion sets, insulin reservoirs, and glucose monitoring sensors. All of these items, I was told, were considered diabetic supplies. Despite this, we had troubles with the claims for the sensors from the beginning, and both my pharmacy and I had to make phone calls to my insurance company to straighten the bugs out of the system."

14.3.4 Enablers to obtaining the technology

The participants also described a number of enablers to obtaining and using a glucose monitor. Despite some of the challenges related to getting 3rd party insurers to cover glucose monitors, having the cost of a glucose monitor covered by an insurer was described as incredibly helpful; this is what often enabled people to obtain a monitor. Health care professionals and specifically endocrinologists played an instrumental role here. More insurance companies are covering glucose monitors, particularly flash monitors; with most seeming to require an endocrinologist to complete paperwork saying that the patient requires the glucose monitor.

> "I was very lucky because [the CGM] was easy for me to get, I have great benefits that allowed me to use this tool to manage my diabetes and cost was never an issue for me."

Many of the participants interviewed described learning how to use the flash monitors and the new continuous glucose monitors as being easy. Most of the patients interviewed who were using a continuous glucose monitor were also using an insulin pump. They describe obtaining support from a number of sources to help them learn how to how to apply the sensors, obtain and read the data, and then use the data to make needed changes. Some people describing not seeking any help from healthcare professionals, doing all of the learning on their own and through online resources including social media, through the manufacturer's websites and through support groups. Others indicate their health care professionals, and particularly diabetes educators and endocrinologists, are playing an active role in supporting them to use this technology.

Many participants spoke about learning to use the monitor by reading the instructions that came with the monitor, and going to the manufacturer's website and watching the videos on how to insert the sensor. This is also how many learned how to download the information to their computer.

> "I learned to use it on my own…watched a few Youtube videos to figure things out. I am fairly tech savvy. If you are new to diabetes, think it would be a bigger challenge as you are trying to learn a lot all at once."

Participants felt learning about what the data was telling them was fundamental to their success. Participants describe using this information to better manage their blood glucose levels, people described learning through practice or "trial and error"; working with their endocrinologist and/or diabetes educator; online resources; and both virtual and in-person peer support groups. Some of these groups are led by patients, such as the Calgary Insulin Pumpers, and others are supported by the healthcare system.

> "About 5 years ago, I discovered that [hospital] in Edmonton, started doing a pump optimizing workshop. They were offered at different times in the day, one in morning, afternoon and evening. I wish I had found about them earlier because I had no one to speak to when I was first diagnosed. I'll never forget, one of the settings I use on my pump a lot was being talked about. We are able to learn from other diabetics and people that live with this every day. I found them really helpful and valuable, so much so in fact, I still attend them after 5 years."

As with learning anything new, however, there is a learning curve involved. Participants described, for example: feeling increasing comfortable inserting a new sensor after they had done it a few times; developing strategies to prevent the sensors from falling off, either due to bumping them or sweating while exercising; understanding the data they were receiving; and then using this data to make any needed changes to how they are managing their diabetes (e.g., adjust their insulin administration, eating and/or activity levels).

In the early days of their diabetes journey, many participants felt as though they were educating their healthcare team on these technologies. As time went on, more and more physicians and educators have become more aware and are more comfortable with the different tools people can

use to manage their diabetes. Some participants, however, still feel they are the most knowledgeable about this technology and about how to use the information to make necessary changes to their insulin, diet and activity levels.

> "My doctor was excited to see it [the device], he was like a kid at Christmas. He had never seen one before. He was so impressed and kept saying over and over 'this is a game changer…wow, you even get your data. This is such a game changer.' Now he recommends them to everyone."

Some participants living in rural jurisdictions have been able to find supportive arrangements with their healthcare professionals saving them much time and aggravation of having to come into the doctor's office everything there was a concern.

The experience and service received from the manufacturers of both the CGM and Flash devices were described positively. Despite having to provide additional information such as serial numbers for a malfunctioning device or sensor, replacement parts were made available without much issue.

> "I had problems with the sensors. I called the Libre folks and told them that my sensor wasn't working, and they shipped a new one via courier, it arrived in two days!"

> "They needed the model and sensor number, but this was on the back of the box, which of course, I tossed away so it wasn't easy to find. This made things somewhat challenging."

A few patients described calling the Flash monitor manufacturer when their sensors fell off, and getting replacement sensors sent for no-charge. In addition, the manufacturer was able to provide advice regarding sensor placement to decrease the changes of it getting bumped and falling off, and information about better adhesives (e.g., "skin tac").

14.3.5 Experience with using the CGM

Participants shared their stories of having tremendous challenges managing their diabetes after their diagnosis, including the big swings in their glucose levels at different times of the day and their fears of the long-term damage to their health due to their blood glucose variability. Many people also expressed fear about the shorter-term safety issues related to incidents of severe hypoglycemia. All of the participants using a glucose monitor feel this technology has been an exceptionally effective tool to help them better manage their diabetes. Everyone appreciated the ability to be able to easily see both what their blood glucose levels were throughout the day and during the night.

Participants describe having to constantly explain their diabetes or what they were doing (injecting insulin or finger pricking) to non-diabetic individuals. Participants spoke of being able to check their blood glucose levels both quickly and discreetly, instead of having to use finger pricks. In addition, they reported that using a monitor had positive impact on their employment, especially if work required travelling or being outside. Participants appreciated being able to test safely in unclean environments, such as when working in the garden, when working in other countries where conditions may not be as sanitary.

> “Generally, blood tests make other people uncomfortable. I used to do it at the table in a restaurant because I had the table where I could spread out all my gear. I am not going into the washroom in an unsanitary and very uncomfortable place. Now all I have to do is scan.”

> “I am very active and work in construction so using this at work is good. In the summer I am mostly outside, and the monitor allows me to quickly get my levels. I have not had any issues.”

> “When I go on longer distance bike rides, it’s so easy to pull transmitter out of pouch and scan it right there.”

> “Because I do a lot of back country skiing and I've had some serious lows in the back country self-injecting and the pump, it's cured the lows, I've never had a serious low since

> I've been on the pump. But having that CGM when you're out in the cold and to be able to scan it and get a result without having to take your pack off and pull your meter out and prick your finger and keeping everything warm. The meter is small, it just fits in my pocket."

> "Freedom part is really nice...Being able to keep on top of blood sugar levels when doing things like hiking…Having to do finger pokes every 5 minutes when doing something strenuous is really difficult."

A few participants commented on how they were initially concerned about the small difference in the readings between the monitor and the finger prick methods of measuring blood glucose. Once individuals had more experience with using the technology and once they understood there was a slight but consistent difference between interstitial fluid and blood glucose levels they felt comfortable using this tool to help manage their diabetes. This was part of the learning curve.

> "There is one drawback, it not as accurate as a finger prick, but it will give you a general sense of where you are. If it is telling you are low, go test your blood. As soon as you know the results are about 15 minutes behind a blood result you know what to do. It gives me a better idea."

The majority of participants who have used these technologies believe that having more knowledge is the key to being able to manage their diabetes. The ability to see the variability within the data, with a trending up or trending down indicator, supported individuals to not only learn about what certain activities do to their blood glucose levels but also enables them to make decisions about how best to react so they can continue or modify an activity.

> "CGM also tells you how you are trending. So, if you get more down arrows, your sugar is going down too far, and same thing with going up. If you have one down arrow, maybe you're going a bit low. If you have three, you're going low fast."

> "This device has given me the knowledge to own my diabetes. I am managing my chronic illness; the illness is not managing me."

> "The biggest takeaway is the patterns in my blood. This is the most powerful tool I have ever used. It gives a minute by minute pattern. We all want to live our 'normal' lives and this helps me to do that."

Participants also appreciated the immediate access to their blood glucose levels and the immediate feedback, which some people described as motivating them to make better choices and decisions.

> "When I didn't have a CGM, if knew my blood sugar wouldn't look great I just wouldn't check. I had the ability to ignore the spikes in the middle. Now that I can see when and how much it spikes, and can see what kinds of food works and what a challenge other foods are [e.g., Sushi]… It helps me to avoid certain foods [or she makes sure she gives herself more insulin in advance, and/or take a short walk after she eats]. It helps me make better choices… No denial possible."

14.3.6 Impact

The most common diabetes-related impacts of using glucose monitors these participants described was a decrease: in the variability of their blood glucose levels (i.e., time in range); in the number of hypoglycemia incidents, including the number of "dangerous lows"; in the amount of snacking required to prevent hypoglycemia; in the daily amount of insulin they injected/delivered; and, in their HbA1c levels. Participants described being able to get rid of the peaks and valleys in their blood glucose levels and being able to adjust to avoid adverse events primarily because they are able to intervene more quickly.

> "I'm knocking the peaks and valleys off the curves, far better than I would otherwise. I'm not accidentally driving myself into lows as often… So yeah…the valleys aren't as deep, far, far more convenient, far better blood sugar control, far better quality of life."

> "I believe that it is worthwhile for you to know that through the use of this monitoring system, my average blood glucose has dropped significantly. As a person who has always had a great deal of difficulty managing my diabetes, this is something that has been life-changing. Through this tiny piece of technology, I have discovered that my body needs

varying amounts of insulin at numerous and varying times of the day. This is not something that I could have ever accomplished using the traditional syringe and vial (or insulin pen) system. The changes in my blood sugar readings, sometimes which are very subtle and quickly changing, could never have been discovered through the system of pricking my finger and testing using strips."

"I have been using the Libre monitoring system since it became available in Calgary. The positive changes that this product has made to myHbA1c speak for itself. Since I started using this device, I have reduced myHbA1c by almost 2 mmols to under seven. Additionally, my family doctor who diagnosed me with diabetes says he has never seen myHbA1c this low. He is encouraging all of his diabetic patients to use this system."

"These guys have covered the spectrum. I started CGM to get better control, to get lower HbA1c you have to be precise. It's changed my life. I work in construction; it's busy you don't have time to notice lows, but it gives alerts. I'm active, I curl, I ride a motorcycle, and so I don't want to be on the road [and have a hypo]. It's great, it's a great tool, it's changed my life, but there's a lot of effort."

One participant who was pregnant and diabetic shared her appreciation for how the monitor supported her to better manage her diabetes.

"When I was pregnant, I was testing upwards of 12-16 times per day and never managed the kind of control I have found using the sensors. I was monitored closely by numerous specialists during my pregnancy, including the "top" endocrinologist that deals with the most difficult cases of diabetic mothers-to-be, because my body was so unpredictable when it came to my blood sugar readings and diabetic control. Even the help of all these people did not have the kind of impact I have found since changing to an insulin pump that can monitor my levels on a minute to minute basis."

Many participants described the ability to stop dangerous lows (i.e., hypoglycemia), as having a positive impact on their quality of life. They were able to work and do activities they enjoyed, much more safely, including driving, biking, running, hiking and skiing. It also decreased

anxiety and gave people greater peace of mind. Continuous glucose monitors, which can send out an alarm, were described as particularly helpful for people who had hypoglycemia unawareness, and for preventing hypoglycemia ("hypos") during sleep.

Overall, people described having more control over their blood glucose levels, as well as having more freedom and flexibility in their lives, since starting to use a continuous glucose monitor. Many participants described feeling more comfortable being able to try different things (travel, activities, food) knowing that they could monitor their blood glucose more easily and make any necessary adjustments to their insulin.

14.4 Conclusion

Speaking with individuals during the focus groups and interviews affirmed the findings of the systematic review of patient experiences with continuous glucose monitors and emphasized the immense impact the monitors had on their ability to manage their diabetes and their lives. These technologies benefit the person living with diabetes themselves, but participants also spoke of the benefits to their friends and family members.

Participants describe using these technologies to manage their diabetes as a powerful tool, enabling them to take more ownership over their chronic disease. Many shared the impact these technologies have on their overall quality of life. They described being able to make more informed decisions, which contributed to helping them feel more "normal." Participants highlight the ability to sleep, work, exercise and even drive with more confidence, as they are able to quickly check or receive notification when blood glucose levels are increasing or decreasing, helping to prevent adverse events.

Most participants choose to try a glucose monitor in response to large variations in their blood glucose levels or experiencing problems with and/or fear of hypoglycemia. Cost was the biggest barrier for individuals in deciding to use these technologies. Some participants shared inconsistencies in insurance coverage and confusion with determining if they had adequate coverage. Others had little to no issues with coverage and even received support from the manufacturer to get set up with the technology. Participants learned how to use these

technologies mostly on their own, searching online websites, social media or watching online videos. With respect to learning how to use the data collected by the monitor people described learning through practice or "trial and error" and working with their endocrinologist and/or diabetes educator and peer support groups.

Participants spoke of being able to check their blood glucose levels both quickly and discreetly. The ability of having more knowledge was the key to being able to manage their diabetes. Participants described being able to get rid of the peaks and valleys in their blood glucose levels, primarily because they are able to intervene more quickly. Individuals describe being able to work and do activities they enjoyed, much more safely, including driving, biking, running, hiking and skiing. Using the continuous monitoring decreased anxiety and gave people greater peace of mind.

This study has strengths and limitations. Recognizing that the participants who volunteered for the focus group or interviews were primarily older, well educated, and from an urban center, it is important to recognize the limitations of these findings. Many participants were well connected to diabetes associations and support groups and were very knowledge able about their diabetes and how to manage it. Although these experiences are important, they do not represent other individuals who do not have private insurance, or whose public plan does not have to the same level of insurance described in this report.

Participants shared the desire to have a choice about which technology was right for them and expressed a desire for additional financial support, so they did not have to minimize use or make compromises as a cost savings measure. Some participants also revealed challenges with getting information about whether they were covered by their insurance, and then getting the necessary paperwork completed to be eligible to get a glucose monitor covered. Healthcare professionals need support and training, so they are better aware of the challenges in using and adopting these technologies. Diabetes clinics and support groups are a valuable resource and could be expanded as these technologies become more mainstream. Future work should consider marginalized populations, individuals on limited income, individuals without insurance and those on other

social assistance programs. It is postulated that the needs of children and adolescents may be different than the adult population and work in this area should be encouraged.

15 Cost-Effectiveness Evaluation of Management Options for Insulin-Dependent Diabetes

Summary

- In the clinical effectiveness systematic review, no difference in HbA1c or number of hypoglycemic events requiring assistance was identified.
- Interviews with clinicians and patients suggest that these metrics are frequently evaluated after the decision-making process. The most important factors in the decision between diabetes management technologies are related to their ability to integrate into the patient's life; and their ability to provide understandable and actionable blood glucose management information.
- Published economic models rely on the connection between HbA1c and hypoglycemic events to predict long-term risk of complications. With no evidence of a difference in terms of these outcomes, a model based on these findings would add little value to the decision-making process.
- Both patients and the Ministry of Health consider cost in decision-making. Therefore, cost is analyzed in more detail in a budget impact analysis.

15.1 Purpose

To evaluate the cost-effectiveness of continuous glucose monitors, flash glucose monitors, and hybrid insulin delivery systems for the management of insulin-dependent diabetes. After completion of the clinical review, a cost-effectiveness model was not undertaken. The rationale is explained below.

15.1.1 Clinical Effectiveness

In the previously described systematic review of clinical effectiveness, many studies reported the effects of the intervention on glycated hemoglobin (HbA1c). However, for both adult and pediatric populations with type 1 diabetes, no significant differences in HbA1C or hypoglycemic events requiring assistance was observed between any of the treatments assessed in the network meta-analysis.

15.1.2 Key Informant Interviews

Interviews with patients and clinicians suggest that decisions about glucose monitoring and insulin management focus mainly on the ability of the patient to integrate the technology into their lives; and in terms of glucose monitoring, the ability to understand and act on measured blood glucose.

Although improvements in HbA1c may have been noted following a switch in technology, a difference in HbA1c was not the precipitating factor for the switch. Patients and clinicians consider these predicted effects of technologies as one facet of their decision making; but there are other considerations. Both the

patients and the Ministry of Health would also consider the cost of a technology within their decision-making framework.

15.1.3 Overall

HbA1c has been connected to long-term diabetes complications, and has been identified as an independent risk factor for coronary artery disease and stroke in patients with and without diabetes.[73] Many published economic models for patients with diabetes rely on this connection between HbA1c and the long-term risk of complications. A previous HTA by Health Quality Ontario found 20 economic evaluations of continuous glucose monitoring interventions compared to usual care.[255] In the 20 studies identified, CGM resulted in increased cost with small increases in quality-adjusted life years; incremental cost-effectiveness ratios (ICER) ranged from $592,206 to $1,108,812 per quality adjusted life-year, with significant uncertainty in ICERs noted.[255] These large ICERs suggest that any difference in QALYs is minimal.

In the systematic review and network meta-analysis conducted in this HTA, no evidence of a difference in terms of HbA1c, and no evidence of a difference in terms of number of hypoglycemic events requiring assistance was identified. Therefore, an additional model based on these outcomes will add little to current understanding of these technologies. The prominence of cost in decision-making for the management of insulin-dependent diabetes suggests that cost must be considered. Therefore, cost outcomes are considered in greater detail in the succeeding budget impact analysis.

16 Implementation analysis

Summary

- Drawing on all the evidence in this report, implementation options were developed for consideration
- Populations for which public funding could be provided are:
  - All people living with insulin dependent diabetes, both Type 1 and 2
  - People living with Type 1 diabetes
  - People living with Type 1 or 2 diabetes where there is a clinical need
- Four implementation considerations that could be applied across all three of these population are:
  - Support varies by patient income
  - Support varies by patient's blood glucose control
  - Access is limited to one specific technology
  - Access is limited to people that need extra help

16.1 Overview

Drawing on all the evidence compiled in this report, implementation options were developed for consideration. These options are described here along with implementation considerations that would apply across all of these populations. A summary is presented in Table 16.1.

16.2 Populations and general considerations

Three broad populations have been identified for which some public funding could be provided for glucose monitors. These are briefly described below along with some general considerations.

16.2.1 All people living with insulin dependent diabetes, both Type 1 and Type 2

In this scenario, public funding for glucose monitoring could be considered for all people living with insulin dependent diabetes, either Type 1, Type 2, regardless of clinical need (e.g., frequent unpredictable hypoglycemic events, frequent diabetic ketoacidosis, or frequent swings in blood glucose). At this time, there is no clinical research evidence to support this scenario. It is not possible to draw meaningful conclusions about positive change in outcomes for patients with Type 2 diabetes both because of the high heterogeneity between interventions, and the few studies reporting outcomes.

Some healthcare professionals and patients, however, feel that any person living with diabetes could benefit from using glucose monitoring technology, as they believe that more frequent monitoring of blood glucose can provide valuable information about how diet, activity and/or

insulin affects blood glucose levels. People then can use that information to make needed adjustments, and thereby potentially achieve better control over their blood glucose. All patients using insulin and needing to do frequent blood glucose testing, described a big improvement in their quality of life, after starting to use glucose monitoring technology, including feeling that they have more freedom and are able to live a more normal life.

This option does not currently align with the PharmaCare eligibility criteria for pumps[256] or for glucose testing[257], as this coverage is dependent on clinical need, leaving some people with insulin-dependent diabetes without coverage. This would be potentially be the costliest option, should many people with Type 2 diabetes seek PharmaCare coverage for a flash or continuous glucose monitor.

16.2.2 People living with Type 1 diabetes

In this scenario, public funding could be considered for people living with Type 1 diabetes. Again, at this time there is no clinical research evidence to support this scenario. With respect to clinical and surrogate outcomes (i.e., HbA1C, time in range, and number of hypoglycemic events requiring assistance), there was no difference between any included interventions. Looking at patient reported outcome measures, it was not possible to draw meaningful conclusions about positive change in outcomes for patients with Type 1 diabetes both because of the high heterogeneity between interventions, and the few studies reporting outcomes.

This scenario not does align with most healthcare professionals' and patients' experience and views, in that the many believe that any patient requiring insulin has the potential to benefit from using either a flash or continuous glucose monitor. This option does not align with the current PharmaCare eligibility criteria for pumps or for glucose testing, in that currently people with type 2 diabetes taking insulin are eligible for coverage for both pumps and up to 3000 test strips/year. This is likely to be a less costly option.

16.2.3 People living with Type 1 or Type 2 diabetes where there is a clinical need

In this scenario, public funding could be considered for people living with Type 1 diabetes, or those living with Type 2 diabetes where there is a clinical need. Again, at this time there is no clinical research evidence to support this scenario. Again, as with population #1, it is not possible to draw meaningful conclusions about positive change in outcomes for patients with Type 2

diabetes both because of the high heterogeneity between interventions, and the few studies reporting outcomes.

This option aligns with the current PharmaCare eligibility criteria for pumps and for glucose testing. BC PharmaCare currently covers insulin pumps for eligible individuals of all ages with Type 1 diabetes or with other forms of diabetes requiring insulin, as long as the following conditions apply: the patient/family is checking blood glucose at least 4X/day and recording the results, they agree to comprehensive and age-appropriate diabetes education by an interdisciplinary diabetes healthcare team, and they commit to regular follow up. The patient must also be experiencing some problems with blood glucose control. BC PharmaCare also currently cover the costs of up to 3000 test strips/year for any patient with diabetes who is taking insulin.

This scenario also aligns most closely with the views of most physicians and patients, as the majority believe that any patient requiring insulin to manage their diabetes should be eligible for some public funding for a flash or continuous monitor; and most particularly those requiring multiple daily injections of insulin. Some endocrinologists also feel that patients who are not taking insulin, but who are on Sulphonylurea, should also be eligible, as these medications can lower blood glucose rapidly and therefore increase the risk of hypoglycemia.

16.3 Implementation considerations

For each of these three population scenarios there are a number of implementation considerations; four of these are briefly described here. Again, there is currently no clinical research evidence to inform these considerations. Rather, the information generated through the other data collection strategies used in this health technology assessment, are drawn upon, including the systematic review of the qualitative research on patient experience, the jurisdictional scan, the BC health professional interviews, and the patient interviews and focus groups.

16.3.1 Support varies by patient income

The first implementation consideration is that the amount of public support provided varies by patient income. BC PharmaCare, under its income-based fair PharmaCare program[258], already operates in this way and test strips are covered through this program; so this would align with how test strips for glucose monitoring are currently covered. This is not aligned with the way

that PharmaCare provides support for insulin pumps, as they fund 100% of one kind of pump (i.e., Omnipod). Other types of pumps can also be 100% funded, but only through 'special authority'.

Patients and healthcare professionals told us that people with no extended health coverage and those on limited incomes currently experienced the greatest challenges accessing flash or continuous glucose monitors. Some patients limited their use of flash monitors, not using them all the time, so as to not have to pay for two sensors a month; and others had no access at all to the technologies. A number of healthcare professionals felt that the patients who could not afford the technology are likely those that would benefit the most.

16.3.2 Support varies by patient's blood glucose control

The second implementation consideration is that the amount of public support provided varies by patients' blood glucose control. This aligns with the current BC PharmaCare pump policy, as well as with policies for funding continuous glucose monitors in some other jurisdictions (e.g. Australia, US Medicare[259]). Both patients and health professionals interviewed believe that all patients who are committed to using the data obtained to make adjustments to their insulin, diet, and other activities could benefit from the provision of a glucometer. They also said that those who have more variability in their blood glucose levels and have frequent and/or severe hypoglycemic episodes are likely to benefit the most.

This kind of policy, however, may appear to penalize patients who work hard to achieve good control of their blood glucose using finger pokes (self-monitoring blood glucose). Being able to test blood glucose using continuous or flash glucose monitoring technology is described by patients and healthcare professionals working with them, as having a big positive impact on quality of life, in that finger poking can be challenging to do in many situations and is painful.

16.3.3 Access is limited to one specific technology

The third implementation consideration is that access to public support is limited to a specific technology, unless special authority is granted. This aligns with the current BC PharmaCare pump policy which provides 100% funding for one type of pump, the Omnipod. This can help limit costs, in that there is a high potential of being able to negotiate for a lower price if a decision is made to go with a single vendor.

This option, however, does not align well with a strong theme related to patient choice that emerged through the interviews and focus groups with patients and healthcare professionals. A number of healthcare professionals and patients recommended that a good implementation option to consider would be for PharmaCare to cap the amount of dollars they would provide to support patients with glucose monitoring, but leave it up to patients to decide what works best option for them, whether it be blood testing with finger pokes or using a flash or continuous glucose monitor. This approach also allows those patients who have already selected a technology to continue using it.

16.3.4 Access is limited to groups that need help

The fourth implementation consideration is that access is limited to groups that need help. There are some populations of people living with diabetes that are not able to manage their blood glucose levels without considerable help. These could include children as well as adults with some level of either cognitive and/or physical disability requiring caregiver assistance. The latter group would include the frail elderly, many of whom require considerable support from healthcare providers, including diabetes education centres. Children require help from a 'community' of people to optimally manage their diabetes; this community may include parents, other family members, school personnel and day care or camp personnel.

These patients, and the families and healthcare professionals supporting them, describe very positive experience with flash and continuous glucose monitoring. The data generated by this technology helps others to optimally support these patients. Both flash and continuous monitor data can be downloaded and viewed by others, which enables more accurate adjustment of insulin and diet. Continuous monitor data can also be shared with family members or friends, which enables them to support the patient remotely. For example, parents are able to see their child's blood glucose data when they are apart, and either directly communicate with the child or others caring for their child, if needed.

Limiting access to flash and continuous glucose monitors to just these groups, however, is not aligned with current BC pump or test strips policy. It is also not aligned with most patient and healthcare professional experiences and views. Having said that, many did recommend different criteria for public support of flash verses continuous glucose monitors.

Table 16.1 Implementation analysis

Populations	**1. All people living with insulin dependent diabetes (Type 1 & 2)**	**2. People living with Type 1 diabetes**	**3. People living with insulin dependent diabetes (Type 1 & 2) where there is a clinical need**
General considerations	• No clinical research evidence to support • Does not align with current eligibility criteria for insulin pumps & glucose test strips • Aligns with some clinician's experience & views • Aligns with some experience & patient views • Would be most costly option	• No clinical research evidence to support • Does not align with current eligibility criteria for insulin pumps & glucose test strips • Does not align with patient views & experience • Does not align with clinician views & experience	• No clinical research evidence to support • Aligns with current eligibility criteria for insulin pumps & glucose test strips • Aligns most closely with most clinician views • Aligns most closely with most patient views
Implementation considerations			
1. Support varies by patient income	• Can align with current PharmaCare deductibles, which is aligned with the current test strip funding policy • Not aligned with current pump funding policy, which provides 100% funding for one type of pump (i.e., it doesn't have any deductible) • Aligns with many healthcare professionals and patients experience and views (i.e., that people who have no extended health insurance and those with limited incomes, have no access to flash or continuous glucose monitors, and that these same people may benefit the most)		
2. Support varies by patient's blood glucose control	• Aligns with current BC PharmaCare pump policy • Aligns with policies in some other jurisdictions (e.g., US Medicare; Australia) • Aligns with some healthcare professionals' experiences and views • Not aligned with many patient experience and views • May appear to penalize patients who work hard to achieve good control		
3. Access is limited to one specific technology	• Aligns with current pump policy, which 100% funds one technology (the Omnipod pump) • There is potential to negotiate for a lower price • May pose a challenge given the potentially rapid changes in technology, and the recent introduction of the closed loop system • Not aligned with many healthcare professionals and patients experience and views • Limits patient choice		
4. Access is limited to people that need extra help	• Does not align with the current pump or testing strip policies • Somewhat aligned with healthcare professional and patient experience & views, in that they believe people who need extra help should have access; however, also feel that many people living with diabetes should also have access		

16.4 Conclusion

Drawing on all the evidence compiled in this report, a number of implementation options were developed for consideration. Three general populations of people living with diabetes were outlined identified for which public funding for flash and/or continuous glucose monitors could be considered. These are: 1) all people living with insulin dependent diabetes, both Type 1 and 2; 2) people living with Type 1 diabetes and 3) people living with Type 1 or 2 diabetes where there is a clinical need. Of these, the population that is most closely aligned with the evidence in this report, and with current BC PharmaCare policy is the third group.

Four implementation considerations were identified that could be applied across all three of these population, as follows:

1. Support varies by patient income
2. Support varies by patient's blood glucose control
3. Access is limited to one specific technology
4. Access is limited to people that need extra help

17 Budget Impact Analysis

Summary

- This budget impact analysis considers four funding scenarios for the management of insulin dependent diabetes in British Columbia. Costs are predicted over a three-year time horizon.
- [redacted]
- In scenario one funding is based on the patient's family income, like the Fair PharmaCare program. Costs to the province are predicted to range from $266 million over three years if income-based funding is provided to all patients with insulin dependent diabetes, to $1.1 million over three years if funding is provided to patients with significant difficulty managing their own diabetes.
- In scenario two, funding is provided to patients with glycated hemoglobin (HbA1c) greater than or equal to 7.0%. Costs to the province range from $397 million over three years if funding is provided to all patients with insulin dependent diabetes and HbA1c ≥ 7.0%, to $1.7 million depending on the population funded.
- In scenario three, only one technology is funded by the province. If all patients with diabetes are eligible and all patients with diabetes select the most expensive technology considered, costs to the province could be as high as $15.7 billion.
- In scenario four, funding is limited to patients with limited functional capacity. Over three years, the predicted budget impact to the province is $15.6 million.

17.1 Purpose

To predict the budget impact of various implementation scenarios for continuous glucose monitors, flash glucose monitors, and hybrid insulin delivery systems for the management of insulin-dependent diabetes.

17.2 Methods

17.2.1 Overview

Populations of interest were: all patients with insulin dependent diabetes, patients living with type 1 diabetes, and all patients determined to have significant clinical need (based on those within the current insulin pump programme). Technologies considered were self-monitoring of blood glucose (SMBG), continuous glucose monitors (CGM), continuous glucose monitors with continuous subcutaneous insulin infusion (CGM, CSII), flash glucometers, and closed loop hybrid insulin delivery systems. Costs are predicted over a three-year time horizon – with year 1

corresponding to 2020, year 2 to 2021, and year 3 to 2022. Costs to both the British Columbia Ministry of Health and patients are considered in each scenario. Costs considered include monitoring of blood glucose, and management with insulin. Oral anti-hyperglycemic agents and other therapies are not considered in this analysis. [redacted]

[redacted]

HbA1c has been connected to long-term diabetes complications, and has been identified as an independent risk factor for coronary artery disease and stroke in patients with and without diabetes[73]. Many published economic models for patients with diabetes rely on this connection between HbA1c and the long-term risk of complications. In the systematic review and network meta-analysis conducted in this HTA, no evidence of a difference in terms of HbA1c, and no evidence of a difference in terms of number of hypoglycemic events requiring assistance was identified. Therefore, cost considerations that may be associated with changes in HbA1c or severe hypoglycemic events avoided are not considered.

17.2.2 Eligible Population

According to the British Columbia Ministry of Health, there were approximately 445,436 patients living with diabetes in the province in 2016/2017[260]; of which approximately 100,000 require the injection of insulin to manage blood glucose[261]. This is similar to the prevalence of insulin use reported in a retrospective cohort study conducted in the United Kingdom, suggesting that the proportion of patients with T2D requiring insulin is slightly greater than 20%[262]. Between 2016 and 2018, the annual population growth rate in Canada was approximately 1.3%[263]. It was assumed that the prevalence of diabetes mellitus in British Columbia was consistent from 2016/2017 forward, and the same population growth rate was applied to the number of patients with diabetes requiring insulin to manage blood glucose.

Populations considered in this analysis were: all patients with insulin-dependent diabetes, patients living with type 1 diabetes, and all patients determined to have significant difficulty controlling their diabetes. Identification of type 1 versus type 2 diabetes in administrative data requires admission to hospital, and therefore the sum of estimates for the population of type 1 diabetes and type 2 diabetes is much smaller than the size of the population determined to have diabetes. In 2016/2017, there were 3,180 adults with diabetes and hospital diagnosis of type 1; and 53,854 adults with diabetes and hospital diagnosis of type 2[264]. Relative sizes of these populations were multiplied by the total population with diabetes to estimate the number of patients by type of diabetes. The number of patients with diabetes determined to have significant difficulty controlling their diabetes is approximated with the number of patients with PharmaCare coverage for insulin pumps. To be eligible for funding for an insulin pump, it is required that the patient has frequent unpredictable hypoglycemic events, frequent unpredictable diabetic ketoacidosis episodes, or unpredictable swings in glucose[265] – any of which would suggest difficulty controlling blood sugar. Differences in average annual cost of insulin between children/youths (age 1-18) and adults (age 18+) were less than $100.00 per patient[264]. The number of blood glucose tests per day are also unlikely to vary significantly by age. Therefore, no distinction was made between children/youths and adults with each type of diabetes. Predicted numbers of patients with diabetes falling into each population category considered are below in Table 17.1.

The provincial funding specific to each scenario was applied to each population separately. The size of the patient population with diabetes is consistent between scenarios. The specific number of patients covered by the province varies depending on the population specified. Costs to the province and to the patients (either out of pocket or by private insurance) with diabetes are presented separately for each scenario and population. Throughout this analysis, patient populations are rounded to the nearest whole number, which introduces error when used in further calculations. Relative to the budget impacts predicted, this error is small.

Table 17.1 Number of eligible patients in each population considered in this budget impact analysis

	All Patients with Insulin-Dependent Diabetes (n)	**Patients with Type 1 Diabetes (n)**	**Patients with Significant Clinical Need (n)**
Eligible Population in 2017	100,000	24,836	424
Predicted Population in 2018	101,300	25,158	429
Predicted Population in 2019	102,616	25,485	434
Predicted Population in 2020 (Year 1)	103,950	25,816	439
Predicted Population in 2021 (Year 2)	105,301	26,151	444
Predicted Population in 2022 (Year 3)	106,669	26,490	449

17.2.3 Costs of Technologies

17.2.3.1 Self-Monitoring of Blood Glucose

Technologies considered were SMBG, CGM, CGM+CSII, flash, and closed loop systems. Within SMBG, costs of the monitor, testing strips, lancets, and glucometer battery were considered. The mean annual cost of insulin-related prescriptions for all patients with diabetes in British Columbia, excluding those patients on insulin pumps, was $927.57. This cost (and all others where appropriate) was converted to January 2019 Canadian dollars with purchasing power parity[266] and the consumer price index for all goods[267]. Significant variety exists in the costs for glucometers and testing strips. Some examples of SMBG costs are presented below in Table 17.2. Given that SMBG monitors are provided with purchases of 100 testing strips[261], the cost used for the monitor in the base case analysis was zero; [redacted] It was assumed that the monitor would last for one year, and each battery would last for 1,000 tests (with the cost of the battery at $2.50[268]). The cost per lancet used was $0.08[269], and the cost per testing strip used in the base case analysis was $0.80 on the basis of

expert clinician opinion[261]. Assuming four glucose tests are conducted per day, the annual cost of testing strips is $1,168.00 and the annual cost of lancets is $116.80.

Table 17.2. Costs for glucometers and testing strips used in SMBG.[270]

Device	Type	Cost	Testing Strip Cost
OneTouch Ultra2	SMBG	$53.49	$1.22/strip
Abbott Freestyle Precision Neo	SMBG	$55.99	$1.32/strip
TRUEtrack Starter Kit	SMBG	$17.79	$0.60/strip
OneTouch UltraMini	SMBG	$50.99	$1.22/strip
Abbott FreeStyle Lite	SMBG	$61.99	$1.32/strip
OneTouch Verio	SMBG	$39.99	$1.21/strip
OneTouch VerioFlex	SMBG	$34.99	$1.21/strip
Ascensia Contour Next One	SMBG	$60.99	$1.26/strip
Ascensia Contour Next EZ	SMBG	$60.99	$1.26/strip

17.2.3.2 Continuous Glucose Monitors

CGMs require transmitters, receivers, and sensors. For this analysis, it was assumed that all patients had a smartphone capable of functioning as the receiver [redacted] In this analysis, the cost for the CGM transmitter used was $606.06, which reflects the cost of the Medtronic Guardian 3[271]. The costs from an Australian subscription plan were used as the Australian plan is considered an exemplar programme. The cost of the Medtronic Guardian 3 Transmitter was available in 2019 Australian dollars, and the latest data for purchasing power parities was from 2017[266]. The Medtronic Guardian 3 transmitter has a rechargeable battery, therefore no additional battery costs were considered for this glucometer[272]. The expected transmitter service life is one year[272]. Alternate costs for CGM transmitters and sensors are included below in Table 17.3. For the Medtronic Guardian 3, it was assumed that calibration with SMBG was required twice per day[273]. Costs of the SMBG monitor, batteries, lancets, and testing strips for these calibrations were also included.

Table 17.3. Costs for CGM transmitters and sensors.

Device	Type	Cost	Sensor Cost
Dexcom G4 Transmitter (has warranty of six months)	CGM	$661.79[269]	$102.99[269] (lasts 10 days)[269]
Dexcom G5 Transmitter (shuts off at three months, and has warranty of three months)	CGM	$333.99[269]	$102.99[269] (lasts 10 days)[269]
Medtronic Guardian 3 Transmitter	CGM	$606.06[271]	$43.35[271] (lasts 7 days)[274]

17.2.3.3 Continuous Glucose Monitor with Continuous Subcutaneous Insulin Infusion

In addition to the costs of CGM described above, the CGM in combination with insulin pump was included. Annual costs of the insulin pump to the ministry of health in 2016/17 were inflated to January 2019 values, and were $7,657.22[264]. This cost was included in the expected annual cost of the CGM with CSII.

17.2.3.4 Flash Glucometer

The only flash glucose monitor currently available is the FreeStyle Libre, at a cost of $49.00.[275] The expected lifetime for this device is three years[276]. With capital costs of 1.5% and device lifetime of 3 years, the equivalent annual cost is $16.83. Sensors for this device cost $89.00, and are expected to last 14 days[275]. This sensor requires no calibration, therefore no costs for testing strips or lancets was included[277]. The FreeStyle Libre uses a rechargeable battery, therefore no costs for additional batteries were included[276]. The same annual cost for insulin as SMBG and CGM was used with this technology.

17.2.3.5 Closed Loop Hybrid Insulin Delivery System

The Canadian Agency for Drugs and Technologies in Health estimates that the annual operating cost of a closed-loop system is between $8,500 and $9,500[278]. Little evidence exists to inform a cost estimate for the closed loop technology and no details regarding how this cost was arrived at were provided[278]. However, this cost was used in the budget analysis herein.

17.2.4 Market Share

No data were available to inform estimates of market share. Thus, the same estimates of market share were used for all populations not eligible and eligible for funding, and in all scenarios analyzed unless otherwise specified (Table 17.4). It was assumed that most patients would use self-monitoring of blood glucose to manage their diabetes. Among the other technologies, flash

would be the most frequently used, and increase annually by 4%. Glucose monitoring with flash technology compared to CGMs is similar, but available at a much lower cost. In 2016/17, there were a total of 424 patients receiving insulin pumps funded by PharmaCare[264]. It was assumed that this proportion would increase by 0.5% to year 1, and annually by 0.5%. Similar proportions and increases were assumed for the closed loop.

Table 17.4. Estimated market share by technology used in all scenarios, unless otherwise specified.

	SMBG	CGM	CGM, CSII	Flash	Closed Loop
Year 1	88.999%	2.000%	0.501%	8.000%	0.500%
Year 2	82.999%	3.000%	1.001%	12.000%	1.000%
Year 3	76.999%	4.000%	1.501%	16.000%	1.500%

17.2.5 Summary of Inputs

All budget impact analysis inputs described above are summarized below (Table 17.5, Table 17.6.

Table 17.5. Budget impact analysis default inputs.

Description	Value
SMBG: monitor cost	$0
SMBG: number of tests per day	4
SMBG: test strip cost	$0.80
SMBG: lancet cost	$0.08
SMBG: cr2032 battery cost	$2.50
SMBG: battery lifetime	1,000 tests
CGM: daily SMBG calibrations	2
CGM: transmitter cost	$606.06
CGM: receiver cost	$0.00
CGM: sensor cost	$43.35
CGM: sensor lifetime	7 days
Flash: monitor cost	$49.00
Flash: sensor cost	$89.00
Flash: sensor lifetime	14 days
Number of patients with insulin dependent diabetes in British Columbia in 2016/17	100,000
Population Growth Rate	1.30%
Insulin pump: annual cost per patient	$7,657.22
Insulin: annual cost per patient	$927.57

Table 17.6. Annual costs per patient, by technology.

Costs Per patient year	SMBG	CGM	CGM, CSII	Flash	Closed Loop
Monitor(s) and Batteries	$3.65	$607.89	$607.89	$16.83	$9,000.00
Testing Strips	$1,168.00	$584.00	$584.00	NA	
Lancets	$116.80	$58.40	$58.40	NA	
Sensors	NA	$2,260.39	$2,260.39	$2,320.36	
Insulin	$927.57	$927.57	$7,657.22	$927.57	
Total Cost Per Patient Year	$2,216.02	$4,438.25	$11,167.90	$3,264.75	$9,000.00

17.2.5.1 Scenario One: Support varies by patient income

In this scenario, it is assumed that diabetic supplies are covered by a program like Fair PharmaCare, with family deductible and family maximum specified by family income. On the Fair PharmaCare program, for families with net income between $28,750 and $30,000, the family deductible is $0.00[279]. Once the family deductible has been met, this program covers 70% of eligible costs until the family maximum of $800.00 is met[279]. Gross income stratified by amount is available for individuals only on the Statistics Canada website, which does not match the way that Fair PharmaCare deductibles and maximum are calculated[280]. Therefore, an alternate data source and simplifying assumptions were required.

In 2014, the median after-tax family income in British Columbia was $48,140[281]. One metric for understanding poverty is the low income measure (LIM), which is calculated as the proportion of households living on less than half the median after-tax income, adjusted for family size. In 2014, the LIM in British Columbia was 13.4%[282]. Given the small difference between the low income measure cut-off for income of $24,070.00 ($25,684.92 in 2019 CAD) and the cut-off for the family deductible at $30,000, it was assumed that 13.4% of individuals with diabetes fell into this category. The proportion of individuals with diabetes categorized as low-income was assumed to be the same each year, and to have income of $30,000. For all individuals not classified as low income, it was assumed that their family income was equal to the median after-tax family income.

In 2016, the median after-tax family income (which is the most recent data available from Statistics Canada) was $50,430.00[281] – $52,472.34 in 2019 CAD. With this annual income, the family deductible on the Fair PharmaCare program is $1,600.00, and the family maximum is

$2,150.00.[279]

17.2.5.2 Scenario Two: Support varies by glucose control.

In the primary care setting, it was estimated that 49% of patients with diabetes in Canada had glycated hemoglobin (HbA1c) greater than or equal to 7.0%, with mean HbA1c of 7.3%[283]. This estimate was generated from a sample of 2,473 eligible patients with type 2 diabetes. Given the overwhelming number of patients with type 2 diabetes relative to type 1 diabetes prevalent in British Columbia, this estimate is applicable this scenario. British Columbia specific diabetes guidelines suggest that HbA1c greater than or equal to 6.5% is indicative of the presence of diabetes[284]. These guidelines suggest that HbA1c targets between 7.1 and 8.5 should be considered in patients with limited life expectancy, high functional dependency, extensive coronary artery disease, multiple co-morbidities, history of recurrent severe hypoglycemia, hypoglycemia unawareness, or longstanding diabetes for whom it is difficult to achieve HbA1c of less than or equal to 7.0% despite effective doses of anti-hyperglycemic agents (including insulin)[284]. Interviews previously described in this HTA suggest that these patients are the most likely to benefit. In this scenario, it is assumed that for the predicted 49% of patients with mean HbA1c of greater than or equal to 7.0%, all interventions are funded. For the remaining 51% that are meeting the treatment target of less than 7.0%, no interventions are funded. Given that no differences in mean HbA1c were found in the network meta-analysis, it is reasonable to assume that market shares do not change in this scenario.

17.2.5.3 Scenario Three: Support is limited to one specific technology

In this scenario, the most expensive intervention, CGM+CSII is the only intervention funded. It was assumed that the market share for this technology in patients eligible for funding would be the same in year one as the default values. In years two and three, this market share would increase to five and ten percent, respectively. This is intended to reflect the change in patient's decision making for these technologies depending on funding provided by the province.

[redacted]

17.2.5.4 Scenario Four: Support is limited to people with limited functional capacity

In this scenario, it was assumed that funding would be provided only to those patients with limited functional capacity. In this scenario, only one population size was considered. To approximate the population with limited functional abilities, the number of residential care facility beds in British Columbia was used as the denominator. It was assumed that the province wide prevalence of insulin dependent diabetes, or 100,000 out of 4.92 million in 2016/17[285], is the same in long-term care. This results in a prevalence of 0.2%. In 2016/17, there were 27,142 publicly subsidized beds in residential care facilities[286]. Assuming the prevalence of diabetes is consistent in long-term care in British Columbia, there would be approximately 551 patients with diabetes eligible for funding in 2016/17 in this scenario (Table 17.7). It is assumed that all patients would receive the closed-loop to minimize the frequency of healthcare provider intervention required for injection of insulin or blood-glucose checks. The market share for all other technologies for the province is zero in this scenario. The population growth rate of 1.3% was also applied in this scenario.

Table 17.7. Number of eligible patients predicted each year

Population	All Patients with Diabetes (number)
Eligible Population in 2017	551
Predicted Population in 2018	558
Predicted Population in 2019	565
Predicted Population in 2020 (Year 1)	572
Predicted Population in 2021 (Year 2)	579
Predicted Population in 2022 (Year 3)	586

17.3 Results

17.3.1 Scenario One: Support varies by patient income.

If 13.4% of the population is classified as low income with annual income of $30,000, and all technologies are covered under a program like Fair PharmaCare, the budget impact for the province over three years for all patients with diabetes is predicted to be $266,973,481. Over the same time period, it is predicted that patients will spend a total of $544,073,510 (Table 17.8).

Table 17.8. Scenario One: Patient and province costs by technology for **all patients with insulin dependent diabetes**.

	Description of Costs (n)	SMBG ($)	CGM ($)	CGM, CSII ($)	Flash ($)	Closed Loop ($)	Total Cost ($)	Percent of Total Costs
Year 1	Patient Costs (n=103,950)	$151,236,687	$4,635,854	$1,747,250	$16,011,265	$1,743,500	$175,374,556	70%
	Province Costs (n=103,950)	$53,778,403	$4,591,263	$4,071,225	$11,138,420	$2,936,500	$76,515,811	30%
						Total	**$251,890,368**	
Year 2	Patient Costs (n=105,301)	$142,872,155	$7,045,634	$3,536,550	$24,328,417	$3,532,800	$181,315,556	67%
	Province Costs (n=105,301)	$50,803,561	$6,974,791	$8,234,414	$16,925,000	$5,944,200	$88,881,967	33%
						Total	**$270,197,523**	
Year 3	Patient Costs (n=106,669)	$134,266,536	$9,515,798	$5,373,250	$32,859,114	$5,368,700	$187,383,398	65%
	Province Costs (n=106,669)	$47,744,051	$9,422,206	$12,517,722	$22,860,423	$9,031,300	$101,575,702	35%
						Total	**$288,959,101**	

If only patients with type 1 diabetes are funded under a program like Fair PharmaCare, funding based on income level would be provided for approximately 25% of the total number of patients living with insulin-dependent diabetes in the province. The predicted budget impact for the province over three years is $66,285,406.; the predicted budget impact for patients is $744,707,735. (Table 17.9).

Table 17.9. Scenario One: Patient and province costs by technology, if funding is provided for patients with type 1 diabetes only.

	Description of Costs (n)	SMBG ($)	CGM ($)	CGM, CSII ($)	Flash ($)	Closed Loop ($)	Total Cost ($)	Percent of Total Costs
Year 1	Patient Costs (n=103,950)	$191,656,821	$8,083,552	$4,800,248	$24,385,443	$3,943,600	$232,869,665	92%
	Province Costs (n=25,816)	$13,356,053	$1,139,127	$1,007,059	$2,767,507	$727,400	$18,997,145	8%
						Total	**$251,866,810**	
Year 2	Patient Costs (n=105,301)	$181,061,472	$12,284,952	$9,724,225	$37,051,663	$7,994,500	$248,116,811	92%
	Province Costs (n=26,151)	$12,616,460	$1,731,035	$2,046,739	$4,205,020	$1,473,500	$22,072,754	8%
						Total	**$270,189,566**	
Year 3	Patient Costs (n=26,490)	$170,154,155	$16,597,514	$14,767,381	$50,042,808	$12,159,400	$263,721,258	91%
	Province Costs (n=106,669)	$11,856,432	$2,340,489	$3,101,255	$5,676,730	$2,240,600	$25,215,507	9%
						Total	**$288,936,765**	

For the patients with significant difficulty managing their diabetes, approximated with the insulin pump population, funding would be provided for approximately 0.4% of the total population with insulin-dependent diabetes in this scenario. The predicted budget impact for the province over three years is $1,134,174; and the predicted budget impact for patients is $809,919,601 (Table 17.10).

Table 17.10. Scenario One: Patient and province costs by technology for patients with significant difficulty managing their diabetes.

	Description of Costs (n)	SMBG ($)	CGM ($)	CGM, CSII ($)	Flash ($)	Closed Loop ($)	Total Cost ($)	Percent of Total Costs
Year 1	Patient Costs (n=103,850)	$204,786,461	$9,207,585	$5,792,471	$27,102,402	$4,660,500	$251,549,418	100%
	Province Costs (n=439)	$226,413	$19,532	$14,836	$47,284	$10,500	$318,565	0%
						Total	**$251,867,984**	
Year 2	Patient Costs (n=105,301)	$193,462,149	$13,993,745	$11,742,093	$41,182,559	$9,456,800	$269,837,347	100%
	Province Costs (n=444)	$213,567	$31,118	$40,039	$70,858	$29,200	$384,782	0%
						Total	**$270,222,129**	
Year 3	Patient Costs (n=106,669)	$181,810,298	$18,894,500	$17,836,097	$55,622,640	$14,369,300	$288,532,835	100%
	Province Costs (n=449)	$200,289	$39,065	$54,875	$96,898	$39,700	$430,827	0%
						Total	**$288,963,662**	

This scenario assumes that any amount paid by patients towards a deductible or family maximum would go towards an included technology.

17.3.2 Scenario Two: Support varies by patient's blood glucose control

If all patients with diabetes and HbA1c of greater than or equal to 7.0% are funded by the province, the predicted budget impact for the province over three years is $397,411,570; and the predicted budget impact for patients is $413,611,836 (Table 17.11). If market shares for both funded and non-funded patients are the same, the proportion of all money spent on diabetic technologies matches the proportion of patients with HbA1c of greater than or equal to 7.0%.

Table 17.11. Scenario Two: Patient and province costs by technology for all patients with insulin dependent diabetes.

	Description of Costs (n)	SMBG ($)	CGM ($)	CGM, CSII ($)	Flash ($)	Closed Loop ($)	Total Cost ($)	Percent of Total Costs
Year 1	Patient Costs (n=53,015)	$104,558,472	$4,708,981	$2,959,493	$13,845,817	$2,385,000	$128,457,763	51%
	Province Costs (n=50,936)	$100,456,619	$4,522,575	$2,847,814	$13,303,868	$2,295,000	$123,425,875	49%
						Total	**$251,883,638**	
Year 2	Patient Costs (n=53,704)	$98,776,875	$7,150,017	$5,997,161	$21,041,332	$4,833,000	$137,798,386	51%
	Province Costs (n=51,597)	$94,901,057	$6,870,408	$5,762,635	$20,215,350	$4,644,000	$132,393,449	49%
						Total	**$270,191,836**	
Year 3	Patient Costs (n=54,401)	$92,824,646	$9,657,627	$9,113,005	$28,416,409	$7,344,000	$147,355,687	51%
	Province Costs (n=52,268)	$89,185,941	$9,280,376	$8,766,800	$27,303,129	$7,056,000	$141,592,246	49%
						Total	**$288,947,933**	

Among the patients with type 1 diabetes only and HbA1c of greater than or equal to 7.0% are funded by the province, the predicted budget impact for the province over three years is $98,685,881; and the predicted budget impact for patients is $712,345,553 (Table 17.12).

Table 17.12. Scenario Two: Patient and province costs by technology for patients with type 1 diabetes.

	Description of Costs (n)	SMBG ($)	CGM ($)	CGM, CSII ($)	Flash ($)	Closed Loop ($)	Total Cost ($)	Percent of Total Costs
Year 1	Patient Costs (n=91,300)	$180,067,137	$8,104,241	$5,103,729	$23,845,755	$4,113,000	$221,233,862	88%
	Province Costs (n=12,650)	$24,947,953	$1,122,877	$703,578	$3,303,930	$567,000	$,30,645,337	12%
						Total	**$251,879,200**	
Year 2	Patient Costs (n=92,487)	$170,108,343	$12,316,138	$10,341,473	$36,232,228	$8,325,000	$237,323,182	88%
	Province Costs (n=12,814)	$23,567,373	$1,704,287	$1,429,491	$5,021,190	$1,152,000	$32,874,341	12%
						Total	**$270,197,523**	
Year 3	Patient Costs (n=93,689)	$159,863,683	$16,630,115	$15,702,064	$48,938,646	$12,654,000	$253,788,508	88%
	Province Costs (n=12,980)	$22,149,120	$2,303,451	$2,177,740	$6,780,892	$1,755,000	$35,166,202	12%
						Total	**$288,954,710**	

For the patients with significant difficulty managing their diabetes, approximated with the insulin pump population, the predicted budget impact for the province over three years is $1,663,290; and the predicted budget impact for patients is $809,353,539 (Table 17.13).

Table 17.13. Scenario Two: Patient and province costs by technology for patients with significant difficulty managing their diabetes.

	Description of Costs (n)	SMBG ($)	CGM ($)	CGM, CSII ($)	Flash ($)	Closed Loop ($)	Total Cost ($)	Percent of Total Costs
Year 1	Patient Costs (n=103,735)	$204,589,614	$9,209,364	$5,807,307	$27,090,920	$4,671,000	$251,368,205	100%
	Province Costs (n=215)	$423,260	$17,753	$11,168	$55,501	$9,000	$516,682	0%
						Total	**$251,884,887**	
Year 2	Patient Costs (n=105,083)	$193,276,832	$13,993,795	$5,372,419	$41,168,534	$9,459,000	$269,368,205	100%
	Province Costs (n=218)	$401,100	$31,068	$22,336	$84,884	$18,000	$557,387	0%
						Total	**$270,193,009**	
Year 3	Patient Costs (n=106,449)	$181,636,079	$18,898,059	$17,846,301	$55,605,272	$14,364,000	$288,349,711	100%
	Province Costs (n=220)	$374,507	$39,944	$33,504	$114,266	$27,000	$589,222	0%
						Total	**$288,938,933**	

17.3.3 Scenario Three: Support is limited to one specific technology

If the province funds the CGM+CSII only and no other technologies for all patients with diabetes, the predicted budget impact over three years for the province is $183,745,423. The predicted budget impact for patients over three years would be $746,164,698 (Table 17.14). This scenario is predicted to be the most representative of the status quo of the scenarios and populations considered in this budget impact analysis. If the market share for CGM, CSII is increased to 100%, this represents the maximum financial exposure for the province, and the predicted budget impact would be $3,528,162,291 over three years.

Table 17.14. Scenario Three: Patient and province costs by technology for all patients with insulin dependent diabetes.

	Description of Costs (n)	SMBG ($)	CGM ($)	CGM, CSII ($)	Flash ($)	Closed Loop ($)	Total Cost ($)	Percent of Total Costs
Year 1	Patient Costs (n=103,429)	$205,015,090	$9,227,117	$0	$27,149,685	$4,680,000	$246,071,893	98%
	Province Costs (n=521)	$0	$0	$5,818,475	$0	$0	$5,818,475	2%
						Total	**$251,890,368**	
Year 2	Patient Costs (n=100,036)	$184,346,272	$14,020,425	$0	$41,253,418	$9,477,000	$249,097,114	81%
	Province Costs (n=5,265)	$0	$0	$58,798,982	$0	$0	$58,798,982	19%
						Total	**$307,896,097**	
Year 3	Patient Costs (n=96,002)	$161,920,149	$18,938,004	$0	$55,719,538	$14,400,000	$250,977,691	68%
	Province Costs (n=10,667)	$0	$0	$119,127,966	$0	$0	$119,127,966	32%
						Total	**$370,105,657**	

If only patients with type 1 diabetes are eligible for funding, the predicted budget impact over three years for the province in this scenario is $45,632,031. The predicted budget impact over three years for patients would be $794,920,350 (Table 17.15).

Table 17.15. Scenario Three: Patient and province costs by technology for patients with type 1 diabetes.

	Description of Costs (n)	SMBG ($)	CGM ($)	CGM, CSII ($)	Flash ($)	Closed Loop ($)	Total Cost ($)	Percent of Total Costs
Year 1	Patient Costs (n=103,821)	$205,015,090	$9,227,117	$4,377,816	$27,149,685	$4,680,000	$250,449,709	99%
	Province Costs (n=129)	$0	$0	$1,440,659	$0	$0	$1,440,659	1%
						Total	**$251,890,368**	
Year 2	Patient Costs (n=103,993)	$191,359,975	$14,020,425	$8,844,975	$41,253,418	$9,477,000	$264,955,793	95%
	Province Costs (n=1,308)	$0	$0	$14,607,610	$0	$0	$14,607,610	5%
						Total	**$279,563,403**	
Year 3	Patient Costs (n=104,020)	$177,022,326	$18,938,004	$13,434,981	$55,719,538	$14,400,000	$279,514,848	90%
	Province Costs (n=2,649)	$0	$0	$29,583,761	$0	$0	$29,583,761	10%
						Total	**$309,098,610**	

Limiting the patient population to only patients with significant difficulty managing their diabetes, the predicted budget impact over three years for the province in this scenario is $770,585. The predicted budget impact for patients is $810,768,759 (Table 17.16).

Table 17.16. Scenario Three: Patient and province costs by technology for patients with significant difficulty managing their diabetes.

	Description of Costs (n)	SMBG ($)	CGM ($)	CGM, CSII ($)	Flash ($)	Closed Loop ($)	Total Cost ($)	Percent of Total Costs
Year 1	Patient Costs (n=463,031)	$205,015,090	$9,227,117	$5,796,139	$27,149,685	$4,680,000	$251,868,032	100%
	Province Costs (n=2)	$0	$0	$22,336	$0	$0	$22,336	0%
						Total	**$251,890,368**	
Year 2	Patient Costs (n=469,030)	$193,638,044	$14,020,425	$11,726,293	$41,253,418	$9,477,000	$270,115,179	100%
	Province Costs (n=22)	$0	$0	$245,694	$0	$0	$245,694	0%
						Total	**$270,360,873**	
Year 3	Patient Costs (n=475,104)	$181,926,378	$18,938,004	$17,801,629	$55,719,538	$14,400,000	$288,785,549	100%
	Province Costs (n=45)	$0	$0	$502,555	$0	$0	$502,555	0%
						Total	**$289,288,104**	

17.3.4 Scenario Four: Support is limited to people with limited functional capacity

If funding is limited to patients living with diabetes and limited functional capacity, the predicted budget impact over three years to the province is $15,633,000. The predicted budget impact over three years to patients is $806,566,394 (Table 17.17).

Table 17.17. Scenario Four: Patient and province costs by technology for patients with limited functional capacity.

	Description of Costs (n)	SMBG ($)	CGM ($)	CGM, CSII ($)	Flash ($)	Closed Loop ($)	Total Cost ($)	Percent of Total Costs
Year 1	Patient Costs (n=103,378)	$203,884,920	$9,178,297	$5,784,971	$26,999,507	$4,653,000	$250,500,694	98%
	Province Costs (n=572)	$0	$0	$0	$0	$5,148,000	$5,148,000	2%
						Total	**$255,648,694**	
Year 2	Patient Costs (n=104,722)	$192,612,026	$13,944,975	$11,703,957	$41,028,150	$9,423,000	$268,712,108	98%
	Province Costs (n=579)	$0	$0	$0	$0	$5,211,000	$5,211,000	2%
						Total	**$273,923,108**	
Year 3	Patient Costs (n=106,083)	$181,011,162	$18,831,486	$17,779,293	$55,412,651	$14,319,000	$287,353,592	98%
	Province Costs (n=586)	$0	$0	$0	$0	$5,274,000	$5,274,000	2%
						Total	**$292,627,592**	

Costs for the first year in all four scenarios considered and populations eligible for funding is presented below in Table 17.18.

Table 17.18. First year costs predicted for patients and province, by population, scenario, and technology.

Patient Population	Scenario	Perspective	SMBG Cost ($)	CGM Cost ($)	CGM, CSII Cost ($)	Flash Cost ($)	Closed Loop Cost ($)	Total Cost ($)	Percent of Total Cost
All patients with insulin dependent diabetes	1	Patient (n=103,950)	$151,236,687	$4,635,854	$1,747,250	$16,011,265	$1,743,500	$175,374,556	70%
		Province (n=103,950)	$53,778,403	$4,591,263	$4,071,225	$11,138,420	$2,936,500	$76,515,811	30%
							Total	**$251,890,368**	
	2	Patient (n=53,015)	$104,558,472	$4,708,981	$2,959,493	$13,845,817	$2,385,000	$128,457,763	51%
		Province (n=50,936)	$100,456,619	$4,522,575	$2,847,814	$13,303,868	$2,295,000	$123,425,875	49%
							Total	**$251,883,638**	
	3	Patient (n=103,429)	$205,015,090	$9,227,117	$0	$27,149,685	$4,680,000	$246,071,893	98%
		Province (n=521)	$0	$0	$5,818,475	$0	$0	$5,818,475	2%
							Total	**$251,890,368**	
Patients with type 1 diabetes	1	Patient (n=103,950)	$191,656,821	$8,083,552	$4,800,248	$24,385,443	$3,943,600	$232,869,665	92%
		Province (n=25,816)	$13,356,053	$1,139,127	$1,007,059	$2,767,507	$727,400	$18,997,145	8%
							Total	**$251,866,810**	
	2	Patient (n=91,300)	$180,067,137	$8,104,241	$5,103,729	$23,845,755	$4,113,000	$221,233,862	88%
		Province (n=12,650)	$24,947,953	$1,122,877	$703,578	$3,303,930	$567,000	$,30,645,337	12%
							Total	**$251,879,200**	
	3	Patient (n=103,821)	$205,015,090	$9,227,117	$4,377,816	$27,149,685	$4,680,000	$250,449,709	99%
		Province (n=129)	$0	$0	$1,440,659	$0	$0	$1,440,659	1%
							Total	**$251,890,368**	
Patients with significant difficulty managing their diabetes	1	Patient (n=103,850)	$204,786,461	$9,207,585	$5,792,471	$27,102,402	$4,660,500	$251,549,418	100%
		Province (n=439)	$226,413	$19,532	$14,836	$47,284	$10,500	$318,565	0%
							Total	**$251,867,984**	
	2	Patient (n=103,735)	$204,589,614	$9,209,364	$5,807,307	$27,090,920	$4,671,000	$251,368,205	100%
		Province (n=215)	$423,260	$17,753	$11,168	$55,501	$9,000	$516,682	0%
							Total	**$251,884,887**	
	3	Patient (n=475,104)	$181,926,378	$18,938,004	$17,801,629	$55,719,538	$14,400,000	$288,785,549	100%
		Province (n=45)	$0	$0	$502,555	$0	$0	$502,555	0%
							Total	**$289,288,104**	
Patients with limited functional capacity	4	Patient (n=103,378)	$203,884,920	$9,178,297	$5,784,971	$26,999,507	$4,653,000	$250,500,694	98%
		Province (n=572)	$0	$0	$0	$0	$5,148,000	$5,148,000	2%
							Total	**$255,648,694**	

17.4 Conclusions

In scenario one, in which funding is provided through a program like Fair PharmaCare, costs are shared between patients and the province. Patients consistently pay more than the province does. With an income-based funding strategy, the province is providing diabetes management technologies for the patients least able to afford them independently. In the second strategy, in which funding is provided based on HbA1c, the same market shares as scenario one were used. Therefore, overall costs are the same as scenario one – differences are in which patients are funded by the province.

In the third scenario considered, in which the province funds CGM+CSII for all patients, patients with type 1 diabetes, or patients with significant difficulty managing their diabetes, overall costs are significantly higher than in other scenarios. CGM+CSII was the most expensive technology considered in this budget impact analysis; and this scenario was designed to represent the maximum financial exposure to the province. In this scenario, costs to the province ranged from $3.5 billion to less than $1 million. Costs to patients ranged from $0 to $4.4 billion – with differences in cost exposure reflecting differences in market share.

In the fourth scenario, funding by the province would only be provided to patients with limited functional capacity. In this scenario, it was assumed that the closed loop would have 100% of the market share for provincially funded technologies. This technology has the potential to limit required healthcare provider intervention for the monitoring of blood glucose and administration of insulin in this patient population.

In all four of the scenarios considered, the size of the population with diabetes significantly affects the cost. Cost outcomes were sensitive to the size of the predicted market share, and the costs associated with the technologies considered. Controlling costs will require limits placed on the eligible population, the costs of technologies considered, or the market share for each technology. All costs outcomes in this budget impact analysis are functions of these three variables. The three populations considered in this analysis represent one way to define the eligible population, and so limit costs to the province.

If the entire population of patients living with diabetes is considered for funding, not just the insulin dependent population, the predicted population in years 1, 2 and 3 are 463,033, 469,052, and 475,149, respectively. If all of these patients were to receive the most costly option,

CGM+CSII at an expected cost of $11,167.90 per year, the predicted budget impact over three years is $15.7 billion. Although unlikely to be observed, this represents the greatest expenditure possible for patients living with diabetes in BC for the included technologies.

Although the estimates of market share used in this analysis are reasonable estimates, little data exists to inform them. This is a major limitation. It is likely that SMBG is the most prevalent technology in use among patients with diabetes – with cost playing a major role in this choice. If technologies are not funded equally, or patient choice is not incorporated into the funding decision, it is likely that changes in market share will follow. This may introduce unintended incentives for patients to use technologies that reflect financial need rather than clinical need.

18 Conclusion

In an effort to validate time in range (TIR) as a clinically meaningful outcome for diabetes management, a systematic review of clinical outcomes associated with TIR was conducted (Chapter 7). Two studies were identified for inclusion. One study explored the association between TIR and internalizing and externalizing behaviours, and concluded that higher percent time spent in range was associated with lower levels of externalizing behaviour. The second study explored the association between TIR and the risk for developing diabetic retinopathy and microalbuminuria in children and adults (age 13-39 years old). This study found that lower percent TIR was associated with higher risk of developing retinopathy and microalbuminuria. Given the lack of evidence, TIR should not be considered a validated surrogate marker for diabetes-related complications until more robust body literature on this topic exists.

A second review was conducted to synthesize health technology assessments (HTAs) on glucose monitoring technologies, including CGMs, flash glucose monitors (FGMs), or sensor augmented pumps (SAP; continuous subcutaneous insulin infusion [CSII] + real-time-CGM [rt-CGM]) for people with insulin-dependent diabetes (Chapter 8). Ten HTAs were included for review. Seven HTAs examined CGMs (two of which also included SAPs and one included FGMs); the other three HTAs examined FGMs. In terms of clinical effectiveness, four HTAs favoured the use of CGM over SMBG; three determined that the evidence did not support the superiority of CGMs compared to SMBG; and three HTAs found that FGMs were superior to SMBG in some aspects and similar in others. Three HTAs identified literature on the cost-effectiveness of CGMs. Four HTAs conducted their own cost analyses of glucose monitoring technologies. In all HTAs that conducted cost analyses, glucose monitors were unlikely to be the cost-effective option for any of the included comparators. Only two HTAs provided specific recommendations regarding the use of glucose monitors; one noted that the evidence supported the recommendation for CGMs to be used by children and adolescents over the age of eight; another noted that rt-CGM should not be offered routinely to adults with T1D, only to select groups of patients.

Current guidelines and best practice recommendations on the use of glucose monitoring technologies were synthesized to determine if differences in recommendations and guidelines exist between Canada and elsewhere (Chapter 9). Ten relevant guidelines were identified for the

use of CGMs, SAPs, or FGMs (Canada, USA, UK, and Germany). The guidelines generally agreed that people at risk for severe hypoglycemia, and people not achieving their HbA1C goals may benefit the most from CGM and FGM technologies. With the exception of the Dexcom G6 CGM, non-adjunctive use of CGM is not recommended. Recommendations note that CGM should be used by patients willing to use the device more than 70% of the time. Children, especially those who cannot recognize or articulate symptoms of hypoglycemia, may benefit from CGMs. Individuals at low risk of severe hypoglycemia may benefit from FGMs.

A systematic review and a series of network meta-analyses were conducted on the clinical effectiveness of CGMs, FGMs, and hybrid insulin delivery systems for the management of insulin-dependent diabetes. Sixty-three studies of 70 sample populations were included in this review. The populations of interest were adults with T1D, children with T1D, adults with T2D that require insulin to manage their blood glucose, and pregnant women with T1D. Among the included studies, there was little overlap in the interventions described – resulting in sparse networks of evidence for network meta-analysis. Network meta-analysis was conducted on HbA1c, number of hypoglycemic events requiring assistance, and time-in-range (percent of time with blood glucose between 3.9-10.0mmol/L), in adults with T1D and children with T1D. No significant differences between interventions were identified for outcomes of HbA1c or number of hypoglycemic events requiring assistance. Although some significant differences between interventions in the outcome of time-in-range were identified in both adults and children with T1D, further study is required to connect this device evaluation metric to meaningful clinical outcomes. Other outcomes of interest were: number of diabetic ketoacidosis (DKA) events, DTSQ, HFS, and health-related quality of life. Few interventions resulted in any DKA events. Other outcomes were not reported with sufficient frequency for quantitative analysis, or meaningful comparisons. Little evidence was identified for T2D or T1D in a pregnant population, and no conclusions about efficacy could be drawn.

To synthesize the literature exploring the patient perspectives of glucose monitoring technologies, a systematic review was completed (Chapter 11). Patient perspectives offer valuable insight into how the technologies influence the experience of living with insulin-dependent diabetes. Patients found continuous monitoring to be an effective tool in managing

their glucose levels, and this message was remarkably consistent across patient groups, countries, and study designs. Additional findings included improvement in sleep, a greater freedom when making life decisions and an improved ability to make informed life decisions such as vacations and exercise. Negative findings were primarily with technical issues such as calibration and trusting the technology.

With some background information on what is currently known about glucose monitoring (HTA review; clinical effectiveness review), what is currently being offered (guidelines/best practice recommendations review), and the lived experience of glucose monitoring (patient perspectives review), an environmental scan was conducted to determine the level of financial support offered to people living with insulin-dependent diabetes across Canada and elsewhere. In Canada, all jurisdictions have programs in place to provide full or partial funding of insulin pumps to qualifying patients with type 1 diabetes. Coverage for health-related expenses other than insulin pumps and pump supplies (e.g., blood glucose test strips) is provided through provincial drug programs. CGMs are provided for children and youth in Yukon, and FGMs are recommended to be provided to select patients in Quebec and Ontario; these recommendations have not been translated into policy yet. In international jurisdictions, insulin pump programs exist in the UK, Australia, and New Zealand. CGMs are less readily available for funding in these jurisdictions. Safety of insulin pumps was also a consideration. In recent years, insulin infusion pumps have been considered one of the top ten medical devices associated with medical complications and death. To address this, Health Canada plans to allow medical professionals to apply to conduct investigations into medical devices as early as 2019.

Building on what is known about the patient experience living and managing insulin-dependent diabetes, interviews with health care professionals (Chapter 13) and patient focus groups (Chapter 14) were conducted. The perspectives of health care professionals and patients were largely consistent. The biggest barrier to CGMs was cost. Alternatively, patients reported that the strongest enabler of using a CGM was having extended benefits that would cover the cost of the device. Patients and clinicians found CGM devices to be relatively easy to use and integrated well into the patient's daily life, allowing for more control and better planning for daily activities (e.g., diet, exercise, and travel). Clinicians reported that CGMs lessened the frequency and

severity of hypoglycemic events, and would be most beneficial for patients who have severe problems with hypoglycemia or patients who require considerable support from others to manage their diabetes (e.g., children, persons with disabilities, or people residing in assisted living).

Drawing on all the evidence in this report, several implementation options were developed for consideration (Chapter 16). Populations for which public funding could be provided are: 1) All people living with diabetes (T1D and T2D); 2) People living with T1D only; or, 3) People living with T1D or T2D where there is a clinical need for financial assistance. The current British Columbia PharmaCare program most closely aligns with the third population (financial need). Four implementation considerations could be applied across the three populations: 1) Support varies by patient income; 2) Support varies by patient's blood glucose control; 3) Access is limited to one specific technology; or, 4) Access is limited to people with limited functional capacity. The first implementation scenario (support varies by patient income) has the strongest support from the current evidence.

After completion of the clinical review, a cost-effectiveness model was not undertaken for a variety of reasons (Chapter 15). Both patients and the Ministry of Health consider cost in decision-making, therefore, a budget impact analysis was conducted to support the policy implementation scenarios (Chapter 17). This budget impact analysis considers four funding scenarios for the management of insulin dependent diabetes in British Columbia. Costs are predicted over a three-year time horizon [redacted] In scenario one funding is based on the patient's family income, like the Fair PharmaCare program. Costs to the province are predicted to range from $266 million over three years if income-based funding is provided to all patients with insulin dependent diabetes, to $1.1 million over three years if funding is provided to patients with significant difficulty managing their own diabetes. In scenario two, funding is provided to patients with glycated hemoglobin (HbA1c) greater than or equal to 7.0%. Costs to the province range from $397 million over three years if funding is provided to all patients with insulin dependent diabetes and HbA1c ≥ 7.0%, to $1.7 million depending on the population funded. In scenario three, only one technology is funded by the province. If all patients with diabetes are eligible and all patients with diabetes select the most expensive technology

considered, costs to the province could be as high as $15.7 billion. In scenario four, funding is limited to patients with limited functional capacity. Over three years, the predicted budget impact to the province is $15.6 million.

In summary, this HTA has presented clinical, budgetary, clinical and patient evidence to inform implementation scenarios for glucose monitoring technology within British Columbia. Each implementation scenario, and a variety of others that could be modelled based on the evidence presented herein, achieve different policy goals and align with different aspects of the evidence-base.

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20 Appendices

20.1 Appendix A: Search Strategy for Systematic Review of HTAs

HTA Database Glucose Monitoring: Sept 10 2018

1. Blood Glucose Self-Monitoring/
2. exp Blood Glucose/ and exp Self Care/
3. ((blood sugar* or glucose or glycated hemoglobin) adj3 (biosens* or control* or measur* or monitor* or sens*)).tw.
4. 1 or 2 or 3
5. diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/
6. (diabetes or diabetic*).tw.
7. 5 or 6
8. 4 and 7
9. (automated insulin delivery or closed loop or dexcom or enlite or eversense or flash monitor* or freestyle libre or insulin pump* or minimed or paradigm revel or paradigm veo or sensor augmented pump*).tw.
10. (bgm or cgm or sap or smbg*).tw.
11. (automated or continuous or constant or continual or continuing or flash or glucose sens* or intermittent or ongoing or real time or realtime).tw.
12. insulin infusion systems/
13. 9 or 10 or 11 or 12
14. 8 and 13
15. limit 14 to (english or french)

20.2 Appendix B: Search Strategy for Systematic Review of TIR Clinical Validity

CINAHL TIR Search Dec 10 2018 (total abstracts 597)

1. ((MH "Diabetes Mellitus, Type 1") OR (MH "Diabetes Mellitus, Type 2") OR (MH "Diabetes Mellitus") OR (MH "Blood Glucose") OR (MH "Blood Glucose Self-Monitoring") OR (MH "Blood Glucose Monitoring") OR (MH "Blood Glucose Meters")) OR TI ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM or blood glucose or glucose monitor*)) OR AB ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM or blood glucose or glucose monitor*)
2. TI (time N5 (range* or target or targets or euglycemi* or euglycaemi* or normoglycemi* or normoglycaemi* or normal fasting glucose or NFG)) OR AB (time N5 (range* or target or targets or euglycemi* or euglycaemi* or normoglycemi* or normoglycaemi* or normal fasting glucose or NFG)) OR TI tir OR AB tir
3. 1 and 2
4. Limit 3 to English or French
5. Limit 4 to Scholarly Peer Reviewed Journals

Time in Range Cochrane CENTRAL Register of Trials Dec 10 2018

1. diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/2. Blood Glucose/
3. Blood Glucose Self-Monitoring/
4. (diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM).tw,kf.
5. (blood glucose or glucose monitor*).tw,kf.
6. 1 or 2 or 3 or 4 or 5
7. (time adj5 (range* or target or targets)).tw,kf.
8. (time adj5 (euglycemi* or euglycaemi* or normoglycemi* or normoglycaemi* or normal fasting glucose or NFG)).tw,kf.
9. tir.tw,kf.
10. 7 or 8 or 9
11. 6 and 10
12. limit 11 to (english or french)

Time in Range Cochrane Systematic Reviews Dec 10 2018

1. (diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM).tw,kf.
2. (blood glucose or glucose monitor*).tw,kf.
3. (time adj5 (range* or target or targets)).tw,kf.
4. (time adj5 (euglycemi* or euglycaemi* or normoglycemi* or normoglycaemi* or normal fasting glucose or NFG)).tw,kf.
5. tir.tw,kf.

6. 3 or 4 or 5
7. 1 or 2
8. 6 and 7

Time in Range EMBASE Dec 7 2018
1. diabetes mellitus/ or exp insulin dependent diabetes mellitus/ or exp non insulin dependent diabetes mellitus/
2. glucose blood level/
3. blood glucose monitoring/
4. (diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM).tw,kw.
5. (blood glucose or glucose monitor*).tw,kw.
6. 1 or 2 or 3 or 4 or 5
7. (time adj5 (range* or target or targets)).tw,kw.
8. tir.tw,kw.
9. (time adj5 (euglycemi* or euglycaemi* or normoglycemi* or normoglycaemi* or normal fasting glucose or NFG)).tw,kw.
10. 7 or 8 or 9
11. 6 and 10
12. limit 11 to (english or french)
13. limit 12 to animal studies
14. limit 12 to (human and animal studies)
15. 13 not 14
16. 12 not 15
17. case report/
18. 16 not 17
19. limit 18 to (conference abstract or editorial or letter)
20. 18 not 19
21. limit 20 to "review"
22. 20 not 21
23. limit 20 to (meta analysis or "systematic review")
24. ((critical or systematic of scoping or evidence-based) adj2 (review or overview or synthesis)).tw.
25. 20 and 24
26. 22 or 23 or 25

Time in Range MEDLINE Dec 7 2018
1. diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/
2. Blood Glucose/
3. Blood Glucose Self-Monitoring/
4. (diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM).tw,kf.
5. (blood glucose or glucose monitor*).tw,kf.
6. 1 or 2 or 3 or 4 or 5
7. (time adj5 (range* or target or targets)).tw,kf.

8. (time adj5 (euglycemi* or euglycaemi* or normoglycemi* or normoglycaemi* or normal fasting glucose or NFG)).tw,kf.
9. tir.tw,kf.
10. 7 or 8 or 9
11. 6 and 10
12. limit 11 to (english or french)
13. limit 12 to animals
14. limit 12 to (animals and humans)
15. 13 not 14
16. 12 not 15
17. limit 16 to (case reports or editorial or letter)
18. 16 not 17
19. limit 18 to "review articles"
20. 18 not 19
21. limit 18 to (meta analysis or systematic reviews)
22. ((systematic or critical or scoping or evidence-based) adj2 (review or overview or synthesis)).tw.
23. 18 and 22
24. 20 or 21 or 23

20.3 Appendix C: Search Strategy for Systematic Review of Clinical Effectiveness

CINAHL (EBSCO Total 1056 abstracts Sept 11 2018)

1. (MH "Blood Glucose Self-Monitoring")
2. (MH "Blood Glucose Monitoring") AND (MH "Self Care")
3. TI (((blood sugar* or glucose or glycated hemoglobin) N5 (biosens* or control* or measur* or monitor* or sens*))) OR AB (((blood sugar* or glucose or glycated hemoglobin) N5 (biosens* or control* or measur* or monitor* or sens*)))
4. 1 or 2 or 3
5. ((MH "Diabetes Mellitus, Type 1") OR (MH "Diabetes Mellitus, Type 2")) OR TI (diabetes or diabetic*) OR AB (diabetes or diabetic*)
6. 4 and 5
7. TI (automated insulin delivery or closed loop or dexcom or enlite or eversense or flash monitor* or freestyle libre or insulin pump* or minimed or paradigm revel or paradigm veo or sensor augmented pump*))) OR AB (automated insulin delivery or closed loop or dexcom or enlite or eversense or flash monitor* or freestyle libre or insulin pump* or minimed or paradigm revel or paradigm veo or sensor augmented pump*)
8. TI (bgm or cgm or sap or smbg*) OR AB (bgm or cgm or sap or smbg*)))
9. (MH "Insulin Infusion Systems")
10. 7 or 8 or 9
11. 6 and 10
12.
13. 11 and 12
14. Limiters - Randomized Controlled Trial
15. TI (random* or trial or trials) OR AB (random* or trial or trials)
16. 13 and 15
17. 14 or 16
18. Limiters - Published Date: 20030101-20181231; Language: English, French

Clinical Effectiveness Glucose Monitor Cochrane CENTRAL Register Sept 9 2018 (**815** records)

1. Blood Glucose Self-Monitoring/
2. 2. exp Blood Glucose/ and exp Self Care/
3. ((blood sugar* or glucose or glycated hemoglobin) adj3 (biosens* or control* or measur* or monitor* or sens*)).tw.
4. 1 or 2 or 3
5. diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/
6. (diabetes or diabetic*).tw.
7. 5 or 6
8. 4 and 7
9. (automated insulin delivery or closed loop or dexcom or enlite or eversense or flash monitor* or freestyle libre or insulin pump* or minimed or paradigm revel or paradigm veo or sensor augmented pump*).tw.
10. (bgm or cgm or sap or smbg*).tw.
11. (automated or continuous or constant or continual or continuing or flash or glucose sens* or intermittent or ongoing or real time or realtime).tw.
12. insulin infusion systems/

13. 9 or 10 or 11 or 12
14. 8 and 13
15. limit 14 to yr="2003 -Current"
16. limit 15 to (controlled clinical trial or randomized controlled trial)
17. prediabet*.ti.
18. 16 and 17
19. 16 not 18

Clinical Effectiveness Glucose Monitor EMBASE Sept 9 2018 (1504 records)

1. blood glucose monitoring/
2. 2. exp self care/ and exp glucose blood level/
3. ((blood sugar* or glucose or glycated hemoglobin) adj3 (biosens* or control* or measur* or monitor* or sens*)).tw.
4. 1 or 2 or 3
5. insulin dependent diabetes mellitus/
6. (diabetes or diabetic*).tw.
7. 5 or 6
8. 4 and 7
9. (automated insulin delivery or closed loop or dexcom or enlite or eversense or flash monitor* or freestyle libre or insulin pump* or minimed or paradigm revel or paradigm veo or sensor augmented pump*).tw.
10. (bgm or cgm or sap or smbg*).tw.
11. (automated or continuous or constant or continual or continuing or flash or glucose sens* or intermittent or ongoing or real time or realtime).tw.
12. insulin pump/
13. 9 or 10 or 11 or 12
14. 8 and 13
15. limit 14 to (randomized controlled trial or controlled clinical trial)
16. crossover procedure/
17. double blind procedure/
18. single blind procedure/
19. (random* or factorial* or crossover* or cross-over* or placebo* or (doubl* adj1 blind*) or (singl* adj1 blind*) or assign* or allocat* or volunteer*).tw.
20. 16 or 17 or 18 or 19
21. 14 and 20
22. 15 or 21
23. limit 22 to yr="2003 -Current"
24. limit 23 to (english or french)
25. limit 24 to animals
26. limit 24 to (human and animals)
27. 25 not 26
28. 24 not 27
29. limit 28 to (conference abstract or editorial or letter)
30. 28 not 29

Clinical Effectiveness Glucose Monitor MEDLINE Sept 9 2018 (1700 records)

1. Blood Glucose Self-Monitoring/
2. exp Blood Glucose/ and exp Self Care/
3. ((blood sugar* or glucose or glycated hemoglobin) adj3 (biosens* or control* or measur* or monitor* or sens*)).tw.
4. 1 or 2 or 3
5. diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/
6. (diabetes or diabetic*).tw.
7. 5 or 6
8. 4 and 7
9. (automated insulin delivery or closed loop or dexcom or enlite or eversense or flash monitor* or freestyle libre or insulin pump* or minimed or paradigm revel or paradigm veo or sensor augmented pump*).tw.
10. (bgm or cgm or sap or smbg*).tw.
11. (automated or continuous or constant or continual or continuing or flash or glucose sens* or intermittent or ongoing or real time or realtime).tw.
12. insulin infusion systems/
13. 9 or 10 or 11 or 12
14. 8 and 13
15. limit 14 to (controlled clinical trial or randomized controlled trial)
16. (random* or trial or trials).tw.
17. 14 and 16
18. 15 or 17
19. limit 18 to yr="2003 -Current"
20. limit 19 to (english or french)
21. limit 20 to animals
22. limit 20 to (animals and humans)
23. 21 not 22
24. 20 not 23

20.4 Appendix D: Search Strategy for Systematic Review of Patient Perspectives

CINAHL (EBSCO Total 163 abstracts Sept 11 2018)

1. (MH "Blood Glucose Self-Monitoring")
2. (MH "Blood Glucose Monitoring") AND (MH "Self Care")
3. TI (((blood sugar* or glucose or glycated hemoglobin) N5 (biosens* or control* or measur* or monitor* or sens*))) OR AB (((blood sugar* or glucose or glycated hemoglobin) N5 (biosens* or control* or measur* or monitor* or sens*)))
4. 1 or 2 or 3
5. ((MH "Diabetes Mellitus, Type 1") OR (MH "Diabetes Mellitus, Type 2")) OR TI (diabetes or diabetic*) OR AB (diabetes or diabetic*)
6. 4 and 5
7. TI (automated insulin delivery or closed loop or dexcom or enlite or eversense or flash monitor* or freestyle libre or insulin pump* or minimed or paradigm revel or paradigm veo or sensor augmented pump*))) OR AB (automated insulin delivery or closed loop or dexcom or enlite or eversense or flash monitor* or freestyle libre or insulin pump* or minimed or paradigm revel or paradigm veo or sensor augmented pump*)
8. TI (bgm or cgm or sap or smbg*) OR AB (bgm or cgm or sap or smbg*)))
9. (MH "Insulin Infusion Systems")
10. 7 or 8 or 9
11. 6 and 10
12. (MH "Qualitative Studies") OR (MH "Phenomenology") OR (MH "Phenomenological Research") OR (MH "Grounded Theory") OR (MH "Naturalistic Inquiry") OR (MH "Focus Groups") OR (MH "Interviews") OR (MH "Semi-Structured Interview") OR (MH "Unstructured Interview")) OR TI ((focus group* or grounded theory or interview* or lived experience* or narrati* or naturalistic inquiry or qualitative)) OR AB ((focus group* or grounded theory or interview* or lived experience* or narrati* or naturalistic inquiry or qualitative)
13. 11 and 12
14. Limiters - Published Date: 20030101-20181231; Scholarly (Peer Reviewed) Journals; Language: English, French

20.5 Appendix E: WinBUGS Codes for Network Clinical Effectiveness Meta-analysis

20.5.1 WinBUGS Code used for Network Meta-Analysis of HbA1c

Random Effects Model: Normal likelihood, identity link, shared parameter model. Adapted from Dias et al. [96]

```
# Normal likelihood, identity link
# Arm and Trial-level data (treatment differences)
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns.a){                       # LOOP THROUGH STUDIES WITH ARM DATA
    w.a[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)            # vague priors for all trial baselines
    for (k in 1:na.a[i]) {              #  LOOP THROUGH ARMS
        var.a[i,k] <- pow(se.a[i,k],2)   # calculate variances
        prec.a[i,k] <- 1/var.a[i,k]      # set precisions
        y.a[i,k] ~ dnorm(theta[i,k],prec.a[i,k]) # normal likelihood
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- (y.a[i,k]-theta[i,k])*(y.a[i,k]-theta[i,k])*prec.a[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na.a[i]])
    for (k in 2:na.a[i]) {              # LOOP THROUGH ARMS
# trial-specific RE distributions
        delta[i,k] ~ dnorm(md[i,k],taud.a[i,k])
# mean of RE distributions, with multi-arm trial correction
        md[i,k] <-  d[t.a[i,k]] - d[t.a[i,1]] + sw.a[i,k]
# precision of RE distributions (with multi-arm trial correction)
        taud.a[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w.a[i,k] <- (delta[i,k] - d[t.a[i,k]] + d[t.a[i,1]])
# cumulative adjustment for multi-arm trials
        sw.a[i,k] <- sum(w.a[i,1:k-1])/(k-1)
      }
  }
for(i in 1:ns.t){        # LOOP THROUGH STUDIES WITH TRIAL DATA
    w[i,1] <- 0  # adjustment for multi-arm trials is zero for control arm
    delta[i+ns.a,1] <- 0          # treatment effect is zero for control arm
    for (k in 2:na[i]) {          #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)   # calculate variances
        prec[i,k] <- 1/var[i,k]      # set precisions
        y[i,k] ~ dnorm(delta[i+ns.a,k],prec[i,k]) # normal likelihood
#Deviance contribution
        dev[i+ns.a,k] <- (y[i,k]-delta[i+ns.a,k])*
                         (y[i,k]-delta[i+ns.a,k])* prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i+ns.a] <- sum(dev[i+ns.a,2:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific RE distributions
        delta[i+ns.a,k] ~ dnorm(md[i+ns.a,k],taud[i,k])
# mean of RE distributions, with multi-arm trial correction
        md[i+ns.a,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of RE distributions (with multi-arm trial correction)
```

```
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i+ns.a,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# pairwise mean differences for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
   for (k in (c+1):nt)  { diff[c,k] <- d[k]-d[c] }
 }
# ranking on relative scale
for (k in 1:nt) {
#  rk[k] <- nt+1-rank(d[],k)  # assumes higher values are "good"
  rk[k] <- rank(d[],k)        # assumes higher values are "bad"
   best[k] <- equals(rk[k],1) #calculate probability that treat k is best
# calculates probability that treat k is h-th best
  for (h in 1:nt){  prob[h,k] <- equals(rk[k],h)  }
 }
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k]  }
}                                     # *** PROGRAM ENDS
```

20.5.2 WinBUGS Code used for Network Meta-Analysis of Number of Hypoglycemic Events Requiring Assistance

Random Effects Model: Poisson likelihood, log link. Code from Dias et al. [96]

```
# Poisson likelihood, log link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         # LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0                     # treatment effect is zero for control
arm
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
    for (k in 1:na[i]) {                # LOOP THROUGH ARMS
        r[i,k] ~ dpois(theta[i,k])    # Poisson likelihood
        theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure
        log(lambda[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))
}
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {                # LOOP THROUGH ARMS
# trial-specific RE distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of RE distributions (with multi-arm trial correction)
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of RE distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1] <- 0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
       for (k in (c+1):nt)  {
              lhr[c,k] <- d[k]-d[c]
              log(hr[c,k]) <- lhr[c,k]
         }
     }
# ranking on relative scale
for (k in 1:nt) {
#      rk[k] <- nt+1-rank(d[],k)    # assumes events are "good"
      rk[k] <- rank(d[],k)          # assumes events are "bad"
      best[k] <- equals(rk[k],1)    #calculate probability that treat k is
best
# calculates probability that treat k is h-th best
      for (h in 1:nt){  prob[h,k] <- equals(rk[k],h)  }
     }
```

```
# Provide estimates of treatment effects T[k] on the natural (rate) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { log(T[k]) <- A + d[k]  }
}                                    # *** PROGRAM ENDS
```

20.5.3 WinBUGS Code used for Network Meta-Analysis of Time-in-Range

Fixed Effects Model: Normal likelihood, identity link. Code from Dias et al. [96]

```
# Normal likelihood, identity link
# Fixed effects model
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         #   LOOP THROUGH STUDIES
  mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
  for (k in 1:na[i]) {                  #  LOOP THROUGH ARMS
    var[i,k] <- pow(se[i,k],2)    # calculate variances
    prec[i,k] <- 1/var[i,k]       # set precisions
    y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood
# model for linear predictor
    theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
    dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
   }
#  summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
 }
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
# pairwise mean differences for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
   for (k in (c+1):nt)  { diff[c,k] <- d[k]-d[c] }
 }
# ranking on relative scale
for (k in 1:nt) {
  rk[k] <- nt+1-rank(d[],k)   # assumes higher values are "good"
#  rk[k] <- rank(d[],k)       # assumes higher values are "bad"
   best[k] <- equals(rk[k],1) #calculate probability that treat k is best
# calculates probability that treat k is h-th best
  for (h in 1:nt){  prob[h,k] <- equals(rk[k],h)  }
 }
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k]  }
}                                       # *** PROGRAM ENDS
```

20.6 Appendix F Clinical Effectiveness Supplementary Material

20.6.1 Study Characteristics Table

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
DirecNet (2005)[144]	USA	Type 1	Pediatric (7-18 years)	7-18 yrs; T1DM for at least 1 yr; HbA1c level 7 -11%; stable insulin regimen;	Use of Gluco Watch Biographer; cystic fibrosis; chronic illness; corticosteroid use	Randomized with equal probability; permuted blocks stratified by clinical center and age group (7-<12)and (12-18)	Parallel	6 months	SMBG, insulin unspecified (n=101)	SMBG plus GlucoWatch G2 Biographer; insulin unspecified (n=98)	HbA1c; Hypos
Abraham (2018)[145]	Australia	Type 1	Pediatric (8-20 years)	8-20 years; had T1DM of at least 1 year duration; HbA1c of <10%; used insulin pump for >6 months	If any had hypoglycemia; oral hypoglycemic agents; pregnant; not able to comply and meet protocol requirements.	NR	Parallel	6 months	CGM+SMBG, CSII (n=74)	CGM+SMBG, CSII (predictive low glucose suspend) (n=80)	HbA1c; Ketoacidosis; HFS; PedsQL
Ajjan (2016)[102]	UK	Type 1	Adults	18 yrs or older with T1DM; treated with MDI for ≥6 months; HbA1c between 7.5% and 12%; capable of using the Freestyle Navigator.	Had concomitant disease; pregnant; currently using CGM for the last 6 months;	Permuted block randomisation with stratification by site and diabetes type in a 2:1 ratio into one of two groups (intervention or control); computer-generated	Parallel	100 days	SMBG+MDII (n=13)	CGM+MDII (n=29)	HbA1c; DTSQ
Ajjan (2016)[102]	UK	Type 2	Adults	18 yrs or older with T2DM; treated with MDI for >6 months; HbA1c between 7.5% and 12%;	Had concomitant disease; pregnant; currently using CGM for the last 6 months;	Permuted block randomisation with stratification by site and diabetes type in a 2:1 ratio into one of two groups (intervention or control); computer-generated	Parallel	100 days	SMBG+MDII (n=15)	CGM+MDII (n=30)	HbA1c; DTSQ

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				capable of using the Freestyle Navigator.							
Aleppo (2017)[103]	USA	Type 1	Adults	Age ≥18 years; T1D for ≥1 year being treated with an insulin pump for at least 3 months; HbA1c <9%	Occurrence of severe hypoglycemic event; significant hypoglycemia unawareness;	Computer-generated sequence to the CGM-only or CGM+BGM group in a 2:1 ratio on the basis of a permuted block design with stratification by clinical site	Parallel	26 weeks	SMBG+CGM + CSII (n=75)	CGM+CSII (n=142)	HbA1c; TIR; Hypos; DKA; HFS; DTSQ
Bally (2017)[104]	UK, Switzerland, Austria	Type 1	Adults	Adults aged 18 years with T1DM; HbA1c 7.5-10%; on insulin pump for at least 6 months	physical or psychological disease; living alone; allergy against insulin; reduced hypoglycaemia awareness; pregnant	Randomly determined with an automated web-based programme with locally stratified, randomly permuted blocks of four.	Crossover		Usual Care (n=28)	CL (n=29)	TIR; Hypos; DKA
Barnard (2014)[39]	UK	Type 1	Pediatric (12-18 years)	adolescents with T1DM;	NR	NR	Crossover	21 days	OL (n=15)	CL (n=15)	HFS
Battelino (2017)[146]	Slovenia, Israel	Type 1	Pediatric (8-18 years)	8-18 years diagnosed with T1DM ≥12 months; treated by CSII; with or without CGM; HbA1c level <10 %	NR	Randomly assigned in a 1:1 ratio	Parallel	2 weeks	CGM+SMBG, CSII	CGM+SMBG, CSII (predictive low glucose suspend) (n=47)	Hypos; ketoacidosis
Beck (2010)[100]	USA	Type 1	Adults	age 25 years or older, has type 1 diabetes treated for at least 1 year with multiple	Pregnancy, use of personal RT-CGM 3 months prior to study entry, use of CSII 3 months prior to study entry, plan to use	Random assignment 2:1 to CGM	Parallel	26 weeks	SMBG, insulin unspecified	CGM+SMBG, insulin unspecified	HFS

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				daily insulin injections, HbA1c level 7.5% to 10%, no home use of a personal CGM device	personal CGM, addition of any new oral or injectable hypoglycemic agents, use of pre-mixed insulin						
Beck (2017)[105]	USA, Canada	Type 1	Adults	25 yrs or older; T1DM; using MDI for at least 12 months; HbA1c of >7.7% to <10%; stable control of diabetes and medication, stable weight; willing to wear CGM; performing SMBG at least 3 times per day	Use of RT-CGM or CSII 3 months prior to study; use of CGM or pump during study; use of pre-mixed insulin; acute uses of glucocorticoids; pregnancy; medical conditions that may affectHbA1c; visual impairment; psychiatric, psychological disorder; renal disease; skin changes/disease; allergy; recent hospitalization; current abusing illicit drugs or alcohol; conditions that may affectHbA1c measurement	From a computer-generated sequence to either the CGM or control group in a 2:1 ratio, with a permuted block design (block sizes of 3 and 6) stratified by HbA1c level (<8.5% and ≥8.5%)	Parallel	24 weeks	SMBG+MDII (n=53)	CGM + SMBG+MDII (n=105)	HbA1c; TIR; Hypos; DKA
Beck (2017)[105]	USA, Canada	Type 2	Adults	Age at least 25 yrs; T2DM treated with MDI of insulin for at least 1 yr; HbA1c levels of 7.5 - 1.0%; stable diabetes medication; self-reported	NR	Randomly assigned by a computer-generated sequence in 1:1 ratio using permuted block design stratified by HbA1c level (<8.5% and >8.5%	Parallel	24 weeks	SMBG+MDII (n=79)	CGM+SMBG+MDII (n=79)	HbA1c; Hypos; Keto; EQ-5D

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				blood glucose meter testing averaging 2 or more times per day; GFR 45 mL/min/1.73m							
Beck (2017)[105]	USA, Canada	Type 1	Adults	Adults with T1DM; using multiple daily insulin injection; HbA1c level of 7.9% to 9.9	Pregnancy, use of personal RT-CGM 3 months prior to study entry, use of CSII 3 months prior to study entry, plan to use personal CGM, addition of any new oral or injectable hypoglycemic agents, use of pre-mixed insulin	Random assignment 2:1 to CGM and a random permuted block design (block sizes of 2 and 4) stratified by HbA1c (≤7·0% , 7·1% to 7·4% , and ≥7·5%)	Parallel	28 weeks	CGM+MDI+SMBG (n=53)	CGM+CSII+SMBG (n=105)	HbA1c; TIR; Hypos; DKA
Bergenstal (2010)[107]	USA, Canada	Type 1	Pediatric (7-18 years)	Age 7-70 years with T1DM; long-acting analogue insulin during past 3 months; HbA1c 7.4 to 9.5%; access to computer;	Use of insulin pump therapy for the previous 3 years; history of at least 2 severe hypoglycemic events last year; use of pharmacologic noninsulin treatment for previous 3 months; pregnancy or planning.	Block design, stratified according to age group: adults (19–70 years of age) or children (7–18 years of age).	Parallel	52 weeks	SMBG, MDII (n=163)	CGM+SMBG, CSII (n=78)	HbA1c; Hypos; ketoacidosis
Bergenstal (2010)[107]	USA, Canada	Type 1	Adults	Age 7-70 years with T1DM; long-acting analogue insulin during past 3 months; HbA1c 7.4 to 9.5%; access to computer;	Use of insulin pump therapy for the previous 3 years; history of at least 2 severe hypoglycemic events last year; use of pharmacologic noninsulin treatment for previous 3 months; pregnancy or planning.	Block design, stratified according to age group: adults (19–70 years of age) or children (7–18 years of age).	Parallel	52 weeks	MDI+SMBG (n=241)	CGM+CSII+SMBG (n=166)	HbA1c; Hypos; DKA

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
Blauw (2016)[108]	Netherlands	Type 1	Adults	18–75 years; T1DM; treatment with an insulin pump for at least 6 months	Impaired awareness of hypoglycaemia; BMI >35 kg/m2; HbA1c >11%; pregnancy or breastfeeding; and use of heparin, coumarin derivatives or oral corticosteroids.	NR	Crossover	4 days	SMBG, CSII (n=10)	Bihormonal AP algorithm not specified+SMBG (n=10)	TIR; DKA
Bolinder (2016)[109]	Sweden, Austria, Germany, Spain, Netherlands	Type 1	Adults	18 years or older, diagnosed with type1 diabetes for 5 years, had been on insulin regimen for at least 3 months before the study, HbA1c concentration 58 mmol/mol	Diagnosed with hypoglycaemia unawareness; diabetic ketoacidosis; myocardial infarction in last 6 months; used CGM within preceding 4 months; were pregnant or planning to; receiving oral steroid therapy	1:1 ratio by central interactive web response system (IWRS) using the biased-coin minimisation method; study centre and type of insulin administration were prognostic factors	Parallel	26 weeks	SMBG, insulin delivery not reported (n=119)	Flash+SMBG, insulin reported together (n=120)	HbA1c; TIR; Hypos; DKA; HFS; DTSQ
Breton (2014)[110]	USA	Type 1	Adults	T1DM duration of 23.6 – 4.4 years; body weight of 68.9± 3.1 kg; HbA1C level of 6.9 ± 0.2%; experienced insulin pump users (> 6 months)	HbA1c level of >10.5%; with recent diabetic ketoacidosis or severe hypoglycemia (< 3 months); at increased cardiovascular risk during exercise; use of a medication that significantly lowers HR	NR	Crossover	24 hour	CL (control to range algorithm) (n=12)	CTR + HR (heart rate) (n=12)	TIR; DKA
Breton (2017)[147]	USA	Type 1	Pediatric (10-16 years)	insulin-treated T1D >1 year; insulin pump use >3 months	history of severe hypoglycemia or diabetes ketoacidosis (within the last 6 months); pregnancy; conditions incompatible with the	Randomly assigned	Parallel	5 days	CGM+SMBG, CSII (n=16)	CL(CTR algorithm)+SMBG (n=16)	TIR

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
					practice of winter sports in altitude.						
Breton (2018)[111]	USA	Type 1	Adults	Adults and adolescents with T1DM; 17-65 years;	NR	NR	Crossover	48 hours	CGM+SMBG, insulin reported together (n=24)	CGM(decision support)+SMBG, insulin reported together (n=24)	TIR
Brown (2017)[112]	USA, Italy	Type 1	Adults	Age <21 to<65 yrs; T1DM for ≥ 1 yr; using an insulin pump for ≥ 1 yr; HbA1c <10%.	Diabetic ketoacidosis or severe hypoglycemic event in the last year; adrenal disorder; active gastroparesis; uncontrolled hypertension; oral steroids; uncontrolled active retinopathy; unstable coronary artery disease; acetaminophen use; use of medications for glucose control other than insulin, and the use of b-blockers	NR	Crossover	24 hours	CGM+SMBG, CSII (n=40)	Night: CL (USS Virginia CLC algorithm)+SMBG, day: CGM+SMBG, CSII (n=40)	TIR; Hypos; DKA
Brown (2015)[113]	USA, Italy	Type 1	Adults	21–65 yrs of age; T1DM for at least 1 yr; HbA1c level of < 9%; insulin pump users for at least 1 yr with predefined pump parameters	Episodes of diabetic ketoacidosis or a severe hypoglycemic episode in the past year; pregnant or breast-feeding; uncontrolled thyroid disease; uncontrolled microvascular disease; uncontrolled hypertension; significant cardiovascular	NR	Crossover	60 hours	CGM+SMBG, CSII (n=10)	Night: CL(USS Virginia algorithm), day: CGM+SMBG, CSII (n=10)	TIR; Hypos; DKA

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
					disease or seizure disorders or other conditions known to increase the risk of hypoglycemia, including use of b-blockers; self-reported hypoglycemic unawareness; use of medications known to affect glucose other than insulin and use of substances known to interfere with CGM measures						
Chase (2003)[148]	USA	Type 1	Pediatric (7-16 years)	Poor glucose control; HbA1c ≥8% in last 9 months	Severe hypoglycemia events past 6 months; serious illness other than diabetes; known diabetic complications	Randomized to 1 of 2 groups	Parallel	3 months	Conventional glucose monitoring (n=20)	Glucowatch biographer (n=20)	HFS
DeBoer (2017)[149]	USA	Type 1	Pediatric (5-8 years)	5-8 years old; T1DM with use of daily insulin for≥1 year; use of insulin pump ≥6 months; HbA1c 5% to 10.5%	Severe hypoglycemia within last 3 months; diabetic ketoacidosis within last 6 months; anemia; conditions that may increase risk of hypoglycemia; use of medication that lowers heart rate.	NR	Crossover	3 days	CGM+SMBG unspecified, CSII (n=12)	CL (CTR algorithm) (n=12)	TIR; Hypos
DeBoer (2017)[150]	USA	Type 1	Pediatric (12-17 years)	Age 12-17 years; clinical diagnosis of T1DM; use of insulin pump ≥6 months; and HbA1c 5.0%-10.5%	Severe hypoglycemia within last 3 months; DKA within last 6 months; pregnancy; anemia; weight <40 kg; conditions that may increase risk of hypoglycemia; or use of a medication	NR	Crossover	2 days	CL(CTR algorithm)+SMBG (n=18)	CL(CTR+HR monitor)+SMBG (n=18)	TIR

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
					that lowers heart rate.						
El-Khatib (2017)[114]	USA, Italy	Type 1	Adults	At least 18 years; had T1DM for at least 1 year; using insulin pump therapy for at least 6 months.	Hepatic dialysis or renal failure; congestive heart failure; history of cerebrovascular disease; hypoglycemic seizure in the last year; current participation in another diabetes-related clinical trial; pregnancy; current alcohol abuse; use of marijuana within 1 month; pancreatitis; history of any non-hypoglycemic seizure within the last two years, or ongoing treatment with anticonvulsants, history of pheochromocytoma, history of adrenal disease and tumor, hypertension with systolic blood pressure greater than 160 mm Hg or diastolic greater than 100 mm Hg despite treatment, untreated or inadequately treated mental illness; electrically powered	Randomly assigned (1:1) in blocks of two using sequentially numbered sealed envelopes	Crossover	11 days	Monitoring unspecified, CSII (n=22)	bihormonal bionic pancreas (algorithm unspecified)+SMBG (n=21)	TIR

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
					implants that may be susceptible to radio-frequency interference, history of adverse reaction to glucagon including allergy besides nausea and vomiting; history of eating disorder in the last two years; use of oral medications that assist in glycemic control.						
Elleri (2013)[151]	UK	Type 1	Pediatric (12-18 years)	T1DM of at least 1 year; insulin pump therapy at least 3 months.	HbA1c > 12%; significant insulin resistance; significant retinopathy or nephropathy; hypoglycemia unawareness	A computer-generated allocation sequence, with permuted blocks placed in sealed envelopes	Crossover	36 hour	SMBG, CSII (n=12)	CL(MPC algorithm)+SMBG (n=12)	TIR
Elleri (2015)[152]	UK	Type 1	Pediatric (12-18 years)	T1DM of at least 1 year; insulin pump therapy at least 3 months.	HbA1c > 12%; significant insulin resistance; significant retinopathy or nephropathy.	Random order	Crossover	36 hour	CL (MPC algorithm), SMBG unspecified (n=8)	CL(MPC algorithm with 25% prandial insulin reduction), SMBG unspecified (n=8)	TIR
Farrington (2017)[170]	UK	Type 1	Pregnant women	Age 18 to 45 years; with a pregnancy between 8 and 24 weeks of gestation; HbA1c level between 6.5 and 10.0%; receiving intensive insulin therapy either multiple daily injections or	Use of assisted reproductive technologies; receiving concurrent treatment that might influence glucose control; had a multiple-gestation pregnancy, had nephropathy, neuropathy, or proliferative retinopathy; allergy against insulin	Randomly assigned in permuted blocks of 4	Crossover	4 weeks	CGM+SMBG, CSII (n=12)	Night: CL (model predictive control algorithm), Day CGM+SMBG, CSII (n=11)	HFS

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				an insulin pump.							
Feig (2017)[115]	Canada, England, Scotland, Spain, Italy, Ireland, USA	Type 1	Pregnant women	Pregnant women aged 18–40 years with T1DM for a minimum of 12 months; receiving intensive insulin therapy via multiple daily injections or an insulin pump; had a live singleton fetus confirmed by ultrasound, were at 13 weeks and 6 days' gestation or less, and had HbA1c between 6·5–10%	Regular CGM users; women with severe nephropathy or medical conditions.	1:1 ratio; used a computer generated randomisation list with permuted block sizes and stratification by method of insulin delivery (pump or multiple injections), and baseline HbA1c (<7·5% vs ≥7·5% for the pregnancy trial	Parallel	34 weeks	SMBG, insulin unspecified (n=107)	CGM+SMBG, insulin unspecified (n=108)	HbA1c, Hypos,DKA,HFS
Feig (2017)[115]	Canada, England, Scotland, Spain, Italy, Ireland, USA	Type 1	Women intending to become pregnant	Planning pregnancy women aged 18–40 years with T1DM for a minimum of 12 months; receiving intensive insulin therapy via multiple	Regular CGM users; women with severe nephropathy or medical conditions.	1:1 ratio; used a computer generated randomisation list with permuted block sizes and stratification by method of insulin delivery (pump or multiple injections), and baseline HbA1c <8·0% vs ≥8·0% or for the planning pregnancy trial)	Parallel	34 weeks	SMBG, insulin unspecified (n=57)	CGM+SMBG, insulin unspecified (n=53)	HbA1c, TIR, Hypos,DKA, HFS

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				daily injections or an insulin pump; an HbA1c level between 7·0–10%							
Forlenza (2017)[116]	USA	Type 1	Adults	T1DM; required daily insulin therapy for at least 12 months with a total daily dose (TDD) > 0.3 units/kg/day; used a CSII pump for >3 months	Pregnant or planning pregnancy; diabetic ketoacidosis; severe hypoglycemia in the past 6 months; used a long-acting insulin via injection or other antidiabetic medications within the past 8 weeks; used an oral/inhaled glucocorticoid; had a skin condition affecting sensor placement.	1:1 ratio to either group	Crossover	2 weeks	CGM+SMBG not specified, CSII (n=19)	CL (zone model prediction algorithm) (n=19)	TIR; Hypos
Haidar (2017)[117]	Canada	Type 1	Adults	18 years or older; T1DM	HbA1c> 12 %	3 arm; blocked randomization with a 1:1:1:1:1:1 ratio	Crossover	60 hours	CGM+SMBG, CSII(n=9)	CL (model predictive control)+SMBG (n=7); bihormonal AP (insulin: model predictive control)+SMBG (n=7)	TIR
Heinemann (2018)[118]	Germany	Type 1	Adults	18 years or older with T1DM for 1 year; having had at least one severe hypoglycaemia event in the previous year; impaired hypoglycaemia awareness; treatment with MDI; HbA1c	Treatment with CSII therapy; use of the rtCGM system or rtCGM device in the previous 3 months; pregnancy.	Randomisation sequence was generated with SYSTAT 12.0 with a 1:1 allocation; the study centre was a stratifying variable. Randomisation was done block-wise per site.	Parallel	26 weeks	SMBG, MDII (n= 74)	CGM+SMBG, MDII (n=75)	HbA1c; TIR; Hypos; EQ-5D; HFS

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				75·0 mmol/mol or lower (≤9·0%)							
Hermanns (2014)[119]	Germany	Type 1	Adults	Age > 18 years withT1DM of more than 6 months;	Diagnosis of psychiatric disease	NR	Crossover	5 days	SMBG, insulin not specified (n=41)	CGM+SMBG, insulin not specified(n=41)	TIR
Hommel (2014)[101]	Europe	Type 1	Pediatric (<18 years)	T1DM of more than 1 yr; HbA1c level of 7.5- 9.5%; using CSII fo last 6 months;	NR	NR	Crossover	12 months	CGM+Sensor off (n=72)	CGM+ Sensor on (n=72)	PedsQL
Hommel (2014)[101]	Europe	Type 1	Adults	T1DM of more than 1 yr; HbA1c level of 7.5- 9.5%; using CSII fo last 6 months;	NR	NR	Crossover	6 months	SMBG + CSII (n=81)	CGM +SMBG, CSII (n= 81)	DTSQ
Hovorka (2014)[153]	UK	Type 1	Pediatric (12-18 years)	Age 12–18 years with T1DM >1 year; use insulin pump therapy for at least 3 months; four or more fingerstick glucose measurements per day; HbA1c <10% (86 mmol/mol).	Nephropathy; neuropathy; proliferative retinopathy; total daily insulin dose > 2.0 U/kg; regular use of CGM within 1 month; severe visual or hearing impairment; pregnancy or breastfeeding.	Permuted block-four approach.	Crossover	3 weeks	CGM+SMBG, CSII (n=16)	Night: CL (MPC algorithm); Day:CGM+SMBG, CSII (n=16)	TIR

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
JDRF (2008)[120]	USA	Type 1	Pediatric (8-14 years)	8 or older yrs; T1DM for at least 1 yr; used an insulin pump or received at least three daily insulin injections; HbA1c level of 7.0 to 10.0%, and had not used continuous glucose monitoring at home in the last 6 months; wear a sensor for at least 6 of 7 days before randomization; min. of 96 hours of glucose values; home BGM performed at least 3 times/day	NR	Permuted-block design stratified according to clinical center, age group (≥25 years, 15 to 24 years, and 8 to 14 years), and glycated hemoglobin level (≤8.0% and >8.0%)	Parallel	26 weeks	SMBG, insulin unspecified (n=58)	CGM+SMBG, insulin unspecified (n=56)	HbA1c; Hypos; DKA
JDRF (2008)[120]	USA	Type 1	Adults	8 or older yrs; T1DM for at least 1 yr; used an insulin pump or received at least three daily insulin injections; HbA1c level of 7.0 to 10.0%, and	NR	Permuted-block design stratified according to clinical center, age group (≥25 years, 15 to 24 years, and 8 to 14 years), and glycated hemoglobin level (≤8.0% and >8.0%)	Parallel	26 weeks	SMBG+ MDII (n=7); SMBG+Pump (delivery not specified) (n=39)	CGM+SMBG+MDII (n=9); CGM+SMBG+Pump (delivery not specified) (n=43)	HbA1c

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				had not used continuous glucose monitoring at home in the last 6 months; wear a sensor for at least 6 of 7 days before randomization; min. of 96 hours of glucose values; home BGM performed at least 3 times/day							
Kordonouri (2010)[154]	Germany, Austria, Poland, France	Type 1	Pediatric (1-5; 6-11, 12- years)	Children and adolescents (1-16years) withT1DM within 4 weeks before study entry.	NR	A central randomisation procedure	Parallel	52 weeks	SMBG+CSII (n=78)	CGM+SMBG, CSII (n=76)	HbA1c
Kovatchev (2014)[121]	USA	Type 1	Adults	Adults (21-65 years) with T1DM	History of diabetic ketoacidosis; severe hypoglycemia; pregnancy; breast feeding; or intention of becoming pregnant; uncontrolled arterial hypertension; conditions that may increase the risk of hypoglycemia or infections.	NR	Crossover	40 hours	CGM+SMBG, CSII (n=18)	CL(control to range)+SMBG (n=18)	TIR

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
Kropff (2015)[122]	Italy, France, Netherlands	Type 1	Adults	Age 18–69 years, T1DM at least 6 months; 20 a BMI of less than 35 kg/m²; HbA1c of between 7·5% and 10%.	Severe hypoglycaemia last year; ketoacidosis in the past 6 month; Pregnant or breastfeeding; medication to alter their glucose metabolism except for insulin; uncontrolled hypertension (resting >140/90 mm Hg); change of anthihypertensive medications; worked nightshifts or expected to be away from home for longer than 25% of the study duration; had no assistance; had malignant disease; acute cardiovascular event during the previous year; renal insufficiency (creatinine >150 µmol/L); had impairment of liver function; impaired cognitive or psychological abilities.	1:1 ratio with computer-generated allocation sequence with block sizes of two, four, and six	Crossover	8 weeks	CGM+SMBG, CSII (n= 32)	Night: CL (control-to-range algorithm, Day: CGM+CSII+SMBG (n= 32)	HbA1c; TIR; Hypos; DKA
Lagarde (2006)[155]	USA	Type 1	Pediatric (5-17 years)	Age 5–17 yr; T1DM treated with insulin for 1 yr or more; availability for all study visits; and	Diabetic ketoacidosis within 1 month; medications that affect glucose levels; and pregnancy.	Randomized 2:1 into an intervention group (CGMS data utilized) or control group (CGMS data blinded) using a computer-generated randomization	Parallel	4 months	SMBG, insulin unspecified (n=9)	CGM+SMBG, insulin unspecified (n=18)	HbA1c; Hypos

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				willingness to wear a medical device for 72 consecutive hours.							
Langeland (2012)[123]	Norway	Type 1	Adults	18-50 yrs with T1DM >3 yrs; treated with either insulin pumps or multiple daily insulin injections; HbA1c levels > 7% and < 10%, hypoglycaemic episodes at least once a week; or at least one episode with serious hypoglycaemia	Untreated hypothyroidism; adrenal gland failure; celiac disease; renal failure; unstable coronary heart disease; serious psychiatric or mental disorder	Randomised by drawing lots, to perform either ICFM or CGM	Crossover	4 weeks	SMBG+insulin delivery lumped together (n=15)	CGM+SMBG, insulin reported together (n=15)	HbA1c; DTSQ
Leelarathna (2014)[124]	UK, Austria, Germany	Type 1	Adults	age ≥18 yrs; T1DM; treatment with insulin pump therapy for at least 3 months, willingness to perform at least six fingerstick glucose measurements per day, and HbA1c ≤10%	Concurrent illness or medications; recurrent severe hypoglycemia; significant hypoglycemia unawareness; total daily insulin dose ≥2.0 units/kg; clinically significant nephropathy, neuropathy, or retinopathy; severe visual or hearing impairment; pregnancy; and breastfeeding	Participants underwent two 8-day periods, in random order	Crossover	7 days (home phase)	CGM+SMBG, CSII (n=17)	CL (model predictive control)+SMBG(n=17)	TIR

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
Leelarathna (2013)[125]	UK, Austria, Germany	Type 1	Adults	Age 18–74 years inclusive, 2) T1D according to World Health Organization criteria, 3) serum C-peptide ,50 pmol/L with simultaneous exclusion of biochemical hypoglycemia (glucose ,4.0 mmol/L), and 4) IAH confirmed by a Gold score (6) of$4 with or without history of SH in the preceding 12 months (as defined by the American Diabetes Association [29]).	Any condition precluding informed consent, unwillingness to undertake intensive insulin therapy and use study devices, and history of intolerance to insulin glargine. Additional exclusion criteria were applied to the optional stepped hyperinsulinemic-hypoglycemic clamp studies as follows: age .60 years, history of epilepsy (seizures not primarily induced by hypoglycemia), and known ischemic heart disease or other significant disease that in the judgment of the investigators would increase the risks associated with taking part in the substudy	Randomized to one of four arms	Parallel	24 weeks	SMBG+insulin not specified	CGM+SMBG, insulin reported together	HbA1c
Lind (2017)[126]	Sweden	Type 1	Adults	Age 18 yrs or older with HbA1c of at least 7.5%; treated with MDI injections; a	Patients treated with insulin pumps; pregnancy; planning pregnancy; severe cognitive dysfunction; current CGM use;	randomized 1:1; randomization was performed by a centralized web-based program stratifying patients by site according to a predefined sequence; random block	Crossover	26 weeks	SMBG+MDI (n=142)	CGM+SMBG+MDII (n=142)	HbA1c, Hypos, DKA, HFS, DTSQ

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				fasting C-peptide level < 0.91 ng/mL; diabetes duration > 1 yr	paracetamol use; abnormal skin; history of allergic reaction to chlorhexidine; eGFR < 30 ml/min	size varied between 1 + 1 and 2 + 2					
Little (2014)[127]	UK	Type 1	Adults	18–74 years with T1DM; C-peptide (<50 pmol/L) with simultaneous exclusion of BH (glucose <4.0 mmol/l); impaired awareness of hypoglycaemia	Insufficient proficiency in English; unwilling to undertake intensive insulin therapy; Unwilling to undertake glucose profiles using the subcutaneous continuous glucose monitoring; Unwilling to use SMBG at least 4 times daily; Unwilling to monitor and record signs and symptoms of hypoglycaemia; history of intolerance to insulin glargine.	Allocation sequence was generated by an individual not otherwise involved with participant recruitment.	Parallel	24 weeks	SMBG+insulin not specified (n=43)	CGM+SMBG, insulin reported together (n=43)	HbA1c; TIR; DKA; HFS; DTSQ
Ly (2011)[156]	Australia	Type 1	Pediatric (12-18 years)	Adolescents with T1DM; hypoglycemia unawareness	NR	Randomized to 1 of 2 groups	Parallel	4 weeks	SMBG, insulin unspecified (n=5)	CGM+SMBG, insulin unspecified (n=6)	HbA1c
Mauras (2012)[157]	USA	Type 1	Pediatric (4-10; 11-14 years)	4 - 10 yrs; HbA1c > 7.0%, and basal bolus therapy using either an insulin pump or at least three (MDIs) of insulin for	Diagnosis of diabetes prior to 6 months of age; medication that affect glycemic control; use of CGM during prior 6 months	Randomly assigned using permuted-blocks design stratified by clinical center	Parallel	26 weeks	SMBG, insulin unspecified (n=68)	CGM+SMBG, CSII (n=69)	HbA1c, HYpos, Ketoacidosis, HFS

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				the prior 3 months with no plans to switch the insulin modality within the next 6 months							
Peyrot (2009)[128]	Not specified (presumably USA)	Type 1	Adults	NR	NR	NR	Parallel	16 weeks	MDI +SMBG (n=14)	CSII+rtCGM+SMBG (n=14)	HbA1c, Hypos, DKA
Piona (2018)[158]	Slovenia	Type 1	Pediatric (6-15 years)	Age 6-15 yrs; T1DM for at least 6 month; at least 3 months of current use of an insulin pump; HbA1c between 6.3%-10%; self-reported regular SMBG; BMI within normal range for age; the absence of other medical conditions	Concomitant diseases; significant morbidity; oral antidiabetic therapy; pregnancy or attempting; known hypoglycemia unawareness; diabetic ketoacidosis	Randomly assigned	Parallel	2 weeks	SMBG, CSII (n=20)	Flash+SMBG, CSII (n=25)	TIR; Hypos; ketoacidosis,
Polonsky (2017)[129]	USA	Type 1	Adults	Age ≥ 25 years; T1DM treated with MDI for at least 1 year; HbA1c 7.5–10.0%	CGM use in the 3 months pretrial	Randomly assigned in a 2:1 ratio to either the CGM or control group	Parallel	24 weeks	SMBG, MDI (n=53)	CGM+SMBG, MDI (n=105)	EQ-5D

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
Reddy (2015)[130]	UK	Type 1	Adults	Age 18-75 yrs; T1DM > 1 yr; fasting c-peptide <0.2 nmol/l; treatment with CSII for >6 months; and HbA1c <8.5%.	Recurrent severe hypoglycemia; pregnancy or planning pregnancy; breastfeeding; enrolment in other clinical studies; active malignancy; or being under investigation for malignancy.	Randomly assigned the order of the closed-loop and open-loop study visit using computer generated allocation numbers	Crossover	24 hours	CGM+SMBG, CSII (n= 14)	CL(bio-inspired control algorithm) (n=14)	TIR
Reddy (2018)[131]	USA	Type 1	Adults	Age ≥ 18 yrs with T1D for >3 yrs; with severe hypoglycemic event in last 12 months requiring assistance or Gold score of < 4	CGM or flash glucose monitoring within the last 6 months; used regular paracetamol; were pregnant or planning pregnancy; breast-feeding, enrolled in other clinical trials; active malignancy or were under investigation for malignancy; severe visual impairment, or reduced manual dexterity	Randomly assigned in a 1:1 ratio using an online randomization tool (www.sealedenvelope.com) stratified by HbA1c <58mmol/mol and ≥58mmol/mol	Parallel	8 weeks	Flash, MDI	CGM+no SMBG, MDI	HbA1c; Hypos; HFS; TIR
Russell (2015)[132]	USA	Type 1	Adults	Patients with T1DM; insulin pump therapy;	Pregnancy; cystic fibrosis; pancreatitis; stimulated C-peptide >0.1nmol/l at 90 mins; hypoglycemia unawareness; anemia;heart failure; hypoglycemic seizure;	NR	Crossover	5 days	CSII, monitoring not specified (n=32)	Bihormonal AP (algorithm not specified) (n= 32)	TIR; Hypos
Russell (2015)[132]	USA	Type 1	Pediatric (12-20 years)	Patients with T1DM; insulin pump therapy;	Pregnancy; cystic fibrosis; pancreatitis; stimulated C-peptide >0.1nmol/l at 90 mins; hypoglycemia unawareness; anemia;heart failure;	NR	Crossover	5 days	DHAP (algorithm unspecified)+SMBG (n=32)	CSII, monitoring unspecified (n=32)	TIR; Hypos

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
					hypoglycemic seizure;						
Russell (2016)[159]	USA	Type 1	Pediatric (6-11 years)	6-11 years with T1DM for 1 year or longer; use insulin pump therapy	cystic fibrosis; seizure disorder; eating disorder; intentional inappropriate administration of insulin; pregnancy;	1:1 ratio; blocks of two	Crossover	5 days	CSII, monitoring unspecified (n=19)	DHAP (algorithm not specified)+SMBG (n=19)	TIR; Hypos
Sequeira (2013)[133]	USA	Type 1	Adults	Diagnosis of diabetes mellitus for at least 6 months prior to study enrollment, subject self-report of self-monitoring blood glucose three or more times per day, on multiple daily insulin injections, and at least 18 years of age.	NR	NR	Crossover	28 weeks	CGM+SMBG not specified, MDI	SMBG, MDI	HbA1c
Sharifi (2016)[139]	Australia	Type 1	Pediatric (12-18 years)	12-18 yrs; T1DM of >1 year; C-peptide level <0.15 ng/mL; HbA1c <8.5%	Total insulin dose >150 units/day; episode of diabetic ketoacidosis; >2 severe hypoglycemic episodes; renal impairment; pregnancy; breastfeeding	Computerized sequence generation	Crossover	4 days	Night: CL (proportional integral derivative algorithm), Day: CGM+SMBG not specified, CSII with low glucose suspend (n=12)	CGM+SMBG not specified, CSII with low-glucose suspend function (n=14)	Hypos, ketoacidosis

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
Stewart (2018)[168]	UK	Type 1	Pregnant women	Pregnant women (18-45 yrs); T1DM for at least one year before pregnancy; a singleton pregnancy with ultrasound-confirmed gestational age between 8-24 weeks; intensive insulin treatment (either MDI or CSII); HbA1c level of ≥6.5 and ≤10% ; speak and understand English and have email access.	Physical or psychological disease; medications known to interfere with glucose metabolism; insulin dose of ≥1.5 units/kg	Was created with an automated web-based programme, using permuted four-block schedule maintained in a secure database	Crossover	28 days	CGM+SMBG, CSII(n=16)	closed loop (University of Cambridge algorithm) (n=16)	HbA1c, TIR, Hypos,
Stewart (2016)[167]	UK	Type 1	Pregnant women	Age 18 to 45 years; with a pregnancy between 8 and 24 weeks of gestation; HbA1c level between 6.5 and 10.0%; receiving intensive insulin therapy either multiple daily injections or	Use of assisted reproductive technologies; receiving concurrent treatment that might influence glucose control; had a multiple-gestation pregnancy, had nephropathy, neuropathy, or proliferative retinopathy; allergy against insulin	Randomly assigned in permuted blocks of 4	Crossover	4 weeks	CGM+SMBG, CSII (n=16)	closed loop(model predictive control algorithm (n=16)	TIR; Hypos

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				an insulin pump.							
Tang (2014)[175]	Canada	Type 2	Adults	Recent HbA1c >7%; internet access; received SMBG at a frequency of at least once per day;	NR	1:1 ratio and was produced by a computer random number generator.	Parallel		SMBG + MDII + internet software for reporting and monitoring BGL (n=17)	rtCGM+MDII+endocrinologist feedback (n=15)	DTSQ
Tauschmann (2016)[160]	UK	Type 1	Pediatric (10-18 years	T1DM with insulin pump therapy for at least 3 months; perform 4 fingerstick glucose measure per day; HbA1c <11%	Nephropathy; neuropathy; retinopathy, total daily insulin dose > 2.0 units/kg; significant hypoglycemia unawareness; more than one incident of severe hypoglycemia within 6 months; more than one episode of diabetic ketoacidosis; pregnancy, and breast-feeding	NR	Crossover	21 days	CGM+SMBG, CSII	CL(MPC algorithm)+SMBG	TIR
Thabit (2014)[134]	UK	Type 1	Adults	Age ≥ 18 yrs with T1DM; C-peptide negative; insulin pump therapy for at least 3 months, knowledge of insulin self-adjustment; performing glucose self-	Nephropathy; neuropathy or proliferative retinopathy; total daily insulin dose ≥2·0U/kg; regular use of CGM within 1 month prior to enrolment; severe visual or hearing impairment;	Randomization using computer generated permuted block randomisation	Crossover	28 days	n=25		HbA1c, TIR

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				monitoring at least four times daily, and HbA1c≤10%	pregnancy or breast feeding						
Thabit (2015)[135]	UK, Germany, Austria	Type 1	Adult	18 yrs with T1DM; received insulin-pump therapy; HbA1c 7.5 - 10%	Living alone; lacked telephone facility; C-petide > 100pmol/l with concomitant plasma glucose > 72mg/dl; total daily insulin dose >2U/Kg/day; reduced hypoglycemia awareness; more than 1 episode of severe hypoglycemia; nephropathy;	Randomly assigned			CGM+SMBG, CSII (n=18)	Night: CL (model predictive control algorithm); day: CGM+SMBG, CSII (assumed this is day intervention) (n=14)	HbA1c, TIR, Hypos, DKA
Thabit (2015)[135]	UK, Germany, Austria	Type 1	Pediatric (6-18 years)	At least 6 yrs; on insulin pump for at least 3 months; HbA1c <10%; willing to use closed loop system overnight	Total insulin dose > 2 U/kg/day; recurrent of severe hypoglycemia; untreated celiac disease; nephropathy; neuropathy; retinopathy; medication that might affect glucose metabolism;	Randomly assigned	Crossover	12 weeks	CGM+SMBG, CSII (n=11)	Night: CL (model predictive control algorithm); day: CGM+SMBG, CSII (assumed this is day intervention) (n=14)	Hypos
Tildesley (2013)[176]	Canada	Type 2	Adults	A1C level > 7%; internet access; prior use of SMBG	NR	Randomly were assigned to 1 of 2 groups, IBGMS or RT-CGM, using a computer random number generator.	Parallel	6 months	SMBG + MDII + feedback from an endocrinologist (n=25)	CGM+MDII+feedback from their endocrinologist (n=25)	HbA1c
Tumminia (2015)[136]	Italy	Type 1	Adults	Age 18-60 yrs; T1DM ≥ 1 yr; HbA1c levels > 8.0%; similar school education and socio-	Pregnant women or planning pregnancy; concomitant chronic illness and/or poor compliance to diet; plasma glucose had to be measured at least	Randomization was electronically generated, according to a predefined randomization sequence	Crossover	6 months	SMBG+CSII (n=10)	CGM+CSII, SMBG not specified (n=10)	HbA1c, Hypos, DKA,

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				economic staus	4–5 times/day, correcting the insulin dose when required.						
Van Beers (2016)[137]	Netherlands	Type 1	Adults	Type 1 diabetes (based on American Diabetes Association [ADA] criteria),19 aged 18–75 years, be treated with either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDI), be undertaking at least three SMBG measure ments per day, and have impaired awareness of hypoglycaemia	History of renal, liver or heart disease; current untreated pro liferative diabetic retinopathy; current malignancy; current use of non-selective β blockers; current psychiatric disorders; current substance abuse or alcohol abuse; pregnancy; current use of CGM other than for a short period (3 consecutive months); any hearing or vision impairment; poor command of the Dutch language; any disorder that precluded full understanding of the purpose and instructions of the study; participation in another clinical study; and any known or suspected allergy to trial-related products.	Randomly assigned patients (1:1) using a computer-generated allocation sequence (block size of four) to either CGM or SMBG	Crossover	16 weeks	SMBG, insulin reported together (n=26)	CGM+SMBG not specified, insulin reported together (n=26)	HbA1c, TIR, Hypos, DKA, EQ-D5, HFS
Wysocki (2006)[161]	USA	Type 1	Pediatric (7-18 years)	7-18 yrs; T1DM with use of insulin for 1 yr; HbA1c level of 7-11%; on	Prior home use of GW2B; Skin abnormalities; current or past use of corticosteroids in last	Randomly assigned	Parallel	6 months	CGM+ SMBG (n=101)	GW2B (n=99	PedsQL

First Author (Year)	Country	Diabetes Type	Population	Inclusion Criteria	Exclusion Criteria	Randomization	Study Design	Follow Up	Intervention 1	Intervention 2	Outcome(s)
				stable insulin regimen;	6 months; chronic illness						

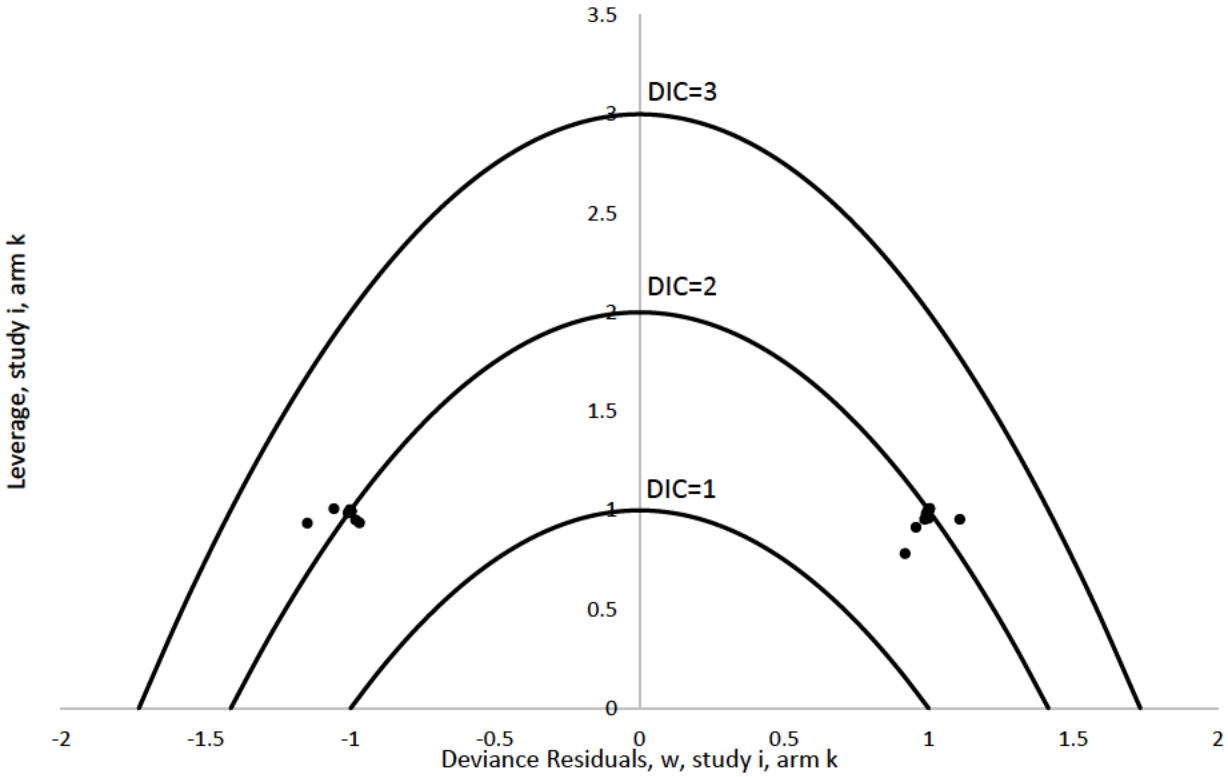
Abbreviations:
T1D/T1DM = Type 1 Diabetes; T2D/T2DM = Type 2 Diabetes; NR = Not Reported; SMBG = Self-Monitoring of Blood Glucose; MDI = Multiple Daily Injections; CGM = Continuous Glucose Monitor; CSII = Continuous Subcutaneous Insulin Infusion; CL = Closed-Loop; MPC = Model Predictive Control algorithm; AP = Artificial Pancreas; GW2B = GlucoWatch G2 Biographer; HbA1c = glycated hemoglobin; TIR = Time in Range; DK = diabetic Ketoacidosis; HFS = Hypoglycemia Fear Survey; DTSQ = Diabetes Treatment Satisfaction Questionnaire; PedsQL = Pediatric Quality of Life

20.6.2 Adult Type 1 Diabetes HbA1c Network Meta-Analysis Model Selection

	Fixed Effects	Random Effects
Posterior mean residual deviance	73.79	31.28
Posterior mean deviance	-2.20	-44.71
Effective number of parameters	24.98	30.34
Deviance information criterion	22.79	-14.38
Between-study standard deviation (posterior mean (95% credible interval))	NA	0.49 (0.21 to 1.07)

The random effects model fits the data better, as evidenced by the lower posterior mean residual deviance. In this model, there were 31 data points, which is similar to the posterior mean residual deviance of the random effects model, and suggests adequate fit. Deviance information criterion of the random effects model is less than that of the fixed effects model, which also supports this choice.

20.6.3 Adult Type 1 Diabetes HbA1c Leverage Plot

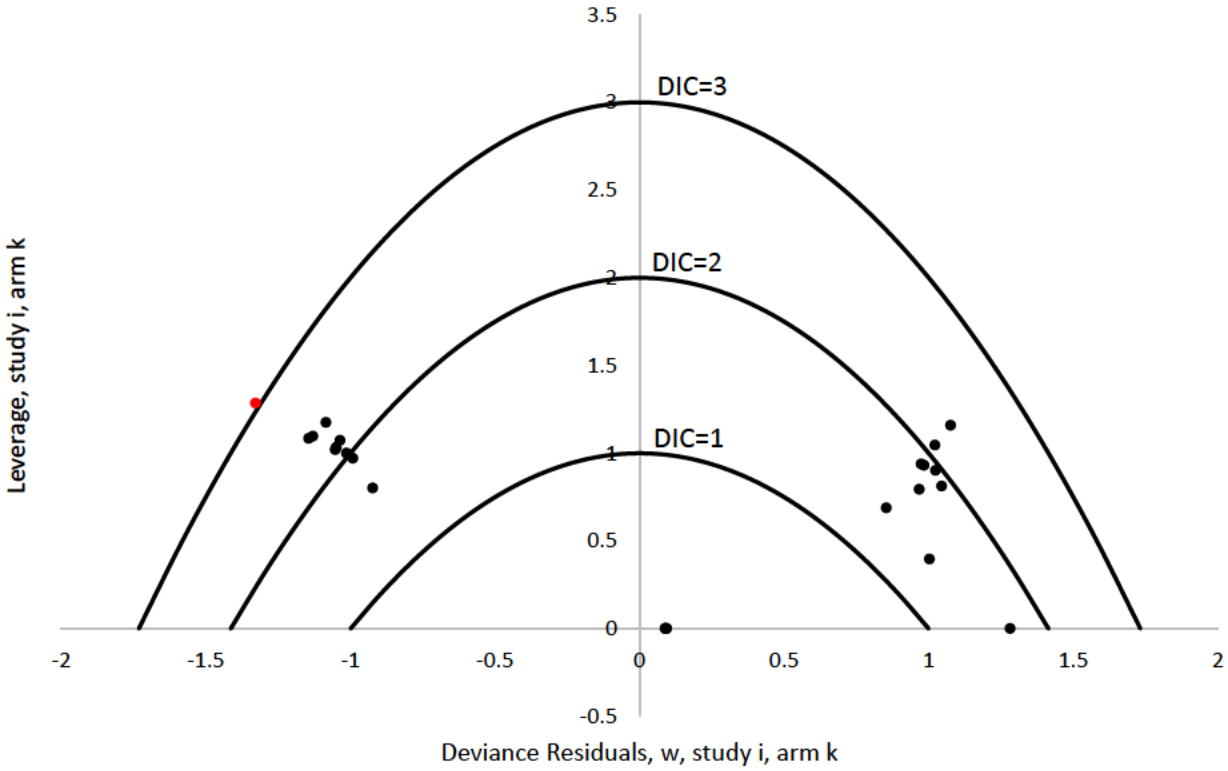


20.6.4 Adult Type 1 Diabetes Number of Hypoglycemic Events Requiring Assistance Network Meta-Analysis Model Selection

	Fixed Effects	Random Effects
Posterior mean residual deviance	33.4	22.27
Posterior mean deviance	102.95	91.81
Effective number of parameters	12.61	17.34
Deviance information criterion	115.56	109.14
Between-study standard deviation, (posterior mean (95% credible interval))	NA	0.87 (0.18 to 2.26)

The random effects model fits the data better, as evidenced by the lower posterior mean residual deviance. For the random effects model, the posterior mean residual deviance was close to the observed number of data points 24, suggesting adequate fit. The posterior mean residual deviance of the fixed effects model was greater than 24, which suggests a lack of fit. The lower DIC associated with the random effects model also supports selection of the random effects model.

20.6.5 Adult Type 1 Diabetes Hypoglycemic Events Requiring Assistance Leverage Plot



20.6.6 Step diagram for all treatment comparisons for relative hazard of hypoglycemic events requiring assistance.

SMBG			
0.8 0.3 to 1.7	CGM		
0.5 0.0 to 5.7	0.6 0.0 to 8.7	Flash	
0.8 0.0 to 46.3	1.0 0.0 to 56.5	1.7 0.0 to 235.4	CL

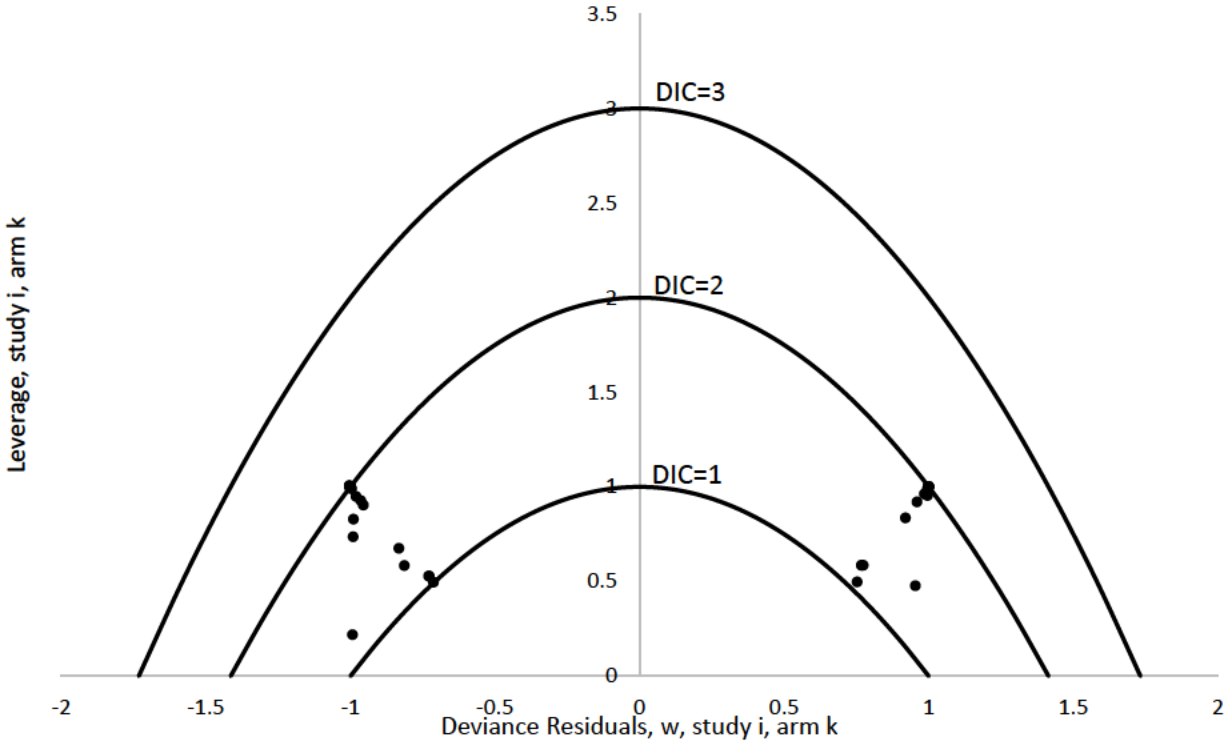
*SMBG=self-monitoring of blood glucose; CGM=continuous glucose monitoring; CL=closed loop

20.6.7 Adult Type 1 Diabetes Percent of Time-in-Range of 3.9-10.0 mmol/L Blood Glucose Network Meta-Analysis Model Selection

	Fixed Effects	Random Effects
Posterior mean residual deviances	43.05	43.23
Posterior mean deviance	219.55	219.73
Effective number of parameters	41.94	42.60
Deviance information criterion	261.49	262.33
Between-study standard deviation, (posterior mean (95% credible interval))	NA	2.00 (0.08 to 4.72)

Fixed effects and random effects models were similar in terms of posterior mean residual, posterior mean deviance, effective number of parameters, and deviance information criteria. Effects of interventions are also similar between models; therefore, the fixed effects model is preferred for ease of interpretation.

20.6.8 Adult Type 1 Diabetes Percent of Time-in-Range of 3.9-10.0 mmol/L Blood Glucose Leverage Plot

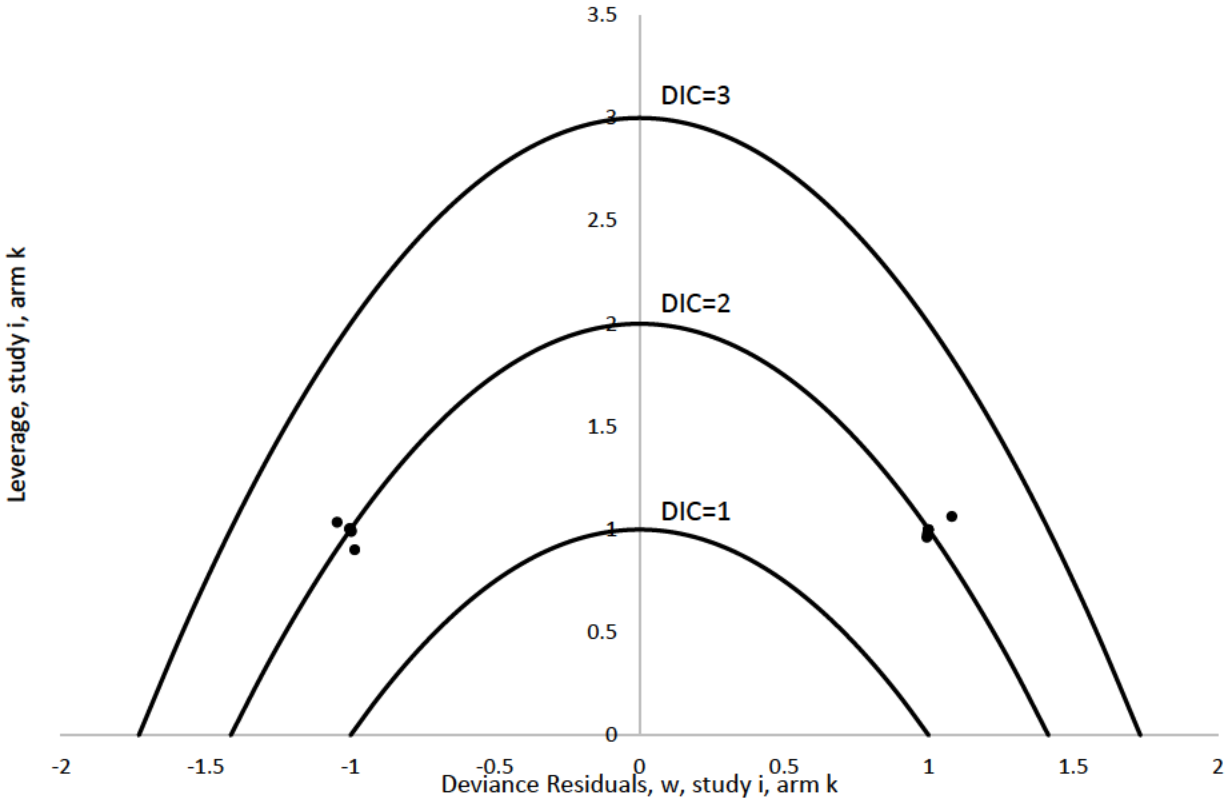


20.6.9 Pediatric Type 1 Diabetes HbA1c Network Meta-Analysis Model Selection

	Fixed Effects	Random Effects
Posterior mean residual deviances	21.31	17.86
Posterior mean deviance	-18.73	-22.17
Effective number of parameters	14.99	17.27
Deviance information criterion	-3.74	-4.90
Between-study standard deviation, (posterior mean (95% credible interval))	NA	0.57 (0.04 to 2.24)

The random effects model fits the data better, as evidenced by the lower posterior mean residual deviance. For the random effects model, the posterior mean residual deviance is close to the observed number of data points 18, suggesting adequate fit. The posterior mean residual deviance of the fixed effects model is greater than 18, which could point to a lack of fit. The difference in DIC between the two models is less than three, and therefore is not meaningful. The random effects model is preferred.

20.6.10 Pediatric Type 1 Diabetes HbA1c Leverage Plot

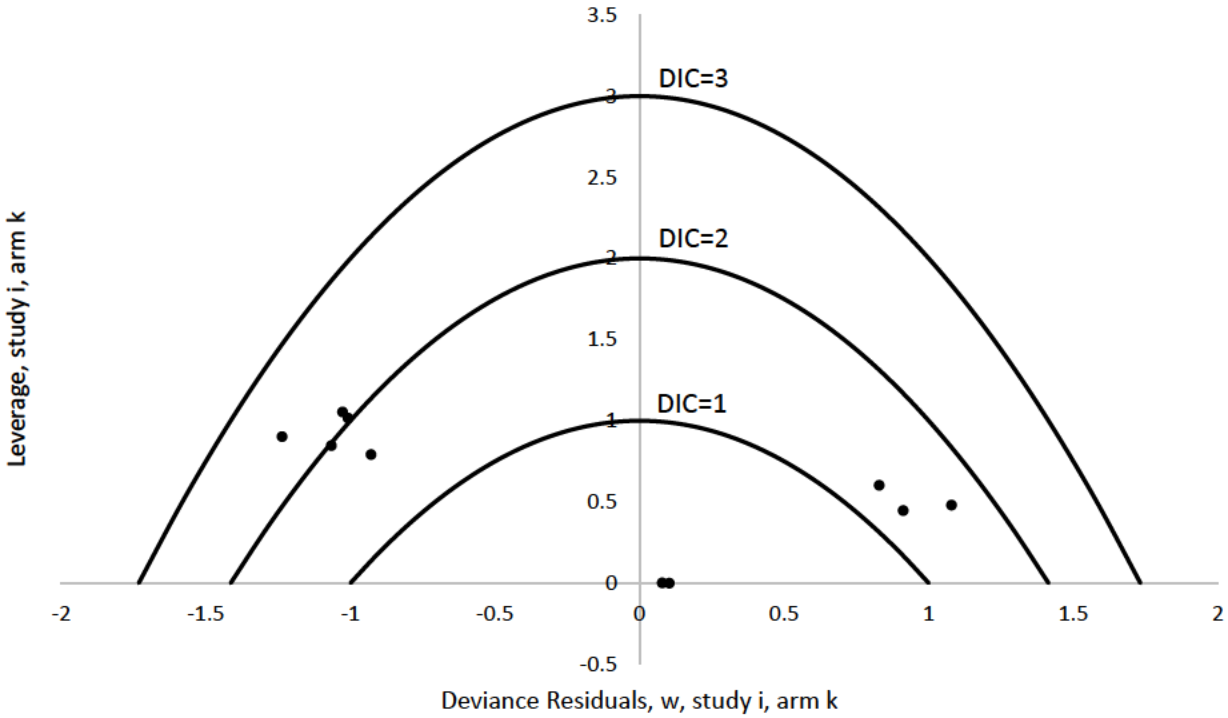


20.6.11 Pediatric Type 1 Diabetes Number of Hypoglycemic Events Requiring Assistance Network Meta-Analysis Model Selection

	Fixed Effects	Random Effects
Posterior mean residual deviances	8.29	7.93
Posterior mean deviance	36.35	35.98
Effective number of parameters	5.91	7.29
Deviance information criterion	42.26	43.27
Between-study standard deviation, (posterior mean (95% credible interval))	NA	1.27 (0.05 to 4.29)

The posterior mean residual deviance, posterior mean deviance, effective number of parameters, and DIC are similar between the fixed and random effects model. The median estimate of effect is also similar between models; therefore, the fixed effects model is preferred for ease of interpretation.

20.6.12 Pediatric Type 1 Diabetes Hypoglycemic Events Requiring Assistance Leverage Plot

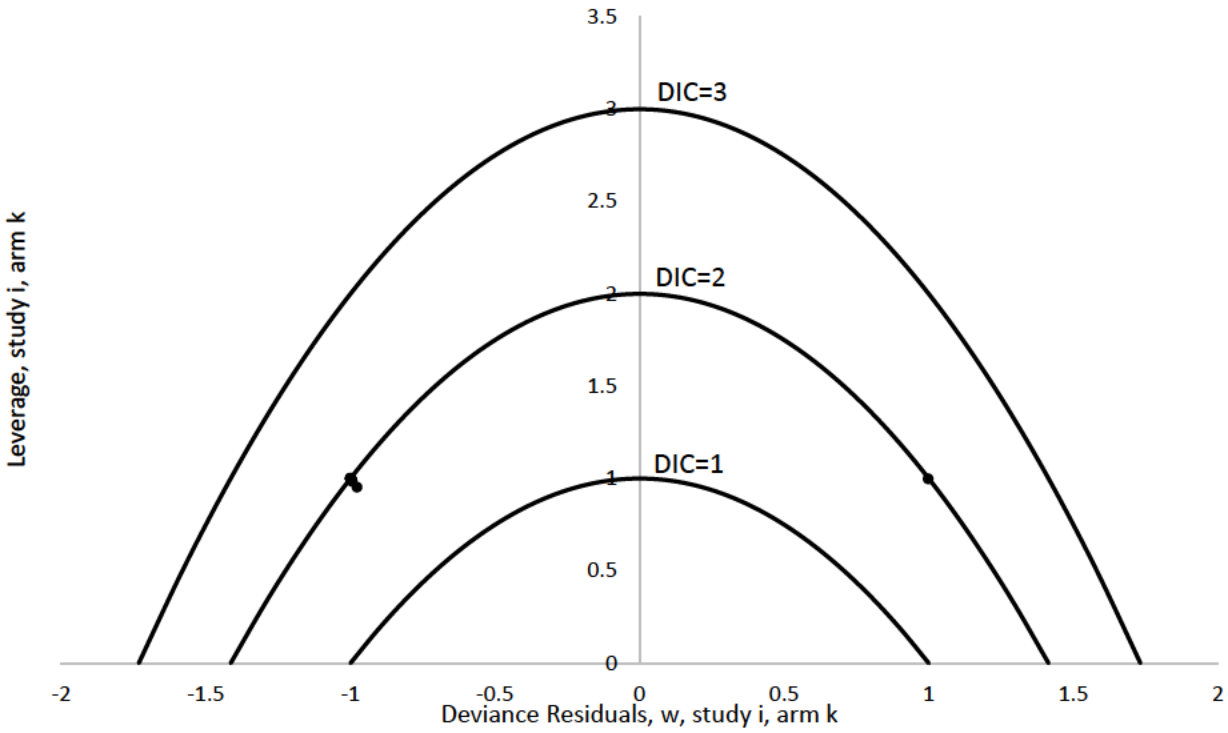


20.6.13Pediatric Type 1 Diabetes Percent of Time-in-Range for Blood Glucose 3.9-10.0 mmol/L Network Meta-Analysis Model Selection

	Fixed Effects	Random Effects
Posterior mean residual deviances	15.88	15.92
Posterior mean deviance	84.01	84.05
Effective number of parameters	15.88	15.91
Deviance information criterion	99.89	99.96
Between-study standard deviation, (posterior mean (95% credible interval))	NA	2.50 (0.14 to 4.87)

Fixed effects and random effects models are similar in terms of posterior mean residual, posterior mean deviance, effective number of parameters, and deviance information criteria. Effects of interventions are also similar between models; therefore, the fixed effects model is preferred for ease of interpretation.

20.6.14 Pediatric Type 1 Diabetes Percent of Time-in-Range of 3.9-10.0 mmol/L Blood Glucose Leverage Plot



20.7 Appendix G: Study Characteristics for Systematic Review of Patient Perspectives

Author	Year	Country	Population	Number of participants	Timeline with "Intervention"	General Findings
Vloemans, A.F., et al.[193]	2017	Amsterdam	Adults; Type 1 with impaired awareness of hypoglycemia	23 adults	Two 16-week intervention periods with a 12- week washout in between.	Sense of control (more control over diabetes, gained better insights into daily trends and patterns, freedom and release of burdening or relying on others, annoyance with frequency of alarms), east of use (machine and features were easy to use, design of sensor was outdated, calibration was a pain, sensor insertion was painful); and handling of CGM information (wide range of responses - some were annoyed at having to respond to the machine in the presence of other, others appreciated the alarms, increased active engagement in self-managing diabetes and others felt it made them more passive).
Hendriechx et al.[191]	2017	Australia	Adults; Type 1	16 participants	4 consecutive nights	Most experienced more stable overnight glucose levels (although for some these levels were similar to usual care or higher than they expected). In comparison to usual care, participants noticed the ability of the system to be able to predict trends and deliver micro amounts of insulin. Participants reported technical issues such as alarms, transmission problems and sensor inaccuracies. Remote monitoring by the trial team and their own hypoglycemic

						awareness contributed to feelings of trust and safety. Some reported safety concerns related to feeling unsure whether the system could respond to falling glucose levels.
Rashotte, J., et al.[190]	2014	Canada	Adolescents and Parents (Type 1)	7 adolescents and 9 parents	Median use was 0-7 years	Managing hopes and expectations of the sensor (thinking it will take away all your worries and concerns but there are a whole host of other issues with the sensor), being ready for SAPT, living with the burden of continuous monitoring. Many parents and adolescents struggle with trying to balance living with the demands of their disease. Pain from sensor insertion. Technology worries, reliability and the worry of an alarm sounding at inconvenient times. Takes a series of partnerships (between parents, adolescents and many others).

Ontario Health Technology Assessment Series[190]	2018	Canada	Adults and parents; Type 1	59	None specified	Diagnosis (overwhelming; emotional, no previous knowledge of experience of T1DM, major life changes and adjustments); day to day (unique to each person, adjustments to work life or social settings, emotional impact contrast fear and anxiety, difficulty allowing children to control their own illness out of fear by parents, sleeping patterns). CGM (not knowing about it, financial barriers, lack of information, social benefits - discretely check levels, social freedom, emotional benefits as individuals and children could manage their illness better without fear, medical and safety benefits (another tool that keeps me away from hospitals), more information is better when managing diabetes, alerts give individuals living on their own increased comfort. Concerns - alarm fatigue and overwhelming data. Initially inserting the device.
Berg, A.K., A.B. Simonsen, and J. Svensson[192]	2018	Denmark	Children and Adolescents	8 children and adolescents	1.3 to 5 years of pump usage	Materials used (adhesive glue, tape and the actual patch material itself were suspected; hard materials used for the patch were also thought); time (getting worse over time) and skin characteristics (dry and sensitive skins seem to cause more challenges); frequency of change.
Scharf, J., et al.[38]	2018	Germany	Mix: Type 1 and 2	30 adults	None specified	Convenience, ease of use, time saving, opportunity to monitor glucose levels, more socially acceptable, attracts less attention, fewer interruptions increased

						concertation at work and ability to work more efficiently.
Bomba, F., E. Muller-Godeffroy, and S. von Sengbusch[40]	2018	Germany	Children: Type 1	9 parents, 8 children/youth	6 months	Adaption occurred over several phases; having already gone through the experience with one child made parents more capable; parents stressed out and frustrated with the sensor; challenging developing a regular structure; calibrating; difference in onions around ease of using the technology. Reduction in number of required blood sugar measurements; feeling of reduced fear a hypoglycemic event would occur; large amount of data is great and helps with understanding. Hassles - finding a good time to calibrate. Setting the sensor is painful and uncomfortable; dissatisfaction with the alarm. Games and school activities were interrupted less, increased transparency between children and parents.
Lawton, J., et al.[188]	2018	United Kingdom	Mixed; not stated	24 interviews	4 weeks	Ease of accessing information regarding blood glucose levels, using glucose level information to make life decisions (predicative information aided short-term lifestyle planning and enabled individuals to prevent hypoglycemic events), developing a better understanding of how insulin, food and activity impact glucose levels. Tolerating experiences with glitches and inaccuracies with the monitor

						(challenges inserting or removing device, finding the right spot on your body) technological issues (alarms, calibrating the machine etc.).
Barnard, K.D., et al.[39]	2014	United Kingdom	Adolescents (Type 1) and parents	16 adolescents	One group - overnight closed loop for 21 days plus CGM. Group 2 - CGM alone for 21 days with a 2-3 washout.	Positive and negative aspects of the closed loop (improved sleep, reduced anxiety, uncomfortable, too big); perceived improvement in blood glucose; difficulties with calibration, alarms and size of the device.
Barnard, K.D., et al.[186]	2017	United Kingdom	Adolescents and adults (Type 1)	32 adults, 25 parents and 26 pediatric participants	None specified	Positive and negative aspects of the closed loop (improved sleep, reduced anxiety, alarms etc.). Pediatric participants - improved blood glucose control, feeling better. Worst - the size of the equipment, sensors having to have a second cannula, getting used to the system. Parents - confidence and reassurance, improved sleep and perceived improved blood glucose control. Worst - size of the pump and technical challenges with connectivity and calibration. Adults - freedom, not having to think about diabetes control. Worst - carrying around the equipment.

Barnard, K.D., et al.[187]	2015	United Kingdom	Adults; Type 1	24 adults (male)	4 weeks overnight only	Positive and negative (reassurance and piece of mind, better sleep); improved blood glucose control resulted in perceived improved health, more energy and a general sense of feeling better. Technical issues or difficulties with the equipment, alarms and overall usability; size of the equipment, having to carry many things; increased anxiety because of the technology.
Ritholz, M.D., et al.[182]	2014	United States	Adults; Type 1	9 younger and 11 older adults	None specified	Overall benefits of continuous monitoring on diabetes management (peace of mind, relief from anxiety, taking vacations, increased personal freedom); continuous monitoring on the relationship (promoted collaboration around diabetes management by increasing understanding, more visible nature of technology encouraged interest and desire to discuss diabetes, increased collaboration between couples planning and managing pregnancy). Conflict (little or no glucose education created frustration around alarms, reluctance from younger males to burden their spouses created distrust).
Iturralde, E., et al.[183]	2017	United States	Mixed; Type 1	17 adults, 15 adolescents	4 to 5 days	Expectations ranged from a system that could handle everything to modest benefits of glycemic control; overall positive glycemic control and quality of life; challenges with limitations around mealtime and exercise. Alarms, entering meal information and calibration

						perceived as burdensome. Impressed by the stability of glucose values and a feeling of a break from diabetes.
Gildersleeve, R., et al.[184]	2017	United States	Clinicians and Parents	5 specialists, 15 parents	None specified	Insulin settings (should require a passcode and some disagreement as to whether only the physician should be able to change them); desire for more custom settings, especially the alarms and remote monitoring; alerts and alarms should be customizable; low and high alarms should persist until treated; gamification options to incentives good behaviours and choices. Simple instructions.
Shepard, J.A., et al.[185]	2012	United States	Adults; Type 1	56 adults	To participate in research, use of insulin pump for minimum of 6 months.	Concerns with the accuracy of the system; trusting the technology and relinquishing personal control of diabetes management to a machine; importance of personalized information in order to provide the best glucose control.
Ritholz, M.D., et al.[181]	2010	United States	Adults; Type 1	20 adults	None specified	Coping with frustrations (mechanical feathers, alarms, calibration), use of continuous glucose monitoring (greater control over glucose levels, increased knowledge of unsafe behaviours), significant other/spousal involvement (increased interest in learning about and understanding glucose monitoring), body image (concerns about public

						appearance, viewed as robotic, self-conscious).