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HEALTH TECHNOLOGY ASSESSMENT REPORT

CONTINUOUS GLUCOSE MONITORING FOR INSULIN-REQUIRING DIABETES PATIENTS

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

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EXECUTIVE SUMMARY

BACKGROUND

One of the major public health concern facing our nation is the widely discussed chronic non-communicable disease (NCD) known as diabetes. According to a national survey report, in Malaysia in 2019, one in five adults in Malaysia had diabetes. Globally, estimation of people with diabetes was 463 million in 2019 and it is projected to reach 578 million by 2030 and 700 million by 2045. Of these, approximately 10% have Type 1 diabetes (T1DM).

Diabetes does end up receiving chronic disease treatment in the form of insulin therapy to help control their blood sugars in conjunction with a blood glucose meter. Without adequate blood sugar control, diabetes can lead to many debilitating complication, life-threatening conditions and ultimately death. Glycaemic control in participants with insulin-treated diabetes remains challenging and suboptimal in the majority of adolescents and young adults with T1DM. Ninety percent (90%) patients with type 2 diabetes (T2DM) contributed to a significant proportion of adults that have poor glycaemic control.

In order to receive the appropriate dose of insulin, an accurate measurement of blood glucose is required, typically with a finger-prick glucose meter. Self-monitoring of blood glucose (SMBG) is now recognised as a core component of diabetes self-management. This procedure is required throughout the day, with measurements taken before meals, after meals, before and after physical activity, before driving, and during the night. Thus, with the advance in diabetes technology, continuous glucose monitoring system (CGMS) devices with or without insulin pumps, allow frequent blood glucose measurements with no need for numerous needle pricks.

Continuous Glucose Monitoring Systems

The development of this new technology allowed patients to monitor their blood sugars by inserting a device subcutaneously. The CGMS measures a patient's glucose levels in their interstitial fluid over the entire day. A CGM works through a tiny sensor inserted under skin, usually on your belly or arm. The sensor measures the interstitial glucose level, which is the glucose found in the fluid between the cells. The sensor tests glucose every few minutes. A transmitter wirelessly sends the information to a monitor. The monitor may be part of an insulin pump or a separate device, which carry in a pocket or purse. Some CGMs send information directly to a smartphone or tablet. With CGMS, instead of the four readings per day, patients and medical providers now have a more in-depth knowledge of the fluctuations each unique patient experiences throughout their day. Real-time (rt-CGM) or flash continuous glucose monitoring displays the current glucose, direction and velocity of glucose change and provides programmable alarms.

Due to the rapid emerging of the diabetes technology using these wearable devices therefore, this assessment will evaluate whether it would be effective, safe and cost-effective to use CGM

in the management of diabetes patients required insulin management in Malaysia as requested by Medical Endocrinologist Consultants from Putrajaya and Malacca Hospital.

Policy Question

Should continuous glucose monitoring devices be utilised and provided as an approach for glucose monitoring for insulin-requiring diabetes patients' management?

Objectives

i. To assess the comparative effectiveness and safety of CGMS for glucose monitoring in insulin-requiring diabetes patients.
ii. To determine the economic, organizational, social, ethical and legal implications of CGMS for glucose monitoring in insulin-requiring diabetes patients.

Research questions

i. How effective and safe are the CGMS for glucose monitoring in insulin-requiring diabetes patients?
iii. How cost-effective are the CGMS or devices for glucose monitoring in insulin-requiring diabetes patients?
iv. What are the organizational, social, ethical and legal implications of CGMS or devices for glucose monitoring in insulin-requiring diabetes patients?
4.2 To assess the economic implication, social, ethical, and organisational aspects related to the used of CGM for glucose monitoring in insulin-requiring diabetes patients

METHOD

PART A: SYSTEMATIC REVIEW

Literature search was developed by the main author and an *Information Specialist* who searched for published articles pertaining to continuous glucose monitoring for diabetes patient who requiring the insulin. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to Jan 2023, EBM Reviews - Health Technology Assessment (4th Quarter 2016), EBM Reviews - Cochrane Database of Systematic Review (2005 to January 2023), EBM Reviews - Cochrane Central Register of Controlled Trials (Jan 2023), and EBM Reviews - NHS Economic Evaluation Database (1st Quarter 2016). Parallel searches were run in PubMed, US FDA and INAHTA database. There was no limitation in language, however, in the end only articles in English were included. Year of publication was limited from year 2000 to 2022 and only human study were included. Detailed search strategy is as in Appendix 3. The last search was performed on 28 February 2023. Additional articles were identified from reviewing the references of retrieved articles.

The risk of bias or quality assessment (methodology quality) of all retrieved literatures was assessed depending on the type of the study design; using the relevant checklist of National Collaborating Centre for Methods and Tools (ROBIS) for Systematic Review and Meta-

analysis, a revised Cochrane Risk of Bias Tool (RoB 2) for Randomised Controlled Trials, and Critical Appraisal Skill Programme (CASP) for Observational and Economic Studies. All full text articles were graded based on guidelines from the *U.S. / Canadian Preventive Services Task Force.*

PART B: LOCAL ECONOMIC EVALUATION

A simplified state transition model, consisted of six health states was used to estimate the cost-effectiveness of continuous glucose monitoring (CGM) for diabetic patients. It followed a hypothetical cohort of intensive insulin regimen patients with CGM versus self-monitoring of blood glucose (SMBG). Effectiveness was based on a meta-analysis and assumptions about the relationship between time in range (TIR), HbA1c reductions, and complications. Acute complications differed between type 1 and type 2 diabetes, and costs were calculated for device acquisition, hospitalization, follow-up visits, and diabetes-related management. The model compared T1DM and T2DM cohorts and applied a cost-effectiveness threshold of one-time per capita GDP of Malaysia in 2022 (MYR 53,043/QALY) from the perspective of MOH with a 3% annual discount rate. A Microsoft Excel cost calculator was created to assess the budget impact of increasing CGM use for T1DM patients. It considered glucose monitoring costs and costs of treating severe hypoglycaemic events. The analysis targeted T1DM patients with more than one severe hypoglycaemic event. Sensitivity analysis was conducted, and scenario analysis examined variations in test strip usage and sensor frequency. The prevalence and incidence of T1DM in Malaysia were estimated based on available data.

PART C: PATIENT AND PUBLIC INVOLVEMENT IN HTA – FOCUS GROUP DISCUSSION ON CGMS FOR DIABETES PATIENTS

A qualitative study was conducted with the aim of exploring patient perspectives on the use of Continuous Glucose Monitoring Systems (CGMS) for diabetes management. The research was conducted through focus group discussions, involving adults, adolescents, and caregivers. Participants were recruited through purposive sampling, and data was collected from May to September 2023. Ethical approval was obtained. The study collected demographic information and conducted discussions using a semi-structured interview guide, exploring the impact of diabetes, benefits, barriers, and attitudes toward CGMS. Thematic analysis was used to analyse the data.

Results:

PART A: SYSTEMATIC REVIEW

All studies included were published in English language between 2012 and till recently 2023 and were conducted in UK, USA, Canada, Italy, Spain, Australia, New Zealand, China and Singapore. The 15 full text articles which were finally selected in this review consist of seven

systematic reviews (SR) with meta-analyses, one SR, two RCTs, two (2) HTA reports and three economic related papers.

1. EFFECTIVENESS

i. GLYCAEMIC CONTROL

- **Hypoglycaemic events in T1DM patient:**

CGM significantly lower severe hypoglycaemic events among patients and also incidence of severe hypoglycaemic events (SHE) in CGM group was significantly lower, RR = 0:52, 95% CI 0.35-0.77, *p* = 0:001 and RR= 0.61; 95% CI 0.33 to 1.15); Z = 1.53, *p*=0.13) when compared with SMBG; (I^2 = 50%, *p*=0.04) when compared with SMBG. (Wang Y, 2022; Teo E, 2022) The risk of getting episode of hypoglycaemia was increased for CGM users, was not significant because of the CIs were wide (RR= 3.26, 95% CI 0.38 to 27.82) vs (RR 1.24, 95% CI 0.67 to 2.29) Langendam M 2012)

- **Hypoglycaemia in T2DM patients: (HTA Ontario 2019)**

CGM was more effective than SMBG in reducing the average time spent in hypoglycemia (−0.47h [95% CI −0.73 to −0.21]) and the average number of hypoglycemia events (−0.16 [95% CI −0.29 to −0.03]) among adults with T2DM requiring intensive insulin therapy. Hypoglycaemia events in T2DM patient, among hospitalised high risk for hypoglycaemia insulin-treated demonstrated that RT-CGM/GTS group experienced 60.4% fewer hypoglycemic events (<70 mg/dL) when compared with point of care/ standard of care or usual care (POC) group = [(0.67 events/patient; 95% CI 0.34 to 1.30] versus [1.69 events/patient [1.11 to 2.58], *P* = 0.024)]; with absolute RRR = 1.02 (RCT by Singh LG, 2022 In addition, the RT-CGM/GTS group experienced 60.4% fewer hypoglycemic events (<70 mg/dL) when compared with POC group = [(0.67 events/patient; 95% CI 0.34 to 1.30] versus [1.69 events/patient [1.11 to 2.58], *P* = 0.024)]; with absolute RRR = 1.02

- **Hypoglycaemia in GDM (Majewska A 2022)**

CGM detects a higher number of hypoglycaemia episodes than SMBG and showed a significant role in pregnant women qualify for insulin therapy. CGM group with GDM had significantly lower number of patients with hypoglycaemic events and also showed significant a difference in the duration of time spent in hypoglycaemia, with lower results in the CGM group

- **Hyperglycaemia in GDM (Majewska A, 2022)**

In this review demonstrated that CGM is better at detecting episodes of hyperglycaemia as compared to SMBG (from 2 studies) found that CGM detected more hyperglycaemic events when compared with SMBG and in all patients the incidence rate of hyperglycaemia = 5.65% using CGM versus 14.2% using SMBG (*p* < 0.05).

- **Episode of diabetic ketoacidosis (DKA)**

There is no statistical difference in the probability of occurrence of diabetes ketoacidosis between the CGM group when compared with the SMBG (RR = 1:34, 95% CI 0.57-3.15, and *p* = 0:5 (Wang Y, 2022) CGM group demonstrated no significant reduction in DKA events (RR= 1.06;

95% CI 0.49 to 2.32); Z = 0.15, *p*=0.88) when compared with SMBG; (I^2= 0%, *p*=0.59) (Teo E, 2022) There is no significant difference in risk of ketoacidosis between CGM and SMBG users.; RR= 0.94, 95% CI 0.36 to 2.40, I^2=0%). (Langendam M 2012)

II. REDUCING HBA1c

- **In T1DM & T2DM:**

CGM was associated with greater reduction in HbA1c from baseline compared with usual care SMBG) (-0.28%, 95% CI -0.36% to 0.21%, I^2 = 0%, *p* < 0.00001). The benefit was observed both in patients with T2DM (-0.31%, 95% CI -0.41% to -0.21%, I*2* = 14%, *p* < 0.00001) and T1DM (-0.27%, 95% CI -0.46% to -0.09%, I^2 = 0%, *p* = 0.004).

The results showed that CGM lowers HbA1c level by 0.17% (95% CI 20.29 to20.06, *p* < 0.003) when compared with the SMBG, among T1DM or T2DM with an extensive insulin regimen. In a subgroup analysis, the mean reduction of HbA1c was 0.23% in the 13 comparisons using rt-CGM. Neither is-CGM nor sensor-augmented pump (SAP) significantly changed mean HbA1c levels, with no evidence of statistically significant heterogeneity for the three comparisons using is-CGM (I^2= 0%) and high heterogeneity for the two comparisons using SAP (I^2=85.5%).

CGM showed greater HbA1c reduction and was aimed at improving glycaemic control MD= (-0.31, 95% CI -0.43 to -0.19, *p*< 0.001) a significant 0.16% decrease of HbA1c was associated with people T1DM but not people with T2DM. Overall, when compared with the usual care, CGM was associated with modest reduction in HbA1c (WMD= 20.17%, 95% CI 20.29 to 20.06, I^2= 96.2%).

- **In T1DM only:**

CGM showed a statistically significant absolute improvement in HbA1c percentage points (MD = -0.22; 95% CI (−0.31 to −0.14) when compared with SMBG. The effects were strongest with adjunctive technology *(Medtronic Paradigm, FreeStyle Navigator, Guardian REAL-Time, Dexcom series, MiniMed series, Enlite and Paradigm Veo)* MD=−0.26%; 95% CI (−0.36 to −0.16), and no evidence of a difference in HbA1c was seen for intermittent scannings – CGM (is-CGM). CGM significantly reducing the HbA1c level when combined with SMBG, the combined result is WMD = −2:69, 95% CI (-4.25, to 1.14), and *p* < 0:001. After six months, Rt-CGM users showed a significant larger decline in HbA1c level in starting insulin pump therapy when compared with patients using MDI and SMBG; MD in change in HbA1c level = (-0.7%, 95% CI -0.8% to -0.5%, 2 RCTs, 562 patients, I^2=84%).

- **In pregnant women (GDM)**

One RCT by Paramasivam S found that CGM significantly lower HbA1c concentration (CGM group: 5.2 ± 0.4% when compared with SMBG group: 5.6 ± 0.6%, p < 0.006.

- **Head-to-head comparison**

Head-to-head comparison between RT-CGM and open-loop continuous subcutaneous insulin infusions (CSII) when compared with RT-CGM Multiple Daily Injections (MDI) group showed that mean in overall HbA1c in RT-CGM+CSII = 63.3 ± 9.2 (mmol/mol) versus RT-CGM+MDI groups = 63.5 ± 10.2 (mmol/mol) and there is no significant reduction of HBA1c between groups.

iii: EFFECTS ON TIME IN RANGE (TIR); TIME SPENT BELOW RANGE (TBR)

- **In T1DM and T2DM**

The CGM group showed beneficial effect on change in TIR from baseline and a greater increase in TIR = (5.59%, 95% CI 0.12 to 11.06, I2 = 0%, p = 0.05) and a neutral effect on change in TBR range from baseline = (-0.11%, 95% CI -1.76% to 1.55%, I2 = 33%, p = 0.90). In patients with T1DM and T2DM with an extensive insulin regimen CGM showed a significant increase of TIR WMD= 70.74 min, 95% CI 46.73 to 94.76, p< 0.001; I2= 66.3%, p< 0.001). In the pre-specified subgroup analysis, TIR increased more in trials using rt-CGM (83.49, 95% CI 52.68 to 114.30, p <0.001) than intermittently scanned (is-CGM) (53.91, 95% CI 28.54 to 79.27, p< 0.001) or SAP (37.10, 95% CI 0.74 to 73.45, p< 0.045). The increase in TIR was significant and robust independently of diabetes type, method of insulin delivery, and reason for CGM use. Another finding from flash CGM demonstrated that CGM group spent on average one hour more in the target glucose range (95% CI 0.41 to 1.59) and 0.37 hours (22 minutes) less in a high glucose range (95% CI −0.69 to −0.05) compared with SMBG.

- **In T2DM among hospitalised high risk for hypoglycaemia insulin-treated**

One RCT by Singh LG (2020) demonstrated that CGM group lower percentage of time spent below range (TBR): <70 mg/dL (0.40% [0.18 to 0.92%] versus 1.88% [1.26 t0 2.81%], p= 0.002) and <54 mg/dL (0.05% [0.01 to 0.43%] vs. 0.82% [0.47 to 1.43%], p= 0.017) when compared with the POC/usual care group.

- **In T1DM patients only**

CGM group showed an overall absolute TIR increased by 5.4% (95% CI 3.5 to 7.2) when compared with control (SMBG), with heterogeneity (I^2= 71%). The effects were strongest with non-adjunctive technology - Dexcom G5 and Dexcom G6; TIR = 6.0% 95% CI 2.3 to 9.7). The CGM improved the percentage of time patients spent in the target glycemic range by 9.6% (95% CI 8.0 to 11.2) to 10.0% (95% CI 6.75 to 13.25).

2. SAFETY

An RCT by Haak T, 2017 (RCT) reported that there is no serious adverse events (SAEs) related to the device or study procedure. There were four hypoglycemia SAEs experienced by four participants (7% in CGM groups versus 9% in control participants) but none of the severe hypoglycemic episodes or hypoglycemic adverse events were associated with the device. Six

(4.0%) in the CGM group reported nine device-related adverse events which were sensor-adhesive reactions and resolved after treatment with topical preparations.

3. COST-EFFECTIVENESS

A CEA study by Roze S (from the U.K. health care payer (National Health Service and personal social services) found that DEXCOM G6 rt-CGM was associated with a mean incremental gain in quality-adjusted life expectancy = 1.49 quality-adjusted life years (QALYs) versus SMBG with (mean [SD] 11.47 [2.04] QALYs versus 9.99 [1.84] QALYs). A total mean (SD) lifetime costs were also higher with rt-CGM (GBP) £14,234
(GBP £102,468 [35,681] VS GBP £88,234 [39,027]) resulting in ICER of GBP £ 9,558 per QALY gained
Ose TK conducted a SR on economic concluded that two studies have explored the CEA of CGM from the payer perspective and have favoured their cost-effectiveness, while another study was inconclusive results due to more data and long-term studies are needed to better understand how CGM use relates to diabetes complications.
Jiao Y et al. conducted a CEA in Australian populations and reported that the estimated ICER range was [$18,734–$99,941] and the (QALY) gain range was [0.76–2.99]. Use in patients with suboptimal management or greater hypoglycaemic risk revealed more homogenous results and lower ICERs. Most studies (n = 17) concluded that CGM is a cost-effective tool.

4.0 ORGANIZATIONAL

- **Patient Reported Outcomes (PRO)**

A systematic review involving six previous systematic reviews found that CGM consistently yielded high patient satisfaction (87.5%) compared to other monitoring methods. Continuous Glucose Monitoring (CGM) was also linked to increased treatment satisfaction for both T1DM and T2DM, despite the presence of study heterogeneity. Additionally, two RCTs demonstrated notable improvements in patient satisfaction, particularly among T2DM patients, when using CGM. In 2020, a study by Pease et al. favored FGM over Self-Monitoring of Blood Glucose (SMBG) based on Diabetes Treatment Satisfaction Questionnaire (DTSQ) results, though statistical significance values were not reported.

- **Guidelines**

International guidelines according to The American Diabetes Association (ADA) released its 2022 Standards of Care, which provides an annual update on practice guidelines and expanded recommendations for CGM and Time in Range (TIR) use in adults and for CGM and automated insulin delivery (AID) use in children. The guidelines also include using diabetes technology in hospital settings. The use of CGM devices should be considered from the outset of the diagnosis of diabetes that requires insulin management. This allows for close tracking of glucose levels with adjustments of insulin dosing and lifestyle modifications and removes the burden of frequent SMBG. In addition, early CGM initiation after diagnosis of type 1 diabetes

in youth has been shown to decrease A1C and is associated with high parental satisfaction and reliance on this technology for diabetes management.

CONCLUSION:
PART A - SYSTEMATIC REVIEW

Based from the review:

1. CGM demonstrated significantly improved of glycaemic control especially in lowers severe hypoglycaemic events (SHE) in T1DM when compared with SMBG, more effective in reducing the average time spent in hypoglycemia and the average number of hypoglycemia events among adults with T2DM requiring intensive insulin therapy. Hypoglycaemia events in T2DM patient, among hospitalised high risk for hypoglycaemia insulin-treated demonstrated that CGM group experienced 60.4% fewer hypoglycemic events (<70 mg/dL) when compared with POC group. In special group such as GDM mothers, CGM detects a higher number of hypoglycaemia episodes than SMBG and showed a significant role in pregnant women qualify for insulin therapy. However, CGM group showed no significant reduction in DKA events or statistical difference in the probability of occurrence of diabetes ketoacidosis between the CGM group when compared with the SMBG.

2. CGM was associated with greater reduction in HbA1c from baseline compared with usual care SMBG) in both T1DM and T2DM patients. CGM group showed a statistically significant absolute improvement in HbA1c percentage points especially in T1DM.

3. CGM group showed beneficial effect on change in TIR from baseline and a greater increase in TIR and a neutral effect on change in TBR range from baseline. In patients with T1DM and T2DM with an extensive insulin regimen CGM showed a significant increase of TIR. TIR increased more in trials using RT-CGM than intermittently scanned (is-CGM) or SAP. The increase in TIR was significant and robust independently of diabetes type, method of insulin delivery, and reason for CGM used. In T2DM among hospitalised high risk for hypoglycaemia insulin-treated CGM group demonstrated a lower percentage of time spent below range (TBR) when compared with SMBG.

4. Limited evidence showed no serious adverse events were related to the device or study procedure. A small percentage of participants experienced hypoglycemia, with similar rates in both the CGM and control groups. Additionally, a few participants in the CGM group reported device-related adverse events, specifically sensor-adhesive reactions, which were resolved with treatment.

5. Patients in CGM group were very satisfied and all the included studies showed better results with the CGMS. In this review also showed that CGM improved treatment satisfaction for individuals with T1DM or T2DM but the quality of this evidence was low due to substantial clinical and statistical heterogeneity.

PART B: LOCAL ECONOMIC EVALUATION

- **Base-Case Analysis**

In both simulated cohorts of T1DM and T2DM patients, the use of Continuous Glucose Monitoring (CGM) was found to be not cost-effective at the current cost-effectiveness threshold. The incremental cost per patient for CGM compared to Self-Monitoring of Blood Glucose (SMBG) was notably high, primarily due to the cost of the CGM system. Key factors influencing the Incremental Cost-Effectiveness Ratio (ICER) were the cost of CGM sensors, SMBG testing frequency, and relative risk (RR) for complications. Shortening the time horizon resulted in varying ICER values (MYR 365,336 for 10 years and MYR 245,581 for 20 years). While CGM reduced hospital resource costs for severe hypoglycemic events in T1DM patients by 48%, it also raised the total annual cost by 28% compared to SMBG under base-case assumptions.

- **Budget Impact Analysis**

The budget impact analysis focuses on increasing the use of CGM among Malaysians with T1DM, considering the reduction in severe hypoglycemic events (SHE). The analysis shows that the yearly cost difference ranges from 4% to 3.6% as CGM usage increases from 10% to 70% over five years. Scenario analysis demonstrates that lower test strip usage in SMBG results in a higher cost difference with CGM, and reducing CGM sensor use can offset monitoring cost with a decrease in SHE management costs. Reducing CGM sensor and reader costs by 30-60% can make CGM more cost-competitive with SMBG.

Conclusion:
PART B -
LOCAL ECONOMIC EVALUATION

Blood glucose monitoring using CGM system was not a cost-effective option when compared to SMBG in both T1DM and T2DM populations with only small gain in the benefit shown in the former population over the simulated lifetime horizon. Nevertheless, CGM system may reduce the health care resource utilisation cost for managing T1DM patients who are at risk for frequent episodes of SHE. Additionally, the combination strategy of CGM and SMBG may improve adherence with lesser financial impact among diabetic patients requiring tight glycaemic control.

Part C: FOCUS GROUP DISCUSSION

The focus group discussions revealed five key themes: the impact of diabetes, perceived benefits of CGMS, perceived barriers to CGMS, issues for long-term use and hopes for CGMS, and overall attitudes and recommendations for CGMS use.

- **Impact of diabetes**

Individuals with diabetes experienced a profound impact across various aspects of their lives, leading to significant lifestyle adjustments, especially in diet, exercise, and daily management. Managing Type 1 diabetes was particularly demanding, with continuous blood sugar monitoring, precise meal planning, and insulin dosing, causing disruptions to daily routines. Emotional challenges were more pronounced among Type 1 diabetes patients and caregivers, manifesting as anger, stress, and feelings of being different. Health and medical consequences included inconvenient monitoring, medication complexities, glucose fluctuations, and susceptibility to diabetic complications. Socially, individuals with Type 1 diabetes faced challenges in socializing and encountered misunderstandings, particularly in school settings.

- **Perceived benefits of CGMS**

Participants found numerous benefits associated with using Continuous Glucose Monitoring System (CGMS) for diabetes management particularly among adolescent and adult Type 1 diabetes patients. These included medical advantages such as real-time monitoring, proactive insulin management, and fewer hypoglycemic events. CGMS served as an educational tool, fostering better understanding of diabetes, while also offering social benefits, saving time and enhancing freedom. It reduced emotional stress and improved quality of life, providing peace of mind, better sleep, and a sense of control over diabetes. Adolescents and caregivers particularly appreciated CGMS for its convenience and impact on independence.

- **Perceived barriers of CGMS**

The financial burden emerged as the primary barrier for CGMS use. High device costs and frequent sensor replacements led some to discontinue use due to financial constraints, exacerbated by a lack of insurance or government support. Participants also faced issues with device malfunctions, including sensor problems, data loss, and dislodgement during physical activities. Limited access to newer CGMS versions, inadequate technical support, lack of awareness, social stigma (especially among adolescents), and occasional skin irritation further hindered their CGMS experience.

- **Issues for long-term use & hopes for CGMS**

Participants shared concerns about the high long-term costs of CGMS, hoping for more affordability and solutions to address skin irritation. A consistent theme across all participants was the desire for CGMS access for specific patient groups and government subsidies for those with lower incomes, the elderly, or high diabetes-related risk. They also expressed a need for improved access to advanced CGMS versions with alarm features in Malaysia. Additionally, they called for healthcare professional training on effective CGMS use and preventive measures to combat the rising prevalence of Type 2 diabetes in the country.

- **Overall attitudes and patients' recommendation**

Findings from this focus group discussion, collectively reflect the overwhelmingly positive attitudes towards CGMS among diabetes patients and caregivers. They strongly recommended

CGMS use, especially for specific groups like Type 1 diabetes patients at high risk of hypoglycemia and adolescents to enhance daily life control. Caregivers particularly suggested early adoption of CGMS during the initial diagnosis stages, aiding patients, caregivers, and healthcare professionals in refining medication regimens and establishing effective diabetes care routines

Conclusion:

PART C - FGD

The focus group discussions have revealed noteworthy insights into the experiences of individuals with diabetes and their caregivers using CGMS. These discussions highlighted a range of perceived benefits for CGMS including medical benefits, social enhancements, emotional well-being, and an overall improvement in their quality of life, particularly among adolescent and adult Type 1 diabetes patients. Most participants regarded CGMS as a valuable educational resource for both patients and caregivers. However, participants also emphasized significant barriers, such as the high financial burden, technical challenges, limited accessibility, and support alongside concerns about social stigma and skin irritation. Participants also stressed issues related to long-term CGMS use, the need for improved technical support and access, as well as the absence of patient support groups. Despite these barriers, both diabetes patients and their caregivers held overwhelmingly positive attitudes towards the utilisation of CGMS for diabetes management and strongly endorsed CGMS use for individuals with diabetes particularly Type 1 diabetes, especially those at high risk of hypoglycaemia. Participants emphasized the need to address financial barriers, access issues, and technical support for CGMS, as well as the need for patient support groups and training for healthcare providers in utilizing CGMS data to improve diabetes care plans.

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ABBREVIATION

AoL	Adjuvant Online
CGM	Continuous glucose monitoring
CGMS	Continuous glucose monitoring system
EVPI	Expected value of perfect information
EVSI	Expected value of sample information
EVPPI	Expected value of perfect parameter information
FISH	Fluorescence In Situ Hybridization
HTA	Health Technology Assessment
HR	Hazard Ratio
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
LR+ / LR-	Positive likelihood ratio / Negative likelihood ratio
LYs	Life Years
MaHTAS	Malaysian Health Technology Assessment Section
MOH	Ministry of Health
NCD	non-communicable disease
NICE	UK National Institute for Health and Care Excellence's
QALYs	Quality adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
T1D	Type 1 Diabetes
T1DM	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes
T2DM	Type
US FDA	United States Food and Drug Administration
WHO	World Health Organization

1 BACKGROUND

One of the major public health concerns facing our nation is the widely discussed chronic non-communicable disease (NCD) known as diabetes. Malaysia has the highest rate of diabetes in Western Pacific region and one of the highest in the world and costing around 600 million US dollars per year. The prevalence of diabetes in Malaysia, based on published articles, ranges from 7.3% to 23.8%. The prevalence of diabetes raised from 11.2% in 2011 to 18.3% in 2019, with a 68.3% increase. According to a national survey report, in Malaysia in 2019, 3.6 million adults (18 and above years) had diabetes, 49% (3.7 million) cases were undiagnosed. Diabetes is expected to affect seven million Malaysian adults aged 18 and older by 2025, posing a major public health risk with a diabetes prevalence of 31.3%.[1] Therefore, diabetes is a major public health concern in Malaysia that is closely related to increased macro and microvascular complications, as well as premature and preventable mortality.[2] Meanwhile worldwide, the global estimate of people with diabetes was 463 million in 2019. This number is projected to reach 578 million by 2030 and 700 million by 2045. Of these, approximately 10% have Type 1 diabetes (T1D).[1,2]

Diabetes does end up receiving chronic disease treatment in the form of insulin therapy to help control their blood sugars in conjunction with a blood glucose meter. Without adequate blood sugar control, diabetes can lead to many debilitating and life-threatening conditions such as heart disease, stroke, vision loss, kidney disease, amputations, and ultimately death. To prevent these conditions from occurring, patients with diabetes are strongly encouraged to make dietary changes and frequently monitor their blood glucose.[3] One of the major barriers to good glucose control is the difficulty and discomfort of frequent blood sugar measurements by the patient before insulin injection and afterward, which results in impairment in patients' quality of life. Glycaemic control in participants with insulin-treated diabetes remains challenging[4,5] and remains suboptimal in the majority of adolescents and young adults with type 1 diabetes (T1DM), with only 17% attaining the 2019 American Diabetes Association’s haemoglobin A1c (HbA1c) target of less than 7.5% and 14% attaining the target of less than 7% in the T1D Exchange clinic registry.[6] Ninety percent (90%) patients with type 2 diabetes (T2DM) with a fifth of whom

are on insulin treatment and contributed to a significant proportion of adults with insulin-treated T2DM are less than 65 years of age and frequently that have poor glycaemic control. [2]

In order to receive the appropriate dose of insulin, an accurate measurement of blood glucose is required, typically with a finger- prick glucose meter. However, patients continue to struggle with the pain associated with finger-pricks before injecting insulin.[3] Continuous glucose monitoring system (CGMS) technologies, with or without insulin pumps, allow frequent blood glucose measurements with no need for numerous needle pricks. Moreover, CGMS may also alert unaware hypoglycaemia events or near hypoglycaemia events. Thus, preventing its deteriorative consequences by 50% with a decrease in both morning ketosis events and life-threatening events following physical exercise.[6,7,8]

CONVENTIONAL METHOD OF GLUCOSE MONITORING

Regular testing of blood glucose is critical to effectively manage T1DM and T2DM diabetes requiring intensive insulin therapy (i.e., multiple daily insulin injections - MDI or a continuous subcutaneous insulin infusion- CSII) to keep their blood glucose levels in the target range. Traditionally, people with diabetes have monitored their glucose levels using finger-prick meters. This method was introduced in the 1970s, is commonly known as self-monitoring of blood glucose (SMBG), and is currently the standard method for monitoring blood. For people whose glucose levels are not well controlled (HbA1C > 7%) and who require insulin, SMBG is required throughout the day, with measurements taken before meals, after meals, before and after physical activity, before driving, and during the night. Periodic SMBG is needed for some adults with T2DM who use oral anti-diabetes drugs. Self-monitoring of blood glucose has drawbacks, including the pain of finger prick (usually done four to six times a day when using insulin) and less comprehensive glycemic data.[10]

Self-monitoring of blood glucose (SMBG) is now recognised as a core component of diabetes self-management. The American Diabetes Association (ADA) recommends that patients on intensive insulin regimens, multiple-dose insulin (MDI) or continuous subcutaneous insulin infusion (CSII) should consider SMBG prior to meals and snacks,

occasionally following meals, at bedtime, prior to exercise, when low glucose is suspected, after treating low glucose and prior to critical tasks such as driving. For many patients, this will require testing six to 10 (or more) times daily.[11] The SMBG has some disadvantages:[12]

1. it is user-dependent and cannot capture nocturnal and asymptomatic hypoglycaemia
2. it cannot predict impending hypoglycaemia as the single-instant reading offers no information regarding the direction of changing glucose; and
3. this method is susceptible to user error, such as contaminated fingers.

However, there are many limitations to SMBG use in individuals with diabetes who are treated with intensive insulin regimens. Many individuals do not test at the recommended frequencies. Additionally, because SMBG only provides a blood glucose reading at a single point in time, hypoglycaemia and hyperglycaemia can easily go undetected, limiting the user's ability to take corrective action. Inaccuracies due to user error, environmental factors and weaknesses in SMBG system integrity further limit the utility of SMBG.

CONTINUOUS GLUCOSE MONITORING SYSTEMS

As of 1999, a new era in diabetes care began as the first-ever CGMS was approved to help people being diagnosed with diabetes. The development of this new technology allowed patients to monitor their blood sugars by inserting a device subcutaneously. The CGMS measures a patient's glucose levels in their interstitial fluid over the entire day. For patients with Type 1 Diabetes Mellitus (T1DM), it is recommended to have four blood glucose readings per day. With CGMs, instead of the four readings per day, patients and medical providers now have a more in-depth knowledge of the fluctuations each unique patient experiences throughout their day[13]

The extremes of hypo- and hyperglycaemia are known to put a patient with diabetes at higher risk of stroke, vision loss, kidney disease, amputations, and even death. Being able to prevent these complications from occurring with CGM can improve the quality of life

(QoL) of the patient and reduce the cost burden of diabetes on the U.S. healthcare system. Continuous glucose monitoring was included in the 2015 American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (AEC) – Clinical Practice Guidelines (CPG) for developing.[13]

Reasons for request

Real-time (rt-CGM) or flash continuous glucose monitoring displays the current glucose, direction and velocity of glucose change and provides programmable alarms. This trending information and 'around-the-clock' vigilance may provide a significant safety advantage relative to SMBG. Therefore, this assessment will evaluate whether it would be effective, safe and cost-effective to use CGM in the management of diabetes patients required insulin management in Malaysia as requested by Medical Endocrinologist Consultants from Putrajaya and Malacca Hospital.

2 TECHNICAL FEATURES

A CGM works through a tiny sensor inserted under skin, usually on your belly or arm. The sensor measures the interstitial glucose level, which is the glucose found in the fluid between the cells. The sensor tests glucose every few minutes. A transmitter wirelessly sends the information to a monitor. The monitor may be part of an insulin pump or a separate device, which carry in a pocket or purse. Some CGMs send information directly to a smartphone or tablet. Several models are available and are listed in the ADA's product guide external link.[11] (See **Table 1** for comparison of personal CGM)

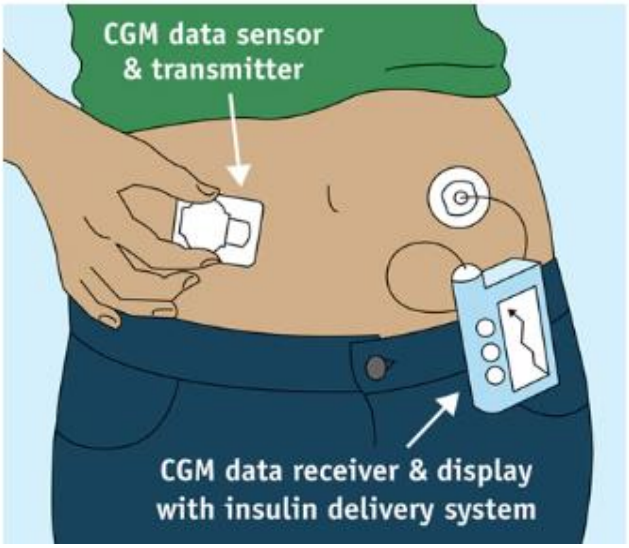

Figure 1: Continous glucose monitoring device

Currently available CGMS devices are considered minimally invasive enzyme-coated electrodes to measure interstitial glucose concentrations and convert these values to blood glucose levels. The information stored in the receiver is then converted into estimated mean values of glucose standardised to capillary blood glucose levels measured during calibration. Using an applicator or self-insertion device, a thin plastic sensor is inserted just under the skin of the abdomen or the upper arm. These devices can display real-time glucose values and glucose trends, and some can also sound an alarm or vibrate when they detect hyperglycaemia or hypoglycaemia. The receiver can store information for later use, and long-term data can be downloaded to a computer. Devices using enzyme-coated catheters require frequent calibrations to correct variations in the reaction between the electrode and the subcutaneous tissue, as well as fluctuations in glucose and oxygen diffusion.[11]

2.1 Approval

The United States Food and Drug Administration (FDA) has approved five continuous glucose monitoring devices, four of which are currently in clinical use. All four devices measure interstitial fluid glucose to calculate blood glucose levels using a mathematical algorithm. These devices include the GlucoWatch® (Redwood City, California, USA), the DexCom SEVEN® PLUS (San Diego, California, USA), the Medtronic MiniMed Paradigm® REAL-Time and the Guardian® REAL-Time (Northridge, California, USA),

and the Abbott Diabetes Care FreeStyle Navigator (Alameda, California, USA).9 **(See Figure 2 and Table 1)**

Figure 2: Continuous Glucose Monitoring devices approved by The United States Food and Drug Administration (FDA)

Table 1: Personal CGM, compared

Specification & capabilities	Freestyle Libre 14 day (Abbot)	Freestyle Libre 2 (Abbot)	Dexcom G6 (Dexcom)	Guardian Connect 3 (Medtronic)	Eversense E3 (Senseonics)
Type	**Intermittently scanned CGM**		**Real-time CGM**		
Approved age of use	≥ 18 y	≥ 4 y	≥ 2 y	14 – 75 y	≥ 18 y
Blood glucose range	40–500mg/dL	40-400mg/dL	40-400mg/dL		
Need to scan sensor	At least every 8H		No		
Frequency of stored glucose level	Every 15 min		Every 5 min		
Overall MARD	9.4%	9.2%	9.8%	9.1% [a]	8.5%
Sensor placement	Back of upper arm		Abdomen	Abdomen or back of upper arm	Subcutaneous implant in upper arm
Patient calibration required	No		No	Every 12 h [b]	Every 12 h
Warm-up period	60 min		120 min	As long as 120 min	24 hr [c]
Sensor life	14 d		10 d	7 d	180 d
Smart-device requirement	Smart device or supplied reader		Smart device or receiver	Smart device	
Glucose alerts	No		Yes		
Can be integrated with insulin pump	No		Yes		
Interfering substances	>500 mg **Vitamin C**: falsely increases scanned glucose level **Salicylic acid**: falsely decreases scanned glucose level	>500 mg **Vitamin C**: falsely increases scanned glucose level	**Hydroxyurea**: falsely increases scanned glucose level	**Acetominophen**: falsely increases scanned glucose level	**Intravenous mannitol or sorbitol**: falsely increases scanned glucose level
Waterproof	1 meter; 30 min		2.4meters;24h	2.4meters;30min	1meter;30min
Data retrieval platform for clinic	Libreview		Dexcom Clarity	Carelink	Eversense Data Management

					System (DMS) Pro
Data sharing platform for family and friends	Librelink up (< 20 people)		Dexcom Follow (<10 people)	Carelink Connect (< 5 people)	Eversense NOW (<5 people)
Patient smartphone app requirement	Reader: N/A Smartphone: LibreLink	Reader: N/A Smartphone: Libre 2	Dexcom Clarity	Guardian Connect	Eversense

CGM, continuous glucose monitor; MARD, mean absolute relative difference; N/A, not applicable.

[a]: When calibrated every 12 h; MARD is slightly better (8.68%) when calibrated 3 or 4 times a day.
[b]: A new sensor requires as long as 2 h to warm up; then needs to be calibrated immediately; then needs to be calibrated 6 h after initial calibration; and then needs to be calibrated every 12 h for the duration of the sensor. The more regularly the sensor is calibrated, the more improved is its accuracy.
[c]: ie, 24 h after the initial sensor placement and 10 min each time the transmitter is removed and replaced.

Source: Schleich K, Ray BE. Make room for continuous glucose monitoring in type 2 diabetes management. J Fam Pract. 2022 Nov;71(9):384-397

2.1.1 Freestyle Libre

Abbott works on a variety of medical devices and holds a separate division for diabetes care, where they have launched multiple glucose monitoring devices. To date, Abbott has launched glucose monitoring devices known as the Freestyle blood glucose meters (Freedom Lite, InsulinX, Lite, and Precision Neo). It is a glucose monitoring system used by adult patients without obtaining a blood sample from the fingertip. An updates from the Freestyle Libre's approval to provide on-demand glucose information to a user for up to 14days. This sensor has to be applied to the back of the person's upper arm, where the electrical signal was generated. The generated electrical signal is converted into a blood glucose reading and transmitted to a dedicated mobile device (reader). It should be used in persons aged 18years and older.[13]

2.1.2 Dexcom® G5/G6 (Dexcom)

Dexcom Inc. is a U.S. based company that works solely on the development, manufacturing, and distribution of CGMS for diabetes management worldwide. Their first CGM technology was launched in 2006, called the Dexcom STS Continuous Monitor.[13] The U.S. Food and Drug Administration (FDA) today expanded the approved use of Dexcom's G5 Mobile CGMS to allow for replacement of fingerstick blood glucose (sugar)

testing for diabetes treatment decisions in people two years of age and older with diabetes. This is the first FDA-approved continuous glucose monitoring system that can be used to make diabetes treatment decisions without confirmation with a traditional fingerstick test. The system was previously approved to complement, not replace, fingerstick testing for diabetes treatment decisions. The G5 Mobile CGMS uses a small sensor wire inserted just below the skin that continuously measures and monitors glucose levels. Real-time results are sent wirelessly every five minutes to a dedicated receiver and a compatible mobile device (e.g., smart phone or tablet) running a mobile app. Alarms and alerts indicate glucose levels above or below user-set thresholds. The system measures glucose in fluid under the skin and must be calibrated at least two times per day using blood obtained from fingerstick tests. However, additional daily fingerstick blood tests are generally no longer necessary because unlike other CGMS, results from this device can now be used directly by patients to make diabetes treatment decisions without confirmation from a traditional fingerstick test.[14]

2.1.3 Guardian Connect 3 (Medtronic)

It is the first FDA approved hybrid closed loop system that monitors glucose and automatically adjusts the delivery of long-acting or basal insulin. It should be used in persons aged 14 years and older. It measures the users' glucose levels for up to seven days, an insulin pump that delivers insulin to the user, and a glucose meter used to calibrate the CGM. This system has two modes: manual and auto mode.[13]

2.1.4 Eversense® E3 (Senseonics)

The Eversense® CGM system uses a small sensor that is implanted just under the skin by a qualified health care provider during an outpatient procedure. After it is implanted, the sensor regularly measures glucose levels in adults with diabetes for up to 90 days. The implanted sensor works with a novel light-based technology to measure glucose levels and send information to a mobile app to alert users if glucose levels are too high (hyperglycemia) or too low (hypoglycemia). The sensor is coated with a fluorescent chemical which, when exposed to blood sugar, produces a small amount of light that is measured by the sensor. Every five minutes, measurements are sent to a compatible

mobile device (e.g., smart phone or tablet) that is running a device-specific mobile application.[13]

2.2 STANDARDISATION OF CGM METRICS

Effective use of CGM data to optimise clinical outcomes requires the user to interpret the collected data and act upon them appropriately. This requires:

- common metrics for assessment of CGM glycaemic status
- graphical visualisation of the glucose data and CGM daily profile, and
- clear clinical targets

In February 2019, the Advanced Technologies & Treatments for Diabetes (ATTD) Congress convened an international panel of individuals with diabetes and clinicians and researchers with expertise in CGM to define core metrics for assessing CGM data. **Refer Table 2**: Standardised CGM metrics

Table 2: Standardised CGM metrics

2017 international consensus on CGM metrics
1. Number of days CGM worn
2. Percentage of time CGM is active
3. Mean glucose
4. Estimated HbA1C
5. Glycaaemic variability (%CV or SD)
6. Time .250 mg/dL (.13.9 mmol/L)
7. Time .180 mg/dL (.10.0 mmol/L)
8. Time 70–180 mg/dL (3.9–10.0 mmol/L)
9. Time ,70 mg/dL (,3.9 mmol/L)
10. Time ,54 mg/dL (,3.0 mmol/L)
11. LBGI and HBGI (risk indices)
12. Episodes (hypoglycaemia and hyperglycaemia) 15 min
13. Area under the curve
14. Time blocks (24-h, day, night)
Use of Ambulatory Glucose Profile (AGP) for CGM report

CV, coefficient of variation; LBGI, low blood glucose index; HBGI, high blood glucose index.

Source: Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care. 2019 Aug;42(8):1593-1603

2.3 Continuous glucose monitoring system devices (CGMS) in Malaysia

Continuous Glucose Monitoring System (CGMS) is among the most important recent advances in diabetes technology that improves glucose control without adding medication. The CGM provides information about glucose concentrations, direction of change, rate of change, and overall glucose trends, whereas self-monitoring blood glucose (SMBG) only provides a single blood glucose measurement at the time of the test.[9] International guidelines according to The American Diabetes Association (ADA) released its 2022 Standards of Care, which provides an annual update on practice guidelines and expanded recommendations for CGM and Time in Range (TIR) use in

adults and for CGM and automated insulin delivery (AID) use in children. The guidelines also include using diabetes technology in hospital settings.[10, 15]

3 POLICY QUESTIONS

3.1 Should continuous glucose monitoring devices be utilised and provided as an approach for glucose monitoring for insulin-requiring diabetes patients' management?

4 OBJECTIVES

4.1 The following are the objectives of this review:

i. To assess the comparative effectiveness and safety of CGMS for glucose monitoring in insulin-requiring diabetes patients.

ii. To determine the economic, organizational, social, ethical and legal implications of CGMS for glucose monitoring in insulin-requiring diabetes patients.

4.2 The following are the research questions of this review:

i. How effective and safe are the CGMS for glucose monitoring in insulin-requiring diabetes patients?

iii. How cost-effective are the CGMS or devices for glucose monitoring in insulin-requiring diabetes patients?

iv. What are the organizational, social, ethical and legal implications of CGMS or devices for glucose monitoring in insulin-requiring diabetes patients?

v. To assess the economic implication, social, ethical, and organisational aspects related to molecular profiling of breast cancer.

5.0 PART A: SYSTEMATIC REVIEW OF LITERATURE

5.1 METHODS

5.1.1 Literature Search strategy

Literature search was developed by the main author and an *Information Specialist* who searched for published articles pertaining to continuous glucose monitoring for diabetes patient who requiring the insulin. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to Jan 2023, EBM Reviews - Health Technology Assessment (4th Quarter 2016), EBM Reviews - Cochrane Database of Systematic Review (2005 to January 2023), EBM Reviews - Cochrane Central Register of Controlled Trials (Jan 2023), and EBM Reviews - NHS Economic Evaluation Database (1st Quarter 2016). Parallel searches were run in PubMed, US FDA and INAHTA database. There was no limitation in language, however, in the end only articles in English were included. Year of publication was limited from year 2000 to 2022 and only human study were included. Detailed search strategy is as in Appendix 3. The last search was performed on 29 February 2023. Additional articles were identified from reviewing the references of retrieved articles.

5.1.2 Study selection

Two dedicated reviewers independently screened the titles and abstracts against the inclusion and exclusion criteria as shown below and evaluated the selected full-text articles for final article selection. Disagreement was resolved by discussion.

Inclusion Criteria

a.	Population	• Patients with Type 1 Diabetes or Type 2 Diabetes • insulin-requiring diabetes patients
b.	Intervention	continuous glucose monitoring
c.	Comparator	i. self-monitoring blood glucose (SMBG) ii. intermittently scanned CGMS versus real-time CGMS
d.	Outcomes	i. **Effectiveness** • hypoglycaemic and hyperglycaemic events • change in HbA1c reduction • CGM accuracy • time in range (TIR), time above range (TAR), time below range (TBR) and average sensor glucose correlated well with HbA1c and change in HbA1c • correlations of HbA1c with various CGM metrics, (calibration) • Various quality of life and treatment satisfaction measure • change in treatment satisfaction, and quality of life measures as secondary outcomes; Health-related quality of life (HRQoL) **ii. Safety** • Adverse events **iii. Economic impact** • Cost-effectiveness • Cost-utility analysis • Cost-benefit analysis • Cost analysis • Any other measure of economic outcome **iv. Organizational, social, ethical and legal implications**
e.	Study design	HTA reports, systematic review with/out meta-analysis, randomised controlled trial (RCT), cohort, diagnostic, cross-sectional, case-control, economic evaluation studies
f.	Full text articles published in English	

Exclusion Criteria:

a. Study design — Animal study, laboratory study, case report, case series, narrative review

b. Non-English full text articles

5.1.3 Critical appraisal of literature/ assessment of risk of bias

The risk of bias or quality assessment (methodology quality) of all retrieved literatures was assessed depending on the type of the study design; using the relevant checklist of National Collaborating Centre for Methods and Tools (ROBIS)[16] for Systematic Review and Meta-analysis, a revised Cochrane Risk of Bias Tool (RoB 2) for Randomised Controlled Trials[17], and Critical Appraisal Skill Programme (CASP)[18] for Observational and Economic Studies. All full text articles were graded based on guidelines from the *U.S. / Canadian Preventive Services Task Force* (Appendix 1).[19]

5.1.4 Analysis and synthesis of evidence

Data extraction strategy

Data were extracted from included studies by a reviewer using a pre-designed data extraction form (*Evidence Table* as shown in Appendix 4) and checked by another reviewer. Disagreements were resolved by discussion and the extracted data was also presented and discussed with the *Expert Committee*. The data extracted was as follows:

i. **Details of methods and study population characteristics**
ii. **Detail of intervention and comparators**
iii. **Details of individual outcomes specified**

Methods of data synthesis

Data on the effectiveness, and cost-effectiveness associated with molecular profiling assays were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review due to high heterogeneity especially in the characteristics of breast cancer populations, and the difference between the assays itself.

5.2 RESULTS

5.2.1 Selection of Included articles

An overview of the systematic search and selection of the studies are illustrated in **Figure 2**. A total of 394 records were identified through the Ovid interface and PubMed while 12 were identified from other sources (references of retrieved articles). Following the removal of 67 duplicates and irrelevant titles, 327 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 105 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 92 full text articles, 83 full text articles were included. Of those, 7 articles were excluded as those primary studies were already included in systematic review and HTA (n =1), irrelevant objective and scope of study (n = 3), other types of CGMS (n = 1), small sample size (n = 1) and narrative reviews (n = 1). The excluded articles were listed as in Appendix 5.

The 15 full text articles which were finally selected in this review comprised of eight systematic reviews, one RCT, two HTA and three economic evaluation studies (cost-effectiveness studies).

All studies included were published in English language between 2012 and 2023 and were conducted in the United States, United Kingdom, Canada, Japan, Italy, Spain, Australia, Nerw Zealand, China and Singapore.

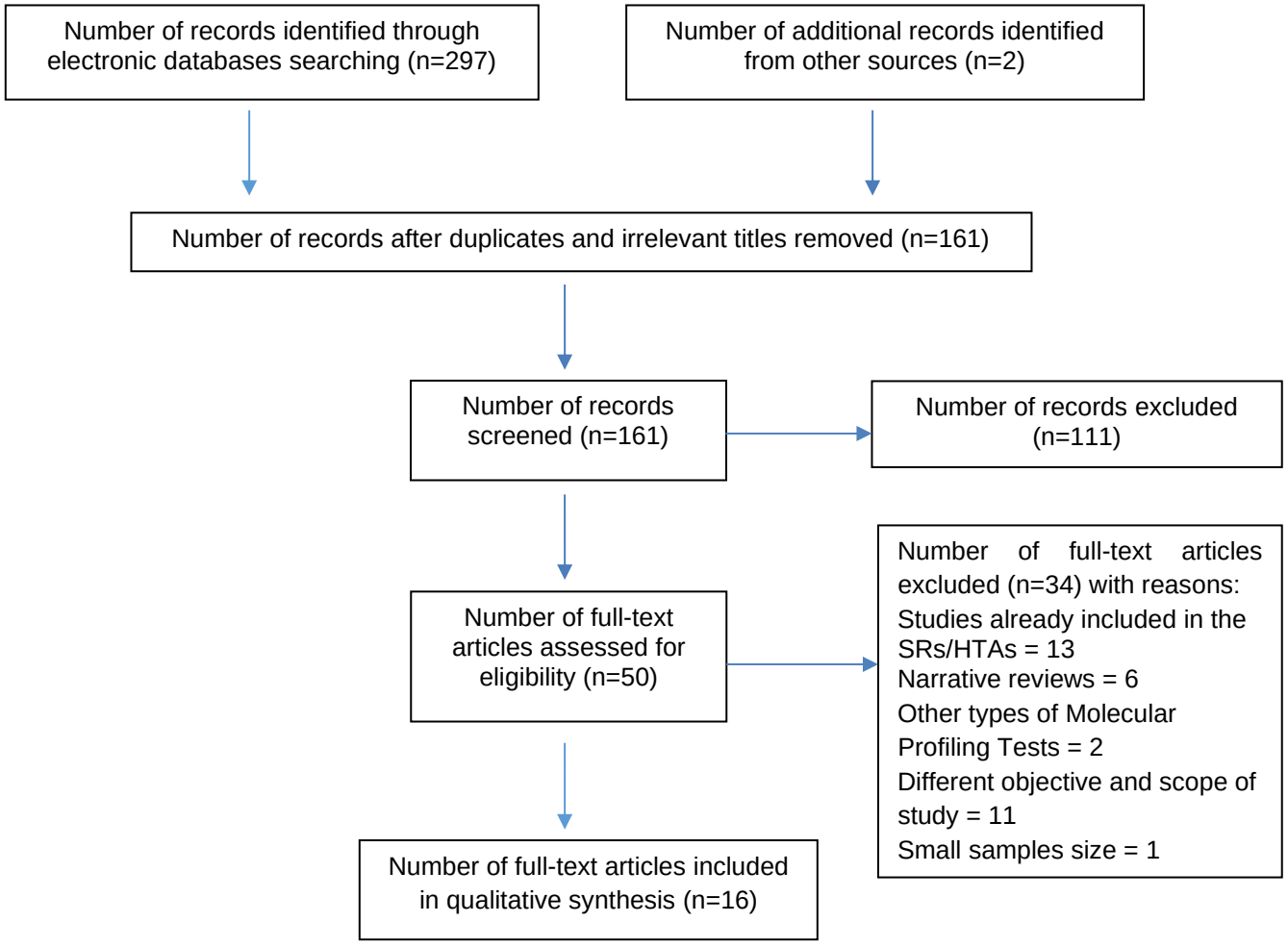

Figure 2: Flow chart of retrieval of articles used in the results

5.2.2 Quality assessment / risk of bias

Risk of bias was assessed using Risk of Bias in Systematic Reviews (ROBIS) for systematic review, and Critical Appraisal Skill Programme (CASP) checklist for observational study. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias.

Risk of bias assessment for included systematic review
(pending)

Figure 3.1: Summary of risk of bias assessment for systematic review using ROBIS

Risk of bias assessment for included RCTs

One RCT was included in this risk of bias assessment (Figure 3.2). Overall, the risk of bias for each study were low, however, three studies have small samples size (<100).

		RISK OF BIAS					
		D1	D2	D3	D4	D5	Overall
Study	Singh S et al.	+	+	+	+	+	+
		D1: Bias arising from the randomisation process. D2: Bias due to deviations from intended intervention. D3: Bias due to missing outcome data. D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result.				Judgement x High - Unclear + Low	

Figure 3.2: Summary of risk of bias assessment for RCT using CASP checklist

5.2.4 Effectiveness

Overall results of CGM (Glycaemic control, HbA1c, Target in range (TIC)

SOURCE: seven (7) SR with Meta-analyses, two (2) systematic review - including one (1) from Cochrane review, two RCTs, three (3) economic related papers and two (2) HTA reports; from 2012 until recent 2023. Most studies conducted in UK, USA, Canada, Italy, Spain, Australia, New Zealand, China and Singapore.

Individualise results of CGMS for diabetes patients based on:

a. Glycaemic control
b. HBbA1c
c. Range (TIR/TBR)

1. Effectiveness

Glycaemic control:

Hypoglycaemic events in T1DM patient:

CGM significantly lower severe hypoglycaemic events among patients and also incidence of severe hypoglycaemic events in CGM group was significantly lower, RR = 0:52, 95% CI 0.35-0.77, *p* = 0:001 when compared with SMBG (Wang Y, 2022)

CGM demonstrated non-significant decrease in severe hypoglycaemia events; RR= 0.61; 95% CI 0.33 to 1.15); Z = 1.53, *p*=0.13) when compared with SMBG; (I^2 = 50%, *p*=0.04) (Teo E, 2022)

The risk of hypoglycaemia was increased for CGM users, but CIs were wide (RR= 3.26, 95% CI 0.38 to 27.82) vs (RR 1.24, 95% CI 0.67 to 2.29) (Langendam M 2012); not significant

Hypoglycaemia in T1DM and T2DM patient: (HTA Ontario 2019)

CGM was more effective than SMBG in reducing the average time spent in hypoglycemia (−0.47 h [95% CI −0.73 to −0.21]) and the average number of hypoglycemia events (−0.16 [95% CI −0.29 to −0.03]) among adults with T2DM requiring intensive insulin therapy

Hypoglycaemia events in T2DM patient, among hospitalised high risk for hypoglycaemia insulin-treated (RCT by Singh LG, 2022)

RT-CGM/GTS group experienced 60.4% fewer hypoglycemic events (<70 mg/dL) VS POC group = [(0.67 events/patient; 95% CI 0.34 to 1.30] vs [1.69 events/patient [1.11 to 2.58], *P* = 0.024)]; with absolute RRR = 1.02

Hypoglycaemia in GDM (Majewska A 2022)

CGM detects a higher number of hypoglycaemia episodes than SMBG; had significant role in pregnant women qualify for insulin therapy

CGM group with GDM had significantly lower number of patients with hypoglycaemic events and also showed significant a difference in the duration of time spent in hypoglycaemia, with lower results in the CGM group

Hyperglycaemia in GDM (Majewska A, 2022)

Five (5) studies found that CGM is better at detecting episodes of hyperglycaemia as compared to SMBG; 2 studies: found that CGM detected more hyperglycaemic events than SMBG and in all patients the incidence rate of hyperglycaemia = 5.65% using CGM versus 14.2% using SMBG ($p < 0.05$)

The duration of time demonstrated that time spent in hyperglycaemia was shorter than in the SMBG group

With one (1) study: found that CGM is a better detector of nocturnal hyperglycaemia than SMBG

Three (3) studies showed no statistical difference between the SMBG and CGM groups in detecting glycaemia above the reference range

Episode of diabetic ketoacidosis (DKA)

There is no statistical difference in the probability of occurrence of diabetes ketoacidosis between the CGM group and the SMBG

(RR = 1:34, 95% CI 0.57-3.15, and p = 0:5) (Wang Y, 2022)

The CGM group demonstrated no significant reduction in DKA events (RR= 1.06; 95% CI 0.49 to 2.32); Z = 0.15, p=0.88) compared with SMBG; (I^2= 0%, p=0.59) (Teo E, 2022)

There is no significant difference in risk of ketoacidosis between CGM and SMBG users.; (RR= 0.94, 95% CI 0.36 to 2.40) in four (4) RCTs, I^2=0%). (Langendam M 2012)

Reducing HBA1c

<u>In T1DM & T2DM</u>:

Personal-CGM was associated with greater reduction in HbA1c from baseline compared with usual care SMBG) (-0.28%, 95% CI -0.36% to 0.21%, I^2 = 0%, p < 0.00001). The benefit was observed both in patients with T2DM (-0.31%, 95% CI -0.41% to -0.21%, I^2 = 14%, p < 0.00001) and T1DM (-0.27%, 95% CI -0.46% to -0.09%, I^2 = 0%, p = 0.004) (Di Molfetto 2023)

CGM lowers HbA1c level was 0.17% (95% CI 20.29 to20.06, p < 0.003) versus SMBG, with high heterogeneity between studies (I^2=96.2%, p < 0.001) among T1DM or T2DM with an extensive insulin regimen. In a subgroup analysis, the mean reduction of HbA1c was 0.23% in the 13 comparisons using rt-CGM, with high heterogeneity (I^2 = 92.2%). Neither is-CGM nor SAP significantly changed mean HbA1c levels, with no evidence of statistically significant heterogeneity for the three comparisons using is-CGM (I^2= 0%) and high heterogeneity for the two comparisons using SAP (I^2=85.5%) (Maiorino MI 2020)

CGM showed greater HbA1c reduction and was aimed at improving glycemic control MD= (-0.31, 95% CI -0.43 to -0.19, p< 0.001) a significant 0.16% decrease of HbA1c was associated with people T1DM but not people with T2DM. Overall, when compared with the usual care, CGM was associated with modest reduction in HbA1c (WMD= 20.17%, 95% CI 20.29 to 20.06, I^2= 96.2%). (Maiorino MI 2020)

<u>In T1DM only:</u>

CGM (pooled 3 categories - adjunctive, non-adjunctive and is-CGM) showed a statistically significant absolute improvement in HbA1c percentage points (MD = -0.22; 95% CI (−0.31 to −0.14) versus SMBG, with heterogeneity (I^2= 79%). The effects were strongest with adjunctive technology *(Medtronic Paradigm, FreeStyle Navigator, Guardian REAL-Time, Dexcom series, MiniMed series, Enlite and Paradigm Veo)* MD=−0.26%; 95% CI (−0.36 to −0.16), and no evidence of a difference in HbA1c was seen for intermittent scannings—CGM (Elbalshy 2022)

CGM could significantly reducing the HbA1c level vs with SMBG, the combined result is WMD = −2:69, 95% CI (-4.25, to 1.14), and p < 0:001 (Wang Y)

CGM showed significantly lower HbA1c level (MD= −2.46 mmol/mol [−0.23%] [95% CI −3.83 to −1.08]; Z = 3.50, *p*=0.0005) versus SMBG (control). Heterogeneity: (I^2 = 72%, p<0.00001) (Teo E 2022)

After 6 months, Rt-CGM users showed a significant larger decline in HbA1c level in starting insulin pump therapy compared to patients using MDI and SMBG; MD in change in HbA1c level = (-0.7%, 95% CI -0.8% to -0.5%, 2 RCTs, 562 patients, I^2=84%). (Langerdam 2012)

In pregnant women (GDM)

One RCT (Paramasivam S, 2018) found that CGM significantly lower HbA1c concentration (CGM group: 5.2 ± 0.4% versus SMBG group: 5.6 ± 0.6%, *p* < 0.006); however, no significant differences in HbA1c concentration between CGM and SMBG groups (Majewske A, 2022)

Head-to-head comparison between RT-CGM+open-loop continous subcutaneous insulin infusions (CSII) VS RT-CGM Multiple Daily Injections (MDI) showed that mean in HbA1c in overall RT-CGM+CSII = 63.3 ± 9.2 (mmol/mol) VS RT-CGM+MDI groups = 63.5 ± 10.2 (mmol/mol) → NO significant reduction of HBA1c between groups (William J, 2022)

Effects on time in range (TIR); time spent below range (TBR)

In T1DM & T2DM

Personal-CGM showed beneficial effect on change in TIR from baseline and a greater increase in TIR = (5.59%, 95% CI 0.12 to 11.06, I^2 = 0%, *p* = 0.05) and a neutral effect on change in TBR range from baseline = (-0.11%, 95% CI -1.76% to 1.55%, I^2 = 33%, *p* = 0.90) (Di Molfetto 2023)

In patients with T1DM & T2DM with an extensive insulin regimen CGM was associated with a significant increase of TIR WMD= 70.74 min, 95% CI 46.73 to 94.76, *p*< 0.001; I^2= 66.3%, *p*< 0.001). In the pre-specified subgroup analysis, TIR increased more in trials

using rt-CGM (83.49, 95% CI 52.68 to 114.30, *p* <0.001) than intermittently scanned (is-CGM) (53.91, 95% CI 28.54 to 79.27, *p*< 0.001) or SAP (37.10, 95% CI 0.74 to 73.45, *p*< 0.045). The increase in TIR was significant and robust independently of diabetes type, method of insulin delivery, and reason for CGM use. (Maiorino MI 2020)

People who used FGM - CGM spent on average 1 hour more in the target glucose range (95% CI 0.41 to 1.59) and 0.37 hours (22 minutes) less in a high glucose range (95% CI −0.69 to −0.05) compared with SMBG (HTA Ontario 2019)

In T2DM among hospitalised high risk for hypoglycaemia insulin-treated

RCT by Singh LG (2020) demonstrated that CGM lower percentage of time spent below range (TBR): <70 mg/dL (0.40% [0.18 to 0.92%] vs. 1.88% [1.26 t0 2.81%], *p*= 0.002) and <54 mg/dL (0.05% [0.01 to 0.43%] vs. 0.82% [0.47 to 1.43%], *p*= 0.017) when compared with the POC group

In T1DM patients only

CGM group showed an overall absolute TIR increased by 5.4% (95% CI 3.5 to 7.2) when compared with control (SMBG), with heterogeneity (I^2= 71%). The effects were strongest with non-adjunctive technology - Dexcom G5 and Dexcom G6; TIR = 6.0% 95% CI 2.3 to 9.7) (Elbalshy 2022)

CGM improved the percentage of time patients spent in the target glycemic range by 9.6% (95% CI 8.0 to 11.2) to 10.0% (95% CI 6.75 to 13.25) (HTA Ontario 2018)

2. Safety

Adverse events: Haak T, 2017 (RCT) reported that:

a. No serious adverse events (SAEs) related to the device or study procedure.

b. There were 4 hypoglycemia SAEs experienced by 4 participants (7% in CGM groups versus 9% in control participants) but none of the severe hypoglycemic episodes or hypoglycemic adverse events were associated with the device.

c. Six (4.0%) in the CGM group reported 9 device-related adverse events which were sensor-adhesive reactions and resolved after treatment with topical preparations.

3. Cost-effectiveness

CEA by Roze S (from U.K. health care payer (National Health Service and personal social services) found that DEXCOM G6 rt-CGM was associated with a mean incremental gain in quality-adjusted life expectancy = 1.49 quality-adjusted life years (QALYs) versus SMBG

= (mean [SD] 11.47 [2.04] QALYs versus 9.99 [1.84] QALYs)

Total mean (SD) lifetime costs were also higher with rt-CGM (GBP) £14,234

(GBP £102,468 [35,681] VS GBP £88,234 [39,027]) resulting in ICER of GBP £ 9,558 per QALY gained

SR on economic by Ose TK conclude that: 2 studies have explored the CEA of CGM from the payer perspective and have favoured their cost-effectiveness, while another study was inconclusive results due to more data and long-term studies are needed to better understand how CGM use relates to diabetes complications

Jiao Y et al. conducted a CEA in Australian populations and reported that the estimated ICER range was [$18,734–$99,941] and the (QALY) gain range was [0.76–2.99]. Use in patients with suboptimal management or greater hypoglycaemic risk revealed more homogenous results and lower ICERs. Most studies (n = 17) concluded that CGM is a cost-effective tool.

4. Patient-reported outcome (PRO)

Díez-Fernández A conducted a SR on patient satisfaction with aims to establish the benefits of FGM in terms of patients' satisfaction and QoL in both type 1 and type 2 diabetes patients using evidence from past systematic reviews and meta-analyses.

Six (6) SR (including two meta-analyses) were included in the meta-review

87.5% of the group FGM were very satisfied and all the included studies showed better results with the FGM system

improve treatment satisfaction for individuals with T1DM or T2DM but the quality of this evidence was low due to substantial clinical and statistical heterogeneity

Cowart et al. (2020), two RCTs reported outcomes on T2D patients' satisfaction, finding statistically significant improvements with the use of FGM.

Pease et al. (2020), which included DTSQ results favoured FGM over SMBG, albeit without reporting statistical significance values

Overall, there is limited evidence for the effectiveness of RT-CGM use in children, adults and patients with poorly controlled diabetes. The largest improvements in glycaemic control were seen for sensor-augmented insulin pump therapy in patients with poorly controlled diabetes who had not used an insulin pump before. The risk of severe hypoglycaemia or ketoacidosis was not significantly increased for CGM users, but as these events occurred infrequent these results have to be interpreted cautiously. There are indications that higher compliance of wearing the CGM device improves glycosylated (HbA1c) to a larger extent.

GUIDELINES

International guidelines according to The American Diabetes Association (ADA) released its 2022 Standards of Care, which provides an annual update on practice guidelines and expanded recommendations for CGM and Time in Range (TIR) use in adults and for CGM and automated insulin delivery (AID) use in children. The guidelines also include using diabetes technology in hospital settings. The use of CGM devices should be considered from the outset of the diagnosis of diabetes that requires insulin management. This allows for close tracking of glucose levels with adjustments of insulin dosing and lifestyle modifications and removes the burden of frequent SMBG. In addition, early CGM initiation after diagnosis of type 1 diabetes in youth has been shown to decrease A1C and is associated with high parental satisfaction and reliance on this technology for diabetes management.

5.2.8 U.S Food and Drug Administration (FDA) Approval

In June 2018, the U.S. FDA approved the Eversense® CGM system for use in people 18 years of age and older with diabetes. This is the first FDA-approved CGM system to include a fully implantable sensor to detect glucose, which can be worn for up to 90 days.[30]

CONCLUSION: PART A - SYSTEMATIC REVIEW

Based from the review:

1. CGM demonstrated significantly improved of glycaemic control especially in lowers severe hypoglycaemic events (SHE) in T1DM when compared with SMBG, more effective in reducing the average time spent in hypoglycemia and the average number of hypoglycemia events among adults with T2DM requiring intensive insulin therapy. Hypoglycaemia events in T2DM patient, among hospitalised high risk for hypoglycaemia insulin-treated demonstrated that CGM group experienced 60.4% fewer hypoglycemic events (<70 mg/dL) when compared with POC group. In special group such as GDM mothers, CGM detects a higher number of hypoglycaemia episodes than SMBG and showed a significant role in pregnant women qualify for insulin therapy. However, CGM group showed no significant reduction in DKA events or statistical difference in the probability of occurrence of diabetes ketoacidosis between the CGM group when compared with the SMBG.

2. CGM was associated with greater reduction in HbA1c from baseline compared with usual care SMBG) in both T1DM and T2DM patients. CGM group showed a statistically significant absolute improvement in HbA1c percentage points especially in T1DM.

3. CGM group showed beneficial effect on change in TIR from baseline and a greater increase in TIR and a neutral effect on change in TBR range from baseline. In patients with T1DM and T2DM with an extensive insulin regimen CGM showed a significant increase of TIR. TIR increased more in trials using RT-CGM than intermittently scanned (is-CGM) or SAP. The increase in TIR was significant and robust independently of diabetes type, method of insulin delivery, and reason for CGM used. In T2DM among

hospitalised high risk for hypoglycaemia insulin-treated CGM group demonstrated a lower percentage of time spent below range (TBR) when compared with SMBG.

4. Limited evidence showed no serious adverse events were related to the device or study procedure. A small percentage of participants experienced hypoglycemia, with similar rates in both the CGM and control groups. Additionally, a few participants in the CGM group reported device-related adverse events, specifically sensor-adhesive reactions, which were resolved with treatment.

5. Patients in CGM group were very satisfied and all the included studies showed better results with the CGMS. In this review also showed that CGM improved treatment satisfaction for individuals with T1DM or T2DM but the quality of this evidence was low due to substantial clinical and statistical heterogeneity.

6.0 PART B: ECONOMIC EVALUATION

COST-EFFECTIVENESS ANALYSIS

6.1 OBJECTIVES

i. To assess the cost-effectiveness of continuous glucose monitoring (CGM) - the direct health care cost - in improving glycaemic control and reducing acute diabetic complications among patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) who are on intensive insulin regimen when compared to self-monitoring of blood glucose (SMBG).

ii. To estimate the incremental cost-effectiveness ratio (ICER) of CGM relative to SMBG in diabetic patients on intensive insulin therapy.

iii. To explore the financial consequences of CGM if the technology were to be reimbursed by the Ministry of Health (MOH).

6.2 METHODS

6.2.1 Analytical Overview and Model Structure

A simplified state transition model was adapted from Garcia-Lorenzo et al. (2018) to estimate the cost-effectiveness of CGM.[1] Based on consensus of the expert committees, it consisted of six health states: no complication, neuropathy, retinopathy, nephropathy, cardiovascular diseases and death (**Figure 1**), with annually cycle length and a lifetime horizon. This model was developed using Microsoft Excel 2019 and followed a hypothetical cohort of diabetic patients who were on intensive insulin regimen and provided with a continuous glucose monitoring system to monitor their glycaemic control. The comparator was a similar cohort of patients but using self-monitoring of blood glucose (SMBG) instead.

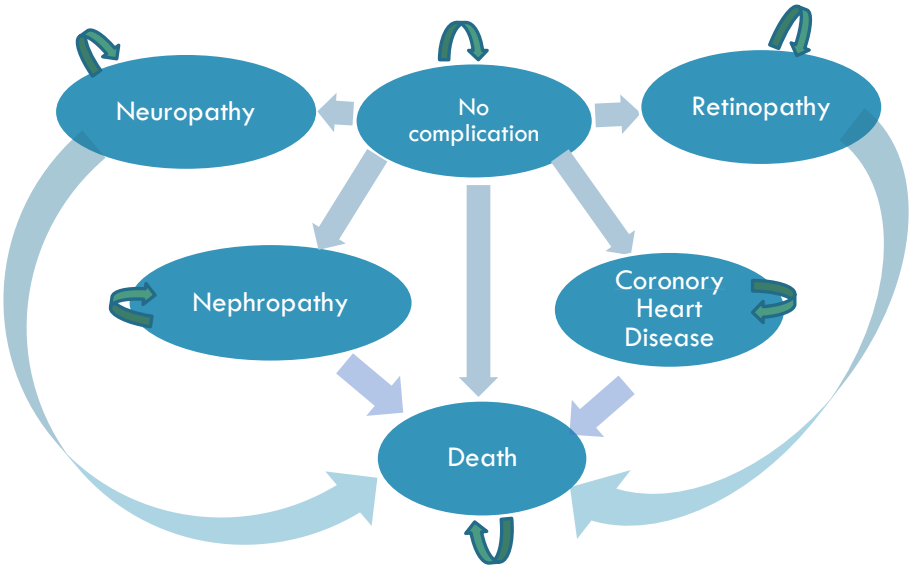

Figure 1: Markov model structure.

The hypothetical cohort was age-weighted to represent Malaysians with diabetes aged 18 years old and above and to estimate the all-cause mortality rate for each age category. This value was obtained by applying the overall estimates of prevalence of diabetics in Malaysia according to their age category to the 2021 Malaysian census data.[2-4]

All simulated patients began at no complication state and then would either remained in their current state or redistribute to one of the complications of diabetes (microvascular or macrovascular) or death states during each Markov cycle state according to the previously published transition probabilities.[1] Hence, after developing a complication, it was assumed patients would not progress to another complication and would stay in the state or die as the result of increased risk from their complications or other causes. Patient can transition to death from all health states during each cycle.

Additionally, acute diabetic complications, such as severe hypoglycaemia (SHE) and diabetic ketoacidosis (DKA) can occur at any time during the cycle but never both at the same time. Table 1 shows the baseline transition probabilities for the simulated cohort of T1DM and T2DM patients.

Table 1: Baseline transition probabilities for SMBG

Parameter	Base case	Lower limit	Upper limit	Rationale for LL & UL	Source
Transition probabilities:					
T1DM with no complication to:					
Retinopathy	0.001	0.001	0.001	95% CI (estimated from SE)	Garcia-Lorenzo, 2018
Neuropathy	0.035	0.018	0.052	95% CI (estimated from SE)	Garcia-Lorenzo, 2018
Nephropathy	0.072	0.037	0.107	95% CI (estimated from SE)	Garcia-Lorenzo, 2018
CHD	0.022	0.011	0.033	95% CI (estimated from SE)	Garcia-Lorenzo, 2018
T2DM with no complication to:					
Retinopathy	0.011	0.006	0.016	95% CI (estimated from SE)	Garcia-Lorenzo, 2018
Neuropathy	0.035	0.018	0.052	95% CI (estimated from SE)	Garcia-Lorenzo, 2018
Nephropathy	0.02	0.018	0.022	95% CI (estimated from SE)	Garcia-Lorenzo, 2018
CHD	0.022	0.011	0.033	95% CI (estimated from SE)	Garcia-Lorenzo, 2018
Increased mortality risk (HR):					
Neuropathy	1.51	-	-		Garcia-Lorenzo, 2018
Nephropathy	2.23	-	-		Garcia-Lorenzo, 2018
CHD	1.96	-	-		Garcia-Lorenzo, 2018
Baseline annual mortality risk:					
T1DM	0.0159	-	-		Bujang, 2018
T2DM	0.0139				Bujang, 2018
Additional probability of death:					
Neuropathy	1.51	-	-		Garcia-Lorenzo, 2018
Nephropathy	2.23	-	-		Garcia-Lorenzo, 2018
CHD	1.96	-	-		Garcia-Lorenzo, 2018
SHE					
Severe hypoglycemia events (SHE) per individual per year:					
Baseline annual risk for SHE					
T1DM	0.817	-	-		Hussein, 2017

	T2DM	0.865	-	-	Hussein, 2017
Proportion of SHE treated at A&E (%)					
	T1DM	9.5	7.6	11.4	varied by ±20%	Heller, 2016
	T2DM	23.2	18.6	27.8	varied by ±20%	Heller, 2016
Proportion. of SHE requiring hospital admission (%)					
	T1DM	8.7	5.0	16.6	estimated from literature	Heller, 2016; Hussein, 2017
	T2DM	5.3	3.2	11.5	estimated from literature	Heller, 2016; Aljunid, 2019; Hussein, 2017

6.2.2 Clinical Parameters and Estimates of Efficacy of Technologies

The effectiveness of CGM reported in one the meta-analysis included in Part A of this report was used to estimate a relative risk reduction in complications as well as reduction in acute diabetes complications.[5,6] The calculation for estimated relative risk (RR) associated with CGM for chronic complications development was carried out in reference to a previously published CE study.[7] It was reported that a hazard ratio (HR) of a 10 per cent increase in daily time in range (TIR), which is equivalent to 2.4 hours (144min)/day, corresponds to 64 per cent and 40 per cent reduction in risk of retinopathy and nephropathy.[8] Meanwhile, estimation of risk reduction of neuropathy and coronary heart disease was based on a finding that a 10 per cent increase in TIR corresponds to an approximately 0.8 per cent decrease in HbA1c.[9] All these calculations assumed there was a linear relationship between TIR, HbA1c reductions, and complication's risks, and the HR to approximate the RR.

For acute complications, only SHE occurrence in T1DM cohort was considered because findings from the conducted systematic review (Part A) did not report significant improvement in the number of SHE among T2DM with CGM in comparison to SMBG users. Similarly, there was also no statistically significant reduction in DKA rates with CGM in both T1DM and T2DM cohorts, hence this acute complication was not included in the model as it was assumed to incur similar healthcare costs and utilisation in both CGM and SMBG users. The baseline for SHE was obtained from a Malaysian cohort sub analysis

of the HAT study.[10] Participants in this study were at the age of 18 years old and above with a mean baseline HbA1c around 8.9% in both T1DM and T2DM cohort. It was reported that the estimated annual rate of SHE was 1.7 events per patient-year of exposure (PYE) and 2.0 events per PYE for T1DM and T2DM, respectively. Proportion of patients with SHE requiring hospitalisation was also estimated using the information from the HAT study.

Additionally, targeted literature search was performed on PubMed database to identify other relevant input to parameterise the model, with a particular emphasis to include as much local data as possible. The health utility values associated with the health states in the Markov structure were taken from published literature.[11,12] The associated QALYs then was calculated by multiplying the person-time spent in each state and its corresponding health utility values. **Table 2** lists all the key parameters inputted in the Markov model.

Table 2: Model input

Parameter	Base value	Lower value	Upper value	Rationale	Source
Effectiveness					
Baseline HbA1c (mmol/mol)					
T1DM	74	51	97	95% CI	Hussein, 2017
T2DM	74	54	94	95% CI	Hussein, 2017
Reduction in HbA1c with CGM relative to SMBG (mmol/mol)					
T1DM	2.69	1.14	4.25	95% CI	Wang, 2022
Improvement in TIR with CGM relative to SMBG (WMD, minutes)					
T1DM & T2DM	70.740	46.73	94.76	95% CI	Maiorino, 2020
Risk for SHE with CGM relative to SMBG (RR)					
T1DM	0.52	0.35	0.77	95% CI	Wang, 2022
Risk for chronic complications with CGM (RR)					
Retinopathy	0.686	0.579	0.792	95% CI	own calculation
Neuropathy	0.837	0.781	0.892	95% CI	own calculation
Nephropathy	0.804	0.737	0.870	95% CI	own calculation
CHD	0.903	0.870	0.936	95% CI	own calculation
Health state utility for T1DM					
Diabetes with no complications	0.81	-	-		Moes, 2023
Retinopathy	0.762	-	-		Moes, 2023
Neuropathy	0.63	-	-		Moes, 2023
Nephropathy	0.762	-	-		Moes, 2023
CHD	0.629	-	-		Moes, 2023
SHE	-0.028	-	-		Moes, 2023
Health state utility for T2DM					
Diabetes with no complications	0.881	0.833	0.929	95% CI	Mok, 2021
Retinopathy	0.858	0.847	0.87	95% CI	Mok, 2021

Neuropathy	0.829	0.817	0.84	95% CI	Mok, 2021
Nephropathy	0.859	0.844	0.874	95% CI	Mok, 2021
CHD	0.852	0.845	0.859	95% CI	Mok, 2021
SHE	0.853	0.833	0.872	95% CI	Mok, 2021
Discount rate	3%	1.50%	5%	varied to extreme values	PE guideline; literature
Time horizon	Lifetime	10	20	varied to extreme values	own estimation

6.2.3 Resources Utilisation and Cost Parameters

Only direct medical costs which included device acquisition cost, hospitalisation cost, routine follow-up visit cost as well as management cost of diabetes-related complications were considered in the analysis.

As this analysis does not intend to compare individual CGM technologies, an average cost of CGM was applied to the model where the share for competing devices available in Malaysian market was assumed to be equal with no significant differences in their sensor efficacy and reliability. The costs for several CGM devices were obtained from their publicly available official website or webstore. The costs of insulin as well as its' different delivery modes were not included in the calculation as the focus was on the cost-effectiveness of glucose monitoring and diabetes-related complications.

The local clinical practice guidelines have recommended T1DM and T2DM patients on insulin to carry out at least four to six capillary blood glucose testing daily.[13,14] However, for the base case analysis, it was assumed that T1DM patients in the SMBG group would monitor their blood glucose nine tests per day, whereas T2DM would do six times instead. The reasoning behind this assumption was in order to achieve a tighter glycaemic control, more frequent, regular monitoring was required to keep track of daily glucose variability as to match those who were on CGM.

Nevertheless, to reflect the reality where the frequency of capillary blood glucose test was much fewer, a scenario analysis had also been conducted. For those on CGM, additional SMBG costs were based on number of test strips used in IMPACT and REPLACE study.[15,16] In both hypothetical populations, the adherence rate to the monitoring

frequency was assumed to be 100 per cent. Additionally, patients' medications including insulin were assumed to have been optimised and their compliance to the treatment regimen was satisfactory.

Hospitalisation costs for the management of diabetes mellitus and diabetes-related complications were obtained from the MOH casemix data and published literature.[17-19] Costs for acute diabetic complications were added to the individual's annual cost along with a corresponding reduction in QALY for that particular year. Casemix's price per case for diabetes with multiple chronic complications were used as a proxy to the estimated management and hospitalisation costs for acute diabetic complications, such as severe hypoglycaemia.[17,20] The management cost for SHE considered was the hospitalisation cost as well as the management cost for such event at the Emergency Department (ED) without hospitalisation. As local data on proportion of patients treated for SHE at ED is lacking, findings from a published literature was applied to the model.[21]

The cost for the routine follow-up visits for diabetic care was also included as a cost incurred by those diabetic patients who have yet to develop chronic complications in this simulation. As local cost input on management cost of diabetic-related complications for T1DM patients is scarce, it was assumed that regardless of the type of diabetes, the health care resources utilisation is similar. All cost inputs were adjusted to MYR 2022 according to the Malaysian consumer price index.[22] Cost inputs are as presented in Table 3.

6.2.4 Outcomes

The described model was analysed separately for T1DM and T2DM cohorts in estimating the total costs, quality-adjusted life-years (QALYs) gained and ICER associated with the use of CGM relative to SMBG. As there was no explicit national cost-effectiveness (CE) threshold, one time of the per capita gross domestic product (GDP) of Malaysia in 2022 was applied in this analysis (MYR 53,043/QALY).[23] This analysis was conducted from the perspective of MOH and an annual three per cent discount rate was applied to both costs and outcomes.[24]

6.2.5 Budget Impact Analysis

A Microsoft Excel-based cost calculator was constructed to estimate the budget impact of increasing utilization of CGM amongst T1DM population. The costs considered in the model included glucose monitoring costs and resource use to treat severe hypoglycaemic events. A net cost difference per patient per year relative to CGM compared with SMBG was then calculated.

Currently, there is no published literature on the prevalence and incidence of T1DM for Malaysians. However, based on the information available from Type 1 Diabetes Index website (available at https://t1dindex.shinyapps.io/dashboard/?loc_id=458), it was estimated that around 7000 Malaysians were diagnosed with T1DM, with estimated annual incidence around 400 people in the year of 2022. Therefore, to explore the financial impact of reimbursing or subsidising CGM for select T1DM patients, the prevalence of T1DM patients reporting more than one SHE in HAT study was proposed as the target population for CGM coverage over five years.

6.2.6 Sensitivity Analysis

One-way sensitivity analysis was performed to determine key drivers that have the biggest impact on the generated base case value. Each relevant parameter was varied one-by-one according to its estimated range based on the reported or estimated 95% confidence interval (CI) from refenced source if available, or by varying it over a range of ±20 per cent of the base-case value. The results of the sensitivity analysis were presented in a tornado diagram.

6.2.7 Scenario Analysis

a) Number of test strips per patient per day

The number of test strips used by T1DM patients in SMBG could varies and may affect the budgetary impact results of covering CGM. Hence, the budget impact that could have resulted from different frequency use in test strips by patients in SMBG group were explored. The number of test strips considered in this analysis ranged from lower values than the base case value (4 test strips per day to 13 test strips per day).

b) Number of sensors per patient per year

In the base case analysis, all simulated patients were assumed to have adhered to continuous use of CGM which can lead to 26, 37, 52 sensors per year (for 7-day, 10-day

and 14-day sensor, respectively). However, due to relatively high cost of the sensor, the cost impact of using the sensor at regular intervals instead of continuous use, complemented with regular SMBG was explored.

Table 3: Cost parameters

Input	Base value		Low value		High value		Rationale	Source
	T1DM	T2DM	T1DM	T2DM	T1DM	T2DM		
Number of test strips per individual per day								
SMBG	9	6	6	3	13	13		CPG, 2015; CPG, 2020; Oyaguez, 2020; Oyaguez, 2021
CGM	0.5	0.2	0.2	0	1.5	0.66		Oskarsson, 2018; Haak, 2017
Number of lancets per individual per day								
SMBG	9	6	6	3	13	13		Oyaguez, 2020; Oyaguez, 2021
CGM	0.5	0.2	0.2	0	1.5	0.66		Oskarsson, 2018; Haak, 2017
Number of CGM sensor and reader per individual per year								
Sensor	31.29		25.03		37.54		varies by ±20%	own calculation based on sensor's lifespan
Reader	1.00						varies by ±20%	
Acquisition cost per patient per year (MYR)								
SMBG								
Glucometer	19.63	19.63	19.63	19.63	19.63	19.63		
Test strips	4,664.70	3,109.80	3,109.80	1,554.90	6,737.90	6,737.90		
Lancets	919.80	613.20	613.20	306.60	1,328.60	1,328.60		
CGM								
Glucometer	19.63	19.63	19.63	19.63	19.63	19.63		
Test strips	259.15	103.66	103.66	0.00	777.45	342.08		
Lancets	51.10	20.44	20.44	0.00	153.30	67.45		
Sensor	9,547.04		7,637.64		11,456.45		based on varying number of sensors by ±20%	

Reader	117.37	93.89	140.84	based on varying number of sensors by ±20%	
Chronic complication management costs per patient per year (MYR)					
Retinopathy:					
First year	3,781.74	3,025.39	4,538.09	varies by ±20%	MOH Casemix, 2020
Subsequent year	560.90	448.72	673.08	varies by ±20%	MOH, 2022
Neuropathy:					
First year	4,920.91	3,936.72	5,905.09	varies by ±20%	MOH Casemix, 2020
Subsequent year	560.90	448.72	673.08	varies by ±20%	MOH, 2022
Nephropathy:					
First year	5,935.16	4,748.13	7,122.19	varies by ±20%	MOH Casemix, 2020
Subsequent year	2,822.96	2,258.37	3,387.56	varies by ±20%	Azmi, 2018
CHD:					
First year	6,889.83	5,511.86	8,267.79	varies by ±20%	MOH Casemix, 2020
Subsequent year	1,918.59	1,534.87	2,302.30	varies by ±20%	Shafie, 2020
Acute complication management cost per case (MYR)					
SHE management cost at A&E	788.77	631.01	946.52	varies by ±20%	Aljunid, 2019
Hospitalisation cost for SHE	7,098.50	5,678.80	8,518.20	varies by ±20%	MOH Casemix, 2020

6.3 RESULTS

6.3.1 Base-Case Analysis

In both T1DM and T2DM simulated cohorts, CGM was not cost-effective at the current assumed CE threshold. The incremental cost per patient using CGM relative to SMBG was high and largely contributed by the CGM system cost. Table 4 shows the summary of cost and QALY per patient for CGM and SMBG groups. In the T1DM cohort, the ICER generated was 3.2 times higher than the set threshold. Meanwhile, in T2DM cohort, it was noted that CGM use has led to a higher incremental cost but its associated benefit was lesser than that of SMBG group. The total cost included costs associated with glucose monitoring system and management of chronic diabetic complications. The cost for glucose monitoring in both groups was noted to contribute a significant portion to the total cost incurred per patient, where it consumed around 60% and 84% of the total cost for SMBG and CGM, respectively.

Table 4: Summary of CEA for CGM relative to SMBG in hypothetical T1DM and T2DM populations

Population	Monitoring strategy	Total cost per patient (MYR)	Total QALY gained per patient	Incremental Cost (MYR)	Incremental QALY	ICER (MYR/QALY)
T1DM	**SMBG***	62,598.05	11.95	-	-	-
	CGM	92,992.08	12.13	30,394.03	0.18	171,920.25
T2DM	**SMBG***	43,304.42	13.56	-	-	-
	CGM	89,091.64	13.42	45,787.22	-0.14	-318,932.58

*reference strategy
QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; SMBG: self-monitoring of blood glucose; CGM: continous glucose monitoring

6.3.2 Sensitivity Analysis

The tornado diagrams illustrated parameters that have remarkable impact of the ICER estimation in the base-case scenario. In the T1DM cohort simulation model, as presented in **Figure 2**, three main parameters identified were cost of CGM sensor, frequency of testing in the SMBG group and RR in complications. As expected, lower cost of CGM sensor would likely drive the ICER closer to the CE threshold value. In contrast, higher number of test strips used per day in SMBG group and RR for complication would improve the generated ICER in the base case. Shortening the time horizon to 10 years and 20 years gave out the ICER of MYR 365,336 and MYR 245,581, respectively.

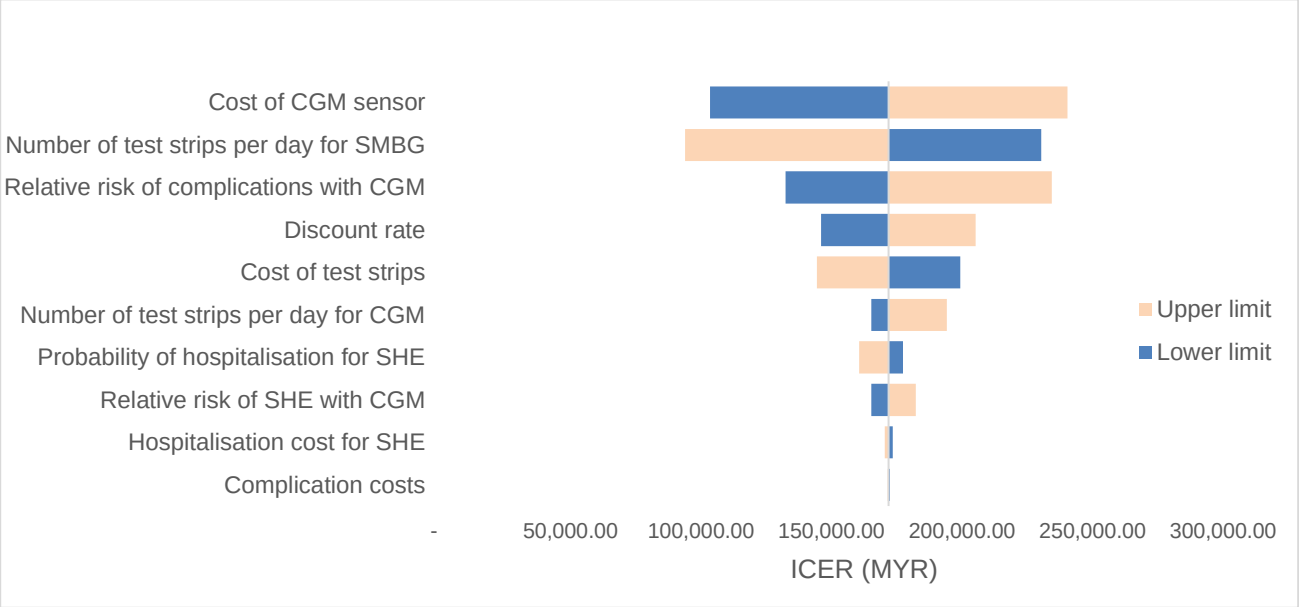

Figure 2: Tornado diagram for one-way sensitivity of ICER difference between CGM system and SMBG in T1DM cohort

6.3.3 Cost per Patient per Year by Technology

As shown in Table 5, in a cohort simulation of T1DM patients, use of CGM has led to 48% reduction in health care resource costs associated with the management of SHE at the hospital level. Despite the apparent benefits, use of CGM under the base case assumptions has resulted in 28% increase in the total cost per patient per year in comparison to SMBG.

Table 5: Different in cost per patient per year treated with CGM relative to SMBG in T1DM cohort

	CGM (A)	SMBG (B)	Cost difference, (A) - (B)	
			Absolute	%
Blood glucose monitoring acquisition cost	9,994.29	5,604.13	4,390.16	78.3
Test strips and lancets	329.88	5,604.13	-5,274.25	-94.1
Sensor and reader	9,664.41			
Health care resource costs				
SHE treated at A&E	212.28	408.23	-195.95	-48.0
SHE requiring hospitalisation	1,749.52	3,364.46	-1,614.94	-48.0
Total cost	**11,956.09**	**9,376.82**	**2,579.27**	**27.5**

6.3.4 Budget Impact Analysis

In the HAT study, 11.5 per cent of Malaysians with T1DM reported more than one episode of SHE.[10] Based on the prevalence, the estimated hypothetical population was 850 people. Hence, the net budget impact of increasing the proportion of T1DM using CGM system from 10 per cent in the first, up until 70 per cent in Year 5 is illustrated in Table 6. Difference in yearly cost ranged from four per cent in Year 2, decreasing to 3.6 per cent in Year 5.

Table 6: Budget impact of increasing uptake of CGM system over 5 years

Parameter	Year 1	2	3	4	5
Hypothetical cohort	805.00				
Proportion of CGM coverage	10%	25%	40%	55%	70%
CGM cost (MYR)	962,465	2,406,163	3,849,861	5,293,559	6,737,257
SMBG cost (MYR)	6,793,508	5,661,257	4,529,005	3,396,754	2,264,502
Total expenditure per year (MYR)	7,755,973	8,067,420	8,378,867	8,690,313	9,001,760
Cost difference from the first year (MYR)	-	311,447	622,893	934,340	1,245,787
Cost increase relative to year 1 per T1DM patient (MYR)	-	387	774	1,161	1,548

6.3.5 Scenario Analysis

The results for the two scenario analyses are illustrated in **Table 7 and Table 8.** In the first scenario, lower number of test strips use in SMBG group resulted in higher cost difference associated with the CGM use. Under the base case assumption, to achieve cost neutrality with CGM, the frequency of capillary blood glucose tests carried out must be more than 13 times daily. In line with the sensitivity analysis conducted earlier, number of glucose test strips used for SMBG greatly affects the cost difference between the two strategies, where four times SMBG daily resulted in the highest net cost difference by 91 per cent with CGM.

Table 7: Scenario 1 - Impact of varying SMBG testing frequency on annual costs difference per patient between CGM and SMBG users in T1DM cohort

	Base case (routine SMBG user: 9 tests per day)	**Scenario 1a (routine SMBG users: 4 tests per day)**	**Scenario 1b (routine SMBG users: 6 tests per day)**	**Scenario 1c (routine SMBG users: 13 tests per day)**
CGM (MYR)	11,956.09	11,956.09	11,956.09	11,956.09
SMBG (MYR)	9,376.82	6274.32	7,515.32	11,858.82
Absolute cost difference (%)	27.5	90.6	59.1	0.82

In the second scenario, CGM sensor use was decreased to 40 per cent of the total recommended annual usage, and complemented with SMBG at nine times daily for the time not on CGM system. The beneficial effect of CGM in reducing rate of SHE was assumed to remain the same. Hence, although the proposed combination strategy has resulted in 29 per cent increase in the monitoring cost, this cost was offset by the decrease in in health care resource utilisation cost for managing SHE.

Apart from the above analyses, it was noted that the cost for CGM sensor and reader need to be reduced between 30 to 60 per cent of the base case value for it to match the total cost consequence of carrying out SMBG six or four times per day, respectively.

Table 8: Scenario 2 - Difference in cost per patient per year treated with CGM relative to SMBG in T1DM (40% use of CGM in a year; complemented by SMBG)

	CGM (A)	SMBG (B)	Cost difference, (A) - (B)	
			Absolute	%
Blood glucose monitoring acquisition cost	7,228.24	5,604.13	1,624.11	29.0
Test strips and lancets	3,362.48	5,604.13	-2,241.65	-40.0
Sensor and reader	3,865.76			
Health care resource costs	1,961.80	3,772.69	-1,810.89	-48.0
SHE treated at A&E	212.28	408.23	-195.95	-48.0
SHE requiring hospitalisation	1,749.52	3,364.46	-1,614.94	-48.0
Total cost	9,190.04	9,376.82	-186.78	-2.0

6.4 DISCUSSION

Overall, CGM was not cost effective at the current set CE threshold in reducing the risk for chronic complications when compared to SMBG. The incremental cost associated with CGM was relatively not too high, however, the benefit, that is the QALY gained associated with CGM was very small. Similar result was noted with a previously published study that reported only 0.046 QALY gained with CGM compared to SMBG in T1DM population.[1] On the contrary, the QALY gained was reported to range between 0.76 to 2.99 in another systematic review, with the ICER ranged from AUD 18,734 to AUD 99,941].[25] Compared to the systematic review whereby many of the included studies used extensive and more complicated IQVIA CORE diabetes model, this analysis was based on a simplified state transition model, based on the agreement of the expert committees. Furthermore, different effectiveness measure applied as well as cost input for CGM technologies being assessed and health care resource utilisation cost for managing acute and chronic diabetes-related complications can vary greatly between different health systems. A simplified model was chosen as to avoid overestimating the CE results, therefore for the purpose of this analysis, conservatively the model only accounted the occurrence of the early major and minor complications.

In the UK, it was reported that 22.5 per cent of T1DM were eligible for CGM reimbursement by NHS England. The eligible patients have to meet at least one of the following conditions: undergoing intensive SMBG, more than eight measurements per day; patients who meet the NICE criteria for continuous insulin infusion pump indication or who have disabling hypoglycaemia; patients who have recently debuted with inadvertent hypoglycaemic episodes; patients with more than 2 hospitalizations per year; and those that require a third party to carry

out monitoring and it is not possible to perform blood tests.[26] However, such information are not available for Malaysia, thus estimated proportion of patients who were at risk for multiple episodes of SHE in a year was used instead to estimate the budget implications, as there was evidence of CGM contributing to the reduction in the number of SHE in T1DM population.

Sensitivity analysis also shown that the cost of CGM sensor has affected the generated ICER greatly. In fact, the sensor cost may pose a financial burden to many eligible diabetic Malaysians, especially given the mean monthly salaries and wages received by employees in Malaysia was only MYR 3,212.[27] Depending on the sensor lifespan, it would cost over MYR 600 to MYR 900 a month, provided the sensor stays intact on the skin until its purported lifetime. However, unlike insulins and other drugs which are required for life-long, the feasibility for occasional use of CGM at regular intervals, in combination with intensive SMBG may be explored in a resource-limited setting. Incorporating patient assistance programme or subsidy (fully or partially) on CGM sensor to select patients may also increase the number of CGM users in Malaysia, thus will enable local data collection on its long-term effectiveness in reducing acute and chronic diabetes-related complications. On a side note, currently, costs for glucose test strips are out-of-pocket, and are not covered by the MOH.

Limitations of this analysis include lack of local data to inform on proportion of patients suffering from one complication then later develop another complication. Besides, as the inputs used to run the model were based on pooled estimates of effectiveness and complication data collected among T1DM and T2DM age more than 18 years, these results may not be applicable to paediatric patients. In addition, almost all input on effectiveness and acute complication rates were drawn from short-term studies which may underestimate or overestimate CGM effectiveness and/or the actual incidence of complications over the select time horizon. This analysis also assumed 100 per cent of adherence to both monitoring strategies, which may not be ideal in a real-world situation.

This economic evaluation has attempted to incorporate as much input as relevant to Malaysian population, yet, the use of CGM, especially in MOH setting is very limited. Hence, the results presented should be interpreted cautiously as long-term effectiveness of CGM in reducing risk for chronic complications especially among Malaysian diabetic patients should be explored further. Furthermore, the uncertainties around CGM effectiveness may have underestimated

or overestimated the estimated costs and outcomes, hence affecting the resulting ICERs for the glucose monitoring strategies described above.

7.0 CONCLUSIONS – COST IMPLICATION

Blood glucose monitoring using CGM system was not a cost-effective option when compared to SMBG in both T1DM and T2DM populations with only small gain in the benefit shown in the former population over the simulated lifetime horizon. Nevertheless, CGM system may reduce the health care resource utilisation cost for managing T1DM patients who are at risk for frequent episodes of SHE. Additionally, the combination strategy of CGM and SMBG may improve adherence with lesser financial impact among diabetic patients requiring tight glycaemic control.

REFERENCES

1. Garcia-Lorenzo B, Rivero-Santana A, Vallejo-Torres L, et al. Cost-effectiveness analysis of real-time continuous monitoring glucose compared to self-monitoring of blood glucose for diabetes mellitus in Spain. *J Eval Clin Pract*. 2018;1–10.

2. Type 1 Diabetes Index. T1D Index Factsheet 2021: Malaysia. Available from https://t1dindex.shinyapps.io/dashboard/?loc_id=458. Accessed on: 9th July 2023.

3. Ministry of Health Malaysia. 2021. National Diabetes Registry Report 2020.

4. Department of Statistics Malaysia. Mid-year population estimates by age group, ethnic group and sex, Malaysia, 2022. Available from https://newss.statistics.gov.my/newss-portalx/ep/epFree DownloadContentSearch.seam?cid=3190. Accessed on: 9th July 2023.

5. Maiorino MI, Signoriello S, Maio A, et al. Effects of continuous glucose monitoring on metrics of glycemic control in diabetes: a systematic review with meta-analysis of randomized controlled trials. *Diabetes Care*. 2020;43:1146–1156

6. Wang Y, Zou C, Na H, et al. Effect of different glucose monitoring methods on blood glucose control: a systematic review and meta-analysis. *Computational and Mathematical Methods in Medicine*. 2022.

7. Rotondi MA, Wong O, Riddell M, Perkins B. Population-level impact and cost-effectiveness of continuous glucose monitoring and intermittently scanned continuous glucose monitoring technologies for adults with type 1 diabetes in Canada: a modeling study. *Diabetes Care*. 2022 Sep 1;45(9):2012-2019.

8. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. Diabetes Care 2019;42(3):400-405.

9. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. Diabetes Technol Ther 2019;21(2):81-5.

10. Hussein Z, Kamaruddin NA, Chan SP, et al. Hypoglycemia awareness among insulin-treated patients with diabetes in Malaysia: A cohort subanalysis of the HAT study. *Diabetes Research and Clinical Practice*. 2017;133:40-49

11. Moes R, Huisman E, Malkin S, et al. Evaluating the clinical and economic outcomes associated with poor glycemic control in people with type 1 diabetes in the Netherlands. *ClinicoEconomics and Outcomes Research*.2023;15 87–96

12. Mok CH, Kwok H, Ng CS, et al. Health state utility values for type 2 diabetes and related complications in East and Southeast Asia: a systematic review and meta-analysis. *Value Health*. 2021;24(7):1059–1067

13. Clinical Practice Guideline. Management of Type 1 Diabetes Mellitus in Children and Adolescents. Ministry of Health. 2015. ISBN: 978-967-0769-40-03.

14. Clinical Practice Guideline. Management of Type 2 Diabetes Mellitus. Ministry of Health. 6th Edition. 2020.

15. Oskarsson P, Antuna R, Geelhoed-Duijvestijn P, et al. Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy: a pre-specified subgroup analysis of the impact randomised controlled trial. *Diabetologia.* 2018;61:539–50.

16. Haak T, Hanaire H, Ajjan R, et al. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicentre, open-label randomized controlled trial. *Diabetes Ther*. 2017;8:55–73

17. MOH Casemix Data. 2020: price per case for DRG diabetes. Medical Development Division, Ministry of Health Malaysia.

18. Azmi S, Goh A, Muhammad NA, et al. The cost and quality of life of Malaysian type 2 diabetes mellitus with chronic kidney disease and anemia. *Value in Health Regional Issues*. 2018;42-49

19. Shafie AA and Ng CH. Estimating the costs of managing complications of type 2 diabetes mellitus in Malaysia. *Malaysian Journal of Pharmaceutical Sciences.* 2020;18(2):15-32

20. Aljunid SM, Aung YN, Ismail A, et al. Economic burden of hypoglycemia for type II diabetes mellitus patients in Malaysia. *Plos One*. 2019.

21. Heller SR, Frier BM, Herslov ML, et al. Severe hypoglycaemia in adults with insulin-treated diabetes: impact on healthcare resources. *Diabetic Medicine*. 2015.

22. Department of Statistics Malaysia. Analysis of Annual Consumer Price Index 2021. Available from: https://newss.statistics.gov.my/newss-portalx/ep/epFree Download ContentSearch.seam?cid=117807. Accessed on: 10th August 2023.

23. Department of Statistics Malaysia. Gross Domestic Product 2015 – 2022. Available from https://www.dosm.gov.my/uploads/release-content/file_20230511170527.pdf. Accessed on: 12th September 2023.

24. Pharmacy Practice & Development Division. Pharmacoeconomic Guidelines for Malaysia. Ministry of Health Malaysia. 2019. eISBN:978-967-5570-86-5.

25. Jiao Y, Lin R, Hua X, et al. A systematic review: cost-effectiveness of continuous glucose monitoring compared to self-monitoring of blood glucose in type 1 diabetes. *Endocrinology, Diabetes & Metabolism*. 2022.

26. NHS. Flash Glucose Monitoring: National Arrangements for Funding of Relevant Diabetes Patients. 2019. Available from https://www.england.nhs.uk/wp-content/uploads/2019/03/National-arrangements-for-funding-of-relevant-diabetes-patients-June-2020-Updated-final.pdf Accessed on: 10th July 2023.

27. Department of Statistics Malaysia. Salaries & Wages Survey Report, Malaysia 2022. Available from https://newss.statistics.gov.my/newss-portalx/ep/epFreeDownloadContentSearch.seam?cid=20917. Accessed on: 10th October 2023.

PART C: PATIENT AND PUBLIC INVOLVEMENT IN HTA
FOCUS GROUP DISCUSSIONS ON CONTINUOUS GLUCOSE MONITORING SYSTEM (CGMS) FOR DIABETES PATIENTS

Background:

In the past, Health Technology Assessment (HTA) primarily concentrated on quantitative evaluations of the clinical effectiveness, safety, and cost-effectiveness of health technologies, sometimes overlooked crucial social, ethical, and political dimensions associated with these technologies.[1] In recent decades, there has been a notable shift in the approach taken by numerous HTA agencies worldwide. Patient and public involvement (PPI) or engagement has gained increasing popularity and is now often integrated into the HTA process.[2]. In the context of HTA, the term 'patient' encompasses individuals living with the specific medical condition under evaluation, as well as patient group representatives and caregivers who may be eligible for the health technology being studied.[3]

The inclusion of patients in the HTA process is designed to enhance the assessment of health technologies' value. Patients bring invaluable first-hand knowledge of living with a clinical condition and can provide insights into the specific diseases and the impact of healthcare technologies related to them.[1] Engagement with patients encompasses an examination of how the condition and its treatment impact not only the patient but also their family, caregivers, and immediate surroundings. Information shared based on personal experiences can also serve as a means to identify disparities or constraints within existing research, such as instances where commonly used outcome measures fail to capture what holds significance for those who have first-hand experience with the condition.[5]

The rapid advancement of technology has led to the widespread adoption of continuous glucose monitoring systems (CGMS) in diabetes care worldwide. Existing evidence has demonstrated clinical benefits for various subpopulations, including children, adolescents, and adults with insulin-requiring Type 1 diabetes, and even some with Type 2 diabetes.[6] However, despite the established effectiveness of CGMS in managing diabetes, previous literature has highlighted concerns about issues related to its use, such as the overwhelming volume of data

and the potential disruptions caused by false alarms, which can adversely affect patients' quality of life.[7]

Existing literature often lacks comprehensive examination of patient perspectives regarding the advantages, disadvantages, and apprehensions related to the use of CGMS in Malaysia. In alignment with global efforts to incorporate patient viewpoints into HTA[8], this qualitative study aims to fill this void. Through focus group discussions, we seek to collect insights and compile valuable patient experiences, especially from individuals with insulin-dependent diabetes, concerning the adoption and use of CGMS in Malaysia.

Objective:

The objective of this focus group discussion is to explore and capture the experience of patients living with diabetes who have incorporated Continuous Glucose Monitoring System (CGMS) technology into their diabetes management.

Research Questions

1. What are patients' perceptions of using CGMS in their diabetes care, specifically in terms of the benefits, barriers, and issues they encounter?
2. What are patients' overall attitudes toward CGMS, and would they recommend its use for diabetes care to other patients?

Methods:

In this research, we utilize focus group discussions (FGDs) as a qualitative research method to gain insights into the perceptions and experiences of patients living with diabetes who have incorporated CGMS technology into their diabetes management. This study follows an exploratory research design with FGDs serving as a primary data collection method. Focus group discussions (FGDs) are used to explore patients' perceptions in terms of the benefits, drawbacks/barriers, challenges, and issues related to the use of CGMS, as well as to allow participants to share their experiences, opinions, and insights on CGMS for diabetes. This study was conducted from May 2023 till September 2023. This study involved insulin-requiring diabetes patients including adults, adolescents, and caregivers, in Kuala Lumpur and Putrajaya, Malaysia.

Participant Recruitment

Participants were recruited through purposive sampling which involves actively reaching out to patients, families, and caregivers with direct experience of CGMS in diabetes management. Insulin-requiring Diabetes patients were invited to participate in this study through a recruitment invitation email that was posted to the members of Persatuan Diabetes Malaysia (PDM) through the representatives from the society along with flyers at the headquarters of the society in Kuala Lumpur. Contacts with diabetes patients and caregivers were also made through clinicians at the Endocrine Institute, Putrajaya. Participants were selected based on the following criteria:

Inclusion Criteria**:**

- Adults aged 18 to 60 years old and adolescents aged 13 to 18 years old.
- Diagnosis of insulin-requiring Type 1 or Type 2 Diabetes.
- Current usage of Continuous Glucose Monitoring Systems (CGMS) or previous user of CGMS
- Proficiency in either Bahasa Malaysia or English.
- Malaysian citizenship.
- Willingness to participate in the study.

Exclusion Criteria:

- Acute illness during the recruitment process.
- Express a refusal to participate in the study.

Participant information regarding the study and an invitation to contact the research team for further information were provided in this manner. Appointments were scheduled for potential participants, during which the patient information sheet was provided and explained to them. Information concerning the conduct of the study, benefits, risks, privacy, and confidentiality was explained to the potential participants by the research team, and they were allowed sufficient time to consider their participation. Any questions from participants were addressed by the research team.

Once consent was obtained from potential participants for the study, they were asked to complete participant information and demographics. They were allocated to a focus group, and details regarding this focus group were communicated to them. Participants were intentionally

grouped into focus groups based on the following categories: (1) Adults with insulin-requiring Type 1 or 2 diabetes, (2) Adolescents with insulin-requiring Type 1 diabetes and their caregivers, with the recruitment of five participants per group as the basis for the sample size.

Data Collection:

Socio-demographic information, including age, gender, race, occupation, duration of diagnosis, type of CGMS used, and duration of CGMS use, was recorded using a form. The focus group discussions were conducted guided by a semi-structured interview guide question. The interview guide had been adapted from the European Network for Health Technology Assessment (EUnetHTA), with additional inputs from clinical experts and the research team.[9] Using this interview guide, the focus groups explored impact of diabetes for patients, patients' experiences and perceptions about using CGMS for their diabetes management in terms of perceived benefits, drawbacks/barriers, challenges, and issues, as well as their attitudes about CGMS and recommendations for its use in diabetes patients.

The focus group discussions were conducted by a team consisting of a moderator and an assistant moderator. While the moderator facilitated the discussion, the assistant moderator was responsible for note-taking. A semi-structured interview guide with questions was employed to guide the focus group discussions, ensuring consistency across groups and interviewers. The focus group discussions took place in an identified meeting room and lasted approximately 90 minutes. They were both audiotaped, and field notes were taken. The data collection period commenced from June 2023 to August 2023, subsequent to the receipt of ethical approval.

Ethics of Study

This focus group discussion was registered under the National Medical Research Register (NMRR) with NMRR ID-23-00721-OKL. Ethical approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia, and other relevant approvals were secured prior to the commencement of any study-related activities. The study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline.

Data Analysis:

Study data included: (1) Demographic data that described participant characteristics, (2) Discussion threads documenting focus group discussions, which were transcribed. Audio-recorded data were transcribed, coded, and analysed using thematic analysis and aided by Atlasti.23 software. The audio records of the interviews were transcribed by four researchers. The transcripts were double-checked against the audio records by one researcher to prevent data loss. The transcripts were analysed using thematic approach and aided by Atlasti.23 software. The interviews were coded by two researchers and the agreement between the two coders was checked. In case of a disagreement, researchers further discussed code differences to reach a consensus. Both deductive and inductive coding were used.[9-11] After completing the coding, codes were categorized, and themes were formed.

Results:

The sample consisted of 28 individuals, comprising 13 adult patients (43% Malay, 29% Chinese and 28% Indian) with Type 1 Diabetes (ranging from 20 to 67 years old) and two Type 2 diabetes (aged 63 to 80 years old), eight adolescent patients (aged 14 to 18 years old), and seven caregivers (aged 42 years old to 53 years old), with CGMS use duration varying from two weeks to eight years; most participants fell within the B40 and M40 income levels. Four focus group discussions were conducted, each involving 6-7 participants, comprising of adults and adolescents with caregivers. Data saturation was achieved after the completion of the fourth group discussion.

Emerging themes and categories

Theme 1: Impact of Diabetes

While the specific situations that led to the diagnosis of diabetes differed among individuals, those who were interviewed consistently expressed the profound emotional and psychological impact of the diagnosis. Furthermore, nearly all interviewees discussed significant and wide-ranging changes in their daily lives, which had consequences for their overall quality of life. These descriptions of the impact generally categorized into four primary groups: health and medical impact, lifestyle and daily management, emotional and psychological impact, social and relationship impact.

Subtheme 1.1: Lifestyle and Daily Management

After being diagnosed with diabetes, nearly all patients reported making substantial changes to their daily dietary habits. This was particularly notable among Type 1 diabetes patients, who exhibited heightened vigilance in managing their food intake. They tended to opt for low-glycaemic index foods and adhered to strict meal timing to align with their insulin regimens. Caregivers of adolescents with Type 1 diabetes also highlighted the significant impact of the condition on the entire family. They mentioned that the entire household had to adjust their dietary choices, meal planning, and daily activities to better support diabetes control for the affected individuals.

“Emmm I'm very cautious about eating. I can go out with friends and they had ice cream, in the back of my mind, whoaa sweet sweet, but it's much, it's much better for me” *Adult Type 1 diabetes*

“"In terms of the family, of course, my mother changed her diet, not just me, but the whole family. My mother uses everything like low GI food, organic items, and when they want something sweet, they use stevia. That's how it changed. We even bought plates with portion divisions." *Adolescent Type 1 diabetes* (translated from Malay)

When it comes to physical activity, adult patients with Type 2 diabetes didn't mention significant limitations in their exercise routines compared to Type 1 diabetes patients, particularly adolescents. Many adolescents expressed their initial reluctance to engage in sports activities after their diagnosis, as they were struggling with diabetes management challenges. However, some of them gradually resumed their sports activities once their diabetes was under better control.

Throughout the focus group discussions, individuals with type 1 diabetes and their caregivers consistently highlighted the ongoing challenges with managing this condition particularly the high burden of consistent blood sugar checking, timing of food intake, and insulin dosing. Those living with type 1 diabetes must maintain a continuous regimen of monitoring their blood glucose levels and administering insulin. As a result, they are required to perform these calculations and decisions multiple times each day, every day, over many years. Participants stressed that while these tasks may eventually become second nature, they remain of utmost medical significance, with errors potentially resulting in severe health complications in both the immediate and long-term.

"Checking the blood sugar 7-9 times a day, doing records and at that times injections with the daily insulins for the food" *Caregiver, adolescent type 1 diabetes*

"I prick my fingers more than 10 times a day because I need to monitor every hour as my blood sugar tends to fluctuate frequently." *Adult type 1 diabetes (translated from Malay)*

"Everyday you have to focus focus focus on your food, lifestyle and your medication timing" *Adult type 1 diabetes*

Caregivers of adolescents with type 1 diabetes also shared their experiences of sleep deprivation, as they need to monitor their children's blood glucose levels during the night and manage hypoglycaemic events. Parents reported the need to wake up multiple times to test their child's blood glucose and make any necessary corrections.

Subtheme 1.2: Emotional and Psychological Impact

During this focus group discussion, it became evident that the emotional and psychological impacts of diabetes were more pronounced in individuals with Type 1 diabetes and their caregivers. Adult Type 1 diabetes patients described experiencing emotions such as anger, denial, and frustration following their diagnosis. Adults with a passion for food and travel particularly voiced frustration, as diabetes restrictions hindered their ability to enjoy these pursuits fully. Adolescents, on the other hand, expressed their challenges in fitting in with their peers, often feeling 'different' or not 'normal.'

"it was a disaster because it's like, you cannot live a normal life anymore" *Adult Type 1 patient*

*"*I thought I was ok, but I think it was stress. I couldn't really accepted it. I am a 'foodie' and I love to travel. So yeah, so I was so mad, and then I really didn't want to be on insulin because it's a whole different change of lifestyle" *Adult Type 1 diabetes patient*

*"*It has effects on my mental health. I feel like I am not normal, I am different" *Adolescent Type 1 diabetes patient*

"I am mentally shattered. Sometimes I just feel like giving up. I feel so stressed out because I need to check my blood sugar frequently and cannot eat anything I want like my friends" *Adolescent Type 1 diabetes patient (translated from Malay)*

Almost all patients conveyed experiencing stress due to the continuous requirement of monitoring their blood glucose levels and adhering to stringent dietary routines to prevent

diabetes-related complications. Adolescents with Type 1 diabetes also shared feelings of inferiority compared to their peers and a sense of responsibility for managing their diabetes during their daily activities at the educational institutions. They also consistently shared their ongoing concern and anxiety related to diabetes management, primarily originating from the fear of complications.

“Then, it's very stressful when we have to keep on checking blood sugar, constantly pricking, all fingers get pricked, it's very traumatic.” *Adult Type 1 diabetes patient*

"I'm always worried and anxious. Worried about food, about anything I do, because I'm afraid I might have a hypoglycaemic episode." *Adolescent Type 1 diabetes patient (translated from Malay)*

As for caregivers, they consistently discussed the emotional toll of type 1 diabetes, frequently mentioning the continuous stress, fear, and anxiety they felt while taking care of their child.

“To me, very stressful, at that time very stressful for the all the family member when everything we have to change, the food also we have to change, the activities, the timing and all. I have fear that he will get into hypos at night, till I could not sleep, keep waking up to check blood sugars.” *Caregiver of adolescent type 1 diabetes patient*

“Really very stressed and afraid, wondering if we're managing her illness correctly, afraid that anything might happen to her." *Caregiver of adolescent type 1 diabetes patient*

Furthermore, caregivers spoke about their conflicting desires to safeguard their children by closely monitoring and checking their blood glucose levels, while also wanting to allow them independence and to be as “normal” as possible. Parents also reflected on the challenge of ensuring their children took responsibilities for their diabetes management. In the case of young children, parents took the responsibility, however, as their children grew older and gained more independence, parents tried to instill a sense of responsibility in their child to self-manage their diabetes, all without provoking resentment or rebellion. Parents mentioned the emotional burden this placed on them and the challenges they faced in enabling their child to independently manage their condition, fully aware of the potential long-term consequences of inadequate diabetes management.

Subtheme 1.3: Health and Medical Impact

All individuals with diabetes emphasized the challenges of continuous blood sugar monitoring and the necessity of taking multiple medications, including daily insulin regimens, which can be inconvenient and bothersome. However, most Type 1 diabetes patients particularly stressed the issues related to fluctuating blood glucose levels and the occurrence of multiple severe hypoglycemic episodes, some of which were so serious that they required admission to the Intensive Care Unit (ICU). Additionally, adolescents with Type 1 diabetes also faced episodes of Diabetic Ketoacidosis (DKA) as they are more susceptible to infections during the course of their diabetes.

“Sometimes I may get hypo and and I may get get it all of sudden I may I may be dizzy or things like that.” *Adult with Type 1 diabetes*

“Sometimes, I was just talking to others and suddenly, I was gone..I woke up already in hospital” *Adult with Type 1 diabetes*

“In the middle of the night. I wake up and shiver. About 2-3 times a week, I experience hypoglycemia.” *Adolescent with Type 1 diabetes (translated from Malay)*

“Then my blood sugar is not stable. When it starts to drop, it will keep decreasing and reaches a hypoglycemic reading, and I often end up going in and out of the hospital." *Adult with Type 1 diabetes (translated from Malay)*

"It's like when I'm at work. I often experience hypoglycemia and end up in the hospital frequently. Hypo during sleep, then not being aware, suddenly I'm in the ward, in an emergency situation like that. No warning signs, like sweating or a pounding heart." *Adult with Type 1 diabetes (translated from Malay)*

"I've been in the ICU twice because of DKA. I get DKA easily because I'm prone to fever." *Adolescent with Type 1 diabetes (translated from Malay)*

Subtheme 1.4: Social and Relationship Impact

The impact on family dynamics and relationships was more evident among individuals with Type 1 diabetes due to dietary changes, restrictions, and scheduling. Both adolescents and adults with Type 1 diabetes consistently mentioned challenges in socializing with friends and colleagues because of the demanding nature of diabetes management. They frequently found themselves having to restrain from fully enjoying food and social occasions.

“It limits yes because you cannot go to a party. You cannot simply friends come to you. They say, OK, let's go out, have an ice cream or you just sit there looking at them eating ice cream. Terrible, just simply terrible.” *Adult with Type 1 diabetes*

“Yes, I mean in one year I didn't go anywhere. I always enjoy travelling for food, trying something viral with friends. But with diabetes, I can’t do that anymore.” *Adult with Type 1 diabetes*

“No matter how good the food is during events, I will get up after the first round.” *Adult with Type 2 diabetes*

“Then yeah, even if I have to go to family functions and all that, it's either I eat at home and go or, I did not go at all. I was really, really strict.” *Adult with Type 1 diabetes*

"So, during my first and second year of degree, I was not very active. I only went to campus and back to the hostel, went to campus and back to the hostel. I didn't go out with friends because it was difficult to manage." *Adult with Type 1 diabetes*

When it comes to employment, most Type 2 diabetes patients didn't face significant challenges at work. However, a few individuals with Type 1 diabetes experienced reduced productivity, required medical leave, or even had to resign due to complications arising from diabetes.

"Yes, I'm still working, but now I can't get too tired. If I get too tired, my blood sugar will drop." *Adult with Type 1 diabetes (translated from Malay)*

"Like now, I can't work because in the beginning, it wasn't stable. I had to come to the hospital frequently, so I had to quit my job." *Adult with Type 1 diabetes (translated from Malay)*

Nearly all adults with Type 1 diabetes expressed that their colleagues at work had a good understanding of how to respond to hypoglycaemia and were aware of the associated symptoms. They provided valuable support and offered positive assistance during work hours. However, adolescents with Type 1 diabetes and their caregivers reported a different set of challenges, primarily in the school setting. Parents often found themselves in the position of educating their children's classmates, teachers, and school staff about Type 1 diabetes, its management, and emergency protocols. This was necessary due to a lack of knowledge and exposure to diabetes among school personnel. Adolescents had to face social stigma and juggle their schedules for blood glucose monitoring and insulin administration, which

sometimes led to time constraints during recess and limited their participation in various school activities.

"While I was in the hostel, I informed all my teachers that I have diabetes, so they didn't allow me to participate in any activities. I was restricted." *Adolescent with Type 1 diabetes*
"When I had a hypoglycemic episode, I drank a sweet drink, and a senior sister saw it. When I was admitted to the ICU, she told the teacher that I often drank sweet drinks, even though it was during my hypoglycemic episode. They checked my locker and found sweet boxed drinks, thinking I often drink that. They didn't know it was my hypo kits and didn't want to ask." *Adolescent with Type 1 diabetes (translated from Malay)*
“Classmates, they don’t really understand. I had to check my blood discreetly. Because many of my friends didn't understand my condition. So, I was worried they would find me strange." *Adolescent with Type 1 diabetes (translated from Malay)*
“Yes, the same. I also wonder why people find it strange. At the same time, when my child has to do the injection, if others look, they will think it's strange, like, 'What is this child doing?'. Our community still has a stigma about things like this. They are not open at all because they don't know what kids go through. They will say, Oh, this child is really bad, he has diabetes.” *Caregivers of adolescent with Type 1 diabetes (translated from Malay)*

Theme 2: Perceived Benefits of Continuous Glucose Monitoring System (CGMS)
All participants, regardless of their group, emphasized numerous perceived benefits associated with using CGMS for diabetes management. These benefits spanned medical advantages, social enhancements, emotional well-being, and an overall improvement in their quality of life, particularly among adolescent and adult Type 1 diabetes patients. Most participants regarded CGMS as a valuable educational resource for both patients and caregivers. Adults might have been handling their diabetes for an extended period, and CGMS represented the most recent addition to their array of tools for managing the condition. In contrast, for parents of recently diagnosed children CGMS held a different significance. It functioned as a means to ensure the safety and well-being of their child. The perceived benefits described by the participants can be broadly categorized into the following areas: medical benefits, social benefits, emotional benefits, improved quality of life, and its role as an educational tool for patients and caregivers.

Subtheme 2.1: Medical Benefits

Both adults with Type 1 and Type 2 diabetes as well as caregivers of adolescents with type 1 diabetes emphasized the perceived medical and safety benefits of the CGMS device. The capability of CGMS to provide real-time blood glucose monitoring and to observe blood glucose level trends, as opposed to relying solely on individual data points obtained through finger-prick monitoring, was a commonly recognised feature with significant medical advantages. In addition to alleviating the necessity for painful and bothersome finger-prick blood glucose testing, individuals noted that having access to trend data facilitated a more proactive approach to insulin dosage management. Parents and adult patients particularly for Type 1 diabetes could make immediate dosage adjustments based on trend data rather than waiting for the next finger-prick test. This was especially valuable for adolescents, as parents noted that factors such as hormonal changes, physical activity, and dietary variations often led to unpredictable fluctuations in blood glucose levels. The increased confidence in managing insulin dosages actively contributed to improved glycaemic control, maintaining lower HBA1C (glycated haemoglobin) levels, improved diabetes management, ultimately benefiting overall health.

“When I check with finger-prick, I get a reading, so what does it mean? Is it rising? Is it dropping? Is it anything doing? How much do I inject? I only need a lot of experience. From one value to do something if it is too high. With CGM, it changed the whole thing. And yes, the most important thing is this arrow is telling me now it's stable. And the curve tells me everything is fine with just taking blood from the finger you cannot do anything. You can just compare with five hours ago. But this is nonsense. So with this thing (showing CGM) you can you can see everything.” *Adult with Type 1 diabetes*

“The recordings will give you trends of some kind. And it does help if you can use it to trace and because I find that the difference the timing of different tablets. You know, sometimes it's fast-acting sometimes it's a slow-acting.” *Adult with Type 2 diabetes*

"With CGMS, it has a graph to view our blood sugar readings, we can see the trends, whether it's going up or down. We can tell when we eat, we can check, oh, it can show how much our blood sugar level is. So, we can control our diet." *Adult with Type 1 diabetes (translated from Malay)*

"Also, this CGMS shows trends with arrows pointing up and down, so we can anticipate our next reading. It's indicative. We can know what our next blood sugar reading prediction will be like." *Adult with Type 1 diabetes (translated from Malay)*

"But CGM is really good. It's easy to monitor, and emotions are okay. Because he had DKA before, emotions can cause blood sugar to go high. Other than fever, it immediately becomes DKA." *Caregiver of adolescent with Type 1 diabetes*

“If without CGM, cannot prick fingers too many times, and then you don't know what you eat. So with CGM, we know where we are and its better. With CGM, he (adolescent) only pricked finger only two times with maximum a day. Morning and then before bed. With the CGM at least we have insight. You know he will not in the dangerous situation especially before sleep.” *Caregiver of adolescent with Type 1 diabetes*

“So a lot of time, people always go back to the doctor. Ask should I adjust the basal? How much do we inject for the long acting? If with CGM then it’ll help a lot. It really help a lot in my opinion.” *Caregiver of adolescent with Type 1 diabetes*

"Far, far different. When I do the prick test, I have to get up, do the finger prick test, swab my finger. With CGMS, I just need to turn on my phone and check. It feels safer, and I can monitor at any time." *Adolescent with Type 1 diabetes*

“CGM controls the disease, without it, disease controlled us.” *Adult with Type 2 diabetes*

Adults and adolescent patients with type 1 diabetes also emphasized a significant benefit of CGMS particularly its alert and alarm features, which contribute to the reduction of hypoglycaemic events. This feature was highly valued by Type 1 diabetes patients who had few or no symptoms during hypoglycaemic events. Many participants mentioned that after using CGMS, the instances of hypoglycaemic events requiring hospitalization had significantly decreased, with some individuals not experiencing any such events for several years.

"Even better because you can see it directly with CGM. Another thing is it gives notifications if it's too low or too high. We can feel it, but what if the glucometer is suddenly left behind? So, with CGMS, it will always be with us." *Adolescent Type 1 diabetes (translated from Malay)*

"For me, it's better for me to use this thing because I'm one of those who don't have signs of hypoglycaemia, so when using CGMS, it helps me in all aspects, for example, during work, or at home. This thing already gives alarms or signals earlier. There haven't been any

hypoglycaemic episodes leading to hospitalization since using CGM." *Adult with Type 1 diabetes (translated from Malay)*

“When you start to use the CGM, they give alarm. Got hypos but when it gives alarm, then you immediately treat.” *Caregiver of adolescent with Type 1 diabetes*

"So with CGMS, when the alarm sounds, it will alert me." *Adolescent with Type 1 diabetes (translated from Malay)*

“Before that, every now and then I used to drop under the table. People have to carry me.Out to the hospital and. With this thing. It won't. It didn't happen once since 2015.” *Adult with Type 1 diabetes*

Subtheme 2.2: Patient Educational Tool

Patients across all groups consistently expressed that CGMS serves as a valuable educational tool, providing them with a comprehensive understanding of their diabetes and empowering them to take proactive charge of their diabetes management. Through the use of CGMS, patients gained a comprehensive education in the real-world influences on their blood sugar levels. It serves as a visual guide, offering insights into how meals, exercise, stressors, and other variables impact their daily glucose patterns. Adolescents with type 1 diabetes found that CGMS not only assists them in managing their condition but also promotes a sense of independence. It equips them with the tools to monitor their blood glucose levels and make informed decisions, empowering them to navigate their daily lives with confidence. The use of CGMS eased the burden on caregivers by providing real-time visibility into their adolescent's diabetes status. Caregivers could remotely monitor blood sugar levels and receive alerts, ensuring timely interventions and minimizing the risk of hypoglycaemic events. Continuous Glucose Monitoring System (CGMS) data was also an invaluable resource for healthcare professionals, enabling them to evaluate medication efficacy and safety. It facilitated evidence-based decision-making, leading to more effective and personalized treatment plans.

“Yes, because with this thing, I can really understand my diabetes. I can really understand my diabetes. I can go out. I can do everything. I can go to the cinema without hesitating and survive the evening. It is really that important for me.” *Adult with Type 1 diabetes.*

“So I know myself well using this CGMS then I know how to control myself.” *Adult with Type 1 diabetes*

"At night, it's better. Before going to sleep, I check my blood sugar levels first. So, I can adjust it myself." *Adolescent with Type 1 diabetes (translated from Malay)*

"Now I can do everything myself; I can manage my own blood sugar, my food, my activities." *Adolescent with Type 1 diabetes (translated from Malay)*

“Yeah, it's supposed to be helping the doctors as well. We have our Endocrine doctor. Every time we want to adjust insulin or even in the hospital, the doctor also based on some basic information to calculate how much basal per hour and what is ICR. That kind of things with the CGM reading then the doctor can adjust better.” *Caregiver of adolescent with Type 1 diabetes*

“When the basal insulin not good or reading always abnormal or high then we install CGMS to monitor from period to period that our endocrine doctor will tell us, then the data will be used to adjust medications” *Caregiver of adolescent with Type 1 diabetes*

“And I think CGMS help to trace and because I find that the difference the timing of different tablets. You know, so the doctors will see the data and should able to tell me.” *Adult with Type 2 diabetes*

Subtheme 2.3: Social Benefits

Patients from all age groups and diabetes types unanimously praised CGMS for its remarkable convenience, allowing them to enjoy social interactions without the constant need to carry a glucometer and perform frequent finger-prick tests during social activities. One common sentiment among patients was the time saved by using CGMS, eliminating the need for multiple finger-prick tests while socialising. They no longer felt restricted by diabetes management and could fully engage in social activities, much like their peers. Adolescent patients particularly highlighted the sense of freedom and carefree living that CGMS afforded them. It allowed them to participate in social events without the constant interruption of glucose monitoring. Patients found it easier to maintain their routines and traditions while effectively managing their diabetes. Caregivers of adolescents with diabetes benefited significantly from CGMS, as it lightened their burden of constant supervision and monitoring. CGMS gave them reassurance and allowed their adolescents to become more independent in managing their diabetes.

“After some time then they get used to the CGM, because they see the reading, they also can have more control, they have more freedom” *Caregiver of adolescent with Type 1 diabetes*

“Easy and quick. If you do finger-prick, it takes time. Previously, she had to do the prick before eating, so it took time during break time, friends had to wait for her, even to buy food, and the

break time was only half an hour. But with CGM, it's faster; she can inject insulin quickly and eat with friends." *Caregiver of adolescent with Type 1 diabetes (translated from Malay)*

"I think when I want to eat out, for example, when going out with friends to have cake, if I want to eat, I will check my blood sugar level. I can check more frequently, anytime, with CGMS. I can know my blood sugar readings." *Adult with Type 1 Diabetes (translated from Malay)*

"Before this, I had to carry a glucometer, strips, and all that, so this is easier. Because before CGMS, I had to carry all this every time I go out with friends and it was bothersome to do glucose checking and everything while my friends asked to go here and there, because they don't need to do any of this." *Adolescent with Type 1 diabetes (translated from Malay)*

"It feels more convenient because there's no need to draw blood anymore. Until now, I had to draw blood, but now, while watching TikTok or whatever, I just look at the side and see your blood sugar level. It's like an advancement. So, I can engage in many activities with my friends." *Adolescent with Type 1 diabetes (translated from Malay)*

"After using CGM, it feels easier because I can see the blood sugar level trend of my child myself, so I can monitor their sugar control, making it more convenient for me." *Caregiver of adolescent with Type 1 diabetes*

"My mother also uses it, she downloaded the app and paired it with mine. When I go to the doctor, they download the data from the app and email it to the doctor to review the data. So, it's very helpful." *Adolescent with Type 1 diabetes (translated from Malay)*

Subtheme 2.4: Emotional Benefits

Patients, especially those with type 1 diabetes, expressed that CGMS instilled a sense of confidence and helped them feel more "normal" in their daily lives. CGMS was noted consistently for its role in reducing the emotional stress associated with frequent finger pricking, which had been a source of discomfort and inconvenience particularly among adolescents with type 1 diabetes. Patients found that CGMS alleviated fears and anxiety related to their ability to optimally control their blood sugar levels, providing a greater sense of control over their diabetes management. The continuous monitoring feature of CGMS offered reassurance to caregivers, as it helped them address concerns about hypoglycaemic events more effectively, ultimately improving their overall emotional well-being.

“You always feel that you're not normal. You're not part of the others who are playing their game, but you're not part of it. And this thing (CGMS) brought this life back now I can play again. With them.” *Adult with Type 1 diabetes*

"She doesn't stand out much with this CGM; it's hidden, so far so good. She appears normal like everyone else." *Caregiver of adolescent with Type 1 diabetes (translated from Malay)*

"Previously, he was very stressed. So, he was very tense, and his fingers even became stiff because of frequent pricking, but he wouldn't check. He was stressed about having to prick so many times. With CGM, he is much, much happier." *Caregiver of adolescent with Type 1 diabetes*

"CGM reduced the stress and anxiety of my child because she couldn't bear to do the pricking anymore, and it was heart breaking to see her." *Caregiver of adolescent with Type 1 diabetes*

"And she doesn't have to suffer anymore with CGM because every time she pricked, she would get emotional and stressed because of the pricking." *Caregiver of adolescent with Type 1 diabetes (translated from Malay)*

"It's convenient, and I'm less worried. I feel safer. We can easily see the glucose readings by looking at the reading trends." *Caregiver of adolescent with Type 1 diabetes*

Subtheme 2.5: Improved Quality of Life

Through the focus group discussions, it became evident that participants overwhelmingly concurred on one crucial point: CGMS offered them a profound peace of mind. Participants across all groups conveyed a shared sentiment that CGMS technology empowered them to regain control over their lives, offering a profound enhancement of overall well-being. Besides its painless nature, an improvement in sleep quality emerged as a tangible and highly valued benefit of CGMS usage, with participants, especially caregivers, reporting that the device alleviated concerns related to nocturnal glucose fluctuations and allowed for more restful nights.

“From black before the time of CGM to white. With this thing I can live. Yeah, I'm living with diabetes with this thing. Without it, I’m just surviving.” *Adult with Type 1 diabetes*

“I think that we can all hear that what we are trying to emphasize here, because of this CGM, it gives you peace of mind.” *Adult with Type 1 diabetes*

“CGM controls the disease, without it, disease controlled us.” *Adult with Type 2 diabetes*

“With CGM, sleeping becomes much better” *Adult with Type 1 diabetes*

“Night-time, its better now. Before going to bed, I check my blood sugar level first. So, I can make adjustments. I can sleep well now.” *Adolescent with Type 1 diabetes (translated from Malay)*

"Before that, one year plus without CGM, I was in the dark, I only sleep for two hours and check and see if everything is OK. Cannot have a good sleep. Now I can sleep with no problem. Everything is good now." *Caregiver of adolescent with Type 1 diabetes*

Theme 3: Perceived Barriers for using Continuous Glucose Monitoring System (CGMS)

Patients and caregivers consistently identified the substantial financial impact as the primary barrier to adopting CGMS for diabetes management. The high costs associated with the device itself and the frequent replacement of sensors significantly contribute to the financial burden of diabetes care. Additionally, participants frequently raised concerns about device-related challenges, including malfunctions, sensor dislodgments, and inadequate technical support. The perceived barriers articulated by participants can be categorized into the following key areas: substantial financial impact, device-related issues, limited access and support, psychosocial issues, and skin irritation.

Subtheme 3.1: Substantial Financial Impact

A common and overarching concern shared by all participants centered on the substantial costs associated with CGMS devices and the need for frequent sensor replacements due to their limited lifespan. Patients unanimously voiced their struggles in affording CGMS, citing the absence of insurance coverage, government subsidies, or financial support as significant barriers to access. Notably, some patients, despite acknowledging the significant advantages of CGMS for their diabetes management, were forced to discontinue its use solely because of financial limitations. Adolescents and their caregivers, too, shared apprehensions about the future affordability of CGMS, especially for adolescents transitioning to adulthood who may face challenges without government support. A noteworthy finding was that a subset of patients could only use CGMS intermittently, given the high cost, highlighting the financial limitations they encounter in maintaining consistent usage.

"At the moments, the problem is the cost. The cost for this device, and cost for sensor is very expensive. The only thing is I wish the price could get lower." *Adult with Type 1 diabetes*

"The main thing is the price. It's just too expensive for me. The price for the device is already expensive, then I have to change the sensor which costed me another RM 200 to 300 every 10-14 days, it is very expensive" *Adult with Type 1 diabetes*

“Cost is a big issue, the device, the sensor, its crazy and too much. I wish to have long term also if cost wasn't the issue.” *Caregiver of adolescent with Type 1 diabetes*

"So, for me, it's also difficult because this CGM is expensive, the cost is high, so I don't know how it will be when I grow up, and my parents are no longer working, so how will I continue, how will I pay for it." *Adolescent with Type 1 diabetes (translated from Malay)*

"Currently, it's my parents who are covering the cost, but now I'm thinking a lot about how the expenses for CGM will be in the future. My parents can afford it, but I still worry that it might be burdensome for them." *Adolescent with Type 1 diabetes (translated from Malay)*

"For every 3 months, I can still manage, but for the long term, I won't be able to afford it. Maybe I won't be able to use it continuously, once a month or every two months, I might be able to manage, but for continuous use, it’s not affordable for me." *Caregiver of adolescent with Type 1 diabetes*

"But overseas, they all have insurance. In Malaysia, we don't have that. There's no room for people with diabetes to get insurance, even if they're willing to pay the premium. There's no subsidy from the government, no assistance for CGMS." *Adult with Type 1 diabetes*

Subtheme 3.2: Device-related Issues

Device malfunctions emerged as a recurring concern, voiced by nearly all participants in various focus groups, with a particular emphasis on sensor-related problems. Participants consistently reported instances where sensors failed to function as expected, displaying 'data not available' or experiencing data loss before reaching their designated lifespan. This issue was notably more frequent during the second week of sensor use. Sensor dislodgement due to contact with the surroundings, including interactions with doors, contact with people, and physical activity such as sports and excessive sweating, emerged as a significant drawback. For some patients, this limitation extended to their ability to engage in contact sports and other physical activities. Interestingly, alarms and alerts generated by CGMS devices appeared to be generally nonintrusive and were not reported as a major concern by most participants.

"But usually, when it's about to reach the 2-week mark, I feel it becomes a bit 'faulty.' It keeps showing 'glucose level not available' suddenly, and during the second week, it's consistently faulty before it should be, unable to detect, sensor not available. You have to wait a few minutes, and even after that, notifications keep saying it's still not working, so you need to have a glucometer with you at that time." *Adolescent with Type 1 diabetes*

“I had sensors who didn't start at all. I had sensor to stopped after five days, 5 to 6 days. And almost none of them lasted 2 weeks. (12 days) yesterday I've changed it to a new one because that one was 10 days. And it will tell you to just change the sensor. Even though it's not yet 14 days” *Adult with Type 1 diabetes*

"Then, if I feel like 'data not available' is taking too long, I'll refresh it, then wait for notifications; sometimes it's okay, and sometimes I have to change the sensor. This often happens during the second week, around day 9-10, and it consistently occurs." *Adolescent with Type 1 diabetes (translated from Malay)*

“My problem is with doors. I had the sensor came off when I accidently bumped into doors. And people. But the only one point is this. Because if somebody hits it, you just cannot fix it back.” *Adult with Type 1 diabetes*

“Contact sport have to be reduced because CGM can get detached.” *Caretaker of adolescent with Type 1 diabetes*

"Yes, it happened few times, it got dislodged because someone bumped into me. So, the sensor was wasted, and I had to replace it with a new one." *Adolescent with Type 1 diabetes (translated from Malay)*

"Earlier this year, I had indeed stopped playing soccer because I want to avoid getting sensor dislodged." *Adolescent with Type 1 diabetes (translated from Malay)*

Subtheme 3.3: Limited accessibility and support

Several patients voiced concerns regarding CGMS access, highlighting the challenges of its limited availability in the market. They frequently found themselves having to visit multiple pharmacies, leading to occasional stock delays and extended waiting time. Patients and caregivers, in particular, emphasized their inability to access the more recent CGMS versions available abroad, known for their advanced features and enhanced convenience. Regrettably, these updated versions have not yet been introduced to the Malaysian market.

“Basically, I don't know where to get it. Then and I travel all the way from my house and I want to get it, this CGM is not available.” *Adult with Type 1 diabetes*

“Problem is to get stock. Normal pharmacies don't sell because expensive and very low demand.” *Caregiver of adolescent with Type 1 diabetes*

“However, the problem is obtaining stock. There's often no stock available, even when we search at pharmacies.” *Adult with Type 1 diabetes (translated from Malay)*

"One thing here in Malaysia we have only old version while people overseas have other better versions with better design and functions. Maybe the demand for this (CGMS) is not that high. And very costly" *Caregiver of adolescent with Type 1 diabetes*

Caregivers highlighted the restricted availability of technical assistance for issues related to CGMS and the absence of peer support groups where users can exchange experiences and seek help. Notably, some Type 2 diabetes patients voiced their frustration about doctors' limited knowledge concerning the effective utilization of CGMS data for medication adjustments. This knowledge gap was perceived as an obstacle to fully harnessing the benefits of CGMS.

"Very stressful for us when we had to set up the CGM and when something is wrong, it's hard to get immediate help." *Caregiver of adolescent with Type 1 diabetes*

"When things are wrong, you cannot just go back to the pharmacy, because they only sell. They cannot fix it" *Caregiver of adolescent with Type 1 diabetes*

"I also feel sorry because we don't have a support group, right? There's no support group for us to share anything about CGM. Because sometimes, parents have their down moments, you know." *Caregiver of adolescent with Type 1 diabetes*

"Sometimes, we need a support group for CGM users to exchange our issues so that we can make it easier to find out where to get CGM, learn from the experiences of those who have been using it for a long time. But there isn't one." *Adult with Type 1 diabetes*

"I found some doctors did not value the data from CGMS. They don't want to interpret the data to adjust medications. Only I do the analysis myself. And I can see that they don't want to analyse because lack of training." *Adult with Type 2 diabetes*

Subtheme 3.4: Psychosocial issues

A minority of participants with Type 1 diabetes raised concerns related to social stigma and public perception surrounding CGMS use. They observed that public awareness in Malaysia is still limited, and CGMS may not yet be universally socially accepted. Patients, especially adolescents, candidly shared their experiences of feeling self-conscious and experiencing stares from the public and peers when using CGMS. One patient openly expressed that fear of social stigma and the perception of not being 'normal' were factors that hindered him from embracing CGMS technology.

“All guys are my age and they are normal and when they are asking what is that, giving me pity eyes. So that's another reason why I didn't want to use it.” *Adult with Type 1 diabetes*

“So I thought. You know, socially in Malaysia is not widely accepted yet. Everybody will start questioning what is it? What is it? Because many people don't know and I don’t want every of them, looking at me like that” *Adult with Type 1 diabetes*

"Many of my friends don't know about my illness. So, some people find me strange." *Adolescent with Type 1 diabetes*

"I also wonder why people find it strange. At the same time, when my child uses CGM and we have to do checks, if others look at us, they'll find it strange, like, 'Why is this child doing that?” *Caregiver of adolescent with Type 1 diabetes*

Additional participants and caregivers highlighted the stress and worry they experience when replacing the sensor by themselves. Their concerns primarily revolved around the fear of device malfunction and the unavailability of immediate technical support.

“So after that when we have to do it ourselves every time, when we want to put in the sensor, we all very stressed. The whole family were stressed” *Caregiver of adolescent with Type 1 diabetes*

“Yes, you’ll be scared, and worried.. oh It's not working anymore. Then I have to take it off and then get another one.” *Adult with Type 1 diabetes*

“Very worried everytime replacing it myself, it might be like just 50-50 if I plug it then it's not working, then it's a waste.” *Adult with Type 1 diabetes*

Subtheme 3.5: Skin irritation

A limited number of participants highlighted the presence of skin irritation in the areas where the CGMS sensor is placed, which acts as a deterrent, restricting their ability to use CGMS continuously.

“CGM cause skin problem, like the skin becomes irritable. Had skin issue when long term and no place to put anymore when the skin irritation problem because you repeatedly use the skin. So, we cannot use continuously. We have to let the skin rest for few weeks.” *Caregiver of adolescent with Type 1 diabetes*

"I found my skin to be irritable and itchy around the sensor area" *Adolescent with Type 1 diabetes*

Theme 4: Issues with long term use and hopes for CGMS

The focus group discussions highlighted a common concern shared by all participants regarding the long-term use of CGMS, with cost emerging as a predominant issue. Participants expressed that while they recognized the ideal nature of CGMS for long-term diabetes control, the high cost presented a significant barrier. Patients conveyed a strong desire to use CGMS consistently over the long term to maintain optimal control of their diabetes. However, due to the financial constraints associated with CGMS, they often found themselves compelled to use it intermittently to ensure they remained on track with their diabetes management goals. Several participants raised concerns related to skin irritation as a consequence of the long-term use of CGMS. They shared experiences of discomfort and skin reactions, emphasizing the importance of addressing these issues to make long-term use more tolerable. Despite the challenges and concerns, participants expressed enduring hopes for CGMS. They saw CGMS as a valuable tool in their diabetes management journey and expressed the desire for more affordable options that would enable them to use it consistently without incurring excessive financial burdens.

"I wish to have long term also if cost wasn't the issue." *Adult with Type 1 diabetes*

"Cost. If it is little or no cost then I will use it long term" *Adult with Type 2 diabetes*

"Currently we already very stable because we monitor for many years and then now we are skipping the CGM not wearing all the time because it's too expensive" *Caregiver of adolescent with Type 1 diabetes*

"For me, there are no material complaints, everything is okay, even in terms of design. The only issue is its price, which is high. I need to use it for the long term, but it's too expensive." *Adult with Type 1 diabetes (translated from Malay)*

"I can manage it for every three months, but for the long term, I'm worried that I can't afford it. Maybe I can use it intermittently, once a month or every two months, I can manage that, but for continuous use, I don't think I can afford it." *Caregiver of adolescent with Type 1 diabetes (translated from Malay)*

“But this cost is the issue and also skin issue when long term and no place to put anymore when the skin cause problem because you repeatedly use the skin area.” *Caregiver of adolescent with Type 1 diabetes (translated from Malay)*

Across all participants in the focus group discussions, a consistent theme emerged: the expressed hope for the provision of CGMS for specific patient groups or, at the very least, government subsidies for CGMS for certain patients with income levels categorized as B40, elderly individuals, or those at high risk of diabetes-related complications.

“So this also if you decide that the people need it and long term government benefit, the cost of health care cost will go down when complications are prevented. So you have to decide that that some categories should get free, you know, maybe senior citizens, you know, some categories of patients. It should be given to selected group of patients because it saves lives.” *Adult with Type 2 diabetes*

"If it's free, I would definitely like it. Even if it's not free but subsidized, it would lessen the cost burden. If more of these can be made available in Malaysia, more people can use it. Because many families can't afford to own CGMS. Parents want the best for their young children who have been diagnosed, but they can't afford to get CGMS." *Caregiver of adolescent with Type 1 diabetes (translated from Malay)*

"Even if it's in the form of a subsidy, it's good. Rather than nothing." *Adult with Type 1 diabetes*

"Maybe it can be given to the B40 group. Even if it's not a lot, at least getting some support from the government is already okay." *Adult with Type 1 diabetes (translated from Malay)*

A common concern raised by most patients was the need to enhance the availability and accessibility of CGMS in Malaysia. Their specific interest lay in accessing newer versions of CGMS equipped with alarm features and other advanced functionalities that are readily available in overseas markets, along with improved design and connectivity options. Furthermore, a subset of patients highlighted the importance of providing training for healthcare professionals, particularly doctors, in the effective use of CGMS. They stressed the significance of optimizing the captured data to deliver superior diabetes care. Lastly, participants emphasized the necessity of intensifying preventive measures to combat the rising incidence of Type 2 diabetes in Malaysia, with the ultimate goal of fostering a healthier population and elevating the overall quality of life for all Malaysians.

Theme 5: Overall attitudes and patients' recommendations for CGMS

The results of the focus group discussions revealed that both diabetes patients and their caregivers held overwhelmingly positive attitudes towards the utilisation of CGMS for diabetes management. Most patients expressed that CGMS provided a convenient and potentially cost-effective solution for their diabetes management needs in the long term. Participants consistently emphasized the profound significance of CGMS in their daily lives. They underscored how CGMS had positively impacted their diabetes management routines and helped them achieve better control. The focus group discussions yielded strong recommendations for the use of CGMS, particularly for specific patient categories. Participants strongly endorsed CGMS use for individuals with Type 1 diabetes, especially those at high risk of hypoglycaemia, as it offered a valuable tool for maintaining optimal glucose levels. Additionally, participants highlighted the importance of CGMS for adolescents with Type 1 diabetes, as it enabled them to maintain better control over their daily routines and activities. Caregivers specifically recommended the early adoption of CGMS, particularly during the initial stages of diagnosis. They believed that CGMS could assist patients, caregivers, and healthcare professionals in fine-tuning medication regimens and establishing effective routines for diabetes care.

"I can only recommend CGMS because it rea
lly gives back your life. In a long period. For me, there's absolutely no issue and I cannot imagine life without it." *Adult with Type 1 diabetes*

"I recommend this CGMS to other diabetes patients. I think cost wise. Healthcare wise cost you reduce substantially with the use the CGM, People benefit, the hospital benefit, yeah all their costs all go down. So instead of spending more time in the hospital, increase the cost of healthcare. So by having this gadget you can reduce all that can reduce the complications and hospitalisations." *Adult with Type 2 diabetes*

"For me, CGM is very helpful, really. Factors like convenience so with CGM, I only need to focus on insulin injections. It makes things much easier for me. So, I feel it's worth it, and I recommend this device for diabetes patients like me." *Adolescent with Type 1 diabetes (translated from Malay)*

"I feel it's really great. I recommend it to other patients to try because it's convenient and doesn't burden us." *Adolescent with Type 1 diabetes (translated from Malay)*

"To me, the use of CGM is good, and this device should be expanded to diabetes patients at risk like me for the convenience of patients as well." *Adult with Type 1 diabetes*
“For me, I highly recommend CGMS for those with Type 1 especially if they're newly diagnosed. That is very. Very helpful. So CGMS for that time very, very beginning stage is very helpful.” *Caregiver of adolescent with Type 1 diabetes*

These findings collectively reflect the overwhelmingly positive perceptions of CGMS among diabetes patients and caregivers. The recommendations emphasize the potential benefits of CGM for specific patient groups and stages of diabetes management.

Discussion

Throughout the focus group discussions, participants revealed how diabetes compelled significant alterations in daily routines, including dietary adjustments, vigilant blood sugar monitoring, and precise timing of food intake and insulin administration. Emotional and psychological strains were particularly noticeable, particularly among Type 1 diabetes patients and caregivers. Health-related challenges, such as frequent blood sugar checks and medication management, compounded the burdens of diabetes. Diabetes also placed restrictions on social activities, limiting the opportunities for patients to engage fully in social and personal relationships. Continuous Glucose Monitoring Systems (CGMS) emerged as a pivotal intervention, significantly mitigating these impacts by providing real-time data, becoming an educational tool, and enhancing glycaemic control, reducing the need for constant vigilance, alleviating anxiety as well as stress, and enabling a more flexible and improved quality of life for diabetes patients and caregivers.

Similar findings were reported in an HTA conducted in Ontario, Canada, where participants in the focus group discussions, especially both adults with type 1 diabetes and parents, emphasized not only the social and emotional advantages of CGMS but also its significant perceived medical and safety benefits. Long-term adult diabetes patients viewed it as an invaluable educational tool, aiding in a deeper understanding of their body's responses to various factors affecting blood glucose levels.[4] Both patients and caregivers in these two settings consistently recognized the capacity of CGMS to track trends in blood glucose levels, as opposed to the singular data points obtained through finger-prick monitoring. This feature was widely acknowledged as having significant medical advantages, as it facilitated more

precise insulin dosing strategies, ultimately leading to improved glycemic control.[4] Both patients and caregivers often spoke of the social freedom that CGMS provided as they could manage their diabetes in a way that was as socially unobtrusive as possible. These findings are consistent with previous research which reported heightened sense of independence and personal control with CGM use especially to patients with Type 1 diabetes.[11] Data from few other qualitative studies also reported CGMS may exert positive effects in terms of functioning at work and relationships.[11,12] The specific benefits of particular brands of CGMS devices were not discussed in this focus group discussions. However, the increased benefit from CGMS with an alarm features was mentioned by several patients largely because they improved awareness, provided peace of mind, and allowed for better diabetes management.

Conversely, participants also shared their experiences regarding perceived barriers to CGMS use. The primary barrier centered around the high financial implications, including the cost of the CGMS device itself and the frequent need for sensor replacements. The lack of insurance coverage and government subsidies added to the financial burden. The participants' stories vividly portray the significant financial challenges individuals encounter when contemplating CGMS adoption underscoring the urgent need for equitable access to this technology, especially for those within the lower income strata. Previous research has shown that when CGMS costs were eliminated through subsidy, both individuals with type 1 and type 2 diabetes had high CGMS uptake and adherence, and its use was associated with improved HbA1c levels, underscoring the effectiveness and broad appeal of CGMS across an underprivileged patient population.[13] Addressing the disparity in CGMS access based on income levels is not only a matter of healthcare policy but also an ethical imperative to ensure that the benefits of this technology reach those who need it most. Expanding government subsidy coverage to encompass CGMS could potentially alleviate the burden of high costs for patients, and stakeholders should advocate for policy reforms that recognize the potential long-term cost savings in preventing diabetes-related complications. Patient advocacy groups play a crucial role in driving policy changes to enhance access to CGMS through lobbying for reforms in healthcare policies.

In this focus group discussion, participants voiced significant concerns about technical challenges, notably sensor malfunctions and dislodgements. Similar findings were reported in few other focus group discussions on CGMS where technical issues were named as one of

important drawbacks.[11,14,15,16] This underscores the pressing need for manufacturers to invest in research and development, aiming to improve the reliability and durability of CGMS sensors. Additionally, the lack of comprehensive technical support and maintenance services, as emphasized by both patients and caregivers, is a critical issue that warrants attention. Ensuring a seamless user experience is vital for unlocking the full potential of this technology. Promoting patient education on sensor maintenance and troubleshooting can empower CGMS users to proactively address technical challenges, reducing their reliance on external support. The establishment of patient support groups or online communities can foster a sense of solidarity among CGMS users, providing a platform for sharing experiences and practical solutions to common device-related issues. While skin irritation was mentioned by only a minority of patients in this focus group discussion, it's important to note that this issue has been reported to varying degrees in a few previous studies, [17,18] highlighting the need for attention and potential solutions to address it.

Overall, the participants expressed positive attitudes towards CGMS which underscore its role in empowering individuals to take control of their diabetes management, resulting in improved lifestyle choices and enhanced overall well-being. Notably, participants expressed a strong willingness to recommend CGMS to others within their diabetes communities, highlighting the potential for peer-driven adoption and an increased awareness of CGMS benefits. However, they emphasized the importance of tackling financial barriers to CGMS adoption, suggesting the need for subsidies or affordable payment options to ensure widespread access to this technology. Participants expressed a strong desire for access to newer CGMS versions boasting advanced features, such as alarms and improved connectivity, emphasizing the need to address this demand and improve access in Malaysia. This could be achieved through a multifaceted approach that may include implementing government subsidies or insurance coverage for CGMS and fostering partnerships with manufacturers for affordability initiatives. Moreover, participants emphasized the need for healthcare providers to receive comprehensive education and training on harnessing CGMS data for more tailored medication adjustments, ultimately leading to enhanced diabetes care plans.

The focus group discussions yielded valuable insights into the experiences of individuals with diabetes and their caregivers using CGMS. Held in a real-world context, these discussions enabled open sharing of experiences, challenges, and recommendations related to CGMS use.

This approach yielded diverse perspectives, including those of patients and caregivers, leading to a more comprehensive exploration of diabetes and CGMS impacts on individuals and their families. By providing qualitative data, these discussions complement quantitative research, offering a holistic understanding of the complexities surrounding CGMS adoption, its benefits, and barriers. The limitations of the focus group discussions include a potentially small sample size, which may restrict the applicability of the findings, emphasizing the potential advantages of larger sample sizes for improved representation. Additionally, there is the possibility of sampling bias, where participants may not fully represent the entire population of CGMS users, introducing variations compared to those who chose not to participate. Social desirability bias may have influenced participant responses, potentially leading to answers that conform to perceived expectations rather than authentic opinions and experiences. Furthermore, the findings from these discussions could be context-dependent, mainly relevant to specific geographic regions or healthcare systems, thus limiting their broad applicability. Lastly, the discussions may not capture long-term changes in experiences or attitudes toward CGMS, as perceptions and challenges can evolve over time. Despite these limitations, the focus group discussions have illuminated the real-life experiences of individuals with diabetes using CGMS, shedding light on the benefits, barriers, and overall impact of CGMS on their lives.

To move forward, several key actions are recommended. Firstly, addressing financial barriers to CGMS adoption through options like subsidies, insurance coverage, and cost-reduction programs is essential. Secondly, healthcare providers and manufacturers should collaborate to enhance technical support for CGMS users, ensuring timely problem-solving. Thirdly, healthcare professionals should undergo training to optimize CGMS data for medication adjustments and improve diabetes patient care. Public awareness campaigns are needed to reduce social stigma around CGMS use. Establishing patient support groups can provide vital platforms for information exchange and emotional support. Expanding research, involving larger and diverse samples, will validate findings from these discussions. In conclusion, addressing the concerns and recommendations from these focus group discussions is vital to enhance CGMS accessibility, usability, and acceptance in diabetes management, necessitating stakeholder collaboration to improve the overall experience for individuals with diabetes and their caregivers.

Conclusion:

The focus group discussions have revealed noteworthy insights into the experiences of individuals with diabetes and their caregivers using CGMS. These discussions highlighted a range of perceived benefits for CGMS including medical benefits, social enhancements, emotional well-being, and an overall improvement in their quality of life, particularly among adolescent and adult Type 1 diabetes patients. Most participants regarded CGMS as a valuable educational resource for both patients and caregivers. However, participants also emphasized significant barriers, such as the high financial burden, technical challenges, limited accessibility, and support alongside concerns about social stigma and skin irritation. Participants also stressed issues related to long-term CGMS use, the need for improved technical support and access, as well as the absence of patient support groups. Despite these barriers, both diabetes patients and their caregivers held overwhelmingly positive attitudes towards the utilisation of CGMS for diabetes management and strongly endorsed CGMS use for individuals with diabetes particularly Type 1 diabetes, especially those at high risk of hypoglycaemia. Participants emphasized the need to address financial barriers, access issues, and technical support for CGMS, as well as the need for patient support groups and training for healthcare providers in utilizing CGMS data to improve diabetes care plans.

7.0 DISCUSSION

The proposed review will address a gap in our understanding about acceptability and feasibility of an emerging health technology that has the potential to transform diabetes self-management, including among more vulnerable groups. Understanding if these devices are acceptable and feasible to a range of people, including users, their carers, and healthcare professionals, is a crucial step. Ongoing assessment of the acceptability of interventions has been identified as crucially important to scale-up and implementation. This review will provide new knowledge with the potential to inform a programme theory of CGM as well as future roll-out to potentially vulnerable populations, including those with severe mental illness.

From the patient perspective, CGM offers the benefit of real-time glycaemic monitoring with glucose trend information indicated by directional arrows. These trend arrows are a visual display of the direction of glycaemic activity (i.e., whether the current glucose level is rising, stable, or decreasing). The visual display of CGM data allows patients to view their glycaemic activity and monitor the effects of different types of food, timing of meals, activity levels, stress, and illness. This opportunity facilitates increased patient engagement with diabetes management. Having glucose data readily available is also relevant for loved ones and caregivers of people with diabetes, allowing them to better assist in care and offering them peace of mind with regard to hypoglycaemia and hyperglycaemia.

Integrating CGM into clinical practice can be challenging for several reasons. Common issues reported include data overload, increased clinic staff time, and the need for HCP education on data interpretation. Orienting practice staff to the use of CGM technology and downloading reports to a standalone computer and printer that are separate from restrictive administrative firewalls can streamline analysis of CGM data.

Although there can be some barriers to CGM use, there is also strong evidence for its utility in patients with either type 1 or type 2 diabetes and with either personal or professional CGM systems. Patient benefits include improvement in HbA1C, reductions in hypoglycaemia and glycaemic variability, and greater treatment satisfaction and improved sense of mental well-being.

Limitations

The authors acknowledge some limitations in the review and these should be considered when interpreting the results. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers. One of the important limitations was the methodological quality of the included studies, particularly in terms of heterogeneity, sample size and the risk of bias. This could due to the differences in the baseline characteristics of the study participants, differences in the inclusion and exclusion criteria of each study, assessment of outcomes, and the differences among the molecular profiling assays itself.

8.0 CONCLUSION

Blood glucose monitoring using CGM system was not a cost-effective option when compared to SMBG in both T1DM and T2DM populations with only small gain in the benefit shown in the former population over the simulated lifetime horizon. Nevertheless, CGM system may reduce the health care resource utilisation cost for managing T1DM patients who are at risk for frequent episodes of SHE. Additionally, the combination strategy of CGM and SMBG may improve adherence with lesser financial impact among diabetic patients requiring tight glycaemic control.

Blood glucose using continuous glucose monitoring device (CGMS) may be offered in aiding glucose monitoring for insulin-requiring diabetes patients especially with Type 1 Diabetes. Blood glucose using CGM for diabetes patients may benefited and improving their QOL where its emphasise of more freedom, convenience and peace of mind.

8.0 RECOMMENDATION

Continuous glucose monitoring device (CGMS) may be offered in aiding glucose monitoring for insulin-requiring especially for Type 1 Diabetes (T1DM) patients.

In view of high cost associated with continuous glucose monitoring device use, it may be considered in selected T1DM patients who are at risk or suffering from frequent severe hypoglycaemic events (SHE), with data collected on its effectiveness in reducing such events to inform further decision on continuation/ expansion of CGM coverage.

While patients recognise CGMS as a valuable resource, significant barriers like cost, accessibility, and support must be addressed to maximise its potential in diabetes management.

10.0 REFERENCES

1. Akhtar S, Nasir JA, Ali A, et al. Prevalence of type-2 diabetes and prediabetes in Malaysia: A systematic review and meta-analysis. PLoS ONE 17(1): e0263139. https://doi.org/10.1371/journal. pone.0263139

2. Zanariah Hussein, Sri Wahyu Taher, Harvinder Kaur et al. Diabetes Care in Malaysia: Problems, New Models, and Solutions, Annals of Global Health, Volume 81, Issue 6, 2015: 851-862

3. R. Naresh Babu, M.Yoshitha, Lakshmi Pravallika et al. Continuous Glucose Monitoring Devices: A Systematic Review. J. Global Trends Pharm Sci, 2020; 11 (2): 7562 - 7568

4. Triki N, Yekutiel N, Levi L, et al. The effects of continuous glucose monitoring system on patient outcomes and associated costs in a real-world setting. Diabet Med. 2021 May;38(5):e14518

5. Young LA, Buse JB, Weaver MA, et al. Glucose self-monitoring in non–insulin-treated patients with type 2 diabetes in primary care settings. JAMA Intern Med. 2017;177(7):920-929.

6. Laffel LM, Kanapka LG, Beck RW, et al. CGM Intervention in Teens and Young Adults with T1D (CITY) Study Group; CDE10. Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults with Type 1 Diabetes: A Randomized Clinical Trial. JAMA. 2020 Jun 16;323(23):2388-2396

7. Maahs DM, Calhoun P, Buckingham BA, et al. A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. Diabetes Care. 2014;37(7):1885-1891

8. Iscoe KE, Campbell JE, Jamnik V, et al. Efficacy of continuous real-time blood glucose monitoring during and after prolonged high-intensity cycling exercise: spinning with a continuous glucose monitoring system. Diabetes Technol Ther. 2006;8(6): 627-635.

9. Moser EG, Crew LB, Garg SK. Role of continuous glucose monitoring in diabetes management. Av Diabetol. 2010; 26: 73-8

10. Julia Kenney, Andrew Briskin. Your Guide to the 2022 Changes to the ADA Standards of Care Assessed on Jan 16, 2023 at https://diatribe.org/your-guide-2022-changes-ada-standards-care

11. NIDDK National of Institute Diabetes and Digestive and Kidney Diseases. Continuous Glucose Monitoring. Assessed on Jan 16, 2023 at https://www.niddk.nih.gov/health-information/diabetes/overview/managing

diabetes/continuous-glucose-monitoring

12. Schleich K, Ray BE. Make room for continuous glucose monitoring in type 2 diabetes management. J Fam Pract. 2022 Nov;71(9):384-397.

13. Oser TK, Litchman ML, Allen NA, et al. Personal Continuous Glucose Monitoring Use Among Adults with Type 2 Diabetes: Clinical Efficacy and Economic Impacts. Curr Diab Rep. 2021 Dec 9;21(11):49

14. American Diabetes Association Professional Practice Committee; 7. Diabetes Technology: *Standards of Medical Care in Diabetes—2022*. *Diabetes Care* 1 January 2022; 45 (Supplement_1): S97–S112

15. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44(Suppl 1): S15-S33

16. Price D, Walker T. The Rationale for Continuous Glucose Monitoring-based Diabetes Treatment Decisions and Non- Adjunctive Continuous Glucose Monitoring Use. Eur Endocrinol. 2016 Mar;12(1):24-30.

17. Paramasivam SS, Chinna K, Singh AKK, et al. Continuous glucose monitoring results in lower HbA1c in Malaysian women with insulin-treated gestational diabetes: a randomized controlled trial. Diabet Med. 2018 Aug;35(8):1118-1129.

APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomised controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomisation.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (HARRIS 2001)

APPENDIX 2: HEALTH TECHNOLOGY ASSESSMENT PROTOCOL

CONTINUOUS GLUCOSE MONITORING FOR INSULIN-DEPENDENT DIABETES PATIENTS

1.0 BACKGROUND INFORMATION:

1.1 INTRODUCTION

One of the major public health concern facing our nation is the widely discussed chronic non-communicable disease (NCD) known as diabetes. Malaysia has the highest rate of diabetes in Western Pacific region and one of the highest in the world and costing around 600 million US dollars per year. The prevalence of diabetes in Malaysia, based on published articles, ranges from 7.3% to 23.8%. The prevalence of diabetes raised from 11.2% in 2011 to 18.3% in 2019, with a 68.3% increase. According to a national survey report, in Malaysia in 2019, 3.6 million adults (18 and above years) had diabetes, 49% (3.7 million) cases were undiagnosed. Diabetes is expected to affect seven million Malaysian adults aged 18 and older by 2025, posing a major public health risk with a diabetes prevalence of 31.3%.[1] Therefore, diabetes is a major public health concern in Malaysia that is closely related to increased macro and microvascular complications, as well as premature and preventable mortality.[2]

Diabetes does end up receiving chronic disease treatment in the form of insulin therapy to help control their blood sugars in conjunction with a blood glucose meter. Without adequate blood sugar control, diabetes can lead to many debilitating and life-threatening conditions such as heart disease, stroke, vision loss, kidney disease, amputations, and ultimately death. To prevent these conditions from occurring, patients with diabetes are strongly encouraged to make dietary changes and frequently monitor their blood glucose.[3] One of the major barriers to good glucose control is the difficulty and discomfort of frequent blood sugar measurements by the patient before insulin injection and afterward, which results in impairment in patients' quality of life.[4,5] Glycaemic control remains suboptimal in the majority of adolescents and young adults with type 1 diabetes, with only 17% attaining the 2019 American Diabetes Association’s hemoglobin A1c (HbA1c) target of less than 7.5% and 14% attaining the target of less than 7% in the T1D Exchange clinic registry.[6]

In order to receive the appropriate dose of insulin, an accurate measurement of blood glucose is required, typically with a finger- prick glucose meter. However, patients continue to struggle with the pain associated with finger-pricks before injecting insulin.[3] Continuous glucose monitoring system (CGMS) technologies, with or without insulin pumps, allow frequent blood glucose measurements with no need for numerous needle pricks. Moreover, CGMS may also alert unaware hypoglycaemia events or near hypoglycaemia events. Thus, preventing its deteriorative consequences by 50% with a decrease in both morning ketosis events and life-threatening events following physical exercise.[7,8]

1.2 TECHNOLOGY DESCRIPTION

A CGM works through a tiny sensor inserted under skin, usually on your belly or arm. The sensor measures the interstitial glucose level, which is the glucose found in the fluid between the cells. The sensor tests glucose every few minutes. A transmitter wirelessly sends the information to a monitor. The monitor may be part of an insulin pump or a separate device, which carry in a pocket or purse. Some CGMs send information directly to a smartphone or tablet. Several models are available and are listed in the ADA's product guide external link.[11] (See **Table 1** for comparison of personal CGM)

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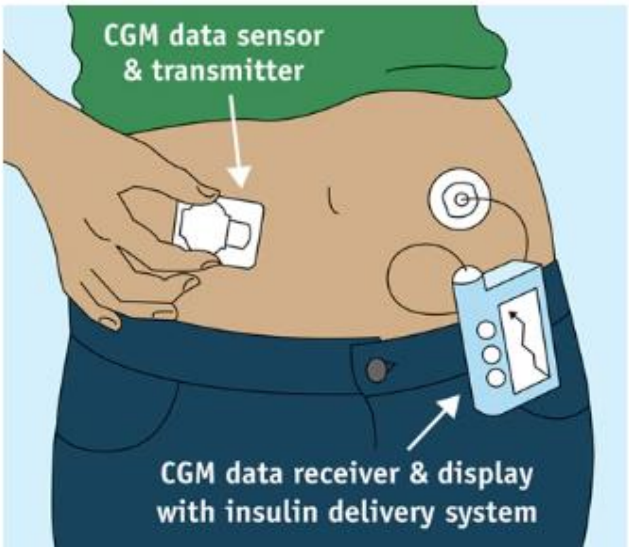

Figure 1: Continous glucose monitoring device

Currently available CGMS devices are considered minimally invasive enzyme-coated electrodes to measure interstitial glucose concentrations and convert these values to blood glucose levels. The information stored in the receiver is then converted into estimated mean values of glucose standardised to capillary blood glucose levels measured during calibration. Using an applicator or self-insertion device, a thin plastic sensor is inserted just under the skin of the abdomen or the upper arm. These devices can display real-time glucose values and glucose trends, and some can also sound an alarm or vibrate when they detect hyperglycaemia or hypoglycaemia. The receiver can store information for later use, and long-term data can be downloaded to a computer. Devices using enzyme-coated catheters require frequent calibrations to correct variations in the reaction between the electrode and the subcutaneous tissue, as well as fluctuations in glucose and oxygen diffusion.[11]

The United States Food and Drug Administration (FDA) has approved five continuous glucose monitoring devices, four of which are currently in clinical use. All four devices measure interstitial fluid glucose to calculate blood glucose levels using a mathematical algorithm. These devices include the GlucoWatch® (Redwood City, California, USA), the DexCom SEVEN® PLUS (San Diego, California, USA), the Medtronic MiniMed Paradigm® REAL-Time and the Guardian® REAL-Time (Northridge, California, USA), and the Abbott Diabetes Care FreeStyle Navigator (Alameda, California, USA).[9] **(See Figure 2 and Table 1)**

Figure 2: Continuous Glucose Monitoring devices approved by The United States Food and Drug Administration (FDA)

Table 1: Personal CGM, compared

Specification & capabilities	**Freestyle Libre 14 day (Abbot)**	**Freestyle Libre 2 (Abbot)**	**Dexcom G6 (Dexcom)**	**Guardian Connect 3 (Medtronic)**	**Eversense E3 (Senseonics)**
Type	**Intermittently scanned CGM**		**Real-time CGM**		
Approved age of use	≥ 18 y	≥ 4 y	≥ 2 y	14 – 75 y	≥ 18 y
Blood glucose range	40–500mg/dL	40-400mg/dL	40-400mg/dL		
Need to scan sensor	At least every 8H		No		
Frequency of stored glucose level	Every 15 min		Every 5 min		
Overall MARD	9.4%	9.2%	9.8%	9.1% [a]	8.5%
Sensor placement	Back of upper arm		Abdomen	Abdomen or back of upper arm	Subcutaneous implant in upper arm
Patient calibration required	No		No	Every 12 h [b]	Every 12 h
Warm-up period	60 min		120 min	As long as 120 min	24 hr [c]
Sensor life	14 d		10 d	7 d	180 d
Smart-device requirement	Smart device or supplied reader		Smart device or receiver	Smart device	
Glucose alerts	No		Yes		
Can be integrated with insulin pump	No		Yes		
Interfering substances	>500 mg **Vitamin C**: falsely increases	>500 mg **Vitamin C**: falsely increases	**Hydroxyurea**: falsely increases scanned glucose level	**Acetominophen**: falsely increases scanned glucose level	**Intravenous mannitol or sorbitol**:

	scanned glucose level **Salicylic acid**: falsely decreases scanned glucose level	scanned glucose level			falsely increases scanned glucose level
Waterproof	1 meter; 30 min		2.4meters;24h	2.4meters;30min	1meter;30min
Data retrieval platform for clinic	Libreview		Dexcom Clarity	Carelink	Eversense Data Management System (DMS) Pro
Data sharing platform for family and friends	Librelink up (< 20 people)		Dexcom Follow (<10 people)	Carelink Connect (< 5 people)	Eversense NOW (<5 people)
Patient smartphone app requirement	Reader: N/A Smartphone: LibreLink	Reader: N/A Smartphone: Libre 2	Dexcom Clarity	Guardian Connect	Eversense

CGM, continuous glucose monitor; MARD, mean absolute relative difference; N/A, not applicable.

[a]: When calibrated every 12 h; MARD is slightly better (8.68%) when calibrated 3 or 4 times a day.

[b]: A new sensor requires as long as 2 h to warm up; then needs to be calibrated immediately; then needs to be calibrated 6 h after initial calibration; and then needs to be calibrated every 12 h for the duration of the sensor. The more regularly the sensor is calibrated, the more improved is its accuracy.

[c]: ie, 24 h after the initial sensor placement and 10 min each time the transmitter is removed and replaced.

Source: Schleich K, Ray BE. Make room for continuous glucose monitoring in type 2 diabetes management. J Fam Pract. 2022 Nov;71(9):384-397

1.3 Continuous glucose monitoring system devices in Malaysia

Continuous Glucose Monitoring System (CGMS) is among the most important recent advances in diabetes technology that improves glucose control without adding medication. The CGM provides information about glucose concentrations, direction of change, rate of change, and overall glucose trends, whereas self-monitoring blood glucose (SMBG) only provides a single blood glucose measurement at the time of the test.[9] International guidelines according to The American Diabetes Association (ADA) released its 2022 Standards of Care, which provides an annual update on practice guidelines and expanded recommendations for CGM and Time in Range (TIR) use in adults and for CGM and automated insulin delivery (AID) use in children. The guidelines also include using diabetes technology in hospital settings.[10]

Self-monitoring of blood glucose (SMBG) is now recognised as a core component of diabetes self-management. However, there are many limitations to SMBG use in individuals with diabetes who are treated with intensive insulin regimens. Many individuals do not test at the recommended frequencies. Additionally, because SMBG only provides a blood glucose reading at a single point in time, hypoglycaemia and hyperglycaemia can easily go undetected, limiting the user's ability to take corrective action. Inaccuracies due to user error, environmental factors and weaknesses in SMBG system integrity further limit the utility of SMBG. Real-time continuous glucose monitoring (CGM) displays the current glucose, direction and velocity of glucose change and provides programmable alarms. This trending information and 'around-the-clock' vigilance may provide a significant safety advantage relative to SMBG. Therefore, this assessment will evaluate whether it would be effective, safe and cost-effective to use CGM in the management of diabetes patients required insulin management in Malaysia as requested by Medical Endocrinologist Consultants from Putrajaya and Malacca Hospital.

2.0 POLICY QUESTION

Should continuous glucose monitoring devices be utilised and provided as an approach for glucose monitoring for insulin-requiring diabetes patients' management?

3.0 OBJECTIVES

3.1 The following are the objectives of this review:

i. To assess the comparative effectiveness and safety of CGMS for glucose monitoring in insulin-requiring diabetes patients.

ii. To determine the economic, organizational, social, ethical and legal implications of CGMS for glucose monitoring in insulin-requiring diabetes patients**.**

3.2 The following are the research questions of this review:

i. How effective and safe are the CGMS for glucose monitoring in insulin-requiring diabetes patients?

ii. How cost-effective are the CGMS or devices for glucose monitoring in insulin-requiring diabetes patients?

iii. What are the organizational, social, ethical and legal implications of CGMS or devices for glucose monitoring in insulin-requiring diabetes patients?

4.0 METHODS:

4.1 Search Strategy

Electronic databases will be searched for published literatures pertaining to CGMS for diabetes patients.

4.1.1 Databases are as follows; MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and FDA database.

4.1.2 Additional literatures will be identified from the references of the related articles.

4.1.3 General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.

4.1.4 There will be no limitation applied in the search such as year and language.

4.1.5 The search strategy will be included in the appendix.

4.2 Inclusion and exclusion criteria

4.2.1 **Inclusion and Exclusion Criteria**

Population Problems	• Patients with Type 1 Diabetes or Type 2 Diabetes • insulin-requiring diabetes patients
Intervention	CGM
Comparators	• self-monitoring blood glucose (SMBG) • intermittently scanned CGMS versus real-time CGMS
Outcomes	i. Effectiveness • hypoglycaemic and hyperglycaemic events • change in HbA1c reduction • CGM accuracy • time in range (TIR), time above range (TAR), time below range (TBR) and average sensor glucose correlated well with HbA1c and change in HbA1c • correlations of HbA1c with various CGM metrics, (calibration) • Various quality of life and treatment satisfaction measure • change in treatment satisfaction, and quality of life measures as secondary outcomes; Health-related quality of life (HRQoL) ii. Safety • Adverse events iii. Economic impact • Cost-effectiveness • Cost-utility analysis • Cost-benefit analysis • Cost analysis • Any other measure of economic outcome iv. Organizational, social, ethical and legal implications
Study designs	HTA reports, systematic review with meta-analysis, systematic review, randomised controlled trial (RCT), and economic evaluation studies
Setting	Hospitals
English full text articles	

4.2.2 Exclusion criteria

a. Animal study
b. Laboratory study
c. Design: Narrative review, cohort, case-control, cross-sectional
d. Non-English full text articles

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Critical Appraisal of Literature

The methodology quality of all retrieved literatures will be assessed using the relevant checklist of Cochrane Risk of Bias tool.

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted:

a. Details of methods and study population characteristics.
b. Details of interventions and comparators.
c. Details of individual outcomes for effectiveness, safety and cost associated with CGMS for diabetes patients

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion

4.4.2 Methods of data synthesis

Data on the effectiveness, safety and cost-effectiveness of CGMS for diabetes patients will be presented in tabulated format with narrative summaries. Meta-analysis may be conducted for this Health Technology Assessment.

6.0 REFERENCES

1. Akhtar S, Nasir JA, Ali A, et al. Prevalence of type-2 diabetes and prediabetes in Malaysia: A systematic review and meta-analysis. PLoS ONE 17(1): e0263139. https://doi.org/10.1371/journal. pone.0263139
2. Zanariah Hussein, Sri Wahyu Taher, Harvinder Kaur et al. Diabetes Care in Malaysia: Problems, New Models, and Solutions, Annals of Global Health, Volume 81, Issue 6, 2015: 851-862
3. R. Naresh Babu, M.Yoshitha, Lakshmi Pravallika et al. Continuous Glucose Monitoring Devices: A Systematic Review. J. Global Trends Pharm Sci, 2020; 11 (2): 7562 – 7568
4. Triki N, Yekutiel N, Levi L, et al. The effects of continuous glucose monitoring system on patient outcomes and associated costs in a real-world setting. Diabet Med. 2021 May;38(5):e14518
5. Young LA, Buse JB, Weaver MA, et al. Glucose self-monitoring in non–insulin-treated patients with type 2 diabetes in primary care settings. JAMA Intern Med. 2017;177(7):920-929.
6. Laffel LM, Kanapka LG, Beck RW, et al. CGM Intervention in Teens and Young Adults with T1D (CITY) Study Group; CDE10. Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults with Type 1 Diabetes: A Randomized Clinical Trial. JAMA. 2020 Jun 16;323(23):2388-2396
7. Maahs DM, Calhoun P, Buckingham BA, et al. A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. Diabetes Care. 2014;37(7):1885-1891
8. Iscoe KE, Campbell JE, Jamnik V, et al. Efficacy of continuous real-time blood glucose monitoring during and after prolonged high-intensity cycling exercise: spinning with a continuous glucose monitoring system. Diabetes Technol Ther. 2006;8(6): 627-635.
9. Moser EG, Crew LB, Garg SK. Role of continuous glucose monitoring in diabetes management. Av Diabetol. 2010; 26: 73-8
10. Julia Kenney, Andrew Briskin. Your Guide to the 2022 Changes to the ADA Standards of Care Assessed on Jan 16, 2023 at https://diatribe.org/your-guide-2022-changes-ada-standards-care

11. NIDDK National of Institute Diabetes and Digestive and Kidney Diseases. Continuous Glucose Monitoring. Assessed on Jan 16, 2023 at https://www.niddk.nih.gov/health-information/diabetes/overview/managing diabetes/continuous-glucose-monitoring
12. Schleich K, Ray BE. Make room for continuous glucose monitoring in type 2 diabetes management. J Fam Pract. 2022 Nov;71(9):384-397.
13. Oser TK, Litchman ML, Allen NA, et al. Personal Continuous Glucose Monitoring Use Among Adults with Type 2 Diabetes: Clinical Efficacy and Economic Impacts. Curr Diab Rep. 2021 Dec 9;21(11):49
14. American Diabetes Association Professional Practice Committee; 7. Diabetes Technology: *Standards of Medical Care in Diabetes—2022*. *Diabetes Care* 1 January 2022; 45 (Supplement_1): S97–S112
15. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44(Suppl 1): S15-S33
16. Price D, Walker T. The Rationale for Continuous Glucose Monitoring-based Diabetes Treatment Decisions and Non- Adjunctive Continuous Glucose Monitoring Use. Eur Endocrinol. 2016 Mar;12(1):24-30.
17. Paramasivam SS, Chinna K, Singh AKK, et al. Continuous glucose monitoring results in lower HbA1c in Malaysian women with insulin-treated gestational diabetes: a randomized controlled trial. Diabet Med. 2018 Aug;35(8):1118-1129.

3: SEARCH STRATEGY

Database: Ovid MEDLINE(R) ALL <1946 to October 27, 2022>

Search Strategy:

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1 Diabetes Mellitus, Type 1/ or Diabetes Mellitus, Type 2/ (198860)
2 Diabetes.tw. (539046)
3 IDMM.tw. (10)
4 NIDDM.tw. (6931)
5 1 or 2 or 3 or 4 (573446)
6 Inpatients/ (22940)
7 Inpatient*.tw. (113300)
8 Hospitali*.tw. (263786)
9 6 or 7 or 8 (359643)
10 Blood Glucose Self-Monitoring/ (7000)
11 Continuous glucose monitoring.tw. (4083)
12 CGM*.tw. (28086)
13 (Real time adj1 Continuous glucose monitoring).tw. (291)
14 RT-CGM*.tw. (111)
15 10 or 11 or 12 or 13 or 14 (35294)
16 5 and 9 and 15 (323)
17 limit 16 to (english language and humans) (261)

APPENDIX 4: EVIDENCE TABLE

<Upon request>

CONTINUOUS GLUCOSE MONITORING FOR INSULIN-REQUIRING DIABETES PATIENTS
HEALTH TECHNOLOGY ASSESSMENT REPORT

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