Application to PHARMAC for the subsidisation of

Dexcom G6™ Continuous Glucose Monitoring System

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Applicant:

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G6™ Continuous Glucose Monitoring System
PHARMAC Submission

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EXECUTIVE SUMMARY

CLINICAL BENEFITS

Diabetes is a highly prevalent chronic disease.[1] A quarter of a million New Zealanders are currently diagnosed with diabetes[206] and a further 90,000[207] are affected but not yet diagnosed In total diabetes affects 7% of the New Zealand population. Poorly controlled diabetes may cause serious acute and chronic complications that negatively impact quality of life and increase healthcare utilisation and costs The total direct health care costs for a person with diabetes are approximately three times those for people without diabetes [204] Diabetes can lower life expectancy by up to 13 years[2]; it is the seventh leading cause of death in New Zealand, and the fifth leading cause of death in people less than 50 years of age [215]

There is no reliable data to determine the split between the number of people with Type 1 diabetes and Type 2 diabetes in New Zealand The Ministry of Health suggests most people with diabetes aged 0–24 years will have type 1 diabetes, while around 90+ percent of those aged 25 years and over are expected to have type 2 diabetes [206] This would mean about 29,000 New Zealanders have type 1 diabetes. The Ministry of Health strategic plan *Living Well with Diabetes* acknowledges it is vital to recognise the specific needs of people with type 1 diabetes [204] Type 1 is usually diagnosed in childhood or adolescence, and throughout their lives Type 1 diabetics are dependent on insulin for survival and the support of their family and other carers in school, work and social settings The *Living with Diabetes* plan aims to *"Support access to technology that provides more effective insulin therapy and to help with self-management, for example 'apps' and insulin pumps*. Further, the plan identifies that *"Parents need to help their child to manage glucose levels, insulin therapy and hypoglycaemia"*.

Intensive therapy that lowers average glucose levels has been shown to reduce the risk of the long term complications of diabetes but also increases the risk of hypoglycaemia.[3-5] Fear of hypoglycaemia is the most important barrier to achieving optimal glycaemic control and is strongly associated with poor adherence to prescribed insulin regimens.[6-9] In addition to compromising diabetes management, fear of hypoglycaemia impairs quality of life for both patients and their family members [10 14]

Recurrent hypoglycaemia induces a maladaptive response that impairs the ability of patients to detect the early warning signs of hypoglycaemia, a condition known as impaired awareness of hypoglycaemia (IAH). IAH significantly increases the risk of severe hypoglycaemia, which requires assistance from a third party to treat[15] and often requires costly emergency medical care [16] Tools are needed that can help patients on insulin therapy achieve target glucose levels without increasing their risk of hypoglycaemia

Real-time continuous glucose monitoring (RT-CGM[a]) is advanced glucose monitoring technology that continuously measures interstitial glucose levels and displays the current blood glucose level, direction, and rate of change; and uses alarms and alerts to inform patients when blood glucose is exceeding or falling below specified thresholds [17,18] This complete picture of glycaemic activity helps guide disease management decisions (e.g., insulin dosage adjustments, changes in diet) to avoid glycaemic excursions.[17,18] For patients with IAH, the alarm function of the RT CGM device may be their only warning of emerging hypoglycaemia. In contrast, traditional fingerstick self-monitoring of blood glucose (SMBG) as well as flash glucose monitoring, which provides intermittent and limited information about blood glucose concentrations at single points in time,[17,19] may fail to detect potentially dangerous glycaemic excursions even when diligently performed [17,18] Whereas RT CGM continuously transfer sensor data in real-time to a receiver, flash glucose monitoring systems rely on intermittent scanning of the sensor with the reader

The Dexcom G5™ Mobile CGM System (G5) and Dexcom G6™ Continuous Glucose Monitoring System (G6) are the only continuous real time CGM (RT CGM) devices approved for therapeutic decision making as a replacement of SMBG by the United States Centers for Medicaid & Medicare (CMS). Ruling CMS 1682 R (https://www cms gov/Regulations and Guidance/Guidance/Rulings/Downloads/CMS1682R.pdf), which designates therapeutic CGM

[a] *Personal RT-CGM technology displays real-time glucose values and is used by patients in the home setting to self-manage diabetes on an ongoing basis This technology also stores blood glucose values, which can be downloaded to analyze patterns of care and optimize treatment. The term RT-CGM used in this dossier exclusively refers to personal use of RT-CGM technology.*

reimbursable under Medicare Part B, designated the G5 as the only RT-CGM meeting criteria as therapeutic CGM The G6 is currently under review by Medicare for the same classification

The G5 is also the only CGM System with CE (Conformité Européenne) certification for both adults and children 2 years and older with two approved sensor placements.

The G6 is first RT CGM indicated by the FDA for use as both a standalone RT CGM device and for integration into automated insulin dosing systems. The G6 is compatible with medical devices and electronic interfaces, including automated insulin dosing systems, insulin pumps, blood glucose meters, and other electronic devices used for diabetes management.

With wireless Bluetooth® technology built into the device transmitter, the G5 and G6 are the only fully mobile RT-CGM systems that send glucose data directly to a smart device, freeing users from the need to carry a separate receiver The device transmitter securely sends glucose information every five minutes directly to an app on iOS and Android enabled devices (see Appendix 1) for real-time diabetes management The G6 can be used as a standalone device when insulin is administered as basal bolus injections or in conjunction with continuous subcutaneous insulin infusion.

The Dexcom Share® feature allows users to select up to five designated recipients or "followers" who can remotely monitor the user's glucose information and receive alert notifications for added protection and peace of mind, particularly for parents of children and for loved ones of elderly individuals who may not be able to reliably measure their own blood glucose values and make insulin dosing decisions on their own Children and elderly diabetes patients who use the G6 and have at least 1 follower have significantly better adherence to RT-CGM, lower mean blood glucose levels, and less exposure to hypoglycaemia than patients without any followers.[20-22]

The overall accuracy of the G6 is equivalent to or better than that of the G5 and Dexcom G4 PLATINUM™ with 505 software (G4 with 505 software) In addition, the G6 offers a longer duration of sensor life (10 days) and better usability due to its improved sensor membrane technology, 30% thinner and contoured wearable sensor, improved applicator, no calibration requirement, and acetaminophen blocking capability. For these reasons, the health outcomes demonstrated for the G5 and G4 with 505 software are expected to be improved in the G6

Three recently published randomized controlled trials (RCTs), the DIAMOND, GOLD, and HypoDE trials, have shown that RT CGM using the G5 or G4 with software 505 in conjunction with multiple daily injections (MDI) therapy significantly improves glycaemic control in insulin-treated patients with diabetes[23 25] and reduces the incidence of hypoglycaemic events in high risk adults with T1DM[26] compared with conventional SMBG. The DIAMOND trial evaluated the effectiveness of RT-CGM in patients with poorly-controlled T1DM or insulin-treated T2DM who were treated with MDI [23,24] After 24 weeks, RT-CGM reduced HbA1c by 0.6% (p<0.001) in patients with T1DM and by 0.3% in patients with insulin-treated T2DM compared with patients who received conventional blood glucose monitoring The multicentre, randomized, open-label GOLD trial utilized a crossover design to compare RT-CGM versus SMBG in 161 patients with poorly controlled T1DM who were treated with MDI [25] The mean HbA1c was 0.43% lower (p<0.001), and time spent in daytime and nocturnal hypoglycaemia significantly less (both p<0.001), during 26 weeks of RT CGM use than during conventional blood glucose monitoring [25,27] The HypoDE RCT evaluated whether RT-CGM reduces the incidence of hypoglycaemic events compared with SMBG in 149 high-risk adults (history of IAH or severe hypoglycaemia) with T1DM treated by MDI compared with SMBG.[26] RT-CGM reduced the incidence of hypoglycaemic events by 72% (incidence rate ratio [IRR] 0 28, 95% CI 0 20 0 39, p<0 0001), the incidence of nocturnal hypoglycaemic events by 65% (IRR 0.35, 95% CI 0.22-0.56, p<0.0001), and the incidence of severe hypoglycaemic events by 64% (IRR 0.36 (95% CI 0 15 0 88, p=0 0247)

Data from three recently published studies show that RT-CGM used in conjunction with MDI is as effective as the combination of RT CGM and insulin pump therapy for improving glycaemic control [28 30]

The majority of RCTs conducted to date have not been designed or powered to detect significant changes in the rate of severe hypoglycaemic events, have often excluded individuals with recurrent severe hypoglycaemia from the study samples, and have not robustly measured hypoglycaemic episodes [31] An exception was the recently published HypoDE RCT which demonstrated that RT CGM reduced the incidence of severe hypoglycaemia events by 64% in high-risk patients who were treated with MDI [26] Additional evidence that RT CGM can substantially reduce the incidence of severe

hypoglycaemia is provided by the IN CONTROL trial and extension phase of the Juvenile Diabetes Research Foundation (JDRF) clinical trial The IN CONTROL trial was a randomized, open label, crossover study conducted in adults with poorly-controlled T1DM and IAH.[32] In this study, RT-CGM reduced the incidence of severe hypoglycaemia by 59% compared with SMBG In a 6 month, open label, extension study of the JDRF clinical trial, children and adults with poorly-controlled T1DM receiving intensive insulin treatment who were initiated on RT CGM experienced a 46% reduction in the incidence of severe hypoglycaemia.[33]

ECONOMIC BENEFITS (PLACEHOLDER)

CONCLUSIONS

Real Time Continuous Glucose Monitoring is expected to reduce the short- and long-term complications associated with diabetes by decreasing average blood glucose levels, glycaemic variability, and the incidence of hypoglycaemia. A strong body of evidence has demonstrated the efficacy of RT-CGM for reducing HbA1c levels and glycaemic variability in children and adults with T1DM, and a recently published RCT showed that RT-CGM significantly reduces HbA1c in adults with poorly-controlled insulin-treated T2DM In addition, data show that RT CGM reduces the incidence of severe hypoglycaemia by 64% in particularly vulnerable T1DM patients (those with a history of severe hypoglycaemia or IAH).[26] RT CGM is estimated to confer cost savings over 1 year by reducing the incidence of costly emergency treatment of severe hypoglycaemia in insulin-treated patients with IAH. Additional cost savings would be expected to accrue over a patient's lifetime as RT CGM has been shown to significantly reduce HbA1c, which is strongly associated with the risk for developing long-term microvascular and neuropathic complications of diabetes

RT-CGM is an evolving technology that is becoming the standard of care for insulin-treated patients with poorly controlled diabetes. Initial FDA approval of the G5 as a replacement of SMBG for therapeutic decision making was made based on the recommendations of a full FDA panel hearing.[34] In addition, results from the REPLACE-BG study,[35] a multicentre, randomized, non inferiority clinical trial, confirmed that the use of CGM without confirmatory blood glucose monitoring measurements is as safe and effective as using CGM adjunctive to blood glucose monitoring in well controlled adults with T1DM Subsequent FDA approval for the G6 as a replacement for SMBG with no calibration and for integration with compatible medical devices demonstrates the rapid evolution in this technology

A recent study found that the G5 has better overall accuracy than many blood glucose meters. The overall accuracy of 17 point of-care SMBG blood glucose meters, as measured by the mean average relative difference (MARD), which represents the difference between RT-CGM readings and contemporaneous blood glucose values assessed by a laboratory standard, ranged from 5 6% to 20.8%, with 9 of the 17 meters having a MARD exceeding 10%.[36] In assessing the safety of insulin dosing based on RT-CGM data, the threshold for accuracy has been recognized at less than 10%.[37] The G5 and G6 have an overall MARD of 9.0%. The high accuracy of these devices may enhance patients' confidence in the device's blood glucose readings and encourage patients to take more aggressive actions in response to this information.[38]

The G6 is as accurate as the G5 while offering improved usability due to its improved sensor membrane technology, 30% thinner and contoured wearable sensor, improved applicator, no calibration requirement, 10-day sensor duration, and acetaminophen blocking capability

1. PRODUCT INFORMATION AND DISEASE DESCRIPTION

1.1 PRODUCT DESCRIPTION

The G6 is a real-time, continuous glucose monitoring device indicated for the management of diabetes in persons aged 2 years and older.

The G6 is intended to replace fingerstick blood glucose testing for diabetes treatment decisions Interpretation of the G6 results should be based on the glucose trends and several sequential readings over time The G6 also aids in the detection of episodes of hyperglycaemia and hypoglycaemia, facilitating both acute and long-term therapy adjustments.

The G6 is also able to autonomously communicate with digitally connected devices, including automated insulin dosing) systems. The G6 can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes

The G6 consists of three major components: sensor, transmitter, and a smart phone or device (iOS or android) for data display

1. Sensor: The sensor is a flexible, round, miniature wire that is placed just under the skin to read glucose levels (Figure 1) The Sensor is inside the applicator and can be inserted with the push of a button. The sensor attaches to the skin with its adhesive patch.

FIGURE 1. G6 SENSOR AND APPLICATOR

2. Transmitter: The transmitter (Figure 2) wirelessly sends glucose information to the smart device. The transmitter snaps into the transmitter holder on the sensor

FIGURE 2 G6 TRANSMITTER

3. Display Device: Data collected by the sensor is processed and displayed using a smart device running the G6™ Mobile Application (Figure 3)

FIGURE 3. SMART DEVICE WITH G6 MOBILE APPLICATION

The sensor wire, transmitter holder, and transmitter are all that remain on the patient's skin during each sensor wear period (Figure 4).

FIGURE 4. SENSOR AND TRANSMITTER ON PATIENT

As shown in Figure 5, Dexcom Share® in the Dexcom G6 Mobile Application allows patients to share their data with up to five people (“followers”). After being invited by the “sharer,” and downloading the Dexcom Follow® App, an individual becomes a “follower ” The user determines what a follower can see, including the user’s sensor glucose readings, trends, alarm/alerts when the user’s glucose is low or high, and messages

FIGURE 5. DEXCOM SHARE®

Dexcom Clarity® is a data management software program that allows the transfer of glucose data from the Dexcom G6™ System to remote servers for data management. The cloud-based Dexcom Clarity® software is intended for use by both home users and healthcare professionals to assist people with diabetes in the review, analysis, and evaluation of historical CGM data to support effective diabetes management. The software provides summary reports, which include average glucose, frequency of calibrations, and patterns of low and high glucose (Figure 6). Healthcare professionals can use the retrospective information presented in Dexcom Clarity® to modify their recommendations for a patient’s diabetes management plan.

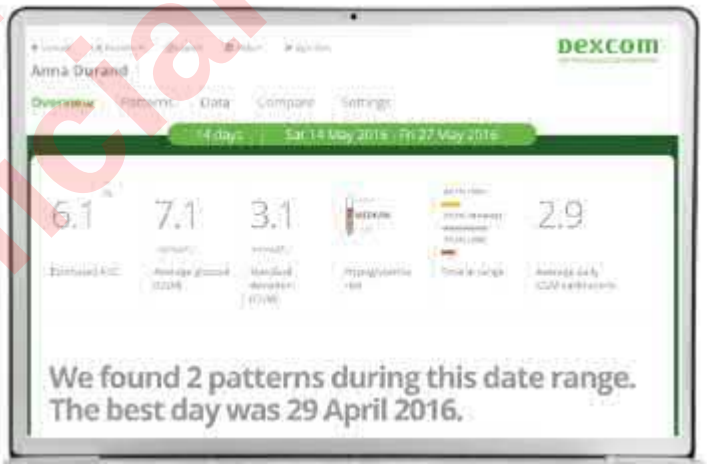


FIGURE 6. DEXCOM CLARITY® OVERVIEW REPORT

1.2 WAND NOTIFICATIONS AND FDA APPROVED INDICATIONS

TABLE 3 DEXCOM DEVICE WAND NOTIFICATION STATUS

Product	Class	GMDN	WAND	Date of Registration
G6 Sensor	IIa	44611	180705-WAND-6QMVJ2	05/07/2018
G6 Transmitter	IIa	44611	180705 WAND-6QMVJJ	05/07/2018
G6 Mobile App	IIa	60702	180705 WAND-6QMVJV	05/07/2018

A De Novo 510(k) application for the G6™ Mobile CGM System was approved by the FDA for the management of diabetes in individuals aged 2 years and older on March 27, 2018 The G6 is intended to replace fingerstick blood glucose testing for diabetes treatment decisions.

On January 12, 2017, the USA Centers for Medicaid & Medicare (CMS) ruling CMS 1682 R created a classification "therapeutic CGM" as "durable medical equipment" under Medicare Part B (https://www.cms.gov/Regulations-and-Guidance/Guidance/Rulings/Downloads/CMS1682R.pdf). The G5™ Mobile CGM System is the only RT CGM device on the market that meets the definition of therapeutic CGM under this ruling The G6 is currently under review by the CMS and is expected to receive the same classification.

1.3 REGISTRATION AND FUNDING STATUS IN OTHER OECD COUNTRIES

TABLE 4. DEXCOM DEVICE REGISTRATION AND FUNDING STATUS IN OTHER OECD COUNTRIES

OECD Countries	Registered	Funded	Guidance
Australia	G5	Yes	Paediatrics
Austria	G6, G5, G4	Yes	T1
Belgium	G6, G5, G4	Yes	T1
Canada	G6, G5 & G4	Yes	IAH
Czech Rep	G6, G5, G4	Yes	T1 & T2 on insulin, co-pay
Denmark	G6, G5, G4	Yes	regional tenders
Finland	G6, G5, G44	Yes	regional tenders
France	G6, G4	Yes	via HAS
Germany	G6, G5, G4	Yes	T1, T2 + insulin, co pay
Israel	G5 & G4	Yes	National tender for paediatrics
Italy	G6, G5, G4	Yes	regional determinations (currently 6/21)
Luxembourg	G6, G5, G4	Yes	T1
Netherlands	G6, G5, G4	Yes	yes, T1 on pump; pregnancy and hypo
Norway	G4	Yes	regional tenders
Poland	G6, G5, G4	Yes	G5 ≤70% reimbursement; G4 100%
Scotland	G6, G5, G4	Yes	Limited ≥ GBP10m
Slovakia	G6, G5, G4	Yes	Paediatrics; limited to sensors

Slovenia	G6, G4	Yes	T1 Paeds, Paeds and adults with Hypo
Spain	G6, G5, G4	Yes	T1 in 3 regions
OECD Countries	**Registered**	**Funded**	**Guidance**
Sweden	G6, G5, G4	Yes	regional tenders
Switzerland	G6, G5, G4	Yes	T1
Turkey	G4	Yes	T1 and hypo, hospital dependent
UK	G6, G5, G4	Pending	Currently limited NG 17 and NG18
USA Commercial	G6, G5, G4	Yes	T1, T2 + insulin
Medicaid	G5	Yes	~25 states have coverage
Medicare	G5	Yes	T1, T2 + insulin. Fee schedule; K codes

1.4 DOSING AND ADMINISTRATION

As detailed in Section 1.1 above the G6 consists of three major components: a sensor, a transmitter, and a display smart device (iOS or android).

The sensor attaches to the skin with its adhesive patch and is replaced every 10 days. The sensor is applied to the abdomen using a unique applicator; patients 2 to 17 years old can also choose to site the sensor on their upper buttocks. Users receive three notifications before each sensor session ends: 6 hours before, 2 hours before, and 30 minutes before. The unique code for each new sensor is entered into the receiver smart device to calibrate the sensor.

The transmitter snaps into the transmitter holder on the sensor. The transmitter has a battery life of 90 days, so can be reused for approximately nine sensor sessions. Users receive notifications as the transmitter nears the end of its battery life. Each new transmitter is paired to the display device.

The smart display devices provide the information needed to make treatment decisions including:

- Dexcom Share (Share): allows users glucose information to be sent to others
- Alert Schedule: allows alarm/alerts to sound different during different times of the day.
- Always Sounds: allows phone settings to be overridden so alarm/alerts will always sound, even when the device is on mute/Do Not Disturb.
- Smart watch: sends G6 sensor information to a smart watch
- Events: records events on the app and displays how they impact the user's trend graph.

The G6 system updates CGM readings every 5 minutes and does not require fingerstick calibration, however the app allows calibration if the user prefers it.

Complete product details are training are available in a variety of resources including the appended User Guide. Two guides are included in the G6 package; a *Start Here* guide and a more detailed *Using Your G6* booklet A tutorial video is included on a USB stick with each system, and is available in the app. All training resources are also available online at dexcom.com/Support.

1.5 CONTRAINDICATIONS/ WARNINGS/ PRECAUTIONS/ INTERACTIONS

The Dexcom G6 Continuous Glucose Monitoring System (Dexcom G6 System) is a real time, continuous glucose monitoring device indicated for the management of diabetes in persons aged 2 years and older

The Dexcom G6 System is intended to replace fingerstick blood glucose testing for diabetes treatment decisions Interpretation of the Dexcom G6 System results should be based on the glucose trends and several sequential readings over time. The Dexcom G6 System also aids in the detection of episodes of hyperglycaemia and hypoglycaemia, facilitating both acute and long term therapy adjustments

Dexcom Share (Share) lets you send your sensor information from your app to your Followers' smart devices Read the indications, warnings, and precautions below to find out how you can safely use this app feature.

- **Keep Followers Informed**
  Use Share to send your sensor information from your smart device to your Followers' smart devices
- **Use as Secondary Notice**
  The information on your smart device is sent directly from your G6 transmitter After it is on your device, Share sends it to your Followers. So your Followers' information is always older than yours Use your current information to manage your diabetes, not your Followers' possibly outdated information. Your Followers can use the information they get to reach out to you and support you in managing your diabetes The information they get is not meant to be used for treatment decisions, analysis, or teaching. Followers can't change your information.

The Dexcom G6 System can also autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. The Dexcom G6 System can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes.

Contraindication

No MRI/CT/Diathermy
Don't wear your CGM (sensor, transmitter or smart device) for magnetic resonance imaging (MRI), computed tomography (CT) scan, or high frequency electrical heat (diathermy) treatment. The G6 hasn't been tested in those situations. The magnetic fields and heat could damage the components of the G6, which may cause it to display inaccurate G6 sensor glucose readings (G6 readings) or may prevent alerts Without G6 readings or alarm/alert notifications, you might miss a severe low or high glucose event.

Warnings

- **Read User Materials**
  Before you use your G6, carefully read the materials included with it If you don't, you might not use the G6 correctly, not understand G6 information, or affect how well it works
- **Don't Ignore Low/High Symptoms**
  Don't ignore how you feel. If your glucose alerts and G6 readings don't match what you're feeling, use your blood glucose meter (meter) to make diabetes treatment decisions or, if needed, seek immediate medical attention. When in doubt, get your meter out.
- **No Number, No Arrow, No CGM Treatment Decision**
  If your G6 doesn't show a number or arrow, or your readings don't match your symptoms, use your meter to make diabetes treatment decisions No number, no arrow, no treatment decision When in doubt, get your meter out.
- **Don't Use If**
  Do not use the G6 if you are pregnant, on dialysis, or critically ill. It is not known how different conditions or medications common to theses populations may affect performance of the system G6 readings may be inaccurate in these populations.
- **Use Meter During Startup**
  When you start a new sensor, you won't get any G6 readings or alarm/alerts until you enter your sensor code or two calibrations Use your meter to make treatment decisions during the 2 hour sensor warmup period.
- **Don't Wait Calibrate!**
  If you have not used the calibration code, you must manually calibrate your G6 using values obtained from a blood glucose meter and fingersticks daily You must calibrate immediately when the G6 notifies you. If you haven't calibrated when notified, your G6 may not be accurate, so use your glucose meter to make treatment decisions until you calibrate your G6
- **Use Fingertips**

Use fingertips only to calibrate from your BG meter. Blood from other places may be less accurate and not as timely

- **Sensor Wire Breaks Off**
  Don't ignore broken or detached sensor wires A sensor wire could remain under your skin If this happens, please contact our 24/7 Technical Support. If a sensor wire breaks off under your skin and you can't see it, don't try to remove it Contact your HCP Also seek professional medical help if you have symptoms of infection or inflammation – redness, swelling, or pain – at the insertion site
- **Where to Insert: Belly or Buttocks?**
  All patients can use their bellies (abdomen) Patients 2 to 17 years old can also choose their upper buttocks. Look for a place on your belly or upper buttocks where you have some padding. The sensor is not tested or approved for other sites Talk to your HCP about the best site for you
- **Sensor Insertion Risks**
  It's uncommon, but inserting the sensor can cause infection, bleeding, or pain, and wearing the adhesive patch can irritate your skin. Only a few patients in the G6 clinical studies got slight redness and swelling No sensor wires broke in the clinical studies; however, there is a remote chance a sensor wire could break or detach and remain under your skin. Sterile broken sensor wires usually don't pose a significant medical risk If a sensor wire breaks off or detaches and remains under your skin, contact your HCP and Technical Support (24/7).
- **Where to Store Sensors**
  You can store your sensors at room temperature or in your refrigerator – as long as it's between 2° C and 30° C Don't store sensors in the freezer
- **Inspect the Transmitter**
  Don't use a damaged or cracked transmitter. A damaged transmitter could cause injuries from electrical shocks and may make the G6 not work correctly.
- **Use as Directed**
  The transmitter is small and may pose a choking hazard. Don't put it in your mouth or let children hold it without adult supervision.
- **Check Smart Device Settings**
  When using your smart device, you should confirm that your volume is turned up, your phone is not muted, and you do not have headphones plugged in. If your volume is not turned up, the device is muted, or headphones are plugged in, you will not hear the sound of any notifications, including important alarms. When you have headphones connected to your Android®, alarm/alerts will sound through the headphones and the speaker On your Apple, they will sound only in the headphones.

  Some notifications are silent during the first visual and vibrate notification and then make a sound on the second notification. If you don't clear the alert, it repeats at half volume after 5 minutes and at full volume after 10 minutes. Your alarm and important alerts sound and display information even when your volume is low or muted. Specifically, if your smart device is on mute, only these notifications make a sound:

  - Glucose Alarm/Alerts:
    - Urgent Low
    - Urgent Low Soon
    - Low Glucose
    - High Glucose
    - Rise Rate
    - Fall Rate
    - No Readings Alert
  - System Alerts:
    - Calibration Required (after 2 hour sensor warmup, only appears when a sensor code is not used)
    - Calibration Error (only appears when a user enters a calibration; calibration is not required)
    - Sensor Expired

    - Replace Sensor
    - Transmitter (not working)
    - No Storage Error
    - App Stopped
    - Exceptions: On Apple® devices, Signal Loss doesn't sound when your volume is low or muted
  - *Bluetooth*: Your transmitter talks to your app with *Bluetooth*. Make sure your smart device *Bluetooth* is on If not, you will not get alarm/alerts or CGM information
  - Notifications:
    - Make sure your smart device settings allow Dexcom app notifications to show on your Lock screen. This will allow you to see notifications without unlocking your phone.
    - Apple: During G6 setup, enable Dexcom app notifications or you won't get alarm/alerts
  - Battery: The app must always be running in the background and may drain your smart device battery Keep the battery charged
  - Compatibility: Before upgrading your smart device or its operating system, check dexcom com/compatibility Automatic updates of the app or your device operating system can change settings or shut down the app. Always update manually and verify correct device settings afterward
  - Time: Let the date and time on your smart device automatically update when you travel across time zones or switch between standard and daylight saving times Don't manually change your smart device time, because it can make the time on the trend screen wrong and the app may stop displaying data
- **Use USB Cable as Directed**
  Use USB cable only as directed, and store safely. Misuse of the USB cable can be a strangulation risk.
- **Use Your G6 to Make Treatment Decisions**
  Don't use Share information for treatment decisions, like treating for a low or dosing for a high. Use the sensor information on your G6 instead
- **Take HCP Advice**
  Has your HCP given you self-monitoring tasks? Keep doing them Having Followers doesn't replace them.
- ***Share* Followers Must Follow and You Must Share**
  You have to turn *Share* on to make it send your sensor information to your Followers. Followers have to download the Dexcom Follow app to see what you send

Precautions

- **Avoid Sunscreen and Insect Repellent**
  Some skin care products, such as sunscreens and insect repellents, can make the plastic used in your G6 crack. Before using your G6, make sure there are no cracks in your transmitter, and transmitter holder. If you find a crack, please contact Technical Support. Do not allow these skin care products to contact your G6. After using skin care products, wash your hands before touching your G6. If any skin care products get on your G6, immediately wipe with a clean cloth
- **Use Correct Sensor Code**
  When you start a new sensor, you must enter a code into your display device to use the G6 without fingerstick calibrations. Each sensor has its own code printed on the back of the adhesive patch. Do not use a code from a different sensor or make up a code. If you do not enter the correct code, your sensor will not work as well and could be inaccurate. If you lost the sensor code, you may calibrate the G6 using fingersticks.
- **Be Accurate, Be Quick.**
  Enter the exact BG value displayed on your meter within five minutes of using your meter. Don't enter the G6 reading as a calibration.
- **Don't Use Sensors if Expired**

Don't use expired sensors, because they may give incorrect results. Check the package label for the expiration date It's in YYYY MM DD (Year Month Day) format

- **Check Sensor Package**
  Don't use sensor if its sterile package has been damaged or opened, because it might cause an infection.
- **Clean and Dry Skin**
  Clean and dry your hands and your insertion site before inserting your sensor. Wash your hands with soap and water, not gel cleaners, and then dry them before opening the sensor package If your hands are dirty when you insert the sensor, you may get germs on the insertion site and get an infection Clean your insertion site with alcohol wipes to prevent infections Don't insert the sensor until your skin is dry. If your insertion site is not clean and completely dry, you run the risk of infection or the transmitter holder not sticking well
  Make sure you don't have insect repellent, sunscreen, perfume, or lotion on your skin.
- **Where to Insert Sensor: Things to Check**
  Keep the safety guard on until you put the G6 applicator against your skin. If you remove the safety guard first, you may hurt yourself by accidentally pushing the button that inserts the sensor before you mean to. Change your insertion site with each sensor. Using the same site too often might not allow the skin to heal, causing scarring or skin irritation.

  Sensor placement is important. Choose a site:
  - At least 8 centimetres from insulin pump infusion set or injection site
  - Away from waistband, scarring, tattoos, irritation, and bones
  - Unlikely to be bumped, pushed, or laid on while sleeping
- **Reuse – Don't Throw Away the Transmitter**
  When ending a session, don't throw away the transmitter The transmitter is reusable until the G6 notifies you that the transmitter battery is about to expire.
- **Use Correct Transmitter, Receiver Device, and Sensor**
  G6 components are not compatible with any previous Dexcom products. Do not mix transmitters, receivers, and sensors from different generations
- **Going Through Security Check Point**
  When wearing your G6 ask for hand-wanding or full-body pat down and visual inspection instead of going through an Advanced Imaging Technology scanner (also called a millimetre wave scanner) or putting any part of the G6 in the baggage x ray machine You can wear the G6 for the walk-through metal detector. If you do, use your meter for treatment decisions until you leave the security area. Because we have not tested every x ray and scanner, we do not know if they damage the G6.
  Not sure what kind of machine it is? Be safe request either hand wanding or full body pat-down
- **Keep Transmitter Close to Display Device**
  Keep your transmitter and display device within 20 feet with no obstacles (like walls or metal) between them. Otherwise, they might not be able to communicate. If water is between your transmitter and the display device for example, if you're showering or swimming keep them closer to each other. The range is reduced because Bluetooth® doesn't work as well through water
- **Get Alarm/Alerts on Display Device You Use**
  To get your alarm/alerts, set them on the display device you use Your receiver smart device won't get the alarm/alerts you set on your app. Likewise, your app won't get the alarm/alerts you set on your receiver device
- **Is It On?**
  If the smart device is turned off (shut down), it will not show G6 readings or alarm/alerts Make sure your display device is turned on.
- **Check Accessory Devices**
  Do you use headphones with your smart device? What about *Bluetooth* speakers or a smart watch? When using peripherals, keep in mind you may get your alarm/ alerts on only one device or

peripheral, not all. After connecting any peripheral devices, make sure that your smart device settings allow you to continue receiving alarms or alerts

- **Test Speaker and Vibrations**
  You have to hear or feel alarm/alerts to react to them, so test your receiver smart device speaker and vibrations regularly.
- ***Followers* Don't Manage Your Diabetes, You Do**
  Don't rely on your *Followers* to let you know you need to make a treatment decision. Stay on top of your diabetes management Look at your G6 often Respond to alarm/alerts Don't wait for a *Follower* to reach out – they may not be getting your sensor information because of a technical issue
- **Check Your Smart Device and Your *Followers*' Smart Devices**
  - Internet access required: Both smart devices need to be connected to the Internet to use *Share*. Try sending your *Follower* an email from your device. If your Follower gets it on their device, both smart devices are connected
  - Batteries charged: Make sure the smart device batteries are charged. If either your or your Followers' smart device batteries aren't charged, *Share* won't work
- **Check Your Smart Device**
  App on: Whenever you power on your smart device, tap the G6 app to open it If the app isn't open, *Share* won't work.
- **Check *Followers*' Smart Devices**
  - Sounds on: *Followers* must keep their smart device volume on, or at least the keep vibration on, so they can hear and/or feel alarm/alerts Smart device settings trump Follow app settings
  - Sharing gaps: *Followers* won't get your sensor information when their smart device is off, not connected to the Internet, or in *Do Not Disturb* or *Airplane* mode. When the *Followers* fix those issues, they'll start getting the current information but they won't get the information they missed
  - Cell carrier supports simultaneous voice and data: Most cell service carriers support using voice and data at the same time. Check yours and have *Followers* check theirs. If it's not supported, *Share* won't work during phone calls *Share* will restart when the call is over and send any waiting notifications
- **Customise *Share* So *Followers* Can Support You**
  - Customise *Share* to make sure your *Followers* have the information they need to help you manage your diabetes
  - Delay feature: Your *Follower* won't get notified until after the delay time you set
  - *Not Share* feature: You can stop sharing with a *Follower* any time by choosing *Not Share* That *Follower* will stop getting any of your sensor information until you choose to *Share* again

Interactions

Paracetamol/Acetaminophen Blocking
In previous generations of Dexcom CGM systems (G4/G5), paracetamol/acetaminophen could affect sensor readings, making them look higher than they really were. However, with the G6, you can take a standard or maximum paracetamol/acetaminophen dose of 1 gram (1,000 mg) every 6 hours and still use the G6 readings to make treatment decisions. Taking higher than the maximum dose of paracetamol/acetaminophen (eg. >1 gram every 6 hours in adults) may affect the G6 readings, making them look higher than they really are

1.6 SUMMARY OF MAIN THERAPEUTIC CLAIMS AND PROPOSED USE

The G6™Mobile CGM System is a real-time, continuous glucose monitoring (RT-CGM) device indicated for the management of diabetes in persons aged 2 years and older

The G6 is intended to replace fingerstick blood glucose testing for diabetes treatment decisions. Interpretation of the G6 results should accordingly be based on the glucose trends and several sequential readings over time. The G6 also aids in the detection of episodes of hyperglycaemia and hypoglycaemia, facilitating both acute and long-term therapy adjustments, which may minimise these excursions and their associated adverse health consequences.

The G6 is also able to autonomously communicate with digitally connected devices, including automated insulin dosing) systems. The G6 can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes

The G6 RT-CGM technology represents a significant advance over SMBG alone because this technology reports glucose every 5 minutes, which facilitates the detection of impending low or high glucose levels that may otherwise be missed with intermittent data captured by SMGB or flash glucose monitoring [162] Nocturnal hypoglycaemia, which accounts for half of all severe hypoglycaemia events,[163] is the primary concern motivating prescription of RT-CGM in two thirds of cases.[164] Most of these hypoglycaemic episodes are asymptomatic and remain undetected by standard SMBG, as fingerstick glucose or flash glucose measurements are rarely performed at night.[18] For patients with impaired awareness of hypoglycaemia (IAH), the alarm function of RT-CGM devices may be their only warning of emerging hypoglycaemia.

RT CGM technology provides information on the direction, rate, and trend in glycaemic activity, thereby offering additional data to guide disease management decisions (eg., insulin dosage adjustments, changes in diet), which enables patients to reduce glycaemic variability and increase the time spent in the target glucose range.[17,18]

Dexcom G5 and G6 are the only continuous RT CGM devices approved in the United States for making treatment decisions and the replacement of confirmatory SMBG. Although the FreeStyle Libre™ is approved for treatment decisions without confirmatory SMBG, the device only provides glucose readings when patients scan their sensors with the reader; thus, the intermittent patient-activated glucose data provided by the FreeStyle Libre cannot alert individuals to potentially dangerous glucose excursions when they are asleep or otherwise not actively checking their sensor readings. A randomized trial comparing the G5 (n=20) and FreeStyle Libre (n=20) in patients with T1DM and IAH found that patients treated with G5 spent significantly less time in hypoglycaemia (<3.9 mmol/L: 6.2% vs 11 0%, p=0 01; <3.5 mmol/L: 3 5% vs 8 2%, p=0 004; <3 3 mmol/L: 2 4% vs 6 8%, p=0 006; <2 8 mmol/L: 0.9% vs. 3.8%, p=0.003) and had significantly less fear of hypoglycaemia (p=0.02) than patients treated with intermittent flash glucose monitoring [165]

Evidence from REPLACE-BG, a multicentre, randomized, noninferiority, clinical trial, demonstrated that the use of the earlier Dexcom G4 CGM device with 505 software (which has equivalent accuracy to the G5) without confirmatory BGM is as safe and effective as using RT-CGM adjunctive to BGM in well-controlled adults with T1DM.[35] Mean time in 3 9 10 0 mmol/L (primary endpoint) was 63 ±13% at both baseline and 26 weeks in the RT-CGM-only group and 65 ± 13% and 65 ±11% in the RT-CGM + BGM group (adjusted difference 0%; one sided 95% CI 22%) No severe hypoglycaemic events occurred in the RT-CGM-only group, and one occurred in the RT-CGM + BGM group. These results indicate that patients using the G5 and G6 devices can reduce their burden of multiple daily finger sticks when using RT CGM without loss of efficacy or safety, and that the cost of RT-CGM may be lowered by reducing the number of BGM test strips required

The Dexcom Share® feature allows users to select up to five designated recipients or "followers" who can remotely monitor the user's glucose information and receive alert notifications for added protection and peace of mind, particularly for parents of children and for loved ones of elderly individuals who may not be able to reliably measure their own blood glucose values and make insulin dosing decisions on their own. Children and elderly diabetes patients who use the G5 and have at least 1 follower have significantly better adherence to RT CGM, lower mean blood glucose levels, and less exposure to hypoglycaemia than patients without any followers.[20 22]

Three recently completed RCTs (the DIAMOND, GOLD, and HypoDE trials) have shown that RT CGM in conjunction with MDI therapy significantly improves glycaemic control in T1DM and insulin-treated

T2DM patients compared to MDI,[23-25] and reduces the incidence of hypoglycaemic events in T1DM individuals with IAH or severe hypoglycaemia,[26] compared with conventional blood glucose monitoring The DIAMOND RCT evaluated the effectiveness of RT-CGM in patients with poorly-controlled T1DM (n=158) or insulin treated T2DM (n=158) who were treated with MDI [23,24] After 24 weeks, RT CGM reduced HbA1c by 0.6% (p<0.001) in patients with T1DM and by 0.3% in patients with insulin-treated T2DM compared with patients who received conventional blood glucose monitoring T1DM patients who received RT-CGM also spent significantly less time in hypoglycaemia (p=0.002), had less diabetes distress (p<0 001) and hypoglycaemic fear (p=0 02), and had better hypoglycaemic confidence (p<0.001) and well-being (p=0.01), compared with conventionally-monitored patients.[23,166]

The GOLD trial, a 26-week, multicentre, randomized, open label, crossover study conducted in 161 patients with poorly-controlled T1DM treated with MDI, evaluated the impact of RT-CGM on glycaemic outcomes, well being, diabetes distress, and hypoglycaemic fear and confidence [25,27] Mean HbA1c was 0.43% lower (p<0.001), and time spent in daytime and nocturnal hypoglycaemia significantly less (p<0 001), during RT CGM use than during conventional blood glucose monitoring. In addition, during treatment with RT-CGM, patients reported better well-being (p=0.02) and hypoglycaemia confidence (p<0 001) compared to when treated with conventional SMBG

The HypoDE study, a 6-month, multicentre, open-label, parallel, randomized controlled trial, was conducted to determine whether RT CGM reduces the incidence of hypoglycaemic events compared with SMBG in 149 high-risk adults (history of IAH or severe hypoglycaemia) with T1DM treated by MDI [26] Compared with SMBG, RT CGM reduced the incidence of hypoglycaemic events by 72% (incidence rate ratio [IRR] 0.28, 95% CI 0.20-0.39, p<0.0001) and the incidence of nocturnal hypoglycaemic events by 65% (IRR 0 35, 95% CI 0 22-0.56, p<0 0001) RT-CGM also significantly reduced glycaemic variability, hypoglycaemia-related distress, and satisfaction with glucose monitoring compared with SMBG

Data from three recently published clinical studies show that RT-CGM used in conjunction with MDI is as effective as the combination of RT CGM and insulin pump therapy for improving glycaemic control [28 30]

The results of these recent RCTs and real world studies support the findings of earlier RCTs, including the landmark JDRF studies, which established the efficacy of RT-CGM in T1DM patients treated with either MDI or insulin pump therapy.[167 171,33,172,173] These studies have shown that, compared to SMBG, RT-CGM significantly reduces HbA1c, glycaemic excursions, and glycaemic variability without increasing hypoglycaemic episodes in children and adults with poorly-controlled T1DM and in adults with well-controlled T1DM who are receiving MDI or insulin pump therapy.[167,171,33,172,173] Similar improvements in glycaemic control are seen when RT-CGM is continued or initiated in a routine clinical practice environment.[169,170,33] The greatest reductions in HbA1c occur in patients who consistently use RT CGM [167,174,23,170,171,33,25]

The majority of RCTs conducted to date have not been designed or powered to detect significant changes in the rate of severe hypoglycaemic events, have often excluded individuals with recurrent severe hypoglycaemia from the study samples, and have not robustly measured hypoglycaemic episodes [31] An exception was the recently published HypoDE RCT which demonstrated that RT CGM reduced the incidence of severe hypoglycaemia events by 64% in high-risk patients who were treated with MDI.[26] Additional evidence that RT CGM can substantially reduce the incidence of severe hypoglycaemia is provided by the IN CONTROL trial and extension phase of the Juvenile Diabetes Research Foundation (JDRF) clinical trial The IN CONTROL trial was a randomised, open label, crossover study conducted in adults with poorly-controlled T1DM and IAH.[32] In this study, RT-CGM reduced the incidence of severe hypoglycaemia by 59% compared with SMBG In a 6 month, open label, extension study of the JDRF clinical trial, children and adults with poorly-controlled T1DM receiving intensive insulin treatment who were initiated on RT CGM experienced a 46% reduction in the incidence of severe hypoglycaemia.[33]

Thus, a strong body of evidence supports the efficacy of highly accurate RT CGM, used in conjunction with MDI or insulin pump therapy, to significantly reduce HbA1c, time spent in hypoglycaemia and fear of hypoglycaemia and improve well being and quality of life in patients with insulin-treated diabetes Burgeoning data also suggest that this technology can significantly reduce the incidence of dangerous and costly severe hypoglycaemic events in high risk patients

2. PROPOSED AMENDMENTS TO THE PHARMACEUTICAL SCHEDULE

2.1 PROPOSED SCHEDULE LISTING AND CRITERIA

It is proposed the Dexcom G6™Mobile Continuous Glucose Monitoring System be listed in Section B of the Pharmaceutical Schedule within the Alimentary Tract & Metabolism / Blood Glucose Testing section. It is suggested the G6 System would be subsidised by endorsement as follows:

The Dexcom G6 should be considered as replacement to conventional SMBG in people aged ≥2 years with diabetes and is particularly appropriate for insulin treated patients who meet any of the following criteria:

- *Frequent hypoglycaemia including all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm All episodes of hypoglycaemia substantially increase the risk of subsequent hypoglycaemia.*
- *Severe hypoglycaemia defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.*
- *Nocturnal hypoglycaemia*
- *Impaired Awareness of Hypoglycaemia (IAH) defined as the inability to detect the early neurogenic warning symptoms of hypoglycaemia. The presence of IAH increases the risk of severe hypoglycaemia by 3-10 times in patients with T1DM1.*

2.2 COMPARISON WITH OTHER CGM PRODUCTS

A comparison of the attributes and performance of the G6 and other commercially available standalone RT-CGM and flash glucose monitoring devices is shown in Table 5.

TABLE 1 COMPARISON OF PRODUCT ATTRIBUTES AND PERFORMANCE

Product Attributes and Performance	G6™ CGM System (Dexcom)	G5™ Mobile CGM System (Dexcom)*	FreeStyle Libre Flash Glucose Monitoring System (Abbott)[39]	Guardian™ Connect (Medtronic)
Indication	≥2 years[40]	≥2 years[41]	≥4 years[39] (Children 4 17 years of age must be supervised by a caregiver ≥18 years.)	≥14 years[42]
Treatment decisions can be made without confirmatory SMBG	Yes[40]	Yes[41]	Yes except: * During times of rapidly changing glucose levels, as reported interstitial glucose levels may not accurately reflect blood glucose levels • In order to confirm existing or impending hypoglycaemia as reported by the Sensor • If symptoms do not match the System reading.[39]	No[42]
Sensor & Transmitter Specifications				
Sensor/Transmitter dimensions	3 8 x 3 0 x 1 5 cm[40]	3 8 x 2 3 x 1 3 cm[41]	3 6 x 2 5 x 0 5 cm[39]	1 9 x 1 1 x 0 7cm[43]‖
Sensor/Transmitter weight	11 9 gm [40]	11 3 gm [41]	5 1 gm[39]	2 8 gm [43]

Sensor duration	10 days[40]	7 days[41]	14 days[39]	7 days[42]
Sensor start-up time	2 h[40]	2 h[41]	12 h[39]	2 h[42]
Moisture protection	Water resistant < 2.4 metres for 24 hrs[40]	Water resistant < 2.4 metres for 24 hrs[41]	Water resistant < 0.9 metres for 30 min[39]	Waterproof < 2.4 metres for 30 min[42]
Transmitter power	Non-rechargeable; silver oxide batteries[40]	Non-rechargeable; silver oxide batteries[41]	Non-rechargeable; silver oxide battery[39]	Rechargeable (charge lasts 14 days)[44]
Communication range	6 metres[40]	6 metres[41]	3.8 cm[39]	1.8 metres[42]
Receiver/Reader Specifications				
Smartphone display option	Yes[40]	Yes[41]	No	Yes[45]
Receiver dimensions	NA	10 0 x 4 6 x 1 3 cm[41]	9 4 x 6.1 x 1.5 cm[39]	No dedicated receiver[45]
Receiver weight	NA	68 gm.[41]	65 gm.[39]	
Memory storage	NA	30 days of glucose data, 7 days of tech support data[41]	90 days of glucose data; reader only collects data when sensor is scanned[39]	
Receiver power	NA	Rechargeable (full charge lasts 3 days)[41]	Rechargeable (full-charge lasts 7 days)[39]	
Calibration				
Minimum calibration	No calibration required[40]	2 h after sensor insertion, then every 12 h[41]	No calibration required[39]	2 and 6 h after sensor insertion, then every 12 h[42]
Range	2.2-22.2 mmol/L[40]	2.2-22.2 mmol/L[41]	2.2-27.8 mmol/L[39]	2.2-22.2 mmol/L[42]
Restrictions	None[40]	Do not calibrate when glucose levels are rapidly changing (>0 1 mmol/L per minute)[41]	Not applicable	None[42]
Interaction with BG meter	Manually enter reading from any meter[40]	Manually enter reading from any meter[41]	Reader incorporates a glucose meter[39]	Reading is manually entered from any meter, or wirelessly uploaded using Bayer Contour® Next Link meter[42]
Alarms				
Hypoglycaemia fixed alarm	Set at 3 1 mmol/L; cannot be adjusted or disabled[40]	Set at 3 1 mmol/L; cannot be adjusted or disabled[41]	No alarms or alerts[39]	Not available[42]
Customisable alarms	Optional; set by user[40]	Optional; set by user[41]	Not applicable[39]	Optional; set by user[42]
Performance Characteristics				
Overall Accuracy MARD (average % discrepancy between CGM and reference YSI, 2.2-22.2 mg/dL)	9.0% (overall) 9 8% (adults) 7.7% (paeds)[40]	9.0% (adults) 10.4% (paeds)[41]	9 7%[39]	10 6%[46]
Accuracy dependent on acetaminophen exposure	No[40]	Yes[41]	No[39]	Yes[46]
Hypoglycaemia Accuracy (% of CGM readings within ±20%/1.1 mmol/L	Adults: <3 0 mmol/L: 91% 3.0 3.8 mmol/L: 95% Children: <3 0 mg/dL: 62% 3.0-3.8 mmol/L: 89% [41]	Adults: 2 2 3 3 mmol/L: 94% 3.4 4.4 mmol/L: 96% Children: 2 2 3 3 mmol/L: 74% 3.4-4.4 mmol/L: 82% [41]	2.2 2.8 mmol/L: 58% 2.8-4.4 mmol/L: 81%[39]	≥2.2-3.3 mmol/L: 97% >3.3-4.4 mmol/L: 88%[46]

of reference YSI, 2.2-4.4 mmol/L)				
Product Attributes and Performance	**G6™ CGM System (Dexcom)**	**G5™ Mobile CGM System (Dexcom)***	**FreeStyle Libre Flash Glucose Monitoring System (Abbott)[39]**	**Guardian™ Connect (Medtronic)**
Hypoglycaemia Detection Rate (% of time BG level was ≤ alert setting of 3.7 mmol/L and alert sounded)	Adults: 86% Children 6 17 yrs: 82%[40]	Adults: 91% Children 2-5 yrs: 100% Children 6-17 yrs: 75%[41]	85%[39]†	88%[46]
Hyperglycaemia Detection Rate (% of time BG level was ≥ alert setting 13.3 mmol/L and alert sounded)	Adults: 98% Children 2-5 yrs: 93% Children 6-17 yrs 97%[41]	Adults: 95% Children 2-5 yrs: 98% Children 6-17 yrs: 94%[41]	95%[39]†	100%[46]
Accuracy Over Time **MARD** (average % discrepancy between CGM and reference YSI, 2.2-22.2 mmol/L)	Days 1 & 2: Adults 10.9% Children 10.9% Days 4 &5: Adults 9.2% Children 9 2% Day 7 &10: Adults 9 6% Children 9.6%[41]	Day 1: Adults 10.7% Children 14.8% Day 4: Adults 8.0% Children 10 7% Day 7: Adults 8.5% Children 11.3% [41]	Day 1: 10 7%[39] Day 4: 9.6%[39] Day 7: 9.1%[39] Day 10: 9 3%[39]	Day 1: 12.4% Day 3: 8.7% Day 7: 10.1%[43]
Sensor Life (% Sensors working at end of maximum indicated use)	Adults: 94% @ 10 days Children: 77% @ 10 days [41]	Adults: 98% @ 7 days Children: 94% @ 7 days [41]	77% @ 10 days[39]	72.3% @ 7 days[46]

BG=blood glucose; MARD=mean average relative difference; YSI=Yellow Springs Instrument

*Performance data are for the G5™ Mobile CGM System with the 505 software. All G5™ Mobile CGM Systems use the 505 software. Unless otherwise specified, the age range for children is 2-17 years.

‖ The dimensions and weight reflect only that of the Guardian 3 sensor and do not include the Guardian Link 3 transmitter that is attached to the sensor.

†The FreeStyle Libre has no alarms or alerts. The hypoglycaemia and hyperglycaemia detection rates reflect the % of high glucose readings that were correct when the Reader was used to scan the Sensor.

The G6 CGM is the first type of CGM system permitted by the FDA for use as part of an integrated system with compatible medical devices and electronic interfaces including automated insulin dosing systems, insulin pumps, blood glucose meters or other electronic devices used for diabetes management.

3. HEALTH NEED AND PUBLIC HEALTH SIGNIFICANCE

3.1 EPIDEMIOLOGY OF DIABETES

Diabetes is a group of metabolic diseases characterized by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both.[47] The prevalence of diabetes continues to increase rapidly worldwide, causing significant morbidity, mortality and cost The rising prevalence reflects a combination of factors, including increasing incidence (true new cases), better detection of cases through increased screening, slower progression from uncomplicated to late stage disease (which means mortality rates are lower) and demographic change (changing ethnic composition and population ageing) [204]

3.1.1 Prevalence of Diabetes in New Zealand

Diabetes is one of New Zealand's fastest growing long-term conditions Addressing the increasing impact of diabetes is specifically recognised by the Government as *"an important focus to support its vision that all New Zealanders live well, stay well and get well".*[204]

Estimates of the prevalence of diabetes in New Zealand have limitations. The annual national health surveys include self-reports of doctor-diagnosed diabetes only. The New Zealand Ministry of Health releases national estimates of the prevalence of diabetes annually based on the Virtual Diabetes Registry (VDR) The VDR counts known diabetes cases using the National Health Index from six databases with information about hospital admissions, attendance at diabetes outpatients or retinal screening, diabetes specific medication prescriptions, laboratory HbA1c testing and mortality.[205] The VDR does not distinguish between the prevalence of Type 1 and Type 2 diabetes however, and persons not enrolled in a Primary Health Organisation are excluded The latest report records a total of 245,680 New Zealanders diagnosed as having diabetes as at 31 December 2017,[206] 5.1% of the total population estimate The total has increased by 30.8% since 2010 (Table 6), at an average of nearly 40 people per day.

TABLE 6. NUMBER OF PEOPLE IN THE VIRTUAL DIABETES REGISTER (V686), 2010–2017[206]

	2010	2011	2012	2013	2014	2015	2016	2017
Total	**187,860**	**200,235**	**211,591**	**220,866**	**228,790**	**236,073**	**241,463**	**245,680**

The prevalence of diagnosed diabetes is higher in people of Pacific and Indian ethnicity, Māori, and people living in lower socioeconomic areas

- The 2016 VDR shows Pacific people as having an estimated prevalence of diagnosed diabetes of 10 6%, followed by Indian people at 8 5% and Maori 6 3%[206]
- Type 2 diabetes is increasingly occurring in Māori and Pacific children under the age of 15 years; an Auckland study found 90 percent of new cases were of Māori or Pacific ethnicity[207]
- Māori are three times as likely to have type 2 diabetes as non Māori, and are more likely to develop complications[208]
- One in three Pacific adults aged 45 years or older has diabetes, rising to 56% of those 75 years or older. A further one third of Pacific adults over 45 years have prediabetes [209]
- Pacific peoples develop diabetes earlier and experience more complications than New Zealand Europeans with the condition.[208]
- Adults living in the most socioeconomically deprived areas are over three times more likely to report that they have been diagnosed with diabetes than adults living in the least deprived areas.[209]
- People with a history of long-term mental illness have significantly higher rates of diabetes [210]

As national diabetes prevalence estimates have not included undiagnosed diabetes cases, the actual burden of disease has been underestimated. The 2008/09 New Zealand Adult Nutrition

Survey (2008/09 NZANS) collected data about doctor diagnosed diabetes and a blood sample was taken for the measurement of glycated haemoglobin (HbA1c), providing an insight into the true national prevalence of diabetes and prediabetes in adult New Zealanders using American Diabetes Association (ADA) criteria Overall, the prevalence of diabetes was 7 0%, and prediabetes was 25.5% [207] (Table 7).

TABLE 7 ADULT AGE-SPECIFIC RATES FOR SELF-REPORTED DOCTOR DIAGNOSED DIABETES, UNDIAGNOSED DIABETES AND PREDIABETES BY AGE GROUP FOR MAORI, PACIFIC, AND NEW ZEALAND EUROPEAN AND OTHER ETHNIC GROUPS [207]

Ethnicity	Age groups (years)	Diagnosed Diabetes† %	Undiagnosed Diabetes‡ %	Total Diabetes‡ %	Prediabetes‡ %
All	15 24	0 0	0 1	0.1	8.4
	25-44	1.4	1 7	3 7	18.9
	45-64	7 0	2 3	9.2	32 5
	65-74	12.8	1.8	14.7	45.1
	75+	15.4	4.6	21.3	43.8
	Total	4.9	1.8	7.0	25.5
Maori	15 24	*	-*	*	12 9
	25-44	2 3	2.3	5.5	31 0
	45-64	16.4	4.4	20.8	42.4
	65-74	28.8	1.1	34.7	51.0
	75+	36.5	-	40.1	44.4
	Total	7.0	2.2	9.8	30.4
Pacific	15 24	-*	-*	*	13 6
	25-44	4.5	6.0	10.7	29.6
	45-64	18.0	12.7	32.9	38.7
	65-74	27.6	10.7	34.2	34.2
	75+	39 0	*	55 8	*
	Total	8.1	6.4	15.4	29.8
NZ European / Other	15-24	0.1	0.1	0.2	7.0
	25-44	1.0	1.3	2.8	16.0
	45-64	5.5	1.7	6.9	31.1
	65 74	11 6	1 6	13 2	44 5
	75+	14.5	4.8	20.3	43.9
	Total	4 5	1 5	6 1	24 6

† Total number completing the survey = 4721. ‡ Total number providing a sample for blood analysis = 3348; * Insufficient data to calculate the rate.

3.2 BURDEN OF DISEASE

3.2.1 Clinical Presentation and Course

T1DM

There is considerable variability in the initial presentation of T1DM in children and adults [53] T1DM is usually diagnosed based on the classic catabolic symptoms suggestive of insulin deficiency, including polyuria, polydipsia, weight loss, and marked hyperglycaemia.[53]

Chronic complications of diabetes, including retinopathy, nephropathy, and neuropathy, rarely have been reported in prepubertal children and children with T1DM duration of only 1-2 years, but may occur after the onset of puberty or after 5-10 years of T1DM.[53]

Most older adults with T1DM have longstanding disease [53] Some may have advanced complications, as detailed below, while some may live with diabetes for many years without the development of complications [53] CVD risks for people with type 1 diabetes are substantially higher than for people with type 2 diabetes (50 percent higher in men and up to 90 percent higher in women).[212]

Insulin is the requisite treatment for all individuals with T1DM [54]

T2DM

T2DM is often undetected for many years because hyperglycaemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes [47] Although some patients with T2DM are diagnosed after developing the classic acute symptoms, the first symptoms in others are nonspecific, (e.g., fatigue, poor wound healing, dry mouth) and may not be recognized as diabetes.[58]

In general, children and adolescents diagnosed with T2DM present with glycosuria without ketonuria, mild thirst, some increase in urination, and little-to-no weight loss; however, up to 33% will have ketonuria at diagnosis, with 5% to 25% having ketoacidosis unrelated to stress, illness, or infection.[58]

Due to the progressive nature of T2DM, many people with the disease eventually require insulin.[47]

Insulin Use in New Zealand

A total of 51,934 people with either T1DM or T2DM regularly used insulin in 2016, that is, 22% of all diagnosed diabetics. Insulin use was highest in the 0–24-year age group with diabetes, with 62% of these regularly dispensed insulin [206]

3.2.2 Complications of Diabetes

a. Hypoglycaemia

The ADA defines hypoglycaemia as “any abnormally low plasma glucose concentration that exposes the subject to potential harm” with a proposed threshold plasma glucose value <70 mg/dL (<3.9 mmol/L).[15] Mild hypoglycaemia is associated with the presence of autonomic symptoms manifested as a cause of activation of the sympathetic nervous system and include trembling, palpitations, sweating, anxiety, hunger, nausea, and tingling; individuals are able to self-treat mild hypoglycaemia [59] Moderate hypoglycaemia is associated with both autonomic and neuroglycopenic symptoms, and the individual is also able to self-treat.[59] Neuroglycopenic symptoms are manifested in response to decreased levels of glucose to the brain and include difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, dizziness and tiredness [59] Severe hypoglycaemia requires the assistance of another person to treat and can lead to seizures, coma, and even death.[15]

Hypoglycaemia is the most common and serious adverse event caused by insulin treatment[60] and is a major barrier to optimal diabetes management.[61] Large landmark randomised clinical trials (RCTs) have shown that intensive diabetes therapy, which aims to achieve lower average blood

glucose results, increases the risk of severe hypoglycaemia by 2- to 3-fold in patients with T1DM and T2DM [62,63,4,64]

Health Consequences of Hypoglycaemia

Recurrent and severe hypoglycaemia can cause significant morbidity and mortality. Profound and prolonged hypoglycaemia may cause transient or persistent neurological deficits. Repeated episodes of severe hypoglycaemia are associated with impaired cognitive function in children, and can have potentially deleterious and cumulative long term effects on intellectual function.[65] Severe hypoglycaemia in older patients has been associated with an increased risk of dementia.[66] A recent history of severe hypoglycaemia is the single most significant factor associated with driving collisions for drivers with diabetes,[67,68] and severe hypoglycaemia may contribute to fatal vehicular accidents by impairing cognitive, motor, and perceptual functioning.[69,68] Among patients who receive emergency inpatient treatment for severe hypoglycaemia, 22% experience persistent neurological deficits that cause disability after discharge.[70]

Among individuals with T1DM, 4-10% of all deaths are attributed to severe hypoglycaemia,[71,72] and risk of death 5 years after an episode of severe hypoglycaemia is 3 4 fold in those who report severe hypoglycaemia.[73] Severe hypoglycaemia is associated with an increased risk of cardiovascular events and sudden cardiac death, although it is not yet clear whether hypoglycaemia is causally linked to cardiovascular risk or is marker of frailty and predictor of adverse outcomes in patients with diabetes.[74]

Diabetes is the 7th leading cause of death in New Zealand, and the 5th leading cause in New Zealanders less than 65 years of age [213]

Quality of Life

Regardless of severity, hypoglycaemia substantially reduces well-being and impairs quality of life by interfering with physical, mental and social functioning, sleep, work productivity, and enjoyment of recreational and leisure activities.[11,12,61] A literature review found that studies consistently demonstrate a lower health related utility associated with hypoglycaemia.[10] Studies also have demonstrated that health-related quality of life decreases with increasing severity and increasing frequency of non severe hypoglycaemic episodes.[10] Nocturnal hypoglycaemia, a particularly feared event, negatively affects well-being and increases fatigue [75]

The negative emotional and physical impact of hypoglycaemia extends beyond the individual with diabetes to their family members. A survey of 2,057 family members of people with diabetes found that 61% experienced distress over a family member experiencing a hypoglycaemic event.[13] Parents of children with diabetes worry about their child's ability to detect/report hypoglycaemia and factors that impacted their child's blood glucose levels and over which they could exercise little control, including leaving their child with other caregivers who could not be trusted to detect hypoglycaemia, difficulties remotely monitoring and regulating their child's food consumption and activity, and physical and social changes accompanying childhood development.[14]

Fear of Hypoglycaemia

The development of fear of hypoglycaemia is associated with both the severity and frequency of past episodes of hypoglycaemia.[10,76] Fear of hypoglycaemia is associated with psychological distress, particular increased anxiety,[77,78] which can make it difficult for patients to differentiate anxiety and hypoglycaemic symptoms[78] and consequently delay or prevent the patient from responding appropriately to hypoglycaemia to prevent a more severe hypoglycaemic episode.[10]

In addition to causing psychological distress, fear of hypoglycaemia can have a negative impact on diabetes management and metabolic control. Fear of hypoglycaemia is strongly associated with poor adherence to prescribed insulin regimens.[8,9] The impact of hypoglycaemia and fear of future hypoglycaemic episodes was assessed via a self-administered survey in 202 patients with T1DM and 133 patients withT2DM.[7] Following a mild or moderate hypoglycaemic episode, 37.8% of T1DM and 29.9% of T2DM patients reported increased fear of future episodes; and 74.1% and 43 3%, respectively, reported modifying their insulin dose After episodes of severe hypoglycaemia, most patients with T1DM and T2DM expressed fear of future events (63.6% and 84.2%, respectively) and reduced their doses of insulin. A survey of 1,404 employed individuals

with diabetes across the US, UK, Germany, and France found that, of the 1,024 individuals taking insulin, 25% decreased their insulin dose following a non severe hypoglycaemic episode [6]

Fear of hypoglycaemia is also common among the parents of children with diabetes.[79]. Scores on the behaviour scale of the Hypoglycaemia Fear Survey, particularly of mothers, suggest that they may maintain slightly higher than optimal glucose levels in their children to avoid hypoglycaemia [80,81]

Fear of hypoglycaemia is a major contributor to the decrease in health-related quality-of-life of patients with diabetes Patients with hypoglycaemia symptoms report more fear and worry of hypoglycaemia and are more affected by their diabetes compared with those without hypoglycaemia symptoms [82]

Incidence of Non-Severe Hypoglycaemia

In a survey of 3,859 people with diabetes in 7 European countries, rates of non-severe hypoglycaemia were 1.8 episodes per week for patients with T1DM and 0.4-0.7 episodes per week for patients with insulin-treated T2DM.[83] These figures likely represent underestimates of the true rate of non severe hypoglycaemia as a majority of respondents in this study had either impaired or absent ability to recognise symptoms of hypoglycaemia.

Prevalence and Incidence of Severe Hypoglycaemia

Approximately 30-40% of adults with T1DM,[84-87] 22% of insulin-treated adults with T2DM,[88] and 6% of youth with insulin-treated T2DM[84] experience at least 1 severe hypoglycaemic event annually.

Five studies of children and adolescents with T1DM have reported rates of severe hypoglycaemia ranging from 0.16 to 0.38 episodes per patient-year.[89-92] Incidence rates for severe hypoglycaemia in adults with T1DM range from 0.5 to 3.2 events per patient year, with most studies reporting an incidence of 1 episode per patient-year [93,85,83,86,94,87,95,96]

The incidence of severe hypoglycaemia in children and adolescents with insulin treated T2DM is 0.12 episodes per patient-year.[97] A systematic literature review (1998-2014) of 11 studies involving 6851 adults with insulin treated T2DM found that the incidence of severe hypoglycaemia was 1.0 episodes per patient-year.[98]

Impaired Awareness of Hypoglycaemia and Risk of Severe Hypoglycaemia

IAH is an acquired complication of insulin therapy whereby patients lose the ability to perceive the early, largely neurogenic, warning symptoms of developing hypoglycaemia [99,100] The prevalence of IAH increases with diabetes duration, and is found in 10 58% of adults with T1DM,[101 108,83,86,109,94,87] 21 29% of children and adolescents with T1DM,[110,91] and 8 20% of adults with insulin treated T2DM.[111,107,83,94,112]

The reduced ability to detect the acute autonomic warning symptoms of hypoglycaemia creates a vicious cycle of recurrent hypoglycaemia and increases the risk of severe hypoglycaemia.[113,114] IAH is associated with a 3-10 times greater incidence of severe hypoglycaemia in patients with T1DM[110,101,103,115,104,116,107,83,94] and a 2 17 times greater incidence of severe hypoglycaemia in patients with insulin-treated T2DM [111,107,94,112]

Data from a randomized clinical study of RT-CGM versus SMBG in adults with T1DM and IAH demonstrated that there is an inverse association between HbA1c and both the number of severe hypoglycaemic events and CGM assessed hypoglycaemia.[117] Thus, reaching target HbA1c values comes with a higher risk of severe hypoglycaemia in this high risk group

b. Chronic Microvascular Complications

The microvascular complications of diabetes include retinopathy, nephropathy, and neuropathy.[47] After 15 or more years of disease, 85% of persons with insulin dependent diabetes will develop diabetic retinopathy and 20% will develop vision-threatening proliferative diabetic retinopathy.[118] Diabetic retinopathy is the leading cause of blindness in adults aged 20 74 years [119] Approximately 20-30% of people with diabetes will develop nephropathy.[120] In T1DM, overt nephropathy will progress to renal failure in 50% of patients within 10 years and 75% within 20 years [120]

Approximately 20% of patients with T2DM who develop overt nephropathy will progress to renal failure within 20 years [120] Diabetic neuropathy affects up to 70% of people with diabetes and is responsible for 60% of all non-traumatic lower-extremity amputations.[121] There were 448 diabetes related lower limb amputations in New Zealand public hospitals in 2016

Chronic Macrovascular Complications and Mortality

Cardiovascular disease is the most common cause of diabetes-related death and disability.[122] US adults with diabetes have a 1.5 to 1.8 times increased risk of heart attack, stroke, and death from CVD compared with those without diabetes.[121] Heart disease and stroke account for 68% and 16% of diabetes related deaths, respectively, in the US[119]

c. Prevalence of Poor Glycaemic Control

Despite adoption of intensive diabetes therapy as the standard of care in diabetes treatment, data from NHANES 2007 2010 indicate that 48% of US adults with diabetes have poor glycaemic control (A1c ≥7.0%).[134] Individuals aged 18-44 years with complications who were receiving less intensive diabetes therapy had the lowest rate of achieving target HbA1c levels (28%), while 70% of adults aged 45-64 years and 84% of those aged ≥65 years with complications who were receiving moderately intensive therapy achieved their HbA1c targets.[134] A lower proportion of older adults with diabetes have poor glycaemic control, with 38% of those aged ≥65 years compared with 51% aged <65 years achieving HbA1c of ≥7.0% in NHANES 2003-3006.[135]

A 2007-2008 retrospective claims analysis of a large US managed care organization (MCO) revealed poor rates of glycaemic control among adults with diabetes, with 68% and 44% of individuals with T1DM and T2DM, respectively, at or above the HbA1c target of 7.0%.[136]

In the SEARCH Study, 56% of US youth with T1DM and 46% with T2DM had poor glycaemic control, as defined by failing to meet the age-specific ADA target or, for individuals aged <6 years, having an HbA1c ≥8.5%.[137]

Recent data from the US T1D Exchange Registry indicate that about more than three quarters of children and two thirds of adults with T1DM fail to achieve target glucose levels (Figure 7).[138]

d. Effects of Glycaemic Control on Risk of Long-term Diabetes Complications

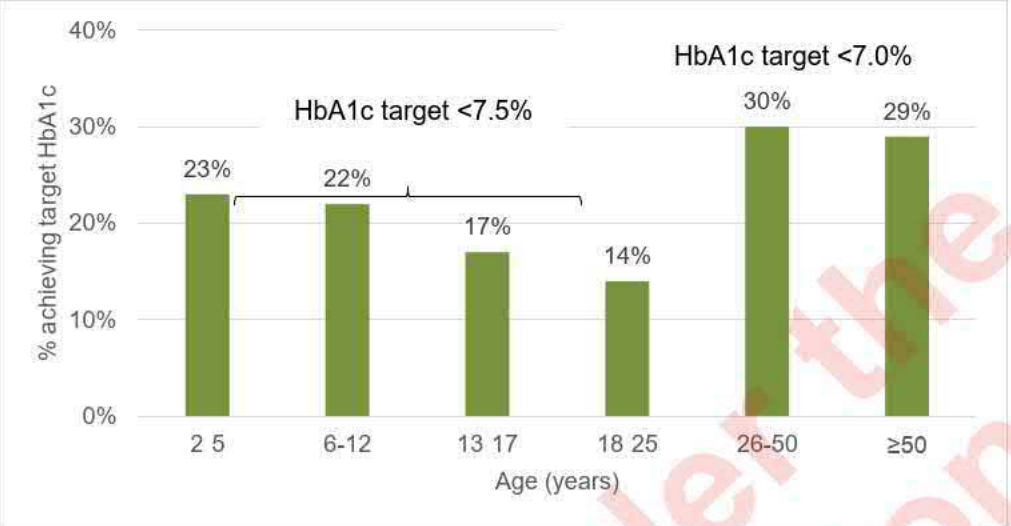
Landmark RCTs, such as the Diabetes Control and Complications Trial (DCCT)[4] and the Stockholm Diabetes Intervention Study (SDIS) in T1DM and the UKPDS (United Kingdom Prospective Diabetes Study)[125] and Kumamoto study[126] in T2DM, have established that intensive diabetes therapy, which aims to reduce HbA1c, delays or prevents long term diabetes complications. In all studies, glycaemic control was directly related to the risk of diabetes complications. For example:

- In the DCCT, a 10% reduction in HbA1c was associated with a 35% risk reduction for retinopathy and a 25-44% risk reduction for nephropathy [127]
- In the UKPDS, each 1% decrease in HbA1c was associated with a 37% reduction in the risk of microvascular complications, a 16% reduction in heart failure, and a 21% reduction in diabetes-related and all cause mortality.[128]

An observational follow-up study to the DCCT, the Epidemiologic Diabetes Interventions and Complications (EDIC) study, demonstrated the importance of achieving early glycaemic control in reducing the risk of long-term complications. During the EDIC study, patients who had received conventional treatment during the DCCT were encouraged to switch to intensive diabetes therapy and those who had received intensive therapy in the DCCT continued receiving this care.[129] During the first 7 years of the EDIC, metabolic control converged between the former DCCT treatment groups (HbA1c of 8.1% for the intensive and 8.3% for the conventional group).[129] Despite the delayed improvement in HbA1c in the former DCCT conventional treatment group, patients in the former DCCT intensive therapy group continued to experience a significantly reduced risk of developing microvascular complications during the EDIC.[130 132] This prolonged protective effect of

early glycaemic control has been called "metabolic memory," and it highlights the importance of early and aggressive interventions to reduce the risk of long-term diabetes complications [133]

FIGURE 6. HBA1C LEVELS AMONG PATIENTS WITH T1DM[138]



3.2.3 Humanistic, Societal, and Economic Burden

a. Hospitalisation due to Diabetes

The latest Ministry of Health published data shows diabetes caused a total of 5,944 public hospitalisation days in the 2014/15 financial year. 214 While over all age groups 61% of hospital days relate to Type 2 DM, in people under 50 years of age Type 1 diabetes caused 77% of hospital admission days. Māori aged under 50 years are particularly over-represented in hospital admission days for both T1 and T2 DM, accounting for approximately 25% of hospital days

TABLE 8. DIABETES PUBLIC HOSPITALISATION DAYS IN 2014/15 [214]

	0-19 Yrs	20-49 Yrs	50-79 Yrs	80 Yrs +	All ages
All Diabetes					
Total	901	1,409	2,820	814	5,944
Māori	228	323	323	19	893
Pacific	88	142	301	29	560
Other	585	944	2,196	766	4,491
T1DM					
Total	855	924	463	51	2,293
Māori	220	220	34	2	476
Pacific	77	52	18	0	147
Other	558	652	411	49	1,670
T2DM					
Total	36	454	2,297	749	3,536
Māori	8	93	281	14	396
Pacific	9	86	279	29	403
Other	19	275	1,737	706	2,737

The Virtual Diabetes Register reports the number of public hospital bed days occupied by people with diabetes for any reason is more than 50-fold higher than shown in Table 8 [206] and accounts for 18.2% of all public hospital bed days. It is suggested this is because people with uncontrolled diabetes may be sicker than the total medical, surgical and disability population

TABLE 9. PUBLIC HOSPITAL BED DAYS OCCUPIED BY PEOPLE WITH DIAGNOSED DIABETES IN 2016 [206]

0-24 Yrs	25-44 Yrs	45-64 Yrs	65+ Yrs	Total
8,113	21,652	97,923	202,910	330,598

b. Mortality due to Diabetes

A total of 839 people were reported to have died as a result of diabetes in 2015 in New Zealand.[213] Consistent with hospitalisation days, over all age groups the majority of deaths resulted from T2DM, however for people under 50 years of age, T1DM caused 55% of diabetes mortality.[213] This disparity was especially true in Pacific people under 50 years, in whom T1DM caused 3 out of 4 deaths from diabetes. Māori were over represented over all age groups for both T1DM and T2DM at 26% of all deaths, with an extraordinarily high 58% of all deaths due to diabetes in people under 50 years of age being Māori. For both Māori and Pacific people 3 out of 4 deaths from T1DM occurred in people under 50 years of age

TABLE 10. DEATHS DUE TO DIABETES IN NEW ZEALAND IN 2015 [213]

	0-49 Yrs	50-79 Yrs	80 Yrs +	All ages
All Diabetes				
Total	31	463	345	839
Māori	18	167	33	218
Pacific	4	68	18	90
Other	9	228	294	531
T1DM				
Total	17	25	4	46
Māori	9	3	0	12
Pacific	3	1	0	4
Other	5	21	4	30
T2DM				
Total	13	432	332	777
Māori	9	162	32	203
Pacific	1	67	18	86
Other	3	203	282	488

c. Cost of Diabetes

While it is well accepted that diabetes related complications exert a substantial economic burden to the healthcare system and society there is limited New Zealand data to quantify this. A 2007 report commissioned by Diabetes New Zealand estimated the direct cost of services and treatment for people diagnosed with T2DM alone to be $590m in the 2006/7 year.[215] The report projected this cost would increase to $1 08 $1 24b by 2016/17, depending on the level of interventional services provided by the Government (Table 11).

TABLE 11. DIRECT COST OF T2DM IN NEW ZEALAND [215]

Intervention Level	2006/07 ($M)	2011/12 ($M)	2016/17 ($M)	2021/22 ($M)
2000 Service Level	540	840	1,240	1,780
Enhanced Services	570	850	1,200	1,660
Optimal Services	590	830	1,080	1,410

A US study also conducted in 2007 found that T1DM accounted for approximately 9.1% of direct treatment costs [51] Table 12 allocates this figure to the projected 2016/17 T2DM cost to approximate the total direct costs of diagnosed T1DM and T2DM in New Zealand.

TABLE 12 ESTIMATED DIRECT COST OF ALL DIAGNOSED DIABETES IN NEW ZEALAND [215,51]

Intervention Level	Projected Direct Costs in 2016/17		
	All Diabetes ($M)	T1DM ($M)	T2DM ($M)
2000 Service Level	1,364	124	1,240
Enhanced Services	1,320	120	1,200
Optimal Services	1,188	108	1,080

d. Cost of Emergency Treatment for Severe Hypoglycaemia

Severe hypoglycaemia requires assistance by a third party to restore glycaemic control and may require ambulance transport/EMS services, Emergency Department visits, and hospitalisation.

In a retrospective cohort analysis of claims data in the United States that assessed the rate and costs of hypoglycaemia among adult patients with T2DM treated with insulin alone, the average cost of hospitalisation (without an Emergency Department admission) due to hypoglycaemia was $10,040 in 2008 USD.[143] Updating this value to 2017 USD (using the Consumer Price Index for Medical Care) yields a cost of $13,108 per severe hypoglycaemia hospitalisation. This figure is similar to the average cost of a diabetes related hospitalisation with documented hypoglycaemia in Belgium in 2014 (€10,258 = $14,893 in 2017 USD),[145] suggesting it has international relevance

3.3 EXPECTED UPTAKE OF REAL-TIME CONTINUOUS GLUCOSE MONITORING

3.3.1 Glycaemic Management and Monitoring Recommendations

Tight Glycaemic Control Reduces Diabetes Medical Costs

Many studies internationally have shown that improving glycaemic control reduces medical costs associated with diabetes.

- In a retrospective analysis of administrative data from a large Washington health maintenance organization, patients with diabetes who achieved a 1% sustained reduction in HbA1c had statistically significant annual cost savings of $685 $950 per patient in the subsequent year [149]
- A prospective study in a large Minnesota health plan found that for patients with T1DM or T2DM and HbA1c >7.5%, higher HbA1c predicted higher total 3-year healthcare costs.[150]
- A study of T2DM patients in a large managed care organization (MCO) found that diabetes related costs during a 1 year follow-up period were 32% higher for patients above the target HbA1c level than for patients at or below the target level [151]
- In a sample of over 10,000 managed care patients with T2DM, patients with good glycaemic control (HbA1c ≤7.0%) had 20% lower diabetes-related medical costs than those with poor glycaemic control (HbA1c >9 0%) [152]
- Among nearly 10,000 MCO patients with T1DM or T2DM and at least 1 diabetes-related hospital stay, the average cost of hospitalization was more than double for patients with poor glycaemic control (HbA1c >10 0%) compared with those with good glycaemic control (HbA1c <7%).[153]
- In a large US MCO with about 15 million covered lives, a 1% decrease in HbA1c was associated with a decrease in diabetes-related costs of 5.7% for T1DM and 4.2% for T2DM.[136] This correlates to a reduction in annual diabetes related medical costs of $423 and $239 ($559 and $316 in 2016 USD) for T1DM and T2DM, respectively.

Goals for Glycaemic Control

Although HbA1c and blood glucose targets are needed, the ADA[154] and the Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)[155] emphasise that glycaemic targets should be individualised with the goal of achieving the best possible control while minimising the risk of severe hyperglycaemia and hypoglycaemia. Table 13 presents the ADA and AACE/ACE recommendations for HbA1c targets for different patient subgroups

TABLE 13. SUMMARY OF ADA AND AACE/ACE GLYCAEMIC RECOMMENDATIONS FOR NON-PREGNANT ADULTS WITH DIABETES

Parameter	ADA[154]	AACE/ACE[155]
A1c	<7.0% (53 mmol/mol)*	≤6.5% (48 mmol/mol)‡
Pre-prandial capillary plasma glucose	80-130 mg/dL (4 4-7 2 mmol/L)*	
Peak postprandial capillary plasma glucose†	<180 mg/dL (<10.0 mmol/L)*	

*More or less stringent glycaemic goals may be appropriate for individual patients Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycaemia unawareness, and individual patient considerations

† Postprandial glucose may be targeted if HbA1c goals are not met despite reaching pre-prandial glucose goals. Postprandial glucose measurements should be made 1-2 h after the beginning of the meal – generally when levels peak in patients with diabetes

‡ Glucose targets should be individualized and take into account life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CVD risk factors, comorbid conditions, and risk for hypoglycaemia, as well as the patient's psychological status

Glucose Monitoring Recommendations

Patients who are receiving MDI or insulin pump therapy should perform SMBG prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycaemic, and prior to critical tasks such as driving.[154] For many patients, this will require testing 6 10 (or more) times daily,[154] causing both inconvenience and expense which would be averted by RT-CGM.

Guidelines and consensus statements from a range of international diabetes societies regarding the use of RT-CGM for monitoring glucose in patients with diabetes are described in detail in Section 10 1 and are summarised below RT CGM should be available to all insulin treated patients with diabetes.[157] In addition, patients with IAH, other patients at risk from hypoglycaemia, including the elderly, patients with renal impairment, and athletes would also benefit from RT CGM.[157]

HbA1c tests should be performed at least twice yearly for patients who meet treatment goals and have stable glycaemic control.[154] HbA1c tests should be performed quarterly for patients whose therapy has changed or who are not meeting glycaemic control goals.[154]

Intensive insulin therapy (MDI or insulin pump therapy) is the standard recommended pharmacologic treatment for patients with T1DM.[54] Most patients with T2DM can be successfully treated with lifestyle intervention and oral antidiabetic agents after initial diagnosis.[54] However, as noted above, many patients will eventually require insulin.[54]

3.3.2 Place in Therapy of Dexcom G6 RT-CGM System

The potential uses of the G6 System summarised below are consistent with the policies of large commercial health plans in the USA regarding coverage of RT-CGM.[158 160]

The G6 should be considered as replacement to conventional SMBG in people aged ≥2 years with diabetes, and is particularly appropriate in insulin treated people with diabetes who meet any of the following criteria:

- Suboptimal glycaemic control, as evidenced by HbA1c exceeding the target specified by consensus guidelines
  - The ADA has defined suboptimal glycaemic control in adults and children as HbA1c >7.0% (53 mmol/mol) and >7.5% (58 mmol/mol), respectively.[154]
- Wide fluctuations in blood glucose levels regardless of A1c
  - Research indicates that the combination of ambient hyperglycaemia, glucose variability, and hypoglycaemia (the “glycaemic triumvirate”) accelerates the development and progression of diabetes complications more so than the additive contribution of the individual glycaemic disorders.[161]
- Frequent hypoglycaemia
  - Hypoglycaemia includes all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm.[61]
  - All episodes of hypoglycaemia substantially increase the risk of subsequent hypoglycaemia [61]
- Severe hypoglycaemia
  - Severe hypoglycaemia is defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions [61]
- Impaired awareness of hypoglycaemia (IAH)
  - IAH is defined as the diminished ability to detect the early neurogenic warning symptoms of hypoglycaemia.[61] The presence of IAH increases the risk of severe hypoglycaemia by 3 10 times in patients with T1DM[110,101,103,115,104,116,107,83,94] and 2-17 times in patients with insulin-treated T2DM.[111,107,94,112]

3.3.3 Expected Uptake of Dexcom G6 System in New Zealand

The projected uptake of the G6 RT-CGM system in New Zealand consistent with the access criteria proposed in Section 2 1 is based on sales of the system in Australia, where it is reimbursed through the National Diabetes Services Scheme under the following eligibility criteria:

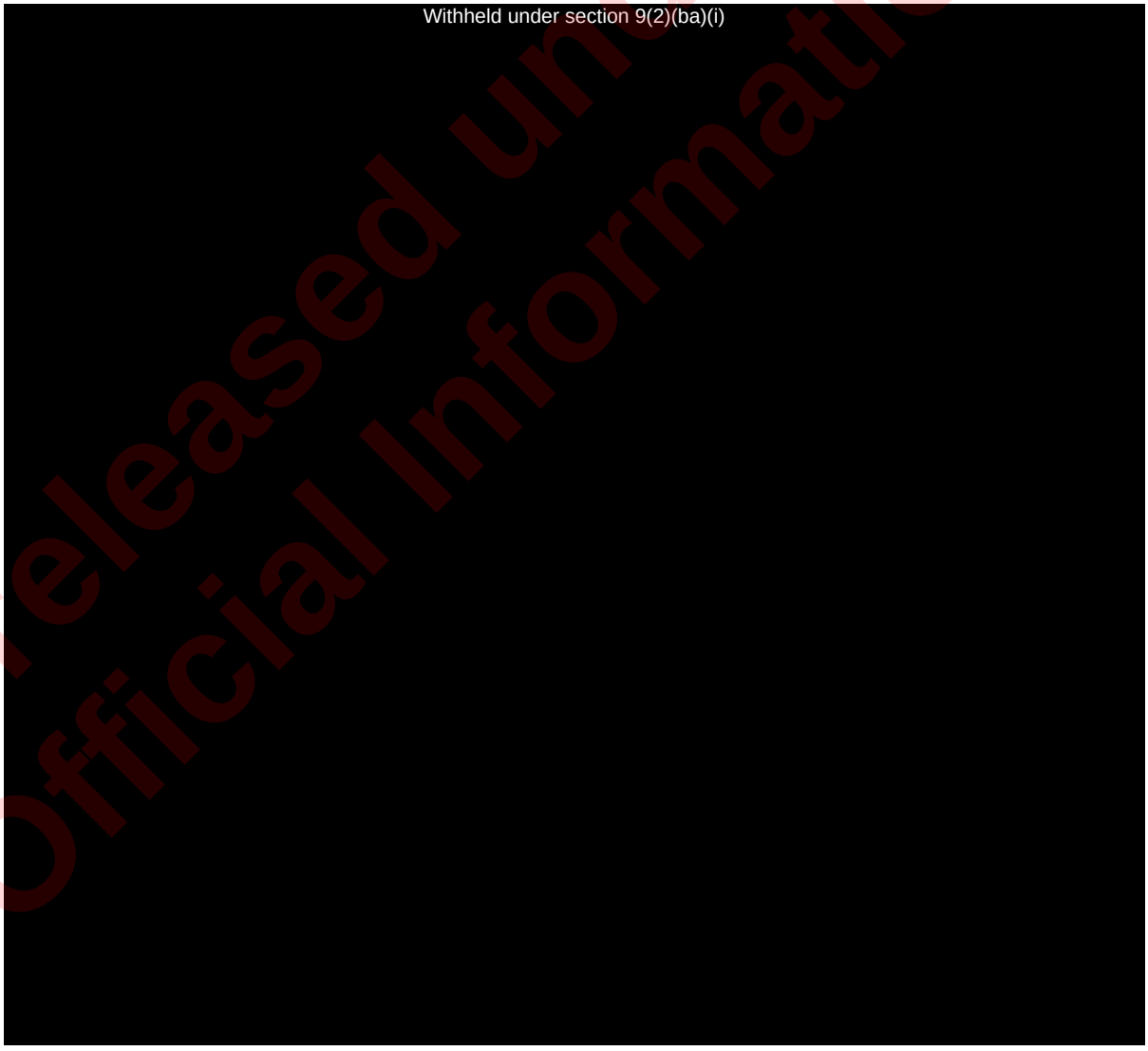
Children and young people with type 1 diabetes aged less than 21 years who:

- *Are expected to benefit clinically from the use of CGM;* ***and***
- *have the willingness and capability to use CGM;* ***and***
- *have the commitment to actively participate in a diabetes management plan which incorporates CGM*

And *fulfil one of more of the following criteria:*

- *frequent significant hypoglycaemia—more than one episode a year of significant hypoglycaemia requiring external, third party assistance;* ***and/or***
- *impaired awareness of hypoglycaemia;* ***and/or***
- *inability to recognise, or communicate about, symptoms of hypoglycaemia;* ***and/or***
- *significant fear of hypoglycaemia for the child/young person or a family member/ carer which is seriously affecting the health and wellbeing of the child or young person or contributing to hyperglycaemia as a reaction to this fear.*

PROJECTED SALES OF DEXCOM G6 SYSTEM ASSUMING REIMBURSEMENT 1 JANUARY 2019 UNDER DESCRIBED SCENARIOS



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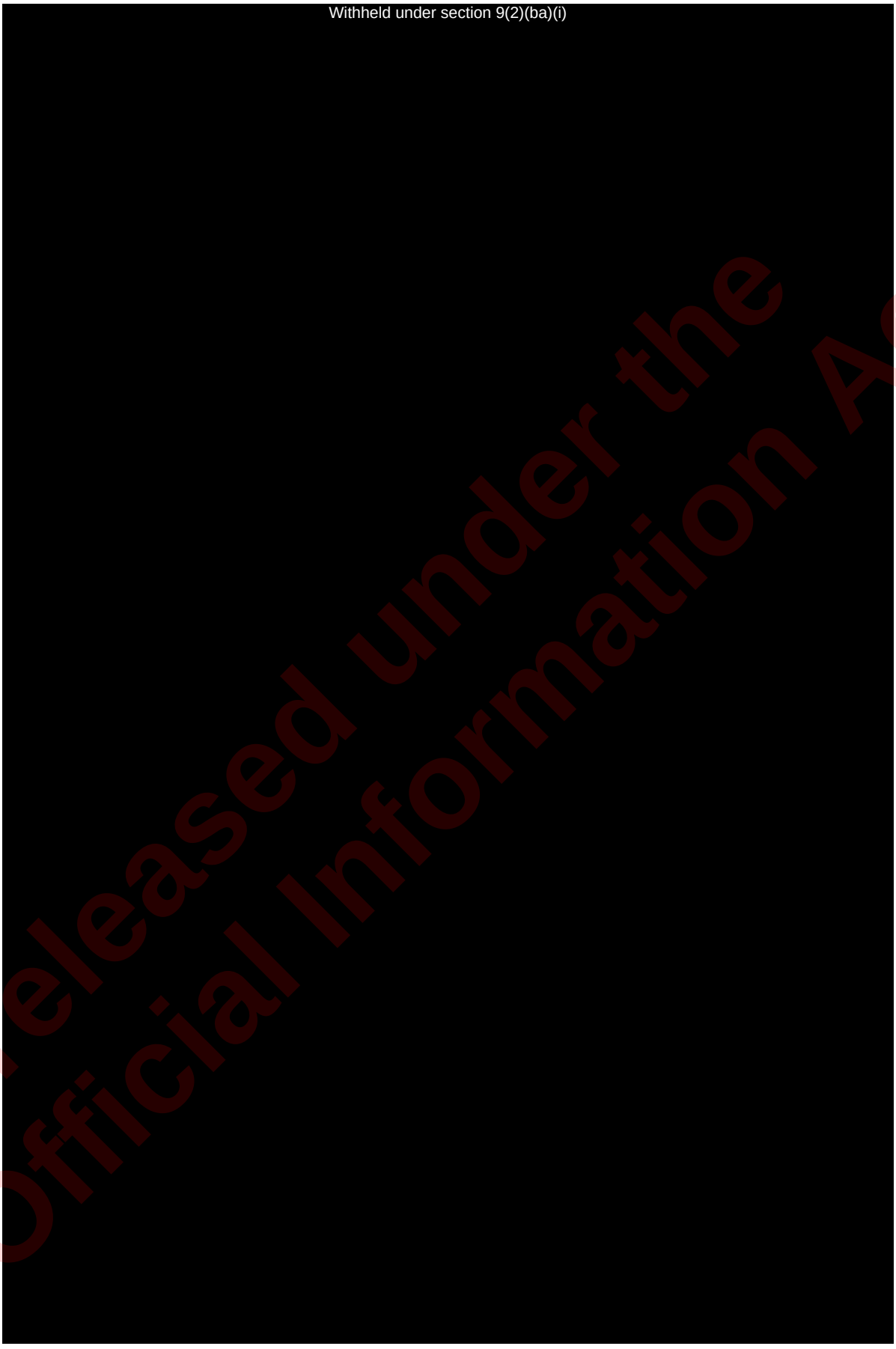


4. PRICE INFORMATION (PLACEHOLDER)

5. PATENT INFORMATION

Dexcom has no patents relating to the G6 System filed in New Zealand at the present time.

6.1 IMPACT ON THE WIDER HEALTH SECTOR (PLACEHOLDER)

SUPPORTING CLINICAL EVIDENCE

7.1 KEY CLINICAL STUDIES

7.1.1 Clinical Studies Supporting FDA Labelled Indications

Real Time Continuous Glucose Monitoring is indicated in children and adults with diabetes. The clinical studies summarized in this section evaluated either the Dexcom G5 or G4 (with or without 505 software) in children and adults with T1DM or insulin-treated T2DM.

- Subsection a) summarizes a pivotal trial demonstrating that use of the most accurate available RT CGM without regular use of confirmatory blood glucose measurements (BGM) is as safe and effective as using RT-CGM with BGM in well-controlled adults with T1DM receiving insulin pump therapy.
- Subsection b) summarizes RCT studies that compared MDI + RT-CGM versus MDI + SMBG.
- Subsection c) summarizes randomized and nonrandomized studies that compared MDI + RT-CGM versus insulin pump + RT CGM
- Subsection d) describes other supporting studies related to use of Dexcom RT CGM. Quality grades were derived from a 2012 AHRQ meta analysis[173] or based on criteria similar to those used in the AHRQ review.

a. RT-CGM Only Versus RT-CGM + Blood Glucose Measurements in Adults with T1DM

Aleppo G, Ruedy KJ, Riddlesworth TD, Kruger DF, Peters AL, Hirsch I, et al. REPLACE-BG: A randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in well-controlled adults with type 1 diabetes *Diabetes Care.* 2017; 40-538-45 [35]

Study Description: This was a 26-week randomized non-inferiority clinical trial to determine whether use of RT CGM without confirmatory blood glucose measurements (BGM) is as safe and effective as using RT-CGM adjunctive to BGM in well-controlled adults with T1DM. The study was conducted from March 2015 to October 2016 14 sites in the US T1D Exchange Clinic Network.

Funding Source: Dexcom, Inc

Methods: Major eligibility criteria included age ≥18 years, T1DM for ≥1 year with insulin pump treatment for at least 3 months (and not currently using a low glucose suspend function), and point-of-care HbA1c ≤9.0% (≤75 mmol/mol). Exclusion criteria included the occurrence of a severe hypoglycaemia event resulting in seizure or loss of consciousness in the past 3 years or an event without seizure/loss of consciousness requiring the assistance of another individual in the past 12 months; >10.0% of baseline CGM glucose concentrations <60 mg/dL (3 3 mmol/L); >1 episode of DKA in the past year; history of seizures other than due to hypoglycaemia; current use of a threshold suspend pump feature; myocardial infarction or stroke in the past 6 months; estimated glomerular filtration rate <30 mL/min/1.73 m^2; abnormal thyroid function; use of a systemic β-blocker; regular use of oral corticosteroids; initiation of a noninsulin drug for glucose control during the past 3 months; pregnant; inpatient psychiatric treatment in past 6 months; and presence of a contraindicated medical condition or medication including ongoing use of acetaminophen.

Patients were randomly assigned from a computer generated sequence to the RT CGM-only or RT-CGM + BGM group in a 2:1 ratio based on a permuted block design with stratification by clinical site Both groups used the G4 with 505 software, which measures glucose concentrations from interstitial fluid in the range of 40-400 mg/dL (2.2-22.2 mmol/L) every 5 min for up to 7 days. The study BGM was the Contour® Next (Ascensia Diabetes Care US, Inc , Parsippany, NJ) The Abbott Precision Xtra® (Abbott Diabetes Care, Alameda, CA) was used to measure blood ketone levels

The run-in phase, which was initiated by 276 participants, lasted for 2-10 weeks, depending on whether the participant was a RT CGM user at the time of study entry There were two parts of the run-in phase of which participants completed various portions, depending on whether they were using RT CGM at study entry: 1) Dexcom RT-CGM system configured to record glucose concentrations not visible to the participant (referred to as a blinded CGM) for 14 days to collect baseline data and 2) standard RT CGM for 2 8 weeks for RT CGM training In both phases, the participant's willingness and ability to use the study RT-CGM and BGM were assessed.

Successful completion of the 14-day blinded phase required study CGM wear on a minimum of 11 of 14 days and an average of three blood glucose measurements per day by the study BGM. Successful completion of the unblinded CGM phase required CGM use on ≥21 days during the past 28 days and an average of four or more BGM measurements on at least 90% of days; for participants whose run in phase was shortened, the number of days of CGM use were reduced accordingly. Of 276 participants who entered the run-in phase, 50 did not enter the randomized trial for the following reasons: 24 did not meet the BGM criterion, 6 had >10% of CGM readings of <60 mg/dL, and 20 were withdrawn for a variety of other reasons.

After randomization, participants in both groups were instructed to calibrate the study RT-CGM per Dexcom specifications and to use it daily. Both groups also were instructed to perform a BGM measurement when the fasting RT CGM glucose concentration was <300 mg/dL or when the RT-CGM glucose concentration during the day was >300 mg/dL for 1 h.

The RT CGM + BGM group was instructed to perform a BGM measurement with the study meter for RT-CGM calibrations whenever an insulin bolus was administered, when treating or attempting to prevent hypoglycaemia, and before going to bed

Clinical Outcomes: Analyses followed the intention-to-treat principle. The primary outcome was a treatment group comparison of time in range of 70 180 mg/dL (3.9-10.0 mmol/L) during the 26 week trial by using an ANCOVA model adjusted for baseline time in range and site as a random effect Secondary outcomes included CGM measures of mean glucose, glycaemic variability (coefficient of variation), and hypoglycaemia (time <70 mg/dL, 60 mg/dL, and 50 mg/dL; area above curve 70 mg/dL; and percentage of days with ≥20 consecutive min of glucose concentrations <60 mg/dL), hyperglycaemia (time >180 mg/dL, 250 mg/dL, 300 mg/dL; area under the curve 180 mg/dL; and percentage of days with ≥20 consecutive min of glucose concentrations >300 mg/dL), change in HbA1c, and proportion of participants with both no worsening of HbA1c by >0 3% (3 3 mmol/mol) and no severe hypoglycaemic event

Sample Characteristics: A total of 226 patients were randomly assigned to the RT-CGM group (n=179) or the RT-CGM + BGM group (n=77) The mean age of patients was 44 ± 14 years and mean duration of T1DM was 24 ± 12 years. The mean HbA1c was 7.0% ± 0.7%. Almost half (47%) of patients were RT-CGM users

One participant in the RT-CGM-only group was determined after randomization to have been ineligible (percentage of time <60 mg/dL during blinded baseline CGM wear was >10%) Seven participants in the RT-CGM-only group and two in the RT-CGM + BGM group withdrew from the trial Thus, the trial was completed by 142 (95%) of the RT-CGM only group participants and by 75 (97%) of the RT-CGM + BGM group participants.

Among participants completing the trial, all in both groups were using RT CGM in month 6 CGM use averaged 6.76 ± 0.5 and 6.86 ± 0.4 days/week in the RT-CGM-only and RT-CGM + BGM groups, respectively, over the 26-week trial, with 91% and 95% averaging ≥6 days/week All participants in the RT-CGM + BGM group and all but one in the RT-CGM-only group averaged ≥5 days/week over the entire 26 weeks Among patients who completed the trial, BGM tests per day from meter downloads (including the two-required daily BGM tests) averaged 2.86 ± 0.9 in the RT-CGM-only group and 5 4 ± 1 4 in the RT CGM + BGM group (p<0 001)

Outcome (Time in Normoglycaemic): Mean percentage time in normoglycaemic (70-180 mg/dL) was 63 ± 13% at both baseline and 26 weeks in the RT CGM group In the RT CGM + BGM group, mean percentage time in normoglycaemic was 65 ± 13% at baseline and 65% ± 11% at 26 weeks (adjusted difference = 0%; one side 95% CI 2 0%)

Outcome (Glucose Control): Other CGM metrics of glucose control for mean glucose, hyperglycaemia, hypoglycaemia, and glycaemic variability also showed little change from baseline to 26 weeks and no significant differences between groups (Table 15).

TABLE 15 STUDY OUTCOMES

CGM Outcome	RT-CGM Only Group		RT-CGM + BGM Group		p value
	Baseline (n=149)	26-week study period (n=148)	Baseline (n=77)	26-week study period (n=76)	
% time in range (70-180 mg/dL)	63 ±13	63 ±13	65 ±13	65 ±11	0 81
Mean glucose (mg/dL)	162 ± 22	162 ± 23	158 ± 22	158 ± 20	>0 99
Coefficient of variation (%)	36 (33-41)	37 (34-41)	37 (33-40)	37 (34-40)	0.58
Hypoglycaemia					
% time <70 mg/dL	2.9 (1.5-4.5)	3.0 (1.6-5.1)	3.6 (1.9-4.8)	3.7 (1.9-4.9)	0.95
% time <60 mg/dL	1.1 (0.6-0.9)	1.3 (0.5-2.4)	1.4 (0.6-2.3)	1.6 (0.6-2.2)	0.57
% time <50 mg/dL	0.3 (0.2-0.5)	0.3 (0.1-0.6)	0.4 (0.2-0.7)	0.5 (0.2-0.8)	0.75
Area above curve 70 mg/dL	0.3 (0.2-0.5)	0.3 (0.1-0.6)	0.4 (0.2-0.6)	0.4 (0.2-0.5)	0.76
% days with ≥20 consecutive min glucose values <60 mg/dL	25 (15 43)	28 (13 42)	33 (15-43)	32 (16-46)	0 68
Hyperglycaemia					
% time <>180 mg/dL	33 (25-43)	35 (25-41)	31 (22-40)	31 (24-38)	0.88
% time >250 mg/dL	8 (4-15)	9 (5-13)	7 (3-11)	7 (4-11)	0.65
% time >300 mg/dL	2 (1-5)	2 (1-4)	2 (1-4)	2 (1-3)	0.72
Area under curve 180 mg/dL	17 (10-25)	17 (10-23)	20 (10-37)	20 (8-36)	0.90
% days with ≥20 consecutive min glucose values >300 mg/dL	25 (12 48)	27 (14-40)	20 (8 36)	20 (10 37)	0 72
HbA1c (%)	7.1 ± 0.7	7.1 ± 0.7	7.0 ± 0.7	7.0 ± 0.6	
HbA1c (mmol/mol)	54 ± 7.7	54 ± 7.7	53 ± 7.7	53 ± 6.6	
Change in HbA1c from baseline (%)		0.0 ± 0.5		0.0 ± 0.5	0.41
Change in HbA1c from baseline mmol/mol)		0 0 ± 5 5		0 0 ± 5 5	0 41
No worsening of HbA1c by >0.3% (3.3 mmol/mol) and no severe hypoglycaemic event		115 (81)		54 (72)	0.15

Data are median (interquartile range), mean ±SD, or n (%) unless otherwise specified.

Outcome (Severe Hypoglycaemia): No severe hypoglycaemia events occurred in the RT-CGM only group and one occurred in the RT CGM + BGM group

Outcome (Adverse Events): There were no occurrences of DKA in either group. Other SAEs, unrelated to the study intervention, occurred in four (3%) of participants in the RT-CGM only group and three (4%) in the RT-CGM + BGM group. A blood ketone level ≥0.6 mmol/L (10.8 mg/dL) occurred at least once in 48 (32%) participants in the RT CGM only group and 26 (34%) in the RT-CGM + BGM group (p=0.79).

Study Limitations: The major limitation of the trial relates to the generalizability of the results based on the participant inclusion and exclusion criteria. The trial cohort included adults with T1DM who used an insulin pump and were well controlled and likely to adhere to the study protocol and excluded individuals with significant hypoglycaemia unawareness or a substantial amount of CGM measured hypoglycaemia Although the trial only included pump users to be able to document when an insulin bolus was given, it seems reasonable to apply the results to

individuals who use MDI who otherwise fit the profile of the study participants because the impact of sensor inaccuracy in determining the amount of a bolus should be similar in pump users and injection users.

Conclusion: In well controlled adults with T1DM at low risk for severe hypoglycaemia, RT CGM without regular use of confirmatory BGM is as safe and effective as using RT-CGM with confirmatory BGM for insulin dosing

Quality Grade: Good

b. RCTs Comparing MDI + RT-CGM Versus MDI + SMBG

Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycaemic control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. *JAMA.* 2017;317:371-8.[23]

Riddlesworth T, Price D, Cohen N, Beck RW. Hypoglycemic event frequency and the effect of continuous glucose monitoring in adults with type 1 diabetes using multiple daily insulin injections. Diabetes Ther 2017;8:947-51.[176]

Polonsky WH, Hessler D, Ruedy KJ, Beck RW. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: further findings from the DIAMOND clinical trial. *Diabetes Care* 2017;40:736-41.[166]

Study Description: This was a 24-week randomized, open-label, parallel-group multicentre clinical trial conducted from October 2014 and May 2016 at 24 endocrinology practices in the US The trial was conducted to evaluate the effect of RT-CGM in adults with T1DM who have elevated HbA1c levels and use MDI

Funding Source: Dexcom, Inc.

Methods: Major eligibility criteria included age 25 years or older, diagnosis of T1DM treated for at least 1year with MDI, central laboratory-measured HbA1c level of 7.5% to 10.0%, no home use of a personal CGM device in the 3 months before the trial, and a negative pregnancy test for women of childbearing potential.

Each participant was required to complete a 2 week prerandomisation phase using a CGM system that was configured to record glucose concentrations not visible to the participant (referred to as a "blinded" CGM). Eligibility required that the blinded CGM be worn on at least 85% of possible days, the CGM be calibrated at least 2 times per day, and blood glucose meter testing be performed at least 3 times daily Fourteen participants did not meet these criteria and did not continue into the randomized trial. One participant had a sudden death during the prerandomisation phase.

On the study website, after verification of eligibility from data entered, each participant was assigned randomly from a computer-generated sequence to either the RT CGM or control group in a 2:1 ratio, with a permuted block design (block sizes of 3 and 6) stratified by HbA1c level (<8.5% and ≥8 5%) A 2:1 randomization was used rather than 1:1 to provide a larger sample size for a separate follow-on randomized trial assessing glycaemic benefits of initiating pump therapy in RT-CGM users using insulin injections

Participants in the RT-CGM group were provided with the G4 with 505 software that measured glucose concentrations from interstitial fluid in the range of 40 to 400 mg/dL every 5 minutes for up to 7 days. Participants in both groups were provided with a Bayer Contour Next USB meter and test strips The RT CGM group was instructed to use RT-CGM daily, calibrate the RT CGM device twice daily, and verify the RT-CGM glucose concentration with the blood glucose meter before injecting insulin The control group was asked to perform home blood glucose monitoring

at least 4 times daily. Participants in both groups were provided general diabetes management education

Follow-up visits for both treatment groups occurred after 4, 12, and 24 weeks. The RT-CGM group had an additional visit 1 week after randomization The control group had 2 additional visits 1 week before the 12- and 24-week visits, at which a CGM sensor in blinded mode was inserted to collect glucose data for 1 week Telephone contacts for both groups occurred 2 and 3 weeks after randomization.

Clinical Outcomes: The primary outcome was change in the central laboratory-measured HbA1c level. Prespecified secondary outcomes included percentage of participants with HbA1c level less than 7 0%; CGM measured time in range (70 180 mg/dL), duration of hypoglycaemia (<70 mg/dL, <60 mg/dL, and <50 mg/dL), duration of hyperglycaemia (>180 mg/dL, >250 mg/dL, and >300 mg/dL), and glucose variability (coefficient of variation); change in IAH; and change in frequency of blood glucose meter testing.

Prespecified exploratory outcomes included CGM measured mean glucose concentration and the following binary HbA1c outcomes to assist in translation of the primary HbA1c analysis to a participant level: HbA1c level less than 7 5% and relative HbA1c reduction greater than or equal to 10%. Post hoc outcomes included HbA1c reduction of 1% or more, HbA1c level less than 7 0% or reduction of 1% or more, CGM measured area above the curve 70 mg/dL and area under the curve 180 mg/dL, change in insulin dose, and change in body weight.

The World Health Organization (Five) Well being Index (WHO-5) and the EQ 5D-5L were used to assess non-diabetes-specific quality of life. The Diabetes Distress Scale (DDS), the Hypoglycaemia Fear Survey (HFS III), and the Hypoglycaemia Confidence Scale (HCS) were used to assess diabetes-specific quality of life. Treatment satisfaction was measured in the RT-CGM group at 24 weeks suing the CGM Satisfaction Survey (44 items on a 1 5 Likert scale, with the computed score representing the mean of the 44 items and subscales of benefits and lack of hassles)

A hypoglycaemic event was defined as a series of at least two sensor glucose values less than 54 mg/dL, lasting at least 20 min, with no intervening values of 54 mg/dL or more The end of a hypoglycaemic event was defined as a minimum of 15 consecutive minutes with at least two sensor glucose values of at least 54 mg/dL and at least 10 mg/dL above the nadir of the event A new event was temporally separated from any previous event by 15 min or more, with no intervening values less than 54 mg/dL.

Analyses followed the intent-to-treat (ITT) principle. The primary analysis was a treatment group comparison of the change in HbA1c level from baseline to 24 weeks, adjusted for baseline HbA1c level and clinical site as a random effect.

Sample Characteristics: A total of 158 participants were assigned to the RT CGM group (n=105) or control group (n=53). Mean (SD) age was 48 (13) years (range, 26-73 years, with 34 participants [22%] ≥60 years); 44% were women Median diabetes duration was 19 years (IQR, 10-31 years), and mean baseline HbA1c level was 8.6% (SD, 0.6%; range, 7.5%-9.9%).

The 24-week primary study outcome visit was completed by 102 participants (97%) in the RT CGM group and all 53 (100%) in the control group. Overall visit completion was 99% and 98%, respectively. Three participants in the RT CGM group (4 total visits) and 3 in the control group (3 total visits) had additional visits, not required in the protocol, for diabetes management.

Outcome (HbA1c): Mean reduction in HbA1c level from baseline was 1 1% at 12 weeks and 1.0% at 24 weeks in the RT-CGM group and 0.5% and 0.4%, respectively, in the control group (primary analysis repeated measures p<0 001) At 24 weeks, the adjusted treatment group difference in mean change in HbA1c level was -0.6% (95% CI, -0.8% to -0.3%; p<0.001; Figure 8) There was no significant interaction of the effect of treatment on 24-week HbA1c level according to baseline HbA1c, age (Figure 9), education level, or type of site.

FIGURE 8. MEAN HBA1C TREATMENT GROUP DIFFERENCES

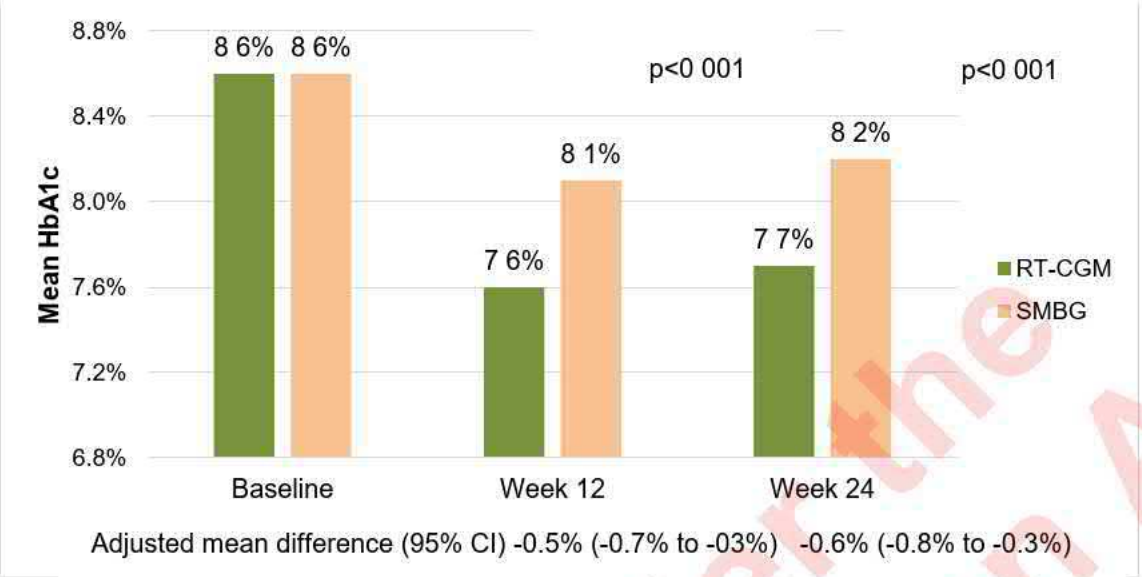


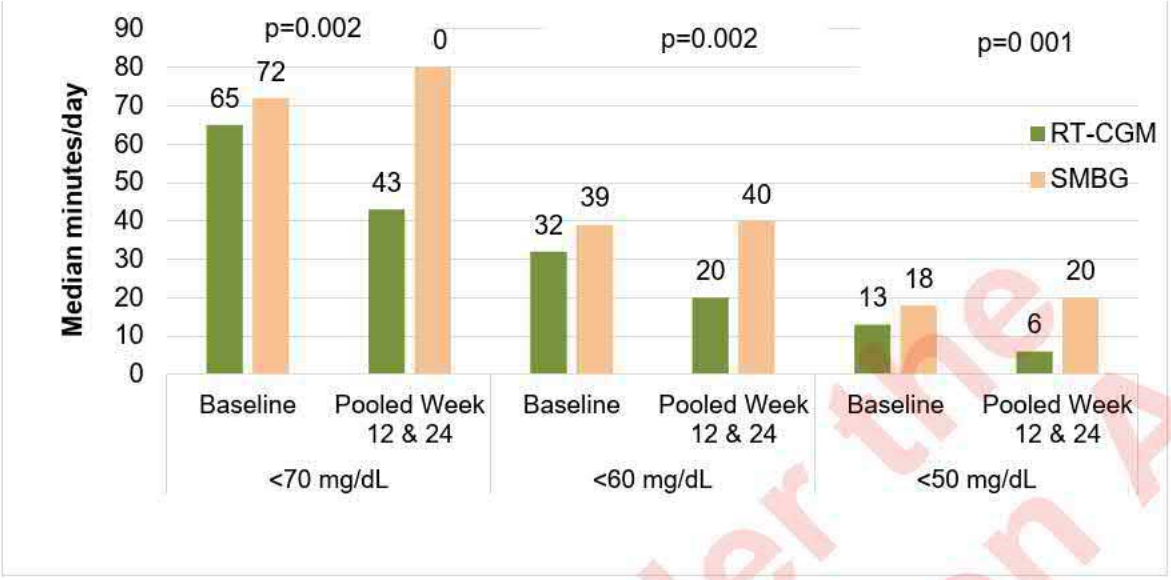
FIGURE 9 MEAN HBA1C CHANGE BY AGE

Outcome (Sensor Use): Among the 102 participants in the RT-CGM group who completed the trial, median RT-CGM use was 7 0 days/week (IQR, 7 0 7 0) at 4, 12, and 24 weeks; only 2 (2%) discontinued RT-CGM before the 24-week visit. During month 6 (weeks 21-24), RT-CGM use was 6 or more days/week for 93% of the 102 participants

Outcome (SMBG Frequency): Mean (SD) frequency of SMBG was 5.1 (1.8) per day in the RT-CGM group and 5 1 (1 4) per day in the control group during the baseline period of blinded CGM wear and 3.6 (1.6) per day and 4.6 (1.6) per day, respectively, at 24 weeks (adjusted mean difference for the change, 1 0; 99% CI, 1 7 to 0 4; p<0 001)

Outcome (Time in Normoglycaemic, Hyperglycaemia, and Hypoglycaemia): CGM metrics for time in the range of 70 to 180 mg/dL, hyperglycaemia, hypoglycaemia (Figure 10), and glycaemic variability favoured the RT-CGM group compared with the control group. In exploratory analyses, hypoglycaemia treatment group differences favoured the RT CGM group during both daytime and night-time, but hyperglycaemia treatment group differences favouring the RT-CGM group were present only during the daytime

FIGURE 10. TIME SPENT IN HYPOGLYCAEMIA



Outcome (Insulin Use): At 24 weeks, in post hoc analyses there were no significant differences between the RT-CGM group and control group in median change in total daily insulin dose per kilogram of body weight (-0 02 vs 0 03 U/kg; p=0.23), median ratio of long-acting to rapid acting daily insulin dose (0.9 vs 1.0; p=0.54), or proportion of participants with an increase in number of injections of rapid acting insulin per day (26% vs 26%; p=0 90).

Outcome (Body Weight): At 24 weeks, there were no significant differences between the RT-CGM group and control group in mean change in body weight (1 7 vs 0 7 kg; mean difference, 1.0 kg; 99% CI, -0.7 to 2.8; p=0.12).

Outcome (Hypoglycaemia Unawareness): Clarke Hypoglycaemia Unawareness scores did not differ between groups at 24 weeks (mean difference, -0.1; 99% CI, -0.7 to 0.5; p=0.64).

Outcome (Quality of Life): RT CGM participants reported significantly greater increases in hypoglycaemic confidence than SMBG participants. Modest decreases in diabetes-related distress in the RT CGM group and increases in the control group resulted in a mean ± SE cumulative difference for total distress of 0.23 ± 0.07 between groups (p=0.02). Between-group differences for diabetes related distress and hypoglycaemia confidence persisted in models that further adjusted for participant demographic factors.

No significant group differences were observed in hypoglycaemic worry or in the non diabetes specific quality of life measures.

Outcome (Satisfaction with RT-CGM): In the RT CGM group, satisfaction with use of RT CGM was high, as indicated by the mean (SD) score of 4.2 (0.4) on the CGM Satisfaction Survey, with mean (SD) scores of 4 2 (0 5) on the perceived benefits subscale and 4 3 (0 5) on the subscale for lack of hassles. Overall RT-CGM satisfaction was moderately related to decreases in total diabetes related distress (B = -0 31, p<0 001) and hypoglycaemic worry (B = 4 22, p=0 03) and increases in hypoglycaemic confidence (B = 0.49, p<0.001) and overall well-being (WHO-5: B = 7 61, p=0 02)

Outcome (Hypoglycaemic Event Rate): In the RT-CGM group, the median hypoglycaemic event rate fell by 30% from 0 23 per 24h at baseline to 0 16 per 24 h during follow-up, whereas in the control group, the rate was nearly unchanged (0.31 per 24h at baseline and 0.30 per 24h at follow-up; p=0 03)

Outcome (Severe Hypoglycaemia): Severe hypoglycaemic events occurred in 2 participants in each group (p=0 67)

Outcome (Adverse Events): There were no occurrences of DKA. Other serious AEs, unrelated to the study intervention, occurred in 2 participants in the RT CGM group and none in the control group.

Study Limitations: The study included only adults with T1DM who use MDI and may not generalize to other patient groups of interest, such as teens and insulin pump users with T1DM or individuals with T2DM Study participants were racially homogenous, with the majority being non-Hispanic white with a high education level. The study was limited to a 24-week period, so it is not known whether the observed benefits would be maintained over longer periods Although the noted effect sizes were small/moderate to moderate, improvement within the RT-CGM group itself was modest, and the potential clinical significant in unknown

Conclusion: Among adults with T1DM who use MDI, the use of RT-CGM compared with usual care resulted in a greater decrease in HbA1c level over 24 weeks, improved glycaemic control, a statistically significant reduction in the frequency of hypoglycaemic events, and statistically significant improvements in diabetes specific quality of life Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects.

Quality Grade: Good

Beck RW, Riddlesworth TD, Ruedy K, et al. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. *Ann Intern Med*. 2017;167:365-74.[23]

Study Description: This was a 24 week randomized, open-label, parallel group multicentre clinical trial conducted from October 2014 and May 2016 at 25 endocrinology practices in the US. The trial was conducted to evaluate the effect of RT-CGM in adults with insulin treated T2DM who have elevated HbA1c levels and use MDI and was run in parallel with the DIAMOND RCT in patients with T1DM

Funding Source: Dexcom, Inc.

Methods: Major eligibility criteria included age 25 years or older, diagnosis of T2DM treated for at least 1year with MDI, central laboratory-measured HbA1c level of 7.5% to 10.0%, stable diabetes medication regimen and weight over past 3 months, self reported SMBG average of ≥2 times per day, and glomerular filtration rate ≥45 mL/min/1.73 m^2.

Each participant was required to complete a 2-week pre-randomization phase using a CGM system that was configured to record glucose concentrations not visible to the participant (referred to as a "blinded" CGM) Eligibility required that the participant wear the blinded CGM on at least 85% of possible days, calibrate it at least 2 times per day, and perform blood glucose meter testing at least 2 times daily Ten participants did not meet these criteria and did not continue into the randomized trial.

On the study website, after verification of eligibility from data entered, each participant was assigned randomly by a computer-generated sequence to either the RT CGM or control group in a 1:1 ratio using a permuted block design (random block sizes of 2 and 4) stratified by HbA1c level (<8.5% and ≥8.5%).

Participants in both groups were provided with a Contour Next USB meter (Ascensia Diabetes Care) and test strips. Participants in the RT-CGM group were provided with the G4 with 505 software which measures glucose concentrations from interstitial fluid in the range of 40 to 400 mg/dL every 5 minutes. Participants used RT CGM as an adjunct to SMBG, according to FDA labelling at the time of the study The control group was asked to monitor their blood glucose at least 4 times daily.

Follow-up visits for both treatment groups occurred after 4, 12, and 24 weeks. The control group had 2 additional visits 1 week before the 12 and 24-week visits, to initiate blinded CGM use for 1 week. Both groups were contacted by telephone 2 and 3 weeks after randomization.

Clinical Outcomes: Change in HbA1c level from baseline to 24 weeks was the primary outcome. Prespecified secondary outcomes included the proportions of participants with HbA1c levels below 7 0%, HbA1c levels below 7 5%, relative reduction of at least 10%, reduction of at least 1%, reduction of at least 1% or HbA1c level below 7.0%, and CGM metrics. Additional outcomes included scores on the Clarke Hypoglycaemia Unawareness Survey, 2 general quality-of-life measures (5-level EuroQol-5D and 5-item World Health Organization Well-Being Index), and 3 diabetes specific quality of life measures (Hypoglycaemia Fear Survey, Diabetes Distress Scale, and Hypoglycaemic Confidence Scale). The RT-CGM group's satisfaction was assessed using the CGM Satisfaction Scale at 24 weeks

Power calculations indicated that a sample size of 132 was necessary to provide at least 90% power to detect a difference in mean HbA1c level between treatment groups, assuming a population difference of 0.4%, effective SD of 0.7 for the 24-week values after adjustment for the correlation between baseline and 24 week values, and a 2 sided α level of 0 05 Sample size was set at 150 to account for potential loss to follow-up.

Analyses followed the ITT principle The primary analysis was a treatment group comparison of the change in HbA1c from baseline to 24 weeks in a mixed-effects linear model with baseline HbA1c level as a fixed effect and clinical site as a random effect The analysis was repeated post hoc with clinical site as a fixed effect. Confounding was assessed by including baseline variables imbalanced between treatment groups as covariates Multiple imputation was used to replace missing 24-week HbA1c data when both central laboratory and local values were missing. If the central laboratory measurement was missing but the local measurement was known, the value used in the analyses was imputed using a regression line based on the site's local HbA1c measurements An analysis using a repeated measures mixed-effects linear model also was conducted. To assess for interaction between baseline factors and treatment effects on the change in HbA1c level from baseline to 24 weeks, interaction terms were included in the mixed effects models. Binary HbA1c outcomes were evaluated in mixed-effects logistic regression models with baseline HbA1c level as a fixed effect and clinical site as a random effect using an adaptive quadrature estimation routine. Adjusted differences for the binary outcomes were calculated using Kleinman and Norton's method and CIs using bootstrapping Frequency of SMBG according to meter download data was compared between groups using the Wilcoxon rank-sum test All p values were 2 sided.

Sample Characteristics: A total of 158 participants were assigned to the RT-CGM group (n=79) or control group (n=79) and the 24-week primary study outcome visit was completed by 77 participants (97%) in the RT-CGM group and 75 (95%) in the control group. Mean (SD) age was 60 (10) years (range, 35-79 years), with 52% of participants ≥60 years; 56% were female Medan diabetes duration was 17 years (interquartile range, 11 to 23 years), and mean baseline HbA1c level was 8 5% ± 0.6% (range, 7 5% to 9 9%)

Outcome (HbA1c): Mean HbA1c at baseline (8.5 ± 0.6% in the RT-CGM group and 8.5 ± 0.7% in the Control group) decreased to 7 5 ± 0 7% and 7 9 ± 0 8%, respectively, at 12 weeks with an adjusted difference in mean change of -0.3% (95% CI, -0.6% to -0.1%; p=0.005). In both groups, mean HbA1c levels increased slightly between 12 and 24 weeks (mean HbA1c level at 24 weeks, 7.7% ± 0.7% in the RT-CGM group vs. 8.0% ± 0.9% in the control group). The adjusted difference in mean change in HbA1c from baseline was 0 3% (CI, 0 5% to 0 0%; p=0 022)

Secondary HbA1c outcomes tended to favour the RT-CGM group, although none of the prespecified secondary outcomes reached statistical significance

Outcome (CGM Metrics). Median CGM-measured time in the range of 70 to 180 mg/dL increased more in the RT CGM group than in the control group (from 802 minutes per day at baseline to 882 minutes per day at 24 weeks in the RT-CGM group and from 794 to 836 minutes per day in the control group), reflecting a greater reduction in time above 180 mg/dL in the RT CGM group than in the control group (Table 16). The groups did not differ meaningfully in

changes in CGM-measured mean glucose concentrations or glycaemic variability (coefficient of variation) The amount of CGM measured hypoglycaemia was extremely low at baseline (median time below 70 mg/dL, 11 minutes per day in the RT-CGM group and 12 minutes per day in the control group), which limited our ability to assess the effect of RT CGM on reducing hypoglycaemia in this cohort.

Table 16 CGM Metrics at Baseline, 12 Weeks, and 24 Weeks in the RT-CGM and Usual Care Groups*

	RT-CGM			Control		
	Baseline (n=79	12 Weeks (n=77)†	24 Weeks (n=74)†	Baseline (n=78)†	12 Weeks (n=74)†	24 Weeks (n=72)†
Data collected, h	311 (294 319)	161 (152 165)	159 (153 163)	312 (293 318)	150 (140-154)	149 (137-156)
Mean glucose concentration, mg/dL	155 (154-191)	166 (149-187)	171 (149-195)	175 (155-191)	172 (155-199)	171 (156-199)
Time spent 70-180 mg/dL, min/day	802 (604-974)	937 (664-1083)	882 (647-1077)	794 (665-976)	822 (537-1025)	836 (551-965)
Hyperglycaemia						
Time spent >180 mg/dL, min/day	612 (411-809)	501 (323-746)	549 (353-789)	607 (392-775)	560 (382-818)	571 (422-883)
Time spent >250 mg/dL, min/day	150 (68-265)	100 (37-180)	105 (37-246)	154 (66-281)	137 (53-251)	118 (48-288)
Time spent >300 mg/dL, min/day	33 (9 77)	19 (0-56)	23 (0 66)	42 (9-96)	33 (1-95)	18 (0 83)
Area under curve 180 mg/dL	22 (13-32)	14 (7-26)	16 (8-30)	21 (11-33)	18 (11-34)	18 (12-24)
Hypoglycaemia						
Time spent <70 mg/dL, min/day	11 (1-33)	9 (1-25)	4 (0-17)	12 (3-39)	11 (0-37)	12 (0-34)
Time spent <60 mg/dL, min/day	3 (0-15)	1 (0-7)	0 (0-6)	4 (0-17)	1 (0-12)	2 (0-12)
Time spent <50 mg/dL, min/day	0 (0-8)	0 (0-0)	0 (0 1)	0 (0 7)	0 (0-3)	0 (0 5)
Area above curve of 70 mg/dL	0.1 (0.0-0.3)	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.0 (0.0-0.3)	0.0 (0.0-0.3)	0.0 (0.0-0.2)
Glucose variability, coefficient of variation %	31 (27-38)	30 (26-34)	30 (26-33)	32 (27-37)	30 (25-37)	29 (25-36)

CGM = continuous glucose monitoring; RT-CGM = real-time continuous glucose monitoring.

*Values are medians (interquartile ranges). To convert glucose values from mg/dL to mmol/L, multiple the values by 0 0555

† CGM metrics were not calculated for participants with <72 h of data: 1 control participant at baseline, 1 RT-CGM and 3 control participants at 12 weeks, and 3 RT-CGM and 3 control participants at 24 weeks.

Outcome (Sensor Use): Among the 77 RT CGM participants who completed the trial, mean RT CGM use was 6.9 ± 0.4 days per week in month 1, 6.7 ± 1.0 days per week in month 3, and 6.7 ± 1.0 days per week in month 6

Outcome (SMBG Frequency): Based on meter downloads, frequencies of SMBG averaged 4.1 ± 1 1 per day in the RT CGM group and 4 0 ± 1 2 per day in the control group during the baseline period of blinded CGM use. At 24 weeks, frequencies averaged 2.9 ± 1.1 per day in the RT-CGM group and 3 8 ± 1 5 per day in the control group (p<0 001)

Outcome (Insulin Use): At 24 weeks, change from baseline in total daily insulin dose per kilogram of body weight was 0 1 units (SD, 0 3) in the RT CGM group and 0 0 units (SD, 0 3) in the control group. The groups did not differ meaningfully in the ratio of basal–bolus daily insulin dose or number of injections per day of rapid acting insulin New noninsulin diabetes medications were added during follow-up for 2 participants (3%) in the RT-CGM group and 2 (3%) in the control group

Outcome (Body Weight): Mean weight change from baseline to 24 weeks was 1.3 kg (SD, 3.6) in the RT CGM group and 0 2 kg (SD, 4 5) in the control group

Outcome (IAH): The group did not differ meaningfully in Clarke Hypoglycaemia Unawareness scores at 24 weeks

Outcome (Quality of Life): The treatment groups did not differ meaningfully in any of the 5 quality of-life measures

Outcome (RT-CGM Satisfaction): The RT-CGM group had high satisfaction with use of RT-CGM, as indicated by the mean score of 4 3 (SD, 0 4) on the CGM Satisfaction Scale (score range, 1 to 5). Mean scores were 4.4 (SD, 0.5) on the benefits subscale and 1.8 (SD, 0.5) on the hassles subscale, indicating that perceived benefits were high and perceived hassles low On almost all items, most participants responded with scores indicating high satisfaction.

Outcome (Severe Hypoglycaemia): Severe hypoglycaemia did not occur in either group

Outcome (Adverse Events): DKA did not occur in either group. In the RT-CGM group, 1 participant died of a myocardial infarction and 2 others were hospitalized for chest pain and fully recovered, all considered to be unrelated to RT-CGM use. No serious adverse events occurred in the control group

Study Limitations: The trial duration was limited to 6 months.

Conclusion: This randomized trial demonstrates that RT-CGM can be beneficial for adults withT2DM treated with basal–bolus insulin therapy, as has been shown in prior studies for adults with T1DM A high percentage of the study participants used RT CGM on a daily or near-daily basis over 6 months with a limited number of visits and phone contacts, none after 3 months prior to the 24 week primary outcome visit Use of RT CGM was associated with a high degree of patient satisfaction, reduced hyperglycaemia and consequently HbA1c levels, and increased time in the target glucose range. Because few insulin-treated patients with T2DM are currently prescribed RT-CGM, the study results indicate an additional management method that may be beneficial for these patients

Quality Grade: Good

Ruedy, K Riddlesworth, TD, Graham C Continuous glucose monitoring in older adults with type 1 and type 2 diabetes using multiple daily injections of insulin: results from the DIAMOND trial *J Diabetes Sci Technol* 2017;11:1138 46 [177]

Study Description: This was a 24 week randomized, open label, parallel group multicentre clinical trial conducted from October 2014 to May 2016 at 27 endocrinology practices in the US and Canada This analysis was conducted to evaluate the effectiveness of RT CGM in adults aged ≥60 years with T1DM or T2DM using MDI.

Funding Source: Dexcom, Inc.

Methods: Major eligibility criteria included age ≥60 years, diagnosis of T1DM or T2DM treated for at least 1year with MDI, central laboratory-measured HbA1c level of 7.5% to 10.0%, stable diabetes medication regimen and weight over the prior 3 months, and an estimated glomerular filtration rate ≥45 Major exclusion criteria were use of real-time CGM within 3 months of screening and any medical condition(s) that would make it inappropriate or unsafe to target an HbA1c of <7.0%.

Each participant was required to complete a 2-week prerandomisation phase using a CGM system that was configured to record glucose concentrations not visible to the participant (referred to as a "blinded" CGM). Eligibility required that the blinded CGM be worn on at least 85% of possible days, the CGM be calibrated at least 2 times per day, and blood glucose meter testing be performed at least 3 times daily (T1DM) or 2 times daily (T2DM). Fourteen participants did not meet these criteria and did not continue into the randomized trial. One participant had a sudden death during the prerandomisation phase.

On the study website, after verification of eligibility from data entered, each participant was assigned randomly from a computer-generated sequence to either the RT-CGM or control group in a 2:1 ratio, with a permuted block design (block sizes of 3 and 6) stratified by HbA1c level (<8.5% and ≥8.5%). A 2:1 randomization was used rather than 1:1 to provide a larger sample size for a separate follow-on randomized trial assessing glycaemic benefits of initiating pump therapy in RT-CGM users using insulin injections.

Participants in the RT-CGM group were provided with a RT CGM system (G4 with 505 software) that measured glucose concentrations from interstitial fluid in the range of 40 to 400 mg/dL every 5 minutes for up to 7 days Participants in both groups were provided with a Bayer Contour Next USB meter and test strips. The RT-CGM group was instructed to use RT-CGM daily, calibrate the RT CGM device twice daily, and verify the RT CGM glucose concentration with the blood glucose meter before injecting insulin. General guidelines were provided to participants about using RT-CGM, and individualized recommendations were made by their clinician about incorporating RT CGM trend information into their diabetes management. The control group was asked to perform home blood glucose monitoring at least 4 times daily Participants in both groups were provided general diabetes management education, and clinicians were encouraged to review downloaded glucose data at each visit to inform treatment recommendations, which were at clinician discretion and not prescriptive in the protocol.

Follow up visits for both treatment groups occurred after 4, 12, and 24 weeks The RT CGM group had an additional visit 1 week after randomization. The control group had 2 additional visits 1 week before the 12 and 24-week visits, at which a CGM sensor in blinded mode was inserted to collect glucose data for 1 week. Telephone contacts for both groups occurred 2 and 3 weeks after randomization.

Clinical Outcomes: The primary outcome was change in the central laboratory-measured HbA1c level from baseline to Week 24 Prespecified secondary outcomes included percentage of participants with HbA1c level less than 7.0%; CGM-measured time in range (70-180 mg/dL), duration of hypoglycaemia (<70 mg/dL, <60 mg/dL, and <50 mg/dL), duration of hyperglycaemia (>180 mg/dL, >250 mg/dL, and >300 mg/dL), and glucose variability (coefficient of variation); change in IAH; and change in frequency of blood glucose meter testing

Sample Characteristics: A total of 116 patients were enrolled (T1DM, n=34; T2DM, n=82). Participants with mean age of 67 ± 5 years were randomly assigned to the RT-CGM group (n=63) or Control group (n=53). Median (IQR) of diabetes duration was 21 (14, 30) years and mean baseline HbA1c was 8 5 ± 0 6% The groups were well balanced with respect to education level and diabetes durations. The 24-week primary study outcome visit was completed by 97% (n=61) of the RT CGM group and 100% (n=53) of the Control group

Outcome (HbA1c): Mean HbA1c at baseline (8.4 ± 0.6% in the RT-CGM group and 8.6 ± 0.7% in the Control group) decreased to 7 5 ± 0 7% and 8 0 ± 0 8%, respectively, at 12 weeks with an adjusted difference in mean change of -0.3% (p=0.005). At 24 weeks, HbA1c reduction from baseline was greater in the RT CGM group than Control group (0 9 ± 0 7% vs 0 5 ± 0 7%) with an adjusted difference in mean change of -0.4 ± 0.1% (p<0.001).

Outcome (CGM Metrics): CGM metrics are shown in Table 17 Significant between group differences in improvements in CGM-measured mean glucose, glycaemic variation and in the average time within glucose range (70 180 mg/dL) and in hyperglycaemia (>250 mg/dL) at 24 weeks were observed; however, there was minimal hypoglycaemia at baseline in both the RT-CGM and Control groups (median time <60 mg/dL was 10 vs. 8 minutes/day, respectively), which affected the ability to detect a difference in hypoglycaemia.

Outcome (SMBG Frequency): Among the 61 RT-CGM participants completing the trial, mean RT-CGM use was 6.9 ± 0.2 days/week in month one (weeks 1-4); and 6.8 ± 1.1 days/week in month 6 (weeks 21 24); 97% used RT CGM ≥6 days/week in month 6. The mean reduction in the number of daily blood glucose tests from baseline to week 24 was significantly greater for the RT CGM group compared with the Control group (1 2 ± 1 6 vs 0.2 ± 1 4, p=0 001)

Outcome (RT-CGM Satisfaction): In the RT-CGM group, satisfaction with use of RT-CGM was high as indicated by the mean score of 4 2 ± 0 4 on the CGM Satisfaction Survey (possible score range 1 to 5), with mean scores of 4.3 ± 0.5 on the 'Benefits' subscale and 1.8 ± 0.5 on the 'Hassles' subscale, indicating that perceived benefits were high while perceived hassles were few.

Outcome (Severe Hypoglycaemia): There were no severe hypoglycaemia events in either group.

Outcome (Adverse Events): There were no DKA events in either group

Study Limitations: The study did not address the question of whether RT-CGM would reduce severe hypoglycaemia events in vulnerable populations (e g , patients with hypoglycaemia unawareness).

Conclusion: This randomized trial demonstrates that RT CGM can be beneficial for elderly adults with T1DM and T2DM treated with basal-bolus insulin therapy, as has been shown in prior studies in younger adults with diabetes A high percentage of the study participants used RT CGM on a daily or near-daily basis over 6 months with a limited number of visits and phone contacts RT-CGM use was associated with a high degree of patient satisfaction, reduction in HbA1c, hyperglycaemia and glycaemic variability and an increase in time in glucose range. Given these significant benefits, RT CGM should be considered for older adults with diabetes using MDI.

Quality Grade: Good

TABLE 17. CGM METRICS

	RT-CGM			Control			p value†
	Baseline (n=63)	12 Weeks (n=61)*	24 Weeks (n=58)*	Baseline (n=53)	12 Weeks (n=52)*	24 Weeks (n=50)*	
Mean ± SD glucose, mg/dL	175 ± 25	167 ± 27	168 ± 29	179 ± 30	178 ± 28	180 ± 28	0.01
Glycaemic variability, coefficient of variation, %	34 (28, 42)	33 (28, 37)	31 (28, 36)	34 (29, 38)	33 (28, 38)	33 (27, 39)	0.02
Time spent 70-180 mg/dL, min/day	796 ± 236	892 ± 256	88 9± 251	753 ± 253	767 ± 265	732 ±2 52	<0.001
Time spent >250 mg/dL, min/day	172 (83, 281)	93 (30, 180)	89 (37, 208)	208 (112, 294)	180 (81, 251)	179 (83, 316)	0 006
Time spent <60 mg/dL, min/day	10 (1, 38)	4 (0, 15)	3 (0, 15)	8 (1, 23)	4 (0, 27)	4 (0, 24)	0 11

Median (IQR) is reported for glycaemic variability and for time in the hypoglycaemic and hyperglycaemic ranges. Mean ± SD is reported for mean glucose and time in normoglycaemic

*CGM metrics were not calculated for participants with < 72 h of data: 1 RT-CGM /1 Control at 12 Weeks; 3 RT-CGM/3 Control at 24 Weeks.

† p values are from analysis of covariance models adjusted for the corresponding baseline value, baseline HbA1c and clinical site as a random effect using pooled data from 12 and 24 weeks. Due to skewed distributions, the models for glycaemic variability and time in the hypoglycaemic and hyperglycaemic ranges were based on ranks using van der Waerden scores

Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, et al. Continuous glucose monitoring vs conventional therapy for glycaemic control in adults with type 1 diabetes treated with multiple daily insulin injections: The GOLD randomized clinical trial *JAMA* 2017;317:379-87 [25]

Olafsdottir AF, Polonsky W, Bolinder J, Hirsch IB, Dahlqvist S, Wedel H, et al. A randomized clinical trial of the effect of continuous glucose monitoring on nocturnal hypoglycaemia, daytime hypoglycaemia, glycaemic variability, and hypoglycaemia confidence in persons with type 1 diabetes treated with multiple daily insulin injections (GOLD-3). *Diabetes Technol Ther* 2018; 20:1-11 [27]

Study Description: This was a randomized, open-label, multicentre clinical trial with a crossover design conducted from February 2014 and June 2016 at 15 sites in Sweden After a run in period of up to 6 weeks, patients were randomized to receive RT-CGM or conventional SMBG for 26 weeks with a 17-week washout between treatment periods The aim of this study was to analyse the effect of RT-CGM on glycaemic control, hypoglycaemia, well-being, and glycaemic variability in individuals with T1DM treated with MDI

Funding Source: The NU Hospital Group, Trollhättan and Uddevalla, Sweden

Methods: Individuals aged ≥18 years with HbA1c of at least 7 5% (58 mmol/mol) treated with MDI were included. Patients were required to have a fasting C-peptide level of less than 0.91 ng/mL (0 30 nmol/L) and diabetes duration of >1 year Patients treated with insulin pumps were excluded.

During a 6-week run in, patients completed masked CGM for 2 weeks and questionnaires regarding the following characteristics: subjective well-being (World Health Organization-5 [WHO 5]), treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire [status version and change version]), fear of hypoglycaemia (Hypoglycaemia Fear Survey), hypoglycaemic

confidence (Hypoglycaemia Confidence Questionnaire), and diabetes-related distress (Problem Areas in Diabetes Scale) During masked CGM, glucose levels were recorded but were not seen by the patient. After masked CGM, patients were excluded if they either did not believe they would wear the CGM sensor more than 80% of the time or did not perform adequate calibrations during the run in (on average ≥12 of 14 during a 7-day period).

Patients were randomized 1:1 into the first treatment period to RT CGM using the G4 with 505 software or conventional therapy. Randomization was performed by a centralized web-based program that stratified patients by site according to a predefined sequence; random block size varied between 1 + 1 and 2 + 2.

RT CGM was compared with conventional therapy using only SMBG Patients were not blinded to treatment. All patients received basic instruction on insulin dosing, such as bolus correction, food choices, and the effect of physical activity on glucose control A graph was displayed for patients showing the proportion of insulin at time of injection (100%) and the proportion of insulin remaining to give effect at various time points after injection The patients received general guidelines for interpreting glucose levels and trends obtained by RT-CGM.

During the first week, no alarms were set on the RT-CGM device for low glucose levels except for acute hypoglycaemia (<55 mg/dL or 3.05 mmol/L). Alarm settings were introduced no later than 2 weeks after randomization At each visit, patients were encouraged to use RT-CGM information at least every1 to2 hours during daytime. In the conventional group, patients were encouraged to measure blood glucose levels according to guidelines (i e , ≥4 times daily) Insulin dosing was based on self-measurement of blood glucose and not RT-CGM values. Assessment of HbA1c was blinded to treatment status During the 17-week washout period, patients used conventional therapy and masked CGM was performed for 2 weeks.

Patients were assessed at the start of each treatment period and at weeks 2, 4, 13, and 26 HbA1c was measured at all visits in each treatment period except week 2. Masked CGM was performed 2 weeks before both treatment periods During conventional therapy, masked CGM was also performed during 2 of the 4 last weeks to evaluate total time in hypoglycaemia, euglycaemia, hyperglycaemia, and glycaemic variability. At all visits, CGM and self measurements of blood glucose data were downloaded and used to assess glucose levels, number of self-measurements of blood glucose, time CGM was in use, and for optimizing glycaemic control. To maintain an equal number of visits for both treatment periods, the study did not permit extra patient visits for improving glycaemic control

Clinical Outcomes: The study was powered to detect a difference of 0.3% (3 mmol/mol) in HbA1c between weeks 26 and 69 at 90% power and assuming a standard deviation of 1 1%, which required 144 participants. Assuming a dropout rate of 10%, 160 individuals were required for enrolment.

The full analysis set (FAS) consisted of all randomized patients who had at least 1 follow-up measurement in each treatment period The safety analysis consisted of all randomized patients who received treatment (RT-CGM or conventional therapy) at any time with patients assigned to treatment administered but not randomized treatment The last observation carried forward (LOCF) principle was applied for any missing efficacy measurements from the last weeks of each treatment period

The primary endpoint was the difference in HbA1c between RT-CGM and conventional therapy at weeks 26 and 69 for the FAS with adjustment for treatment period and patient effects using procedure for generalized linear models in SAS software, with sequence, patient (sequence), period, and treatment as class variables A post hoc sensitivity analysis of primary outcome was performed by multiple imputation with 50 study samplings on all patients randomized by using demographics, baseline characteristics, baseline comorbidities, and HbA1c values at run in and randomization as imputation variables. A second post hoc sensitivity analysis investigating the effect of the site and interaction between site and treatment modelled as fixed effects on the primary outcome was performed.

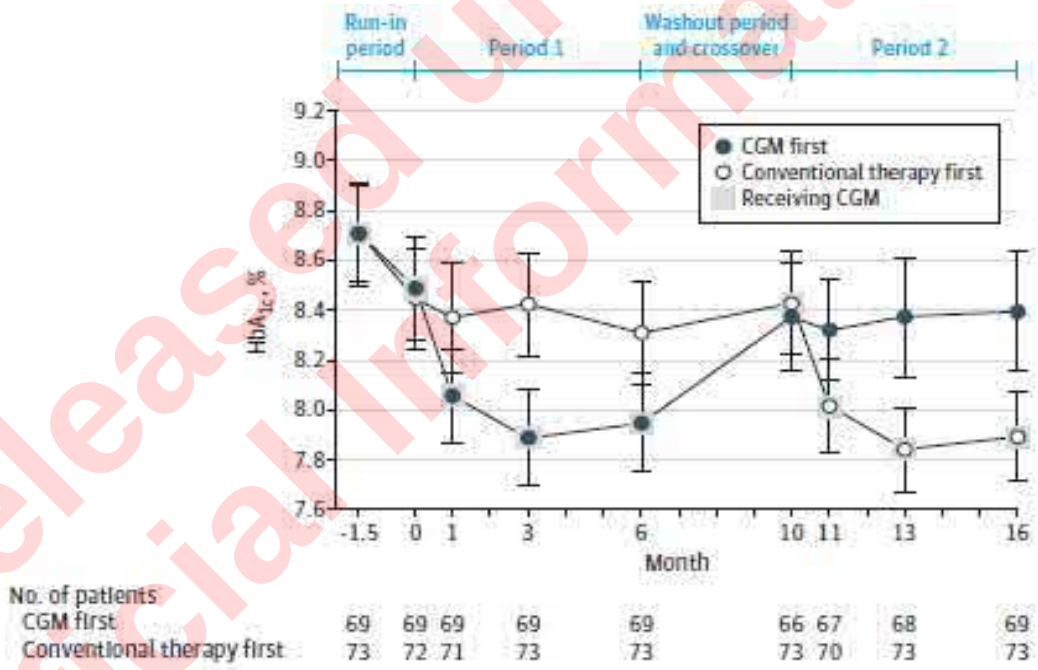
Secondary endpoints included mean amplitude glycaemic excursions; the SD of glucose levels; the percentage of time in hypoglycaemia (<70 mg/dL and <54 mg/dL), the number of min/day spent in hypoglycaemia in the daytime and night-time; hyperglycaemia, and euglycaemia during

RT-CGM use. Other endpoints included Diabetes Treatment Satisfaction status (range 0-36) and change in satisfaction (range 18 to 18), WHO 5 Well Being Index (range 0-100), Hypoglycaemic Fear Behaviour Scale (range 0-4) and Hypoglycaemic Fear Worry Scale (range 0-4), the Problem Areas in Diabetes scale (range 0 100), and the Hypoglycaemic Confidence Scale Other endpoints were the number of self-measurements of blood glucose and rate of severe hypoglycaemia, defined as unconsciousness from hypoglycaemia or requiring assistance from another person.

Sample Characteristics: There were 161 patients randomized with a mean age was 43 7 years; 45.3% were women, and mean HbA1c was 8.6% (70 mmol/mol). Of the 161 randomized patients, 142 (88 0%) had follow up data during both treatment periods in the FAS population The FAS population had a mean (SD) age of 44.6 (12.7) years; 56.3% were men and 99.3% were white Mean HbA1c was 8 7% (SD, 0 8%) (72mmol/mol), and mean diabetes duration was 22.2 (11.8) years. For the primary efficacy outcome HbA1c, FAS population, the LOCF imputation was done for 2 (2 9%) patients at the end of RT CGM therapy and 3 (4 1%) at the end of conventional therapy.

Outcome (HbA1c): Mean (SD) HbA1c during RT CGM use was 7 92% (0 8%) (63 mmol/mol) and during conventional treatment was 8.35% (0.9%) (68 mmol/mol) (mean difference, -0.43% [95% CI, -0 57%to 0 29%] or 4 7 mmol/mol [95%CI, 6.27 to -3.13 mmol/mol]); p<0 001) HbA1c was lower in RT-CGM-treated patients during the first and second treatment periods, whereas levels were similar at the beginning of both periods.

FIGURE 11. HBA1C VALUES AT INCLUSION, RANDOMIZATION, AND DURING THE TWO DIFFERENT PERIODS OF TREATMENT



In a sensitivity analysis (performed by using multiple imputation) of the primary outcome, including all participants in the trial (n=161), the effect on HbA1c by RT CGM was 0 39% (95% CI, 0.24%-0.55% [p<0.001]). The second sensitivity analysis of primary outcome (adjusted for the site effect and interaction between site and treatment) showed an HbA1c reduction of 0 43% (95% CI, 0.22%-0.64% [p<0.001]) for RT-CGM use vs conventional therapy. The interaction between site and treatment term was not significant (p=0 84)

Outcome (Glycaemic Variability): The SD of blood glucose estimated by CGM and compared with masked CGM during conventional treatment was lower during RT CGM use than

conventional therapy (68.49 vs 77.23 mg/dL; p<0.001) as was the case for mean amplitude of glycaemic excursions (161 93 vs 180 96 mg/dL; p<0 001)

Outcome (Well-being and Treatment Satisfaction): Overall well-being, estimated with the WHO-5 questionnaire, improved during RT CGM use (66 1 vs 62 7; p=0 02) Treatment satisfaction was higher during RT-CGM use as measured by the Diabetes Treatment Satisfaction Questionnaire status version (30 21 vs 26 62; p<0 001) and change version (13 20 vs 5 97; p<0.001).

Outcome (Hypoglycaemia Fear Survey): Scores on the Hypoglycaemia Fear Survey behaviour and worry subscales were similar during SMBG and RT-CGM.

Outcome (Hypoglycaemic Confidence Scale): The Hypoglycaemia Confidence Scale score improved significantly from 3.27 to 3.40 (p<0.001) during RT-CGM use and, when analysed separately, 4 of the 9 scale items improved significantly: staying safe from serious problems with hypoglycaemia when in a social situation (p=0.016); confidence in catching and responding in time to hypoglycaemia (p=0 033), avoiding serious problems due to hypoglycaemia (p=0 002), and continue to do the things you really want to do despite the hypoglycaemia risk (p=0.022).

Outcome (Sensor Use): Overall mean time of RT CGM use, estimated by the proportion of CGM data downloaded in relation to follow-up time, was 87.8% during RT-CGM treatment periods RT CGM use ranged between 86 5% and 91.9% during various study visits HbA1c was reduced by 0.46% (0.31%-0.61%) in patients using the CGM sensor more than 70% of the time, and there was no significant difference inHbA1c for those using the CGM sensor for less than 70% of the time.

Outcome (SMBG Frequency): Patients performed a mean (SD) of 2.75 (1 39) self-measurements of blood glucose during RT-CGM therapy and 3.66 (2.30) during conventional therapy

Outcome (% of Time Spent in Hypoglycaemia): The proportion of time spent with hypoglycaemia (<70 mg/dL) during RT CGM use was less than during conventional therapy, 2.79% (40 min) versus 4.79% (69 min), with p<0.001. This was also found for glucose levels of <54 mg/dL, 0 79% (11 min) versus 1.89% (27 min), with p<0 001

Outcome (Time Spent in Nocturnal Hypoglycaemia): Time spent in nocturnal hypoglycaemia was less during RT-CGM use for both the evaluated glucose levels of <54 mg/dL and <70 mg/dL irrespective of the time frames used (time 00:00-05:59 or 22:00-05:59), with p<0.001 in all cases. Time spent with nocturnal glucose levels below 70 mg/dL (Time 00:00-05:59) was reduced by 48% (10.2 vs. 19.6 min) and glucose levels <54 mg/dL by 65% (3.1 vs. 8.9 min).

Outcome (Time Spent in Daytime Hypoglycaemia): Daytime hypoglycaemia was significantly reduced by RT-CGM compared with SMBG for both glucose levels evaluated, and both time frames, with p<0.001 in all cases Time with daytime glucose levels below 70 mg/dL (Time 0:600 23:59) was reduced by 40% (29.5 vs. 48.8 min) and for glucose levels <54 mg/dL by 54% (8.2 vs 18 0 min)

Outcome (Number of Hypoglycaemic Episodes): Episodes of both daytime and nocturnal hypoglycaemia were fewer during RT CGM use for both the evaluated glucose levels and irrespective of time frames used, significant for all time frames for episodes below 54 mg/dL. During a 2-week period, there was overall an average of 9 46 episodes of daytime (time: 06:00 23:59) hypoglycaemia (<70 mg/dL) when using RT-CGM and 11.78 while using conventional therapy (p=0 002) The corresponding episodes for glycaemic value below 54 mg/dL were 3 5 for RT-CGM versus 5.58 for conventional therapy (p<0.001).

Outcome (Glycaemic Variability): The CV was lower during RT CGM compared with conventional therapy (0.37 vs. 0.40, difference = -0.03 [-0.05 to -0.02], p<0.001), and when analysed for the nocturnal period, time frame 00:00-05:59, (0 35 vs 0 38, p<0 001) and daytime

periods, time 06:00-23:59, (0.37 vs. 0.41, p<0.001). Corresponding findings exited when other time frames were used The SD and MAGE were also lower both during nocturnal and daytime periods with p<0.001 in all cases.

Outcome (Hypoglycaemia Confidence): Overall hypoglycaemia confidence was greater at the end of the RT-CGM period than at the end of the SMBG period, 3.40 (95% CI 3.32-3.47) versus 3 27 (95% CI 3 18 3 35) with p<0 001 RT CGM use was associated with greater confidence than SMBG use in being able to avoid serious problems due to hypoglycaemia (p=0.0020), detect and respond to falling glucose levels and thus prevent hypoglycaemia (p=0 0033), and continue with one's chosen lifestyle activities despite the risk of hypoglycaemia (p=0.022). In addition, RT-CGM use was linked to greater confidence in social situations (p=0 016)

Outcome (Severe Hypoglycaemia): There were 5 events of severe hypoglycaemia during conventional treatment (event rate, 0 19 per 1000 patient years) and 1 event occurred during RT-CGM therapy (event rate, 0.04 per 1000 patient-years). There were 7 severe hypoglycaemia events during the washout period when all patients were on conventional therapy (event rate, 0.41 per 1000 patient-years).

Outcome (Adverse Events): In total, there were 77 patients with 137 AEs during RT CGM and 67 patients with 122 AEs during conventional therapy. There were no obvious numerical differences for any AE between the treatments One patient in the RT CGM group discontinued use because of an allergic reaction to the sensor. There were 7 patients with a total of 9 serious AEs during RT-CGM treatment and 3 patients with total of 9 serious AEs during conventional treatment. Ketoacidosis was not reported during the study.

Study Limitations: Nineteen patients (~12.0%) had no follow-up data in the second treatment period and were not included in the primary analysis. Generally, in a parallel-group study, this can lead to an imbalance between groups. However, in the current study, patients served as their own controls and thus no such problem existed. It has therefore been proposed that the full analysis set population should be used in crossover studies as the main analysis In addition, with the crossover design, it can be determined whether results are going in the same direction during the first treatment period from a parallel design perspective Sixteen of the 19 patients who had no follow-up data in the second treatment period hadHbA1c data during the first follow-up period Among these patients, those with RT-CGM had a 1 0% decrease in HbA1c, whereas those with conventional therapy had an increase of 0.1%. There were more patients treated with RT CGM than conventional therapy who discontinued treatment during the first treatment period This was due to patients wanting to continue RT-CGM and therefore not completing the study while receiving conventional therapy in the second period and due to patients experiencing device-related problems. A second limitation is that the study could not be blinded and hence patients were aware of the intervention In addition, the current results are restricted to patients with HbA1c of at least 7.5%.

Conclusion: Among patients with inadequately controlled T1DM treated with MDI, the use of RT-CGM compared with conventional treatment for 26 weeks resulted in lower HbA1c and reduced time and episodes of nocturnal and daytime hypoglycaemia Continuous RT CGM was needed to obtain these effects. Further research is needed to assess clinical outcomes and longer-term adverse effects

Quality Grade: Good

c. Studies Comparing MDI + RT-CGM Versus Insulin Pump + RT-CGM

Beck RW, Riddlesworth TD, Ruedy KJ, Kollman C, Ahmann AJ, Bergenstal RM, et al Effect of initiating use of an insulin pump in adults with type 1 diabetes using multiple daily insulin injections and continuous glucose monitoring (DIAMOND): a multicentre, randomized controlled trial. *Lancet Diabetes Endocrinol* 2017; 5:700-08.[28]

Study Description: This was a 28-week, multicentre, randomized, open-label, parallel-group follow-on study to the DIAMOND RCT The trial conducted from April 2015 and May 2016 at 20 endocrinology practices in the US. The purpose of the study to determine whether there was a benefit from switching from MDI to insulin pump therapy in T1DM patients already using RT CGM.

Funding Source: Dexcom, Inc

Methods: Major eligibility criteria included age 25 years or older, diagnosis of T1DM treated for at least 1year with MDI, and central laboratory measured HbA1c level of 7 5% to 10.0%l Patient in the RT-CGM group of the initial DIAMOND trial were eligible if they used CGM on 21 of the last 28 days of the initial trial and used MDI of <100 units of insulin per day

All 75 participants continued using the G4 with 505 software. On the study website, after programmatic verification of eligibility from data entered, each participant was randomly assigned (1:1) to either insulin pump therapy or continuation of MDI using a computer-generated sequence maintained in an encrypted database and a random permuted block design (block sizes of two and four) stratified by HbA1c (≤7·0%, 7.1% to 7·4%, and ≥7·5%).

The RT CGM plus insulin pump group was provided with an Insulet OmniPod (Insulet, Billerica, MA, USA) insulin pump and pods. Pump training was done according to the study site's routine practice and customized to each participant's need, including a training visit after 2 weeks to troubleshoot any use or device issues and to modify pump settings. Pump basal rate settings and bolus calculator settings were determined by the investigators or clinicians within the clinical practices and were not standardized per protocol.

Participants in both groups were provided with sensors, blood glucose meters, and glucose test strips (Abbott Freestyle; Alameda, CA, USA), built into the Omnipod Personal Diabetes Manager (Insulet) for the RT CGM plus insulin pump group; and Bayer Contour Next USB (Ascenia Diabetes Care, Parsippany, NJ, USA) for the RT-CGM plus MDI group.

Follow-up visits for both treatment groups occurred after 6 weeks, 14 weeks, and 28 weeks Participants in the RT-CGM plus insulin pump group had an additional visit after 2 weeks to troubleshoot pump issues.

Sample Characteristics: Of 102 participants in the RT-CGM group who completed the original trial, 75 continued in this follow-on trial with 37 randomly assigned to the RT CGM plus insulin pump group and 38 to the RT-CGM plus MDI group. Mean age of all participants at the time of randomization was 46 years (SD 14; range 26 72), 35 (47%) of 75 participants were women, and 65 (87%) of 75 participants were non-Hispanic white people. Mean CGM-measured time in glucose range 70-180 mg/dL at baseline was 736 min per day (SD 196; equivalent to 51% of the day) and mean baseline HbA1c was 7.6% (SD 0.8). In the RT-CGM plus MDI group, 27 (71%) of 38 participants used one injection of long acting insulin per day and 11 (29%) of 38 used two injections per day. The 75 participants in this trial were similar to the 105 original participants in the initial DIAMOND RCT n mean age (46 years [SD 14] *vs* 46 years [14]), female sex (47% [n=35] *vs* 45% [n=47]), white race or ethnic origin (88% [n=66] *vs* 86% [n=90]), and education level (college degree or higher: 56% [n=74] *vs* 53% [n=53])

The 28-week primary study outcome visit was completed by 36 (97%) of 37 participants in the RT CGM plus insulin pump group and 35 (92%) of 38 participants in the RT CGM plus MDI group. All 36 participants in the RT-CGM plus insulin pump group who completed the trial were using insulin pump therapy at the end of the trial Two participants in the RT CGM plus MDI

group initiated insulin pump before the primary outcome was assessed (one after 6 weeks and one after 26 weeks) and two in the RT CGM plus MDI group started a non insulin glucose lowering medication during follow-up.

During weeks 25-28, 33 (94%) of 35 participants in the RT CGM plus insulin pump group and 34 (97%) of 35 participants in the RT-CGM plus MDI group used CGM for 6 days per week or more. Based on meter downloads, mean SMBG was 3 8 tests per day (SD 1 8) in the RT CGM plus insulin pump group and 3.7 tests per day (1.4) in the RT-CGM plus MDI group at baseline and 3 0 (2 7) in the RT CGM plus insulin pump group and 3 2 (1 4) in the RT CGM plus MDI group at 28 weeks (p=0·92).

Clinical Outcomes: The primary outcome was change in CGM measured time in the glucose range of 70-180 mg/dL from baseline using all available CGM data after the first 4 weeks of the trial Prespecified secondary outcomes included change in HbA1c from baseline; percentage of participants with HbA1c less than 7·0% at 14 weeks and 28 weeks; CGM-measured mean glucose concentration, time in hyperglycaemia (>180 mg/dL, >250 mg/dL >300 mg/dL), time in hypoglycaemia (<70 mg/dL [<60 mg/dL, <50 mg/dL) and coefficient of variation; self-reported hypoglycaemia unawareness; change in total daily insulin dose; and change in body weight. Insulin data were obtained for the RT-CGM plus insulin pump group by downloading data from the pump and by self-report for the RT CGM plus MDI group

Safety outcomes were frequencies of severe hypoglycaemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions), diabetic ketoacidosis, and serious adverse events, irrespective of causality.

The sample size was determined by the number of participants completing the original trial The trial was projected to have at least 80% power with a type 1 error rate of 5% (two-sided) to show a treatment group difference in the primary outcome of time in glucose concentration target range if the true population difference is at least 7·5% (108 min per day), assuming an SD of 8·0% (115 min per day) for time in range and a minimum of 50 participants completing the trial

The primary analysis was a treatment group comparison using a linear regression model with the change in time in glucose concentration target range (using all data after the first 4 weeks) as the outcome adjusting for baseline time in range, baseline HbA1c concentration, and clinical site as a random effect Confounding was assessed by repeating the analysis including baseline variables imbalanced between treatment groups as covariates. Exploratory analyses assessed the interaction between the treatment effect on the change in time in range and baseline factors by including interaction terms in linear regression models. The interaction between the treatment effect on the change in time in range and the time of day was assessed by including both the day and night time in range in a repeated measures model adjusting for the baseline time in range, baseline HbA1c concentration, and clinical site as a random effect Two per-protocol analyses were done: prespecified analysis including participants meeting these criteria (completion of the 28-week examination within 30 days, CGM usage averaging a minimum of 6 days per week, insulin pump being used at the time of the 28-week visit [RT-CGM plus insulin pump group], and insulin pump not used at any time during the trial [RT-CGM plus MDI group]); and post-hoc analysis excluding participants who started an oral glucose-lowering agent after randomization, who initiated insulin pump therapy when assigned to the RT CGM plus MDI group, or had less than 72 h of follow-up CGM data.

For the additional CGM outcomes, treatment group comparisons were made using linear regression models based on ranks using van der Waerden scores if the metric was skewed, adjusting for the corresponding baseline value, baseline HbA1c concentration, and clinical site as a random effect. The treatment group comparison of change in HbA1c was made using a linear regression model adjusting for baseline HbA1c concentration and clinical site as a random effect, and binary HbA1c outcomes were compared using logistic regression models adjusting for baseline HbA1c concentration and clinical site as a random effect We calculated the adjusted differences for the binary outcomes as in Kleinman and Norton and CIs were calculated with a bias corrected bootstrap We compared the frequency of blood glucose monitoring between treatment groups using a linear regression model adjusting for the baseline value and clinical site as a random effect

Analyses were done in SAS (version 9.4). All p values are two-sided. CIs are 95% for the primary outcome and 99% for all other outcomes

Outcome (Time Spent in 70-180 mg/dL): During follow-up, mean time in range 70-180 mg/dL was 791 min per day (SD 157) in the RT CGM plus insulin pump group and 741 min per day (225) in the RT-CGM plus MDI group, representing a mean change from baseline of 78 min per day (185) in the RT CGM plus insulin pump group and 17 min per day (105) in the RT CGM plus MDI group (adjusted mean treatment group difference favouring the RT-CGM plus insulin pump group: 83 min [95% CI 17 149], p=0 01) Adjusting for the baseline imbalance in diabetes duration did not alter the result. Results were similar when analysed separately at 14 weeks and 28 weeks and in two per protocol analyses The treatment group difference in time in range 7 180 mg/dL was predominately seen during the daytime, with little difference between groups overnight p<0 0001 for day *vs* night) In subgroup analyses, the beneficial effect of insulin pump therapy on the time in range outcome was greatest in participants with higher baseline HbA1c concentration ($P_{interaction}$=0 006)

Outcome (CGM Metrics): The beneficial effect of insulin pump therapy on time in range was reflected in a greater reduction in CGM measured mean glucose (p=0 005) and in all four hyperglycaemia metrics (p=0·04–0·007). However, there also was an increase in CGM-measured hypoglycaemia in the RT CGM plus insulin pump group compared with the RT-CGM plus MDI group (p<0·001 on all four hypoglycaemia metrics). In the RT-CGM plus insulin pump group, there was a net decrease in hypoglycaemia (<70 mg/dL]) at the end of this trial compared with the initial baseline blinded CGM data, from a median of 73 min per day to 47 min per day at 28 weeks (52 weeks from randomization in the original trial). The treatment group difference in hypoglycaemia was largest in participants with less baseline hypoglycaemia ($P_{interaction}$=0·04) and higher baseline HbA1c ($P_{interaction}$=0 0001) Compared with the blinded baseline CGM data from the initial study (before unblinded CGM was started), mean improvement in time in glucose concentration range 70 180 mg/dL at 28 weeks (52 weeks from randomization in the initial trial) was 136 min per day (SD 248) in the RT-CGM plus insulin pump group and 81 min per day (167) in the RT-CGM plus MDI group

Outcome (HbA1c): Mean HbA1c change from baseline to 28 weeks was 0·3% (SD 0.9) in the RT CGM plus insulin pump group and 0 1% (0.4) in the RT CGM plus MDI group (p=0 32) Among participants with baseline HbA1c of 7.5% or higher, mean change in HbA1c from baseline to 28 weeks was -0·1% (0.7) in the RT-CGM plus insulin pump group (n=22) and 0 1% (0 5) in the CGM plus MDI group (n=18; p=0·49). The correlations between change in HbA1c from baseline to 28 weeks with change from baseline to follow up in time in hypoglycaemia 70-180 mg/dL, time in range greater 180 mg/dL, mean glucose concentration, and glucose concentration area under the curve for 180 mg/dL ranged from 0 63 to 0 66 The overall mean change in HbA1c over the 52-week period from randomization in the original trial was -0·8% (0.8) in the RT-CGM plus insulin pump group and 0 9% (0 8) in the RT CGM plus MDI group

Outcome (IAH): IAH did not differ between groups at 28 weeks (p=0·76).

Outcome (Insulin Dose): Median change in total daily insulin dose was –0 18 units/kg per day in the RT-CGM plus insulin pump group compared with 0·01 units/kg per day in the RT-CGM plus MDI group (p<0·0001)

Outcome (Body Weight): Mean change in bodyweight was 0.0 kg (SD 3.6) in the RT-CGM plus insulin pump group and 0 6 kg (3 4) in the RT CGM plus MDI group (p=0 42)

Outcome (Severe Hypoglycaemia): A severe hypoglycaemic event occurred in one participant in the RT CGM plus MDI group (participant had an insulin bolus but fell asleep before eating dinner; RT-CGM device alarmed but did not wake the participant) and none in the RT-CGM plus insulin pump therapy group

Outcome (Adverse Events): There was one occurrence of DKA and one hospital admission for hyperglycaemia without DKA that occurred in the RT CGM plus insulin pump therapy group,

which were presumed to be due to the insulin pump, although attribution in the DKA case was inconclusive because an insulin bolus also was missed One participant in the RT CGM plus insulin pump therapy group reported a skin reaction related to the insulin pump insertion site, which was deemed a non serious adverse event No other adverse events were reported

Conclusions: In adults with T1DM using MDI who had used RT-CGM for 6 months, initiation of insulin pump therapy improved CGM measured time in the glucose concentration range of 70 180 mg/dL without any occurrences of severe hypoglycaemia. However, the benefit of insulin pump therapy on glycaemic control was associated with an increase in biochemical hypoglycaemia and with no significant change in HbA1c. The study participants, whether using insulin pump therapy or MDI, continued to have glycaemic benefit over 12 months and high persistence with near-continuous RT-CGM use.

Quality Grade: Good

Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. *The Lancet* 2018; 391:1367 77 [26]

Study Description: The HypoDE study was a 6-month, multicentre, open-label, parallel, randomized controlled trial conducted from February 2016 to October 2017 at 12 diabetes practices in Germany The aim of the study was to test the hypothesis that use of RT CGM reduces the frequency of hypoglycaemic events when compared with use of SMBG in high-risk adults withT1DM treated by MDI.

Funding Source: Dexcom, Inc.

Methods: Study participants were eligible for inclusion if they had T1DM for 1 year or more and problematic hypoglycaemia, which was defined as having had at least one severe hypoglycaemia event requiring third-party assistance for recovery in the previous year or having IAH as defined by a total score of 4 or more in the hypoglycaemia unawareness questionnaire developed by Clarke and colleagues. Additional inclusion criteria were treatment with MDI, age ≥18 years, and screening HbA1c ≤9.0%). Exclusion criteria were treatment with insulin pump therapy, use of the RT CGM system or another RT-CGM device in the previous 3 months, and pregnancy All study participants had attended a structured diabetes teaching and treatment program.

Following enrolment, participants had to complete a 4 week baseline phase with a masked RT CGM device before they were eligible for randomization. Participants in both groups were required to wear the masked RT CGM system more than 85% of the time during the 4 week period. If a participant was unable to meet this requirement, investigators had the option to allow one additional week of RT CGM system wear

Following the baseline phase, eligible study participants were randomly assigned to one of two groups: RT CGM + MDI or continued use of SMBG +MDI (control group) Randomization was done centrally at the study coordinating centre by staff who were not involved with recruitment or treatment of study participants A randomization sequence was generated with SYSTAT 12 0 with a 1:1 allocation; the study centre was a stratifying variable. Randomization was done block-wise per site (four participants per block)

The study was done in three phases: the baseline phase, therapy phase, and follow-up phase. During the baseline phase, all participants wore a masked RT CGM system (G4 with 505 software) for 4 weeks. In the therapy phase, before randomization, all RT-CGM and SMBG data were uploaded at the study sites and downloaded at the study coordination centre via an electronic data management tool, and participant adherence to use of RT-CGM was checked.

Participants assigned to the RT-CGM group received an unmasked RT-CGM (G5). Glucose alerts were individualized to each participant at their respective study centre Participants in the RT-CGM group received instructions on optimal use of RT-CGM in three sessions. Both groups used their respective glucose monitoring device for the subsequent 22 weeks to make therapeutic decisions. The follow-up phase began at week 22. SMBG participants again wore the masked G4 with 505 software, and participants in the RT CGM group continued with the G5 during the next 4 weeks.

Clinical Outcomes: The primary outcome was the number of hypoglycaemic events measured by RT-GM during the follow-up phase weeks 22 to 26) compared with baseline. A hypoglycaemic event derived from RT-CGM was defined as glucose values of ≤54 mg/dL) or lower for at least 20 min, preceded by a minimum of 30 min with glucose values greater than >54 mg/dL. The number of hypoglycaemic events was examined for each patient during each recording phase and standardized to an incidence of low glucose values per 28 days.

Secondary outcomes were changes in nocturnal hypoglycaemic events (0000 h to 0600 h); percentage and duration of glucose readings derived from continuous glucose monitoring per day in different glucose ranges (≤54 mg/dL, ≤70 mg/dL, >70 mg/dL to 180 mg/dL, and >180 mg/dL), and percentage of blood glucose readings based on SMBG measurements in these different glucose ranges Glycaemic variability assessed by coefficient of variation and the low blood was calculated for the baseline and follow-up phases with RT-CGM and SMBG data. The following changes in patient reported outcomes were also regarded as secondary endpoints: IAH assessed with the hypoglycaemia unawareness questionnaire; diabetes distress assessed with the Diabetes Distress Scale for type 1 diabetes (T1 DDS); fear of hypoglycaemia assessed with the Hypoglycaemia Fear Survey; self-reported health status assessed with the European Quality of Life 5 Dimensions questionnaire (EQ-5D); and satisfaction with glucose measurement assessed with the Glucose Monitoring Satisfaction Survey.

The frequency of severe hypoglycaemia events was defined as the number of hypoglycaemic events requiring third-party assistance to administer carbohydrate, glucagon, or intravenous glucose injections during the therapy and follow up phases. Severe hypoglycaemia was further divided into two additional categories: events requiring medical assistance to inject glucagon or glucose or associated with hospital admission; and events requiring third party assistance without medical assistance.

The full analysis dataset consists of participants who wore the RT CGM system during the baseline and follow-up phases. The ITT analysis was based on all randomized participants. For the ITT analysis, missing values were replaced with multiple imputation technique Missing data at the follow-up phase were imputed by use of a Markov Chain Monte Carlo multivariate imputation algorithm

Sample Characteristics: Among 170 participants recruited and assessed for eligibility; 163 participants started the baseline phase and 149 were randomized to the control group (n=74) or RT-CGM +MDI group (n=75). Among the 21 participants who were not randomized, seven discontinued before the baseline phase and 14 were excluded during or immediately after the baseline phase. All randomized participants were included in the intention-to-treat population. Among the 149 randomized participants, all RT CGM + MDI participants and 66 control group participants completed the study.

The full analysis dataset consists of data from 141 participants (control group, n=66; RT CGM + MDI group, n=75) who completed the baseline and follow-up phases. Mean baseline HbA1c was 7.5% for all study participants Approximately two thirds of participants reported at least one severe hypoglycaemia episode in the past year and more than 90% had IAH. There were no significant differences in demographic characteristics between participants who completed the study and those who discontinued.

Outcome (Sensor Use): Among RT CGM +MDI participants, the average percentage of sensor wear time was 90.7% of study days assessed (first 4 weeks subsequent to randomization, 30 days before 12-week visit, and 30 days before 26 week visit)

Outcome (SMBG Frequency): The mean frequency of daily SMBG was significantly lower in the RT CGM + MDI group than in the control group (3 7 [SD 1 9] vs 6 0 [1 3], p<0 0001)

Outcome (Hypoglycaemia Events): The mean number of hypoglycaemic events per 28 days was reduced from 10 8 (SD 10 0) to 3 5 (4 7) among RT-CGM + MDI group participants and from 14.3 (12.4) to 13.7 (11.6) among control group participants (p<0.0001).

Outcome (Nocturnal Hypoglycaemia Events): The number of nocturnal hypoglycaemic events was significantly reduced in the RT-CGM + MDI group, but not in the control group (Table 1).

Outcome (Mean Percentage of RT-CGM Values ≤54 mg/dL and ≤70 mg/dL): The percentages of glucose values 54 mg/dL or lower and 70 mg/dL or lower were reduced in the RT-CGM + MDI group compared with the control group

Outcome (LBGI): The LBGI was also reduced in the RT-CGM + MDI group, whereas it remained relatively unchanged in the control group (table 2)

Outcome (Time in Target Range): The time in range increased by 0.7 percentage points in the RT CGM + MDI group, whereas the control group showed a reduction by 2 6 percentage points (p=0·0513).

Outcome (% of Hypoglycaemic Glucose Values): The percentage of hyperglycaemic glucose values was increased slightly in both study groups but with no significant between-group differences

Outcome (Glycaemic Variability): Reductions in glycaemic variability were observed in RT-CGM group participants but not in control group participants Glycaemic variability was improved over the whole day by RT-CGM.

Outcome (HbA1c): HbA1c values remained stable in both groups, with only a marginal between group difference.

Outcome (Severe Hypoglycaemia): Severe hypoglycaemia events were observed during the therapy and follow-up phases: 24 in the RT-CGM + MDI group and 39 in the control group. The incidence of all severe hypoglycaemia events among control group participants during follow up was approximately twice the incidence seen in the RT-CGM + MDI group (1.18 [SD 3.46] vs 0.64 [1 92] events per patient-year; IRR 0.36 [95% CI 0 15–0 88], p=0 0247 Severe hypoglycaemia events requiring third-party assistance without medical assistance for recovery were also less frequent in the RT-CGM + MDI group than in the control group (19 vs 36 events), with a similar difference in incidence (0.51 [SD 1.75] vs 1.09 [3.41] events per patient-year; IRR 0.26 [95% CI 0 10 0.69], p=0·0071 Of the eight severe hypoglycaemia episodes requiring medical assistance for recovery, five occurred in RT-CGM + MDI group participants and three in control group participants (0 13 vs 0.09 events per patient year; IRR 1 60 [95% CI 0 30 8 49], p=0 59).

Outcome (Hypoglycaemia Unawareness): The hypoglycaemia unawareness score improved in both groups by approximately 40%, with no between group differences

Outcome (Glucose Monitoring Satisfaction): Participants in the RT-CGM + MDI group were more satisfied with their method of glucose monitoring than were those in the control group

Outcome (Fear of Hypoglycaemia): At study end, fear of hypoglycaemia was lowered in both groups (between group difference p=0 067)

Outcome (Diabetes Distress): The diabetes distress total score was reduced in both groups. A significant between group effect was observed only for the hypoglycaemia distress subscale score of the T1-DDS).

Outcome (Health Status): Self-reported health status, measured by the EQ 5D questionnaire, showed no significant difference between both groups.

Outcome (Serious Adverse Events): 18 serious adverse events were reported for 15 participants: seven events occurred in the control group (two severe episodes of hypoglycaemia,

one kidney transplantation, one myocardial infarction, two colon polyps, and one seizure) and ten occurred in the RT CGM + MDI group (four episodes of severe hypoglycaemia, two diabetic foot ulcers, one allergic reaction following a wasp sting, two fractures, and one kidney tumour removal) One serious adverse event occurred before randomization (whiplash after a car accident). No event was considered related to the investigational device.

TABLE 18: PRIMARY AND SECONDARY GLYCAEMIC OUTCOMES

Outcome	Baseline phase		Follow-up phase		Adjusted between-group difference (95% CI)	p value*
	Control	RT-CGM +MDI	Control	RT-CGM + MDI		
Mean number of hypoglycaemic events per 28 days	14.4 (1.7)	10.8 (10.0)	13.7 (11.6)	3.5 (4.7)	0.28 (0.20 to 0.39)†	<0.0001‡
Mean number of nocturnal hypoglycaemic events per 28 days	2 4 (2 6)	2 3 (2 4)	2 7 (2 8)	1.0 (1.0)	0.35 (0 25 to 0.56)†	0 0982‡
Mean RT-CGM glucose, mmol/L	8.7 (1.5)	9.0 (1.6)	8.9 (1.5)	9.5 (1.6)	0 28 (-0.05 to 0.62)	<0.0001
Median % RT-CGM values ≤70 mg/dL	6.9 (3.6-12 3)	5.0 (2 7 9 0)	6.4 (3 7-12.0)	1.6 (0.9-3.7)	—	<0.0001
Median % RT-CGM values ≤54 mg/dL	2 7 (1 0-5 7)	1 7 (0 7-3 8)	2.5 (1.0-6.1)	0 3 (0 1-0 9)	—	<0 0001
Mean % RT-CGM values >70 mg/dL and ≤180 mg/dL	59.1 (3.3)	57.8 (15.4)	56.5 (12.2)	58.5 (17.7)	3.1 (0.0 to 6.2)	0.0535
Mean % RT CGM values >180 mg/dL	32 8 (15 5)	35.4 (17 5)	35 3 (15 2)	38.8 (18.7)	1.3 (2 3 to 4 9)	0 4681
Median duration RT CGM values ≤70 mg/dL per day. min	99 5 (52.3-178.1)	70 9 (38.8-130.2)	92 2 (51.8-172.6)	23.9 (12.9-54.5)	—	<0.0001
Median duration RT-CGM values ≤54 mg/dL per day. min	36.3 (13.1-78.7)	24.1 (8.9-51.0)	32.9 (13.1-83.9)	3.8 (1.1-11.9)	—	<0.0001
Mean duration of RT CGM values >70 mg/dL and ≤180 mg/dL per day, min	851.0 (191 7)	831 9 (221.5)	814 2 (176 0)	842 9 (225 2)	44 9 (-0.3 to 90.0)	0 0513
Mean duration RT-CGM values >180 mg/dL per day, min	471.7 (223.1)	509.8 (252.2)	509.1 (219.1)	558.6 (268.4)	-18.7 (-70.3 to 32.9)	0.4744
Mean RT-CGM variability, coefficient of variation, %	40 5 (7 0)	39.3 (7 6)	4 1 (6 9)	34 1 (5 6)	6.2 (5 0 to 7 5)	<0 0001
Median low blood glucose index, RT CGM	1 60 (0.88-2.92)	1 26 (0.70-2.15)	1 53 (0.84-2.97)	0.52 (0.25-0.98)	—	<0.0001
Median % SMBG values ≤70 mg/dL	9.0(5.8-14.4)	7.6 (4.1-11.5)	8.6 (4.8-11.7)	2.6 (1.0-6.2)	—	<0.0001§
Median % SMBG values ≤54 mg/dL	2.9 (1.0-7.2)	2.4(0.6-4.8)	2.6 (1.0-4.9)	0.0 (0.0-1.6)	—	<0.0001§
Mean % SMBG values >70 mg/dL and ≤180 mg/dL	55.5 (13.5)	53.9 (14.5)	53.6 (12.7)	54.4 (16.6)	3.4 (1 0 to 7 9)	<0.0001§
Mean % SMBG values >180 mg/dL	33 9 (18 9)	37 5 (16 3)	37 2 (15 2)	41.4 (18 3)	0 2 (4 5 to 4 9)	0 9422§
Mean SMBG variability, coefficient of variation, %	43.7 (6.8)	43.0 (9.7)	43.9 (7.4)	37.8 (7.2)	5 7 (3.4 to 8.0)	<0.0001§
Median low blood glucose index, SMBG	1.85 (1 20-3 24)	1.58 (0 90-2 45)	1.75 (1 11 2 71)	0.61 (0 28 1 45)	—	<0.0001§
Mean HbA1c, %	7 4 (1 0)	7 6 (1 0)	7 3 (0 9)	7.4 (0 8)	0 03 (-0.12 to 0.19)	0 6653

Data are mean (SD) or median (IQR) unless otherwise stated. RT-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose. Nocturnal=between 0000 h and 0600 h, measured by RT-CGM. *Unless stated otherwise, p values are based on covariance analysis with group allocation as independent factor and baseline values as covariates, and p values for data with skewed distributions are based on covariance analysis using van der Waerden scores. †Incidence rate ratio adjusted for baseline (reference category = SMBG group. ‡p values are based on negative binomial regression analysis (model fit: Pearson $\chi^2 = 0.92$. §Adjusted for baseline and frequency of SMBG during follow-up phase

Study Limitations: Neither participants nor study personnel could be masked to the intervention. Participants were required to wear their RT-CGM device 85% of the time during the baseline phase to continue in the study. This requirement might have resulted in selection bias, which could potentially limit the generalizability of the findings to all high risk individuals with T1DM The use of SMBG data to assess the effect of RT-CGM on glycaemic outcomes could be problematic since the control group might have tested blood glucose several times during one hypoglycaemic event. This repeated testing might have biased the effect of SMBG on hypoglycaemia-related outcomes Additionally, the frequency of SMBG was substantially different during the follow up period between the groups, which necessitated the use of a post-randomization covariate. The absence of adjustment for multiplicity for secondary outcomes can be regarded as another limitation.

Conclusions: Individuals with T1DM treated by MDI and with IAH or severe hypoglycaemia can minimise both biochemical and clinical hypoglycaemia through use of RT-CGM without compromising overall glycaemic control

Quality Grade: Good

d. Studies Comparing MDI + RT-CGM Versus Insulin Pump + RT-CGM

Soupal J, Petruzelkova L, Flekac M, Pelcl T, Matoulek M, Dankova M, et al. Comparison of different treatment modalities for type 1 diabetes, including sensor-augmented insulin regimens, in 52 weeks of follow up: a COMISAIR study *Diabetes Technol Ther.* 2016.[30]

Study Description: This was a nonrandomized, prospective, real life clinical trial designed to compare the efficacy of long-term use of sensor-augmented insulin regimens (SAIRs), that is, RT CGM combined with either insulin pumps or MDIs, on glycaemic control compared with more common schemes based on classical SMBG in patients with T1DM seeking treatment at an academic medical centre in the Czech Republic.

Funding Source: Agency for Healthcare Research of the Czech Republic

Methods: Participants were included if they were aged >18 years, had a duration of T1DM of more than 2 years, and had an HbA1c level between 7.0% and 10% (53 and 86 mmol/mol). Only patients with insulin analogues were enrolled in this study Subjects who had used RT CGM during the past 3 months were excluded from the study. Patients with ketoacidosis within the past 3 months and/or severe noncompliance and/or any concomitant therapy influencing glucose metabolism, pregnant women, and women planning pregnancy were not allowed to participate either

A total of 65 patients were divided into three groups with comparable baseline parameters, taking into account their preferences and diabetologist's recommendation At the baseline, 27 patients started to use RT-CGM as part of an SAIR, 20 patients initiated insulin pump therapy (without RT-CGM), and 18 patients continued MDI and SMBG only In the SAIR group, after a further consultation with the diabetologist, subjects could choose a combination of RT-CGM with either an insulin pump (SAP) or MDI Fifteen of them started to use SAP and the remaining 12 continued with MDI (MDI + RT-CGM). A prerequisite for participation in the SAIR group was the willingness to use sensors >70% of the time Similarly, patients in the groups without RT CGM had to be willing to perform SMBG at least 4 times a day.

Subjects were scheduled for a total of seven clinic visits (initial, at 2 weeks, 1 month, then 3, 6, 9, and 12 months). Initially, all patients were monitored by professional CGM for 6 days. Throughout the study, subjects in the groups not using SAIR had professional CGM every 3 months Participants in the insulin pump group wore one of two types of insulin pumps: MiniMed Paradigm Veo (Medtronic, Northridge, CA) and Animas Vibe (Animas Corporation, West Chester,

PA). Participants in the SAP subgroup used either the MiniMed Paradigm Veo System with Enlite sensors (Medtronic) or Animas Vibe system with G4 sensors The subgroup of patients with MDI + RT-CGM used a G4 with 505 software comprising a 7-day transcutaneous sensor, a transmitter, and a receiver

Participants on SAIR were encouraged to make self-adjustments to their treatment using RT-CGM values, hyper- and hypoglycaemic alerts and trends, and to incorporate results of SMBG into treatment changes. The target range for glucose was usually initially relatively wide, but we emphasized to patients that its successive narrowing is usually necessary for reduction of mean blood glucose and glycaemic variability. Subjects in non-SAIR groups were encouraged to measure their blood glucose at least 4 times a day

Clinical Outcomes: The primary endpoint was the difference in HbA1c between the groups after 52 weeks of follow-up HbA1c values were measured at the baseline, then every 3 months, and at the end of this trial. Prespecified secondary endpoints were changes of glycaemic variability expressed by the total SD of blood glucose, average daily glucose from CGM, % of time spent in range (4.0-10.0 mmol/L or 70-180 mg/dL), and the incidence of hypoglycaemia (% of time below 3 9 mmol/L or 70 mg/dL)

At each clinic visit, patients were screened for AEs and sensor insertion sites were inspected. Severe hypoglycaemia was defined as an episode requiring assistance from another person or neurological recovery in response to restoration of plasma glucose to normal. Ketoacidosis was defined as an episode of hyperglycaemia (>14 mmol/L) with low serum bicarbonate (<15 mmol/L), low pH (<7.3), or both together with either ketonemia or ketonuria that required treatment in a healthcare facility

Sample Characteristics: Baseline characteristics were similar in the three groups (Table 13). Of the 65 patients enrolled, 62 completed all study visits One subject from the insulin pump group and one from the SAIR group withdrew from the study after the third visit because of personal reasons One patient from the MDI group was excluded from the analysis due to significant protocol violation.

TABLE 19: BASELINE CHARACTERISTICS OF PATIENTS

	RT-CGM	Insulin pump + SMBG	MDI + SMBG
No. of patients	27	20	18
Age (years), mean (SD), years	34 (10)	35 (9)	38 (17)
Duration of diabetes (years), mean (SD)	15 (9)	13 (10)	14 (9)
HbA1c (%), mean (SD)	8.3% (0.9%)	8.4% (0.6%)	8.3% (0.8%)
MDI=multiple daily injections of insulin; RT CGM=real time continuous glucose monitoring; SMBG=self-monitoring of blood glucose.			

Outcome (HbA1c): After a year, the SAIR group of patients had significantly lower HbA1c (8.3% ± 0 9% vs 7 1% ± 0.8% [67 5 ± 10 4mmol/mol vs 54 5 ± 9 1mmol/mol]; p<0 0001) This improvement in HbA1c was observed both in the subgroup with SAP (8.2% ± 0.9% vs. 7.1% ± 0 9% [66 ± 9 mmol/mol vs 53 9 v10 mmol/mol]; p=0 0025) and with MDI + RT CGM (8 5% ± 1.1% vs. 7.2% ± 0.8% [69.3 v 12 mmol/mol vs. 55.3 ± 8.7 mmol/mol]; p=0.0034) compared with the study baseline

Insulin pump therapy alone also led to significant reduction of HbA1c (8.4% ± 0.9% vs. 7.9% ± 0.7% [68 3 ± 9 mmol/mol vs 62 7 ± 8 mmol/mol]; p=0 048), while in the group just on MDI, no significant decrease of HbA1c was observed (8.3% ± 0.8% vs. 8.0% ± 0.9% [67.2 ± 9 mmol/mol vs 64 4 ± 10 mmol/mol]; p=0 40)

At 1 year, the mean difference in HbA1c between the SAIR group and the MDI group was -0.91% (9 81 mmol/mol) (95% confidence interval [CI], 1 47% to 0 35% [15 96 to 3 67 mmol/mol]; p=0.002). Moreover, both SAIR strategies were superior to insulin pump therapy alone; the mean difference was -0 75% (8 11 mmol/mol) (95% CI, 1 23% to 0 26% [13 41 to 2 81 mmol/mol]; p=0.0032). The difference in HbA1c between the SAIR group and the MDI group was significant

from the third month and the difference between the SAIR group and the insulin pump group was significant from the ninth month Importantly, superiority of both SAIRs in comparison with insulin pump only was not observed just for the SAP version of SAIR but also for the MDI version of SAIR for a between group difference favouring the MDI + RT CGM subgroup of 0 66% (7 4 mmol/mol) (95% CI, -1.23% to -0.10% [-13.64 to -1.6 mmol/mol]; p=0.022). The difference in HbA1c between insulin pump only and MDI + RT-CGM groups started to be significant from the ninth month of this study.

At the baseline, no patient met the ADA/ESDA goal for HbA1c (<7 0% [53 mmol/mol]), while at the end of this trial, 48% of subjects in the SAIR group (eight patients in SAP and five patients in MDI subgroups), 16% (n=3) of patients in the insulin pump group, and 18% (n=3) of individuals on MDI achieved the HbA1c target.

Outcome (Sensor Use): Mean sensor percentage use in the SAIR group was 85% ± 10% of the time (median 85%) with no significant differences between the two subgroups—SAP or MDI + RT CGM (85% ± 10% [median 84%] vs 85% ± 10% [median 87%]; p=0.98)

Outcome (SMBG Frequency): At the end of the study, the average number of blood glucose tests in non SAIR groups was 3 7 ± 1 1 per day (median 3 6/day), with no significant differences between the groups with MDI and insulin pump therapy (3.7 ± 1.4 [median 3.3/day] vs. 3.6 ± 0.7 [median 3 5/day]; p=0 8) In comparison with SMBG groups, the average frequency of finger-stick tests performed per day was numerically, but not statistically, lower in the SAIR group (3.2 ± 1.0 [median 3 1/day] vs 3 7 ± 1 1 [median 3 6/day]; p=0.08) However, regardless of the type of insulin delivery (SAP or MDI + RT-CGM), there was lower frequency of SMBG in subjects who were using the G4 (n=19) in comparison with users of the MiniMed Paradigm Veo System (n=8) (2.7 ± 0.6 vs. 4.3 ± 0.7, p<0.001).

Outcome (Insulin Use): Compared with the baseline, at the end of this study in the SAIR group, there was a significantly higher number of boluses per day and the relative proportion of bolus insulin was higher, while no significant change in these parameters was seen in either SMBG group. No change in the total daily dose of insulin between the baseline and the end of the study was observed for any study group. The average number of boluses per day at the end of the study was lower in both SMBG groups in comparison with the SAIR group (6.8 ± 2.2 vs. 4.3 ± 1 2; p<0 0001) A higher frequency of boluses was seen in patients with insulin pump therapy versus the self-reported boluses in the MDI only group (4.7 ± 1.4 vs. 3.9 ± 0.8; p=0.04), while no significant difference between SAP and MDI + RT CGM was observed (7 2 ± 2 3 vs 6 2 ± 2; p=0.25). At the end of this trial, the total daily dose of insulin and the relative proportion of bolus insulin were not different between study groups

Outcome (Body Weight): No significant change in body weight between the beginning and the end of the study was found for any study group

Outcome (Glycaemic Variability): At 1 year, the average daily glucose level, as measured by RT-CGM or professional CGM, was significantly lower, both in the SAIR group (10 6 ± 1 5 mmol/L vs. 8.7 ± 1.4 mmol/L; p<0.001) and in the insulin pump group (10.7 ± 1.2 mmol/L vs. 9.8 ± 1 1 mmol/L; p=0.04) This improvement in average CGM glucose was accompanied by an increase in the time in range (4.0–10.0 mmol/L or 70-180 mg/dL); 50% ± 11% versus 69% ± 11%; p<0 0001, for SAIR and 51% ± 10% versus 59% ± 11%, p=0 03, for insulin pump

Compared with the baseline, glycaemic variability was lower in the groups on SAIR (SD of blood glucose: 4 0 ± 0 7 mmol/L vs 3 0 ± 0 5 mmol/L; p<0 0001) and with insulin pump therapy (SD of blood glucose 3.9 ± 0.6 mmol/L vs. 3.4 ± 0.6 mmol/L; p<0.05). Additionally, significant reduction of the time spent in hypoglycaemia was observed only in patients with SAIR (8% ±4% vs 6% ± 3%; p< 0.01). For patients just on MDI, no significant change in SD of blood glucose (3.8 ± 1.0 mmol/L vs 3 8 ± 1 1 mmol/L; p=0 93) and in hypoglycaemia (6% ± 4% vs 7% ± 5%; p=0 68) was observed.

No difference in HbA1c (7 2% ± 0 8% vs 7 3% ± 0 9% [54 ± 9 mmol/mol vs 56 ± 10 mmol/mol]; p=0.87), hypoglycaemia (6% ± 4% vs. 6% ± 3%; p=0.91), and SD of blood glucose (2.9 ± 0.5

mmol/L vs. 3.0 ± 0.4 mmol/L; p=0.67) was observed in patients with the two types of RT-CGM systems (G4 and Paradigm Veo)

Outcome (Severe Hypoglycaemia): Throughout the study, two severe episodes of hypoglycaemia were reported, one in the insulin pump only group and one in the MDI group No severe hypoglycaemia in the SAIR group was reported.

Outcome (Adverse Events): There was no DKA or sensor insertion site infection requiring assistance during a year of follow-up.

Study Limitations: This was a nonrandomized study Thus, although baseline HbA1c was similar, the more motivated patients might have selected the insulin pumps and/or RT-CGM. Another possible limitation is the different types of insulin pumps and RT CGM systems used in this study. However, this reflects real-life and day-to-day clinical practice.

Conclusion: In patients with T1DM with suboptimal glycaemic control, both SAIRs, that is, SAP and MDI + RT-CGM, were superior to MDI or insulin pump therapy in reducing HbA1c, hypoglycaemia, and the other endpoints Both SAIRs provided comparable glycaemic benefits Hence, a combination of RT-CGM and MDI can be considered as an equivalent alternative to SAP therapy for patients who are not willing to or cannot use insulin pumps

Quality Grade: Fair

Foster NC, Miller, KM, Tamborlane WV, Bergenstal RM, Beck RW. Continuous glucose monitoring in patients with type 1 diabetes using insulin injections. *Diabetes Care* 2006;39:e81-e82 [29]

Study Description: This observational, cross sectional, real-world analysis assessed the impact of RT-CGM on patients with T1DM using different methods of insulin delivery.

Funding Source: The Leona M and Harry B. Helmsley Charitable Trust

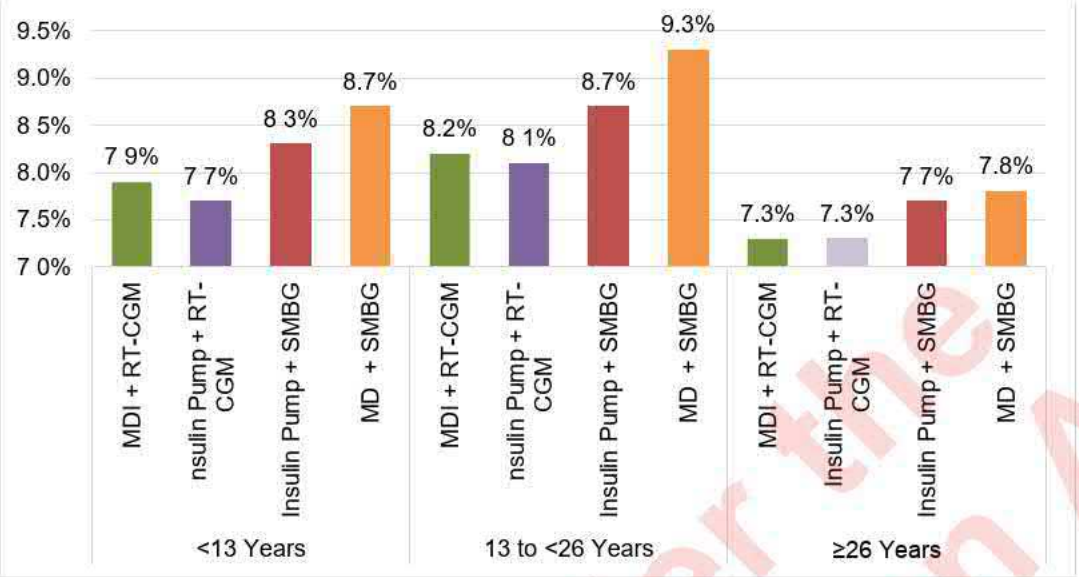
Methods: Participants in the T1D Data Exchange Registry who were diagnosed with T1DM for >1 year; had a clinic visit between June 2014 and October 201e; and used RT-CGM for real time diabetes management during the 30 days prior to the clinic visit were eligible for the study.

Clinical Outcomes: The primary endpoint was mean HbA1c.

Sample Characteristics: Among the 17,731 registry participants who met eligibility criteria, 6,222 (35%) used MDI + SMBG, 8,783 (50%) used an insulin pump + SMBG, 2,316 (13%) used an insulin pump with RT-CGM, and 410 (2%) used MDI with RT-CGM. A Dexcom RT-CGM device was being used by 97% of the MDI + RT-CGM users and by 58% of the insulin pump + RT-CGM users. Of the 2,726 participants using RT-CGM, 85% were receiving insulin pump treatment, and only 15% were receiving MDI The median number of boluses of short acting insulin per day was 3 (interquartile range 3, 4) in both participants using MDI + SMBG and participants using MDI with RT CGM

Outcome (HbA1c): Among RT-CGM users, mean HbA1c was similar in MDI and insulin pump users (7 6 6 ± 3% vs 7 7 ± 1 1%, adjusted p=0 82) and lower in RT CGM users than in non RT CGM users in the insulin pump group (8.3 ± 1.5%, adjusted p<0.001) and in the MDI group (8.8 ± 1.9%, adjusted P <0.001). As shown in Figure 18, this pattern was seen in both adults and youth.

FIGURE 12. MEAN HBA1C ACCORDING TO INSULIN MODALITY/RT-CGM USE STATUS



Study Limitations: Cross sectional analyses are subject to potential bias. For instance, there was no available information on how many injection users tried RT-CGM and discontinued it, and thus, the cohort of injection RT CGM users in the study may be self-selected to be those who are more likely to have lower HbA1c levels.

Conclusion: In this analysis of T1D Exchange registry data, RT-CGM users, irrespective of insulin delivery method, had lower HbA1c levels than non-RT-CGM users even after adjustment for potential confounding factors Importantly, RT CGM users who were using MDI for insulin delivery had HbA1c levels similar to those of RT-CGM users using an insulin pump.

Quality Grade: Fair

e. Other Supporting Studies

Laffel L. Improved accuracy of continuous glucose monitoring systems in pediatric patients with diabetes mellitus: results from two studies. *Diabetes Technol Ther.* 2016;18 Suppl 2:S223-33.[178]

Study Description: Two 1-week open label single arm multicentre studies were conducted to demonstrate the improved accuracy of the G4 with 505 software (SW505) compared with the G4 in paediatric patients treated with MDI or insulin pump therapy Study 1 was conducted from September 2012 to October 2012 at 6 centres in the US. Study 2 was conducted from May 2014 to September 2014 at 5 centres in the US

Funding Source: Dexcom, Inc.

Methods: Patients were youth 2 17 years of age with T1DM or T2DM who were using MDI or insulin pump therapy. Exclusion criteria included haematocrits beyond the range recommended by the study glucose meters, pregnancy, hypoglycaemic unawareness (other than that usually expected for toddlers with diabetes), need for treatment with acetaminophen, and any significant illness that would pose a risk to the patient or to the staff handling the blood specimen

In Study 1, participants wore two CGM systems simultaneously for a 7-day sensor wear period (amounting to 168 h), with one receiver providing real-time data and the other masked In Study 2, participants wore a single unmasked sensor for the 7-day sensor wear period with CGM data displayed in real time Subjects in both studies were required to use a study-provided BG meter and test strips for all BG measurements. In both studies, participants were asked to perform a minimum of seven fingersticks per day and to base all diabetes management decisions on results from the BG meter.

Subjects completed one in clinic session (on Day 1, 4 or 7) to allow for comparison of masked G4 and SW505 sensor glucose measurements with a reference glucose measurement (YSI BG analyser; YSI, Yellow Springs, OH) In Study 2, for the teen subjects, glucose levels during the in-clinic session were manipulated under close supervision according to protocol guidelines in efforts to achieve glucose levels across the range of sensor performance (40-400 mg/dL) The RT-CGM sensor values were compared with the temporally matched glucose values from the reference YSI and BG meter values to evaluate the accuracy of the CGM devices

Sample Characteristics: Study 1 consisted of 176 subjects, with 29 in the 2-5-year age group, 69 in the 6-12-year age group, and 78 in the 13 17-year age group Study 2 included 79 subjects, with 16 in the 2-5-year age group, 17 in the 6-12-year age group, and 46 in the 13-17-year age group Almost all patients had T1DM, with an average duration about 5 years; the majority (68%) were receiving insulin pump therapy. Mean HbA1c values were 8.2 ± 1.3% and 8 5 ± 1 5% in Studies 1 and 2, respectively In Study 1, 40% of participants had previous exposure to RT-CGM, whereas only 13% used RT-CGM devices on a routine basis; in Study 2, 57% had previous exposure to RT CGM, whereas only 19% used it on a routine basis

Outcome (CGM Performance): Table 20 summarizes the performance of the G4 and SW505 devices The overall accuracy of the SW505 was superior to the G4. The mean absolute relative difference was significantly lower with the SW505 than the G4 (10% vs. 17%; $p<0.0001$) when compared with YSI and blood meter values (13% vs 15; $p<0.00001$) The Clarke Error Grid and Parkes Error Grid results indicated superior clinical accuracy with the SW505 algorithm compared with the G4 CGM accuracy improved after Day 1 of sensor use for both devices

The SW505 performed better than the G4 with respect to detection of hypo- and hyperglycaemia. The G4 detected true hypoglycaemia (YSI measurements ≤80 mg/dL) within 15 min 55% of the time with the G4 compared with 91% of the time with the SW505. In this hypoglycaemic range, there was a false alert rate of 34% with the G4 versus 14% with the SW505 With a high glucose alert of 240 mg/dL, CGM detected true hyperglycaemia (YSI measurements ≥240 mg/dL) within 15 min 96% of the time with the G4 and 94% of the time within 15 min with the SW505 In this hyperglycaemic range, there was a false alert rate of 33% with the G4 and 12% with the SW505.

TABLE 20. CGM PERFORMANCE ACCURACY DURING CLINIC (CGM VS REFERENCE YSI) AND HOME USE (CGM VERSUS BLOOD METER VALUES)

	CGM versus YSI		CGM versus Blood Meter	
	G4	SW505	G4	SW505
Number of matched pairs	2,922	2,262	16,318	4,264
Mean/median ARD (%)	17/14	10/8	15/11	13/10
CEG Zone A (%)/A + B (%)	68/98	90/99	75/98	83/93
PEG Zone A (%)/A + B (%)	79/99	93/100	80/99	86/100
%20/20/%30/30 (%)	68/85	91/96	76/89	84/94
Within CGM ranges				
40 ≤ CGM ≤60 mg/dL				
Number of matched pairs	19	86	487	240
Mean/median AD (mg/dL)	19/9	16/13	24/18	17/14
60 < CGM ≤80 mg/dL				
Number of matched pairs	76	142	1,340	399
Mean/median AD (mg/dL)	13/11	12/8	17/11	14/10
80 < CGM ≤180 mg/dL				
Number of matched pairs	1,155	805	7,084	1,650
Mean/median AD (mg/dL)	17/13	11/8	15/11	14/10
CGM >180 mg/dL				
Number of matched pairs	1,672	1,229	7,407	1,975
Mean/median AD (mg/dL)	18/14	9/7	14/10	11/8
CGM >250 mg/dL				
Number of matched pairs	724	608	3,604	964
Mean/median AD (mg/dL)	18/15	10/7	14/10	11/8

AD=absolute differences; ARD=absolute relative difference; CEG=Clarke Error Grid; G4=G4 Platinum; PEG=Parkes Error Grid; SW505=505 software algorithm

Outcome (Adverse Events): There were no SAEs or device related SAEs for either the G4 or the SW505 among the paediatric patients in either study. There was no sensor break-off or infection at the site of sensor insertion. There was a low rate of mild skin irritation in some patients in the adhesive area.

Study Limitations: Longer-term studies are needed to assess whether the substantially improved performance of the SW505 algorithm results in greater uptake, sustained use, and improvements in glycaemic control without an increase in severe hypoglycaemia

Conclusions: This report describes the improved performance of the G4 with the SW505 algorithm in paediatric patients with diabetes

Quality Grade: Fair

Parkin CG, Graham C, Smolskis J Continuous glucose monitoring use in type 1 diabetes: longitudinal analysis demonstrates meaningful improvements in HbA1c and reductions in healthcare utilization *J Diabetes Sci Technol* 2017;11:522-8 [179]

Study Description: This retrospective, longitudinal analysis utilized datasets from T1DM patients enrolled in a commercial health plan to assess changes in HbA1c using RT CGM versus SMBG

Funding Source: Dexcom, Inc.

Methods: The study population included patients with a diagnosis code for T1MD, continuous enrolment in the health plan, use of MDI or insulin pump therapy, and at least one claim for insulin during the study period Patients who were pregnant or had prior experience with RT CGM were excluded from all analyses. Study patients were divided into two groups: patients who initiated RT CGM use with the G4 and patients documented use of SMBG at a frequency of ≥4 test strips per day within the baseline period as indicated by medical claims.

The identification period for eligible patients was from November 2012 through December 2013 The index date for each patient was the date of the first claim for initiation of either RT-CGM or SMBG at a frequency of ≥4 test strips per day The baseline period for each group was one year prior the index date; whereas, the measurement period was a year following the index date, including the index date itself

Data for the study were obtained from the Optum Research Database (Optum, Eden Prairie, USA), which contains eligibility, pharmacy claims, medical claims and laboratory data for more than 14 million enrolees in fully-insured and self-funded healthcare plans. Medical and demographic information, including diagnosis, utilization of healthcare services (e g , inpatient admissions, ER visits, pharmacy costs), age, gender and geographic regions were obtained from health plans' administrative records for this study

Clinical Outcomes: The primary outcome measure was change in HbA1c between and within study groups by insulin delivery method (insulin pump vs. MDI) Secondary outcomes included within- and between-group differences in hospitalizations and ER visits. The primary analysis included patients who had at least one HbA1c value documented in both the baseline and the measurement periods. For the secondary analysis, propensity score matched analysis was performed to reduce selection bias due to imbalances in study covariates The two groups were extensively matched on baseline per-member per-month (PMPM) medical and pharmacy costs, gender, region, Charlson Index Score and sixteen comorbidity Charlson indices Patients in the RT-CGM group were matched to those in the SMBG group in a 1:1 ratio, based on the resultant propensity score probabilities However, patients were not matched for HbA1c due to the relatively smaller number RT-CGM patients with baseline and measurement period values.

Sample Characteristics: A total of 6,467 patients, with 187 in the RT CGM group and 6,280 in the SMBG group, were included in the primary analysis. The distribution of baseline HbA1c values in the two groups was similar

Outcome (HbA1c): Patients in both the RT-CGM and SMBG groups experienced statistically significant reductions in HbA1c from baseline (RT-CG: 0 5%, p=0 004; SMBG: 0 2%, p<0.0001). Comparison of change in HbA1c by insulin administration method showed a clinically and statistically significant HbA1c reduction in patients treated with RT CGM plus MDI (0 6%, p<0.01) but not with RT-CGM plus insulin pump therapy (-0.3%, p=0.16); however, the between-group difference was not statistically significant (p=0 06)

Outcome (Healthcare Utilization): The number of all cause inpatient admissions among RT CGM patients was significantly lower compared with SMBG patients (42 2%, p=0 013), resulting in 17.4% (p=0.556) lower PMPM costs. The number of diabetes-specific inpatient admissions and costs were also lower among RT CGM users than those using SMBG, although these differences were not statistically significant. The number of inpatient admissions coded for DKA

among SMBG patients was more than double the number reported for RT-CGM patients during the *measurement* period (36 vs 16, p=0 068)

The number of all-cause ER visits was 17% lower among RT-CGM patients vs. SMBG patients (p=0 303) with associated lower PMPM costs (p=0 491) The number of diabetes-specific ER admissions was also lower among RT-CGM patients vs. SMBG patients but with higher associated costs The number of ER visits coded for DKA among SMBG patients was more than four times higher than reported for RT-CGM patients during the *measurement* period (17 vs. 4, p=0 0318) Similar differences between RT GM vs SMBG patients also were seen in the number of ER visits coded for hypoglycaemia (2 vs. 7, p=0.353).

Study Limitations: A key limitation of the study is the small sample size of RT-CGM users with pre- and post-HbA1c test values; a larger sample size would have provided a more robust assessment of the impact of RT CGM use on glycaemic control and health service utilization Another limitation was the design of the study. It is well known that retrospective analyses inherently include confounding variables, which may go unrecognized because of inadequate knowledge of how they interrelate with the outcomes. Although the analyses showed associations between treatment modalities and outcomes, causal relationships cannot be inferred. Additionally, the Optum data set provided no information regarding the socioeconomic, educational characteristics or participation in a formal diabetes self-management education program, all of which could have affected outcomes.

Conclusion: Use of RT CGM was associated with reduced HbA1c and utilization of health services compared with SMBG use regardless of insulin delivery method. Additionally, RT-CGM use was associated with notably fewer inpatient admissions and ER visits coded for DKA and hypoglycaemia, which can have long term effects on patient adherence

Quality Grade: Fair

Chamberlain JJ, Dopita D, Gilgen E, et al. Impact of frequent and persistent use of continuous glucose monitoring (CGM) on hypoglycaemia fear, frequency of emergency medical treatment, and SMBG frequency after one year. *J Diabetes Sci Technol* 2015;10:382-8.[180]

Study Description: This was a single-centre survey to assess changes in hypoglycaemia fear, incidence of emergency medical treatment, and utilization of SMBG before and after 1 year of RT CGM use.

Funding Source: Dexcom, Inc.

Methods: Study participants were individuals with T1DM who were treated with intensive insulin regimens and had used their current RT CGM device (G4) for at least 1 year Participants were recruited on an "as seen" basis from a major, urban internal medicine clinic that sees between 700 and 800 patients per year on both an inpatient and outpatient basis and an associated diabetes education centre that sees between 500 and 600 outpatients per year. The average HbA1c level among clinic patients was 7.4%. Participants were asked to complete a 16-item questionnaire.

Clinical Outcomes: The survey assessed changes in hypoglycaemia fear, daily SMBG testing frequency and emergency medical treatment, comparing the year prior to RT CGM to 1 year after CGM use in respondents who reported "almost daily" wear of their RT-CGM device.

Sample Characteristics: A total of 74 patients (38 male, 36 female) completed the survey from June 2014 to March 2015. The average age of participants was 42.9 years (range, 23-71 years). Fifty nine participants had 10 25+ years duration of diabetes, and 59 were currently using an insulin pump. Approximately 76% (n=56) of participants reported participating in at least 1 formal training session with a trainer.

Outcome (Sensor Use): Eighty-four percent of respondents reported wearing their sensor "almost daily" (n=58) or 3 weeks per month (n=4) Among frequent users, "improved glycaemic control" and "knowing glucose at all times" were most commonly reported as primary reasons for frequent use Among less frequent RT CGM users (≤3 weeks per month), the most common reasons reported were "tired of wearing 2 devices" and "sensor did not remain attached." Seventy (94 6%) respondents indicated that they would purchase the G4 again

Outcome (SMBG Frequency): "Almost daily" RT-CGM users reported a significant reduction in daily frequency of SMBG after 1 year of RT CGM use compared with the prior year (6 8 ± 3 2 vs 3.2 ± 1.7, p<0.001).

Outcome (Healthcare Utilization): "Almost daily" RT CGM users reported an 86% reduction in the number of events requiring emergency medical treatment after 1 year of RT-CGM use compared to the prior year (0 4 ± 0 9 events vs 0 1 ± 0 3 events, p=0.0013).

Outcome (Fear of Hypoglycaemia): Among respondents who indicated "almost daily" RT-CGM use, 45 (78%) reported worrying about hypoglycaemia "most of the time" or "frequently" prior to RT-CGM use. After 1 year of RT-CGM use, no respondents reported worrying about hypoglycaemia "most of the time" and 1 (2 0%) reported frequent worry, a 98% decrease in significant hypoglycaemia fear (p=0.7359).

Study Limitations: A significant limitation of this study was the use of self-reported data, which may not accurately reflect participants' actual SMBG utilization or history incidence of emergency medical treatment Lack of objective measurements of clinical and financial outcomes (e g , change in HbA1c, insurance data regarding emergency room visits, SMBG data) further limit the interpretation of our findings Another limitation was the small sample size; a larger number of participants would likely have increased the generalizability of findings, particularly if a larger number included more patients who used RT-CGM less frequently.

Conclusion: After 1 year of RT-CGM use, high-frequency users reported notable reductions in SMBG utilization, incidence of emergency medical treatment/hospitalizations, and hypoglycaemia fear.

Quality Grade: Fair

Reddy M, Jugnee N, El Laboudi, A, Spanudakis E, Anantharaja, S, Oliver N. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with Type 1 diabetes and impaired awareness of hypoglycaemia *Diabet Med* 2018;35:483 90 [165]

Study Description: A randomized, non-masked, parallel-group study evaluated the impact of intermittent flash glucose monitoring (Freestyle Libre) compared to RT-CGM (G5) on hypoglycaemia in adults with T1DM and IAH.

Funding Source: Dexcom, Inc

Methods: After a 2-week run-in with blinded CGM, participants were randomized 1:1 to RT-CGM (G5) or flash glucose monitoring (Free Style Libre) using an online randomization tool Randomization was stratified by HbA1c.The treatment period was 8 weeks. Eligible patients were aged ≥18 years, diagnosed with T1DM for >3 years, had been receiving MDI for ≥3 months, and had a severe hypoglycaemic event in the last 12 months requiring third party assistance or a Gold score of ≥4 Patients who used CGM or the Libre device within the last 6 months, used paracetamol regularly, were pregnant or planning pregnancy, or breastfeeding were excluded. The study was conducted from January 2016 to August 2017 at a single site in the UK

Sample Characteristics: 40 CGM-naïve adults withT1DM and IAH were randomly assigned to RT CGM (n=20) or flash glucose monitoring (n=20) Participants (24 men, 16 women) had a median (IQR) age of 49.5 (37.5-63.5) years, duration of diabetes of 30.0 (21.0-36.5) years, HbA1c of 6 5 7 8%, Gold score of 5 (4 5), and episodes of self reported hypoglycaemia per week of 3.0 (2.0-4.5). There were no significant differences in baseline characteristics between the groups

Outcomes: The primary outcome was change in time spent in hypoglycaemia (<60 mg/dL) from baseline to 8 weeks with RT CGM vs flash glucose monitoring Secondary outcomes were % time spent in hypoglycaemia (<50 mg/dL, <63 mg/dL, <70 mg/dL), % of time spent in normoglycaemic (70 140 mg/dL, 70 180 mg/dL), % of time spent in target (70 140 mg/dL) % of time spent in hyperglycaemia (>140 mg/dL, >180 mg/dL, >270 mg/dL), low blood glucose index (LBGI), severe hypoglycaemia (requiring third party assistance to treat), hypoglycaemia risk, Gold score, hypoglycaemia fear (as assessed by the Hypoglycaemia Fear Survey [HFS]), HbA1c, and diabetes related emotional distress (PAID questionnaire)

Outcome (% Time Spent in Hypoglycaemia): As shown in Table 21, patients using RT-CGM spent significantly less time in hypoglycaemia than patients using the Libre (<50 mg/dL: 2 5%, p=0.003; <60 mg/dL: -4.3%, p=0.006; <63 mg/dL:-4.8%, p=0.0004; <70 mg/dL: -3.3%, p=0.01).

Outcome (% Time Spent in Normoglycaemic): There were no significant differences in change from baseline to endpoint in time spent in target glucose range (70-140 mg/d, 70-180 mg/d) between the two groups

Outcome (% Time Spent in Hyperglycaemia): There were no significant differences change from baseline to endpoint in time spent in hyperglycaemia (>180 mg/dL, >270 mg/dL) between the two groups.

Outcome (HbA1c): There was no significant difference in change from baseline to endpoint in HbA1c between the two groups.

Outcome (Gold score): The percentage of participants with a Gold score of ≥4 decreased in both groups; no significant difference was observed in overall Gold score from baseline to endpoint between the two groups

Outcome (Fear of Hypoglycaemia): Participants in the RT-CGM group reported a statistically significant reduction in fear of hypoglycaemia (p=0 02) and worry about hypoglycaemia (p=0 02) compared with patients using flash glucose monitoring.

Outcome (Severe Hypoglycaemia): No episodes of severe hypoglycaemia were reported during the 8-week intervention phase in either group.

Conclusions: RT-CGM has a significantly greater beneficial impact on hypoglycaemia outcomes and hypoglycaemia awareness than intermittent flash glucose monitoring in a high-risk group of adults with T1DM.

Quality Grade: Good

TABLE 21. PRIMARY AND SECONDARY OUTCOMES*

Outcome	Dexcom G5				FreeStyle Libre				Δ G5 vs Libre	P
	Baseline	Final	Δ	P	Baseline	Final	Δ	P		
% time <60 mg/dL	7.7 (6.8)	3.3 (3.2)	-4.0	0.004	7.0 (3.5)	7.8 (4.5)	0.8	0.433	-4.8	0.004
% time <70 mg/dL	11.5 (8.5)	7.2 (5.1)	-4.3	0.006	11.2 (4.4)	12.5 (6.1)	1.5	0.372	-5.6	0.008
% time <63 mg/dL	8.6 (7.3)	4.6 (3.9)	-3.9	0.005	8.1 (3.6)	9.5 (5.1)	1.3	0.256	-5.2	0.003
% time <50 mg/dL	5.0 (5.5)	1.6 (2.0)	-3.4	0.004	4.3 (2.5)	4.9 (5.1)	0.6	0.401	-4.0	0.003
Low blood glucose index	8.7 (4.6)	5.1 (2.3)	-3.6	<0.001	8.2 (2.7)	5.1 (6.5)	1.0	0.109	-4.6	<0.0001
% time 70-140 mg/dL	36.5 (16.5)	42.9 (14.3)	6.4	0.078	37.5 (13.1)	41.3 (9.2)	3.8	0.064	2.6	0.516
% time 70-180 mg/dL	53.6 (17.1)	63.4 (14.9)	9.7	0.007	54.8 (14.3)	60.9 (10.9)	6.1	0.001	3.6	0.307
% time >140 mg/dL	52.0 (18.3)	49.9 (17.0)	-2.1	0.544	51.4 (14.9)	46.2 (11.2)	-5.2	0.105	3.1	0.496
% time >180 mg/dL	34.8 (18.3)	29.4 (17.1)	-5.4	0.104	34.0 (11.0)	26.6 (11.0)	-7.4	0.007	2.0	0.619
% time >270 mg/dL	11.9 (10.3)	7.3 (9.5)	-4.5	0.005	9.3 (10.5)	5.1 (6.5)	-4.2	0.009	-0.3	0.856
HbA1c (mmol/mol)	58.6 (12.3)	55.1 (13.0)	-3.5	0.039	57.2 (11.1)	53.8 (9.4)	-3.5	0.021	0.0	0.99
Gold Score	5.0 (0.9)	4.2 (1.6)	-0.8	0.046	4.6 (0.9)	4.7 (1.3)	0.1	0.609	-0.9	0.09
Hypoglycaemia Fear Survey-II	59.2 (24.9)	50.5 (24.3)	-8.7	0.01	49.4 (23.0)	50.5 (26.8)	1.1	0.8	-9.8	0.04
Behaviour subscale	21.90 (11.2)	19.65 (10.0)	-2.25	0.15	19.70 (10.6)	18.75 (10.7)	-0.95	0.54	-1,3	0.54
Worry subscale	37.25 (17.1)	30.80 (15.8)	-6.45	0.01	28.39 (11.4)	30.67 (15.9)	2.28	0.36	-8.73	0.01
*Baseline and Final values are mean (SD).										

Parker A, Welsh J, Jimenez A, Graham C Effects of sharing continuous glucose monitoring (CGM) data from young children with diabetes on CGM usage and hypoglycaemic exposure. Poster presented at the ISPAD 43rd Annual Conference; 2017 October 18-21; Innsbruck, Austria.[20]

Parker AS, Welsh JB, Hutchings M, Jimenez A, Walker T. Hypoglycaemic exposure among children using the Dexcom Share Cloud Poster presented at the 17th Annual Diabetes Technology Meeting; 2017 November 2-4; Bethesda, MD.[22]

Parker AS, Jimenez A, Welsh JB, Cooper TB, Walker T. Hypoglycaemic exposure among older adults using the Dexcom Share Cloud Poster presented at the 17th Annual Diabetes Technology Meeting; 2017 November 2-4; Bethesda, MD.[21]

Study Description: A retrospective observational study correlated real-time sharing of data captured by the G5 with CGM usage, mean blood glucose values, and hypoglycaemia exposure children and older adults.

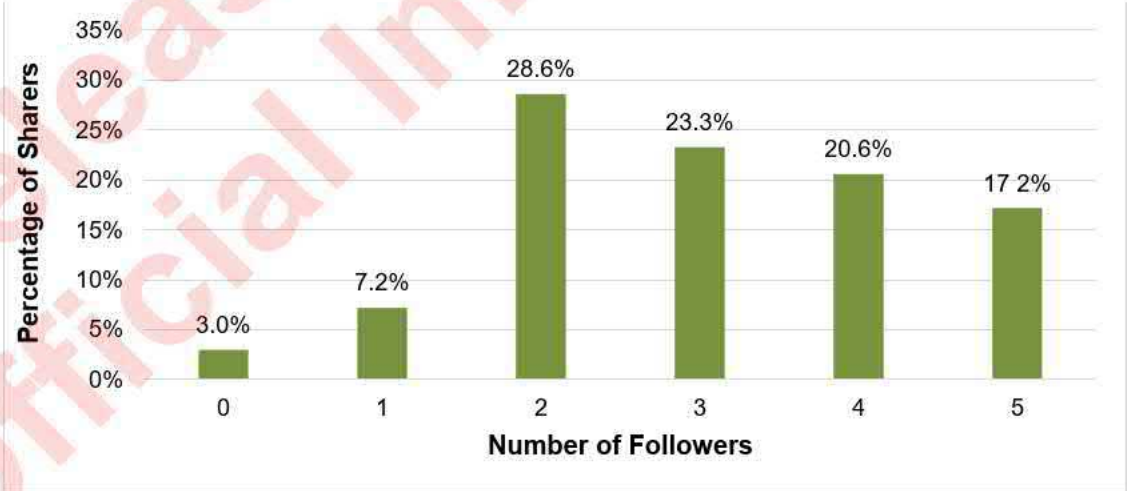
Funding Source: Dexcom, Inc.

Methods: Share/Follow is part of the G5 which allows for monitoring of data from one patient (the "sharer") by up to 5 "followers." It relies on data transfer from the sharer's Dexcom G5 Mobile App to the Dexcom Share Cloud, and then to the linked Follow app on the follower's smart device using either Wi Fi or cellular networks.

A convenience sample of 4,511 children aged 2-10 years, 8,805 children aged 2-14 years, and 1,653 adults ages 65 and older in the US who had uploaded data in May 2017 were identified and categorized according to the number of associated followers on June 2, 2017.

Sample Characteristics: About 97% of children aged 2-10 years had at least one follower; most had either 2 or 3 followers (Figure 13). Children aged 2-14 years in the "No Followers" (n=197) and "≥1 Follower" (n=8,608) categories had mean (±SD) ages of 9 3 ± 3 3 and 10 4 ± 3 1 years, respectively (p<0.0001). Adults in the "no followers" (n=934) and "≥1 follower" (n=719) categories had mean (±SD) ages of 69.9 ± 4.7 and 73.0 ± 8.1 years, respectively (p<0.0001).

FIGURE 13. USE OF FOLLOW IN CHILDREN AGED 2-10 YEARS



Outcomes: CGM utilization for each patient was calculated as the number of days per month with valid sensor glucose (SG) values, with each day equivalent to 288 SG values. Hypoglycaemic exposure was expressed as the percentage of SG values < 70 mg/dL.

Outcome (Sensor Use): As shown in Figure 14, sensor utilization increased from <2 to >4 weeks per month as the number of followers increased from 0 to 5 in children aged 2-10 years.

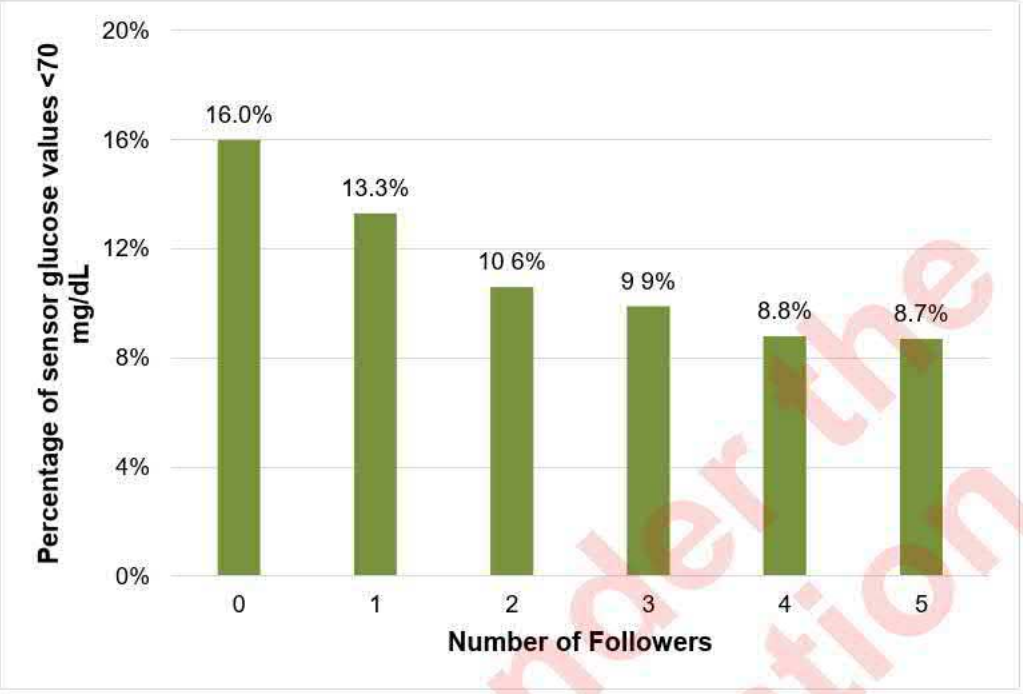
Children aged 2-14 years with followers used the sensor almost twice as much as children without followers (24 9 ± 8 2 vs 12 9 ±10 1 days/month; p<0 0001) Older adults with followers had significantly higher sensor use than those without followers (26.0 ± 7.6 vs. 24.3 ± 8.8 days/month; p<0 0001) Adults in the" ≥1 Follower" category used the sensors 7% more than adults in the "No Followers" category.

FIGURE 14 SENSOR USE BY NUMBER OF FOLLOWERS (CHILDREN AGED 2-10 YEARS)

Outcome (Mean SG Value): Children aged 2 14 years with followers had significantly higher mean SG values than those without followers (165.9 ± 35.3 vs. 156.3 ± 60.7 mg/dL; p<0.03). Older adults with followers had significantly higher mean SG values than those without followers (151.6 ± 35.1 vs. 145.8 ± 36.2 mg/dL; p<0.002).

Outcome (Hypoglycaemia Exposure): Children aged 2-10 years with more followers had progressively lower percentages of SG values that were <70 mg/dL (Figure 15). Children aged 2-14 years with followers had 43% fewer SG readings <70 mg/dL than those without followers (10.9 ± 12.7% vs. 19.0 ± 27.6%; p<0.0001). Older adults with followers had a significantly lower percentage of SG readings <70 mg/dL than those without followers (8 9 ± 12 6% vs 10 3 ± 15.4%; p<0.04). Adults in the" ≥1 Follower" category had 14% fewer senor readings >70 mg/dL than adults in the "No Followers" category

FIGURE 15. PERCENTAGE OF TIME IN HYPOGLYCAEMIA BY NUMBER OF FOLLOWERS (CHILDREN AGED 2-10 YEARS)



Conclusions: Over 97% of young children using the Dexcom Share Cloud had at least one associated follower Compared to young children with no followers, these children had increased sensor usage and 43% fewer SG readings indicative of hypoglycaemia, consistent with appropriate and timely involvement of follower(s) Children aged 2 14 years with ≥1 follower also had slightly higher mean glucose levels, but less glycaemic variability, than children with no followers In this population of young children who are unlikely to entirely self-manage their diabetes, data sharing with Share/Follow may help their parents and caregivers provide appropriate and timely interventions that lead to higher CGM utilization and improved glycaemic outcomes. Over 43% of older adults using the Dexcom Share Cloud had at least one associated follower Compared to those with no followers, these adults had higher mean SG values, used the sensors more frequently, and had 14% fewer SG readings <70 mg/dL. Older adults may benefit from technologies that facilitate involvement of others in diabetes related treatment decisions.

Quality Grade: Fair

7.1.2 Clinical data supporting FDA Off-label Indications including pregnant women with T1DM or T2DM who are treated with insulin

Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet* 2017. [181]

Study Description: This was a multicentre, open label, randomized controlled in women with T1DM who were receiving intensive insulin therapy via MDI who were pregnant or planning pregnancy, designed to evaluate the effectiveness of RT CGM on maternal glucose control and obstetric and neonatal health outcomes.

Funding Source: Juvenile Diabetes Research Foundation

Methods: This study included two parallel trials: a pregnancy trial and a planning pregnancy trial. The study was conducted from March 2013 to March 2016 at 31 hospitals in Canada, England, Scotland, Spain, Italy, Ireland, and the USA.

Subjects were women aged 18 40 years with T1DM for a minimum of 12 months, receiving intensive insulin therapy via MDI or an insulin pump who were pregnant or planning pregnancy. Pregnant women were eligible if they had a live singleton foetus confirmed by ultrasound, were at 13 weeks and 6 days gestation or less, and had HbA1c between 6.5-10.0% (48–86 mmol/mol). Women planning for pregnancy were eligible if they had an HbA1c level between 7 0 10 0% (53 86 mmol/mol).

Regular RT CGM users and women with severe nephropathy or medical conditions such as psychiatric illness requiring hospitalization that could prevent them from completing the trial were excluded Women using automatic insulin delivery options, such as low glucose suspend pumps, were not excluded.

After enrolment, participants had to complete a run-in phase with a masked CGM device before they were eligible for randomization. In the run-in period, glucose values were recorded but were not visible to the user or clinical team Eligibility required that participants wear the sensor for 6 days, provide at least 96 h of glucose values including a minimum of 24 h overnight, and obtain at least four capillary glucose tests daily. Participants meeting these criteria were randomized to receive either RT-CGM (Guardian REAL-Time or MiniMed Minilink system, both Medtronic, Northridge, CA) in addition to capillary glucose monitoring (intervention) or capillary glucose monitoring alone (control). Treatments were allocated in a 1:1 ratio via a web-based system that used a computer-generated randomization list with permuted block sizes and stratification by method of insulin delivery (pump or multiple injections), and baseline HbA_{1c} (<7.5% *vs* ≥7.5% for the pregnancy trial; <8 0% *vs* ≥8 0% for the planning pregnancy trial

Clinical Outcomes: The primary outcome was difference in change in HbA1c from randomization to 34 weeks' gestation in the pregnancy trial and to 24 weeks or conception in the planning pregnancy trial. Prespecified secondary glycaemic outcomes for all groups were percentage of time spent in, above, and below the recommended glucose control target range (63-140 mg/dL); area under the curve for glucose levels; episodes of hypoglycaemia; and glucose variability measures derived from CGM measures For pregnant women, prespecified health outcomes were gestational weight gain, gestational hypertension, pre-eclampsia, mode of delivery, length of hospital stay, insulin dose, and questionnaires relating to fear of hypoglycaemia, coping with diabetes, quality of life, and satisfaction with monitoring device. Prespecified neonatal health outcomes included preterm delivery, neonatal hypoglycaemia requiring intravenous dextrose, neonatal intensive care unit admission requiring a duration of at least 24 h, cord blood gas pH, total length of hospital stay, birthweight, and macrosomia (birthweight ≥4 kg). We included the following outcomes both as individual and as a composite neonatal measure: pregnancy loss (miscarriage, stillbirth, or neonatal death), birth injury, shoulder dystocia, neonatal hypoglycaemia, hyperbilirubinaemia, respiratory distress syndrome, or neonatal intensive care admission To capture clinically important adverse outcomes, neonatal

hypoglycaemia was defined as requiring treatment with intravenous dextrose and neonatal intensive care unit admission as requiring a duration of at least 24 h

Sample Characteristics: 386 participants were assessed for eligibility and 325 participants were randomized, with 215 pregnant and 110 planning pregnancy In the pregnancy trial, 108 women were assigned to the RT-CGM intervention and 107 women were assigned to the control group. One RT-CGM participant withdrew before the baseline assessments, leaving 107 in each group In the planning pregnancy trial, 53 women were assigned to the intervention and 57 to the control group Most participants self identified as of European or Mediterranean origin, were college educated, non-smokers, and had a long duration of T1DM. Approximately half were overweight or obese Half the women in the pregnancy trial took folic acid preconception and slightly more than half used MDI. In the planning pregnancy trial, a greater proportion of women used insulin pump therapy than in the pregnancy trial The mean HbA1c levels at randomization were lower in the pregnant women.

Outcome (HbA1c): In the primary analysis of the pregnancy trial, there was a small but significant between-group difference in the change in HbA1c from baseline to 34 weeks' gestation, favouring RT CGM (mean difference 0 19%, 95% CI 0 34 to -0 03; p=0 0207) In the planning pregnancy trial, the between-group difference was of a similar size but with a wider confidence interval and not significant (0 17%, 95% CI 0.43 to 0.09; p=0=0 20). Outcomes of the 34 women (17 RT CGM and 17 control group) who conceived during the 24-week planning pregnancy trial did not differ.

Outcome (% of time in Target Range, Hyperglycaemia, and Hypoglycaemia): In the pregnancy trial, the women in the RT-CGM group spent increased time in the recommended glucose control target range of 63 140 mg/dL (68% vs 64%, p=0.0034) and less time above target (27% vs. 32%, p=0.0279) compared with those in the control group. There was no difference between groups for time spent during hypoglycaemia (3% vs 4%, p=0 10)

Outcome (Glycaemic Variability): Women in the RT-CGM group had reduced glucose SD (p=0 0359), lower mean amplitude of glucose excursion (0.0455), and non significantly reduced glucose coefficient of variation (p=0.0568) compared with those in the control group.

Outcomes (No of episodes of severe hypoglycaemia): In the pregnancy trial, women receiving RT-CGM had a similar incidence of severe hypoglycaemia episodes as those in the control group (18 vs. 21)

Outcomes (Maternal Outcomes): In the pregnancy trial, there were no observed between-group differences in hypertensive disorders, pre-eclampsia, caesarean delivery, gestational age, or preterm delivery.

Outcomes (Neonatal Outcomes): There was a decreased proportion of large for gestational age (odds ratio 0.51, 95% CI 0 0.27-0.90; p=0=0210) in the infants of mothers randomly assigned to RT CGM Infants of mothers randomized to RT CGM experienced fewer neonatal intensive care admissions lasting more than 24 h (odds ratio 0.48, 95% CI 0.26-0.86; p=0.0157), fewer incidences of neonatal hypoglycaemia requiring treatment with intravenous dextrose (0 45, 0.22–0.89; p=0=0250), and a reduced total length of hospital stay (p=0.0091) than did infants of control participants There were no differences in the composite foetal outcome, cord blood C peptide levels, and neonatal anthropometric measurements.

Outcomes (Patient reported Outcome Measures): There were no between group differences in any of the patient-reported outcome measures, including the Blood Glucose Monitoring System Rating Questionnaire, Problem Areas in Diabetes Short Form 12, and Hypoglycaemia Fear Survey.

Conclusion: This study is the first to show an effect of RT CGM on health outcomes other than glycaemic outcomes, and with substantial reductions in neonatal complications attributed to maternal hyperglycaemia Data indicate a role for offering RT CGM to all pregnant women with T1DM using intensive insulin therapy in the first trimester.

Quality Grade: Good

8. ECONOMIC VALUE AND MODELING REPORT (PLACEHOLDER)

9. OTHER SUPPORTING EVIDENCE

9.1 CLINICAL PRACTICE GUIDELINES

American Diabetes Association

In the 2018 *Standards of Medical Care in Diabetes*, the ADA found strong evidence supporting the value of RT CGM in conjunction with intensive insulin therapy in lowering HbA1c without increasing hypoglycaemia in adults with T1DM (Grade A)[154] and supportive evidence that RT-CGM can help reduce HbA1c in children and adolescents with T1DM (Grade B) [190] The guidelines also note that RT-CGM technology may be particularly useful in people with IAH and/or frequent hypoglycaemic episodes (Grade C).[154] People who have successfully used RT CGM should have continued access after age 65 (Grade E).[154] Given the variable adherence to RT-CGM, clinicians should assess individual readiness for continuing RT CGM use prior to prescribing. (Grade E).[154] When prescribing RT-CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use (Grade E) [154]

American Association of Clinical Endocrinologists/American Academy of Endocrinology (AACE/ACE)

On the basis of available evidence, the 2016 AACE/ACE Consensus Conference on Glucose Monitoring made the following recommendations:[157]

- Consensus conference attendees unanimously agreed that RT-CGM should be made available for all insulin using patients regardless of diabetes type although this conclusion is based entirely on studies conducted in T1DM.
- Few studies have been conducted in patients with IAH due to challenges recruiting a suitable patient population, but it is likely that this population would also benefit from RT-CGM
- Other patients at risk from hypoglycaemia, including the elderly, patients with renal impairment, and athletes should receive next priority
- T2DM patients who use antihyperglycaemic agents other than insulin might also benefit from RT-CGM, but the evidence base is inadequate to make a strong recommendation.

Endocrine Society

The Endocrine Society strongly recommends RT CGM for adult patients with T1DM who have HbA1c levels above target and those with well-controlled T1DM who are willing and able to use RT-CGM on a nearly daily basis (high-quality evidence) [191] The Endocrine Society suggests short-term, intermittent RT-CGM use in adult patients withT2DM (not on prandial insulin) who have HbA1c levels ≥7% and are willing and able to use the device (low-quality evidence)

National Institute for Healthcare Excellence (NICE)

The most current NICE guidelines for the diagnosis and management of adults with T1DM (NG17) recommend that RT CGM be considered for adults with T1DM who are willing to commit to using RT-CGM at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring:[192]

- More than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause;
- Complete loss of awareness of hypoglycaemia;
- Frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities;
- Extreme fear of hypoglycaemia; or
- Hyperglycaemia (HbA1c level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day.

RT-CGM should be continued only if HbA1c can be sustained at or below 5 mmol/mol (7%) and/or there has been a fall in HbA1c of 2 mmol/mol (2 5%) or more

The principles of flexible insulin therapy with either a MDI insulin regimen or insulin pump therapy should be used for adults with T1DM who are using RT CGM

RT-CGM should be provided by a centre with expertise in its use, as part of strategies to optimise a person's HbA1c levels and reduce the frequency of hypoglycaemic episodes

The most current NICE guidelines for the diagnosis and management of diabetes in children and young people (NG18) recommend the use of RT CGM with alarms in children with T1DM who have:[193]

- Frequent severe hypoglycaemia;
- Impaired awareness of hypoglycaemia associated with adverse consequences (for example, seizures or anxiety); or
- Inability to recognize, or communicate about, symptoms of hypoglycaemia (for example, because of cognitive or neurological disabilities)

In addition, the guidelines specify that RT-CGM should be considered for:

- Neonates, infants and pre school children;
- Children and young people who undertake high levels of physical activity (for example, sport at a regional, national or international level); and
- Children and young people who have comorbidities (for example anorexia nervosa) or who are receiving treatments (for example corticosteroids) that can make blood glucose control difficult

Lastly, intermittent (real-time or retrospective) CGM should be considered to help improve blood glucose control in children and young people who continue to have hyperglycaemia despite insulin adjustment and additional support.

European Society for Paediatric Endocrinology (ESPE), Paediatric Endocrine Society (PES), and International Society for Paediatric and Adolescent Diabetes (ISPAD)

A panel of expert physicians convened by the ESPE, the PES, and the ISPAD provided a consensus statement in 2012 regarding the use of RT-CGM in pediatric and adolescent patients with T1DM.[194] The group recommended that RT-CGM be considered in children and adolescents with T1DM who:

- Are performing frequent SMBG;
- Have experienced severe hypoglycaemic episodes;
- Have hypoglycaemic unawareness (especially in young children);
- Have nocturnal hypoglycaemia;
- Have wide glucose excursions; or
- Have HbA1c exceeding target range or who wish to have in-target glycated hemoglobin levels but limit the risk of hypoglycemia.

International Diabetes Federation (IDF)/ISPAD

A global guideline for diabetes in childhood and adolescence, developed by the IDF/ISPAD in 2011, noted that RT-CGM may allow near-normalization of blood glucose and HbA1c while decreasing risk of hypoglycaemia.[195] In addition, the guideline states that RT CGM may particularly benefit patients with IAH.

9.2 HEALTH TECHNOLOGY ASSESSMENTS AND SYSTEMATIC REVIEWS

Health Quality Ontario

The Ontario Health Technology Advisory Committee (OHTAC) recommended publicly funding CGM in patients with T1DM who are willing to use CGM for the vast majority of the time and who meet one or more of the following criteria:

- Severe hypoglycaemia without an obvious precipitant, despite optimized use of insulin therapy and conventional blood glucose monitoring
- Inability to recognize, or communicate about, symptoms of hypoglycaemia.[196]

OHTAC members noted that CGM provides benefit for outcomes that are important to patients, including maintaining their blood glucose in an optimal range. However, CGM is very expensive, and there is considerable uncertainty about whether the technology represents good value for money for many patients with T1DM.

OHTAC members took into account the lived experience of patients with T1DM and parents of children with T1DM, who described the social, clinical, and safety benefits of CGM. Based on these considerations, the OHTAC decided to recommend public funding for CGM for patients who meet certain criteria.

Centre for Evidence-based Policy - Oregon

To develop coverage guidance, the Health Evidence Review Commission (HERC) evaluated relevant research on RT-CGM using an adaptation of the GRADE methodology.[197] The HERC recommended coverage (*weak recommendation)* of RT-CGM in adults with T1DM who 1) have received or will receive will receive diabetes education specific to the use of RT-CGM and who have used the device for at least 50% of the time at their first follow-up visit, and 2) have baseline HbA1c ≥ 8.0%, frequent or severe hypoglycaemia, or impaired awareness of hypoglycaemia. RT-CGM (including the RT CGM enabled insulin pump) was recommended for coverage *(weak recommendation)* in adults with T1DM on insulin pump management who have received or will receive diabetes education specific to the use of CGM and who have used the device for at least 50% of the time at their first follow-up visit.

The rationale for a weak recommendation of coverage in adults with T1DM was due the limited evidence of benefit. The HERC found that use of RT-CGM in adults with T1DM results in greater improvements in HbA1c when compared with SMBG but was not clear that these benefits are clinically significant. In addition, the committee found that there is insufficient evidence on long-term clinical outcomes related to the use of RT CGM, and lack of evidence that RT CGM reduces severe hypoglycaemia or ketoacidosis.

Coverage of RT CGM was recommended (*weak recommendation*) in children and adolescents <21 years with T1DM who have received or will receive diabetes education specific to the use of RT-CGM and who have used the device for at least 50% of the time at their first follow-up visit The recommendation for coverage was based on strongly expressed values and preferences and is a weak recommendation that may be supplemented by further studies of RT CGM use in this population This HERC had high confidence that use of RT-CGM in children with T1DM results in greater parental satisfaction In addition, expert testimony confirms that providers, parents, and these young patients highly value the benefits of improved monitoring capability, especially in reducing anxiety related to potential hypoglycaemia during attempts to improve HbA1c levels Although the evidence does not show benefit in critical or important outcomes, the committee recognized that published RT CGM studies generally do not include the youngest children with T1DM and do not address long-term developmental concerns.

Diabetes Australia

In 2017, Diabetes Australia launched a new position statement on glucose monitoring in patients with T1DM and T2DM.[198] The organization strongly supports the subsidized access to RT-CGM, for children and young people (under 21) with T1DM, which commenced on April 1, 2016 Access to RT-CGM is free for all children aged ≤10 years and for children and young people with T1DM (aged >10 and ≤21 years) who meet one of the following criteria:

- Frequent significant hypoglycaemia, i.e. more than one episode a year of severe hypoglycaemia needing assistance from someone else for recovery;
- IAH;
- Inability to recognize, or communicate about, symptoms of hypoglycaemia; and/or
- Significant fear of hypoglycaemia for the child/young person or a family member/ caregiver, which is seriously affecting the health and wellbeing of the child or young person or contributing to high glucose levels (hyperglycaemia) as a reaction to this fear.

There is currently no subsidized access to RT CGM for adults aged 21 years or older in Australia Diabetes Australia recommends that subsidized access to RT CGM should be extended to adults aged 21 and over in the following groups:

- People with recurrent severe hypoglycaemia (i e , needing assistance for recovery);
- People with IAH who are at high risk of severe hypoglycaemia;
- People with significant fear of hypoglycaemia where this is significantly affecting their diabetes management (leading them to maintain high glucose levels (hyperglycaemia) and/or their quality of life); and
- Women with T1DM while planning for a pregnancy and during pregnancy, due to the adverse effect that high and low glucose levels can have on the unborn child

Institute for Quality and Efficiency in Healthcare (Germany/IQWiG)

This HTA evaluated the benefit of RT-CGM compared with other methods of measuring blood glucose in patients with diabetes receiving insulin [199] The systematic review was limited to randomized controlled trials with a minimum duration of 24 weeks published through 13 August 2014 Thirteen studies compared continuous use of RT-CGM plus SMBG versus SMBG alone The joint consideration of severe hypoglycaemia and HbA1c value produced proof of an advantage of RT CGM plus SMBG versus SMBG alone for the subgroup of adults (>18 years) with T1DM based on proof of superiority regarding HbA1c (a statistically significantly greater proportion of adults in the RT CGM group had HbA1c <7% at the end of the study) and a hint of an effect in favour of the RT CGM group regarding the proportion of patients with at least one severe hypoglycaemic event.

There was an indication of benefit of RT-CGM in children (<18 years) with T1DM regarding the joint consideration of severe hypoglycaemia and HbA1c value, which was based on a hint of superiority regarding severe hypoglycaemia and an indication of superiority regarding HbA1c

There were no harms for adults or children aside from a hint of harm regarding skin reactions.

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