



Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL, STATE AND
TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Australia and New Zealand
Horizon Scanning Network
Continuous glucose monitoring devices
Horizon Scanning Report



Te Whare Wānanga o Ōtago



NEW ZEALAND HEALTH TECHNOLOGY ASSESSMENT
DEPARTMENT OF PUBLIC HEALTH AND GENERAL PRACTICE
CHRISTCHURCH SCHOOL OF MEDICINE AND HEALTH SCIENCES
UNIVERSITY OF OTAGO
CHRISTCHURCH, NEW ZEALAND

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This Horizon Scanning Report was prepared by staff from the New Zealand Health Technology Assessment group, Department of Public Health and General Practice, Christchurch School of Medicine and Health Sciences, University of Otago, New Zealand. <http://nzhta.chmeds.ac.nz/> Mr Peter Day (Research Fellow) prepared the report. The literature search strategy was developed and undertaken by Mrs Susan Bidwell (Information Specialist Manager). Internal peer review was provided by Dr Robert Weir (Director) and Mrs Susan Bidwell.

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The New Zealand Health Technology Assessment Unit, Department of Public Health and General Practice, Christchurch School of Medicine and Health Sciences, University of Otago, on behalf of the Medical Services Advisory Committee (MSAC) and the New Zealand Ministry of Health, has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of continuous glucose monitoring (CGM) devices for patients with diabetes mellitus.

Continuous glucose monitoring (CGM) devices provide in depth information about fluctuations in glucose levels throughout the day and facilitate the prevention of hypo- and hyperglycaemia in patients with diabetes mellitus. A range of technologies are currently being researched for non-invasive and minimally invasive continuous glucose monitoring systems. Only impedance spectroscopy (the application of electromagnetic radiation through the skin to the blood vessels) and interstitial fluid (ISF) technologies are currently approved for clinical use.

Typically these devices consist of a small monitor that reads and displays glucose values in real-time or retrospectively, a glucose sensor which is attached subcutaneously to the abdomen or externally to the arm, and a transmitter to relay information about glucose concentrations between the sensor and monitor. These monitoring devices supplement but do not replace standard blood glucose self-monitoring (SMBG) practices and can be used in home settings. Seven CGM devices are currently U.S. Food and Drug Administration (FDA) approved for clinical use on a prescription basis in the U.S. or CE (Conformité Européene or European Conformity) marked for use in Europe. Other devices are pending FDA approval. In Australia and New Zealand, the CGMS[®] Continuous Glucose Monitoring System (Medtronic MiniMed, Northridge, CA) and its second generation replacement CGMS[®] System Gold[™] are currently available but only for approved physician-supervised use for inpatients and are pending TGA approval in Australia.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an updated assessment of the current state of development of continuous glucose monitoring devices in general, their present use, the potential future application of the technology, and its likely impact on the Australian and New Zealand health care systems. This Horizon Scanning Report is an update statement based on the latest available evidence derived from Randomised Controlled Trials (RCTs) on the safety, effectiveness, cost-effectiveness and ethical considerations associated with continuous glucose monitoring devices for diabetic patients.

Description of the technology

Development of the procedure

The Diabetes Control and Companion Trial (DCCT) (1993) and the U.K. Prospective Diabetes Study (UKPDS) (1998) have shown that tight glycaemic control and intensified insulin therapy reduces long-term complications associated with diabetes mellitus. However, intensified insulin therapy also increases the risk of severe hypoglycaemic events. Frequent and accurate blood glucose monitoring is necessary if the disease is to be managed optimally. Standard self-testing techniques with finger pricks and home glucose meters can be painful, messy, and inconvenient and have poor patient compliance. Due to the importance of achieving euglycaemia in diabetes management and limitations with conventional SMBG methods there has been considerable investment and development in CGM technologies with more than 100 companies currently involved in the research (Sieg et al, 2005).

Glucose monitoring has in the past relied on blood glucose levels. Newer technologies using non-invasive and minimally invasive glucose sensing technologies focus on the interaction of electromagnetic radiation with tissue and the harvesting of interstitial fluid (ISF) across the skin.

Truly non-invasive techniques involve tissue irradiation, the analysis of the absorbed and scattered radiation, the processing of this information, and the measurement of the glucose in the dermal tissue. This includes optical methods such as near-infrared, Raman spectroscopy, polarimetry, light scattering, and photoacoustic spectroscopy. The structural and physiological properties of the skin present difficulties in the reliability of these optical methods for glucose monitoring sensing. At present there are no large-scale clinical studies supporting the efficacy, portability, and affordability of these technologies. Therefore at present minimally invasive technologies are offering the greatest potential for practical continuous glucose monitoring devices for clinical use (Bui et al, 2005; Sieg et al, 2005).

Minimally invasive continuous glucose monitoring techniques sample and monitor glucose concentrations in the ISF and not the blood. These techniques are considered to be minimally invasive because they do not puncture any blood vessels but rather they bring a sensor into contact with ISF by inserting a sensor subcutaneously (into the abdominal wall, wrist or arm) to measure ISF in situ (e.g. direct sensor implantation, CGMS[®]) or by extracting this fluid to an external sensor by various mechanisms which compromise the skin barrier (e.g. reverse iontophoresis, GlucoWatch[®] G2 Biographer) (Klonoff, 2005a).

A wide range of continuous glucose monitoring technologies are currently being researched. At this stage only non-invasive impedance spectroscopy (the application of electromagnetic radiation through the skin to the blood vessels) and minimally invasive technologies (interstitial fluid (ISF) measurement in situ or extraction through the skin) are approved for clinical use.

The procedure

Typical CGM systems consist of:-

- a small monitor (usually a pager sized recording device clipped to the belt) that reads and displays glucose values in real-time or retrospectively
- a glucose sensor (usually a glucose-oxidase based needle-like sensor) which is implanted subcutaneously in the abdomen (or externally to the wrist, arm or forearm)
- a transmitter to relay information about glucose concentrations between the sensor and monitor (via a cable or wirelessly).

Some devices such as the CGMS[®] System Gold[™] have a Com-station, a communication device for downloading sensor data to a computer. Each device has specific attractive features such as sensor placement options, longer sensor life, alarms for out-of range values, real time readings (a feature in more recent devices), and varying degrees in invasiveness. Each device undergoes a warm-up period of 1-2 hours, a device specific calibration process of between 1 and 4 times per day, and each device's sensor provides a blood glucose reading every 1-10 minutes for up to 72 hours and up to 3-months for newer non-invasive technology. The blood glucose information is available to the patient and clinician either in real time or retrospectively and many models have alarms that trigger if glucose levels fall outside of preset euglycaemic ranges (Table 1.) (Klonoff, 2005a).

Stage of development

Seven CGMs have been approved by the U.S. Food and Drug Administration (FDA) for clinical use in the U.S. or carry the CE marking for clinical use in Europe. The basic specifications of these devices are outlined in Table 1.

The devices are the:-

- Continuous Glucose Monitoring System Gold (CGMS[®] System Gold[™]; Medtronic MiniMed, Northridge, CA)
- GlucoWatch[®] G2 Biographer (Cygnus Inc, Redwood City, CA)
- Guardian[®] Telemetered Glucose Monitoring System (Medtronic MiniMed, Northridge, CA)
- Guardian[®] RT Continuous Glucose Monitoring System (Medtronic MiniMed, Northridge, CA)
- GlucoDay[®] (Menarini Diagnostics, Florence, Italy)
- Pendra (Pendragon Medical, Zurich, Switzerland)
- STS[™] Continuous Glucose Monitoring System (Dexcom, San Diego, CA)

One further device, the FreeStyle Navigator[™] Continuous Glucose Monitor (Abbott Laboratories, Alameda, CA), is pending FDA approval.

Minimally invasive CGM systems are available in Australia which measure interstitial blood glucose via an indwelling sensor in the subcutaneous tissue of the abdomen or buttocks. Only the CGMS[®] Continuous Monitoring System (Medtronic MiniMed, Northridge, CA) and its successor the CGMS[®] System Gold[™] are currently available in Australia and New Zealand but are only available in approved hospitals, diabetes clinics

and research centres for physician-supervised use in the management of specialised diabetes cases (Cameron and Ambler, 2004). In Australia it is currently not approved by the TGA and clinicians must apply to the TGA for use in each specialised patient (personal communication, Medtronic Australasia). Non-invasive CGM systems such as the GlucoWatch[®] G2 Biographer are not available in Australia or New Zealand. Some individuals have accessed this CGM technology via overseas contacts and it is likely that increasing patient demand will see this technology introduced.

Table 1: Specifications of continuous glucose monitoring systems approved or pending approval for clinical use

Product	FDA Approved/ CE marked	Year first approved or marked	Sensor type	Sensor mechanism	Sensor location	Sensor warmup (h)	Calibrations per lifetime of sensor	Sensor lifespan (h)	Frequency of testing (min)	Time of blood glucose data display	Alarm
Continuous Glucose Monitoring System (CGMS) Gold (Medtronic MiniMed)	Yes/Yes	1999	Minimally invasive	Enzyme-tipped catheter	Subcutaneous abdomen	2	12	72	5	Retrospective	No
GlucoWatch G2 Biographer (GW2B) (Cygnus Inc)	Yes/ Yes	2001/2002	Minimally invasive	Reverse iontophoresis	External on arm or forearm	2	1	13	10	Real time	Yes
Guardian Telemetered Glucose Monitoring System (Medtronic MiniMed)	Yes/Yes	2004	Minimally invasive	Enzyme-tipped catheter	Subcutaneous arm	2	12	72	5	Retrospective	Yes
GlucoDay (Menarini Diagnostics)	No/Yes	2001	Minimally invasive	Microdialysis	Subcutaneous abdomen	0	1	48	3	Real time or retrospective	Yes
Pendra (Pendragon Medical)	No/Yes	2004	Non-invasive	Impedance spectroscopy	External on wrist	1	20	3 months	1	Real time	Yes
FreeStyle Navigator Continuous Glucose Monitor (Abbott Laboratories)	No/No	—	Minimally invasive	Enzyme-tipped catheter	Subcutaneous arm or abdomen	1	1	72	1	Real time	Yes
Guardian RT Continuous Glucose Monitoring System (Medtronic MiniMed)	Yes/No	2005	Minimally invasive	Enzyme-tipped catheter	Subcutaneous abdomen	2	6	72	5	Real time	Yes
STS System (DexCom)	Yes/No	2005	Minimally invasive	Enzyme-tipped catheter	Subcutaneous abdomen	2	6	72	5	Real time	Yes

Adapted from Klonoff (2005a)

Intended purpose

Testing blood glucose levels is essential for children, adolescents and adults who suffer from Type-1 and Type-2 diabetes requiring treatment with insulin and for people taking oral hypoglycaemic agents. A primary treatment goal in insulin dependent diabetes is tight glucose control to minimise complications associated with diabetes. Insulin dependent patients must monitor their blood glucose to ensure that suitable levels of insulin are circulating. To ensure appropriate glucose control patients may require intensive therapy to administer insulin by injection at least three or more times during the day, or have insulin delivered by an external or implanted pump by continuous insulin infusion. There are varying recommendations regarding the method, technique, timing, and frequency of self-monitoring blood glucose (SMBG) in non-insulin dependent Type-2 diabetes patients (Bergental and Gavin, 2005).

SMBG with the finger prick test and glucose meter adds valuable information that complements glycohaemoglobin (HbA1c) testing in achieving optimal glycaemic control. Conventional point-in-time blood testing provides discrete and highly accurate data about current glucose levels. Given that HbA1c monitoring is a time-averaged result it has limitations as a marker for glycaemic control. This is because it does not represent “real time” monitoring for patients and physicians and excursions in glycaemic control such as post-prandial hyperglycaemia or severe hypoglycaemia may be missed (Bergental and Gavin, 2005). The main limitations with SMBG are that this method is invasive, messy and painful, and inconvenient which can affect testing compliance, especially among paediatric patients.

Minimally invasive continuous glucose monitoring systems obtain multiple readings over time but are not as accurate as SMBG testing and for people taking oral hypoglycaemic agents. CGM devices are used to obtain in depth information about changes in blood glucose levels throughout the day to facilitate optimal glycaemic control for Type-1 and Type-2 diabetes patients requiring insulin therapy. Patients and clinicians have the ability to view real time blood glucose values, to retrospectively review recent blood glucose values, review trend graphs for glucose values, and receive alerts/alarms for impending hypo- or hyperglycaemia. These devices are particularly useful for night time monitoring particularly in preventing episodes of hypoglycaemia unawareness. Continuous glucose monitoring devices supplement but do not replace standard blood glucose self-monitoring (SMBG) practices and can be used in home settings.

CGM is also being used in the management of patients with conditions associated with diabetes. The CGMS[®] monitoring device has been used to monitor children with diseases associated with hypoglycaemia including hyperinsulinism (Conrad et al, 2004), and glycogen storage (Hershkovitz et al, 2001), hyperglycaemia in pregnancy (Buhling et al, 2004; Kerssen et al, 2004), glucose monitoring of neonates in neonatal intensive care (Beardsall et al, 2005; Javid et al, 2005), and to assist with continuous positive airway pressure (CPAP) interventions for obstructive sleep apnea (Babu et al, 2005; Czupryniak et al, 2005). Patients with cystic fibrosis related diabetes have benefited from CGM (Jefferies et al, 2005), as have pregnant women where strict glycaemic control can reduce perinatal complications (Kerssen et al 2005).

CGM has been utilised as an adjunct monitoring system to assess glycaemic control using continuous subcutaneous insulin infusion (CSII) compared with multiple daily injection (MDI) for both Type-1 and Type-2 diabetes patients (Hirsch et al, 2005; Wainstein et al, 2005). Prototype systems for CGM in closed-loop systems with a combination of a continuous glucose monitor, a control algorithm, and an insulin pump have been developed. The main two approaches use either a minimally invasive subcutaneous system for glucose monitoring and insulin delivery or intravenous glucose sampling and intraperitoneal insulin delivery (Hovorka, 2006). Medtronic MiniMed (Northridge, CA) have particularly been involved in closed-loop projects utilising both the CGMS[®] and Guardian[®] monitoring systems and other groups have also utilised Medtronic MiniMed technology. Although feasibility studies into closed-loop systems have been conducted the reliability and accuracy of the glucose monitors remains the main limitation to commercially viable closed-loop systems (Hovorka, 2006).

Clinical need and burden of disease

Type-1 or juvenile diabetes occurs where sufferers produce no (or very little) insulin due to the auto-immune destruction of the insulin producing beta cells of the pancreas. Type-1 diabetes represents approximately 10-15 per cent of all diabetic patients, however 98 per cent of childhood diabetes is Type-1. Type-2 diabetes occurs where sufferers still produce insulin but production is impeded and is characterised by reduced levels of insulin or insulin resistance and represents approximately 85-90 per cent of diabetic sufferers, most of whom are over the age of 40 years. Gestational diabetes is a temporary form of diabetes, which occurs during pregnancy in 3-8 per cent of females not previously diagnosed with diabetes (AIHW, 2002).

It is recommended that blood glucose self-monitoring be performed by checking blood glucose levels at least 3 times per day using the finger prick test and glucose meter (Bergenstal and Gavin, 2005). This method is invasive, messy, and can be painful and difficult to perform.

Burden of disease in Australia

An estimate of the number of patients who could benefit from continuous glucose monitoring was based on estimates of diabetes prevalence. The Australian Institute of Health and Welfare (AIHW) 2001 National Health Survey estimates, based on self-reported information, that 95,000 (0.5%) of Australians have type 1 diabetes and that a further 900,000 (7%) of adults aged 25 years and over had type 2 diabetes based on 1999/2000 data (AIHW, 2004).

Estimates for the age-standardised prevalence of Type-1 diabetes for 1999-2000 was 298 per 100,000 or approximately 37,000 individuals over the age of 25 years (AIHW, 2002). Since 1999, the National Diabetes Register (NDR) has collected information on the number of new users of insulin. There were 4,548 new cases of Type-1 diabetes, aged 0-39 years, for the years 1999-2001, 50 per cent of these cases were children aged 0-14 years. The most recent data on the incidence of childhood diabetes in Australia for the years 2000-2001 indicate an incidence rate of 20.3 and 18.9 per 100,000 for males and females, respectively (AIHW, 2003). Of the 21,346 new insulin users registered on the NDR for the years 1999-2001, 12,167 (57%) suffered from Type-2 diabetes. The majority (90%) of these patients were aged over

35 years (AIHW, 2003). The prevalence of Type-2 diabetes is increasing and has been associated with obesity, poor nutrition and physical inactivity.

Over the period 2001–2003 there were 20,908 diabetes-related deaths registered (5.4% of all deaths) for people aged 25 years or over in Australia. Diabetes was recorded as the underlying cause of death in 9,772 of these cases, representing 2.5% of all deaths registered during the period (AIHW, 2005a).

The total Australian health system expenditure on diabetes in 2000–01 was estimated to be around \$784 million, or 1.7% of allocatable recurrent health expenditure. Diabetes was ranked fifteenth out of around 200 disease groups compared. An estimated \$204 million was spent by the Australian Government on people with diabetes on antidiabetic drugs and diabetes testing reagents. Although only 10% of the 4.6 million prescriptions for antidiabetic drugs in 2000–01 were for insulin, these accounted for 60% of expenditure on antidiabetic drugs. Average health expenditure on diabetes in 2000–01 was \$1,469 per known (self-reported) case of diabetes, or \$42 per Australian (AIHW, 2005b).

Burden of disease in New Zealand

The New Zealand population of adults aged 15 years and over in 2002/03 was estimated at 3,124,690 (Statistics New Zealand, 2005). Self-reported diabetes information from the 2002/03 New Zealand Health Survey indicated that the diabetes prevalence rate in adults aged 15 years and over was 4.2%, of which 85-90% were for type 2 diabetes (Ministry of Health, 2004). Based on these prevalence estimates 131,237 adults aged 15 years and over have diabetes where an estimated 111,551 to 118,113 persons have Type-2 diabetes. The estimated incidence of Type-1 juvenile diabetes was 25.8 cases per 100,000 persons aged up to 19 years in 2001. Over the period from 1999-2001 there were 2,324 deaths registered (2.8% of all deaths) where diabetes was recorded as the underlying cause (Ministry of Health, 2005).

Summary

There is huge potential for the use of CGM within the diabetic population of Australia and New Zealand. Based on self-reported data available approximately one million Australians could possibly benefit from CGM devices. In New Zealand based on self-reported information, more than 131,000 adults over 15 years could potentially benefit from CGM devices.

Treatment Alternatives

Existing comparators

Material on existing comparators was sourced from the ANZHSN report on the GlucoWatch[®] G2 Biographer (Australia and New Zealand Horizon Scanning Network, 2005). The optimal method for assessing long-term glycaemic control is the measurement of glycosylated haemoglobin. Haemoglobin combines with blood glucose to form glycosylated haemoglobin or HbA1c. When plasma glucose is

consistently elevated there is a corresponding increase in levels of HbA1c stored in erythrocytes. Due to the 120 day life span of erythrocytes, the levels of HbA1c will reflect the glycaemic history of the patient over the past 2-3 months. HbA1c levels determined by high-performance liquid chromatography (HPLC) are the standard reference for glycosylated haemoglobin measurements.

Levels of HbA1c should reflect to a certain extent glucose levels determined by self-monitoring of blood glucose (SMBG). When measured by HPLC, a HbA1c level of 6 per cent approximates a plasma glucose level of 6.6 mmol/L or 120 mg/dL. A 1 per cent rise in the HbA1c level equates to a 1.7 mmol/L or 30 mg/dL increase in the mean glucose level (Braunwald et al 2001; FDA 2002). The normal average value for preprandial glucose is <5.5 mmol/L, with an ideal range of 4.4-6.7 mmol/L (Braunwald et al 2001). Patient action should be taken for values <4.4 or >7.8 mmol/L. Similarly the normal average value for bedtime glucose is <6.1 mmol/L, with an ideal range of 5.5-7.8 mmol/L, with action required if values are <5.5 or >8.8 mmol/L. Hypoglycaemia and hyperglycaemia may be defined as plasma glucose levels of <2.5 mmol/L and 28 mmol/L, respectively. However these levels may vary with symptoms and physiologic responses (Braunwald et al 2001).

The current gold standard for SMBG for use by the patient in the home is the glucose meter, which is a small, portable battery operated device. There are currently more than 25 different brands of commercially available glucose meters, including Accu-Chek[®] Advantage[®] (Roche Diagnostic), One Touch[®] (LifeScan Inc) and Accutrend[®] DM (Boehringer Mannheim). SMBG is recommended for all people with diabetes, but especially for those treated with insulin. It is recommended that patients with Type-1 diabetes test glucose levels three or more times per day. SMBG plans may recommend testing glucose levels before all meals, two hours after meals and before retiring for the night. To test glucose levels patients should wash hands thoroughly to remove any trace of glucose and reduce risk of infection, prick the fingertip with a lancet and hold the finger until a large droplet of blood forms. The droplet of blood is placed onto a test strip, which is then inserted into the glucose meter. The test strip is coated with glucose oxidase, which then converts any glucose present in the blood to hydrogen peroxide. A dye impregnated into the test strip combines with the hydrogen peroxide and, when placed into the glucose meter, will reflect light according to the amount of glucose present. Higher glucose concentrations will reflect less light. Glucose meters should be calibrated regularly using a standard glucose solution (FDA, 2002).

All portable blood glucose meters measure the amount of glucose in whole blood. Glucose levels in plasma are generally 10-15 per cent higher than glucose measurements in whole blood. The results are displayed on a digital readout approximately 1-2 minutes after the test strip is placed into the meter. Glucose meters can detect glucose over the range 0-34 mmol/L. Many SMBG meters now give results as "plasma equivalent", using a built in algorithm, allowing comparison of home glucose measurements to those determined from plasma by HPLC (FDA, 2002).

Continuous glucose monitoring devices are only intended to supplement information acquired from conventional SMBG. They are not intended to replace SMBG by the patient in the home with a glucose meter.

The GlucoWatch[®] G2 Biographer and the original CGMS[®] Continuous Glucose Monitoring System and its second-generation replacement the CGMS[®] System Gold[™] (the sensor and software were modified in 2002) were the first clinically approved and commercially available devices and have been studied more extensively in the medical literature than other devices. The RCT studies in this report mainly utilised the original CGMS[®], the GlucoWatch[®] G2 Biographer and in one RCT, the Guardian[®] RT Continuous Glucose Monitoring System and in another the STS[™] Continuous Glucose Monitoring System. Other Horizon Scanning reports have recently been published for the GlucoWatch[®] G2 Biographer (Australian and New Zealand Horizon Scanning Network, 2005; AETSA, 2005a) and minimally invasive blood glucose monitoring systems (CGMS[®] and GlucoDay[®]) (AETSA, 2005b).

Diagnostic Accuracy

Standard glucose monitoring measures blood glucose levels but the development of minimally invasive glucose sensing techniques has focused on measuring glucose in the ISF. Accurate measurement of glucose is dependent upon a strong correlation between glucose in the ISF and the blood. Glucose enters the ISF from the blood and is removed again by uptake into the surrounding cells. Under normal physiological conditions the process of glucose exchange between the plasma and the interstitial space means that changes in the glucose concentration in the ISF are strongly correlated with those in the blood (Seig et al, 2005). However, changes in blood flow and metabolic rate can affect glucose concentrations in the ISF with resulting changes in the ISF not always reflected in the blood. There can be a lag time that can vary between 0 and 45 minutes. Also glucose concentrations in the ISF can also precede the blood level and/or change at a greater rate and can complicate the interpretation of the glucose measurement in the ISF (Seig et al 2005, Kulcu et al, 2003; Aussedat et al, 2000). Models have shown how that a rapid change in blood glucose (e.g. from insulin injection) will be reflected in the ISF with a delay.

The relationship between glucose concentrations in the ISF and blood is also important as all current CGM techniques require calibration with a blood sample obtained by the conventional method prior to sensor monitoring. This calibration value is used in subsequent monitoring. Inaccuracies in calibration will result in inaccurate glucose measurements, hypo- and hyperglycaemic alarm settings and insulin therapy adjustments (Choleau et al, 2002). Deviations from the glucose reference values in the blood may be due not only to technical limitations but also may be due to physiological factors. Further research into the complex relationship between blood and the interstitial compartment is required in order to achieve standardised and objective performance evaluation for CGM devices and accuracy for the optimisation of metabolic control (Sieg et al, 2005).

Point to point glucose comparisons between SMBG and CGM monitoring for determining accuracy are limited in their analysis of glucose trends. Other methods have been developed, such as the continuous grid-error analysis (CG-EGA) which utilises point- and rate-error analysis to capture the point presentation and the direction and rate of blood glucose fluctuations for hypoglycaemic, euglycaemic and hyperglycaemic ranges (Kovatchev et al, 2004). The accuracy of the TheraSense

FreeStyle™ Navigator Continuous Glucose Monitor (Abbott Laboratories, Alameda, CA) was assessed using grid-error analysis and the failure to detect hypoglycaemia at blood glucose extremes (73.5% accuracy) was the most common error. The device was reported to be very accurate in periods of euglycaemia (99%) and hyperglycaemia (95.4%).

The diagnostic accuracy of CGMS® systems and the GlucoWatch® G2 Biographer evaluated in non-randomised controlled trials

The accuracy of the first U.S. FDA approved CGM devices, the original Medtronic MiniMed CGMS® and its modified successor the CGMS® System Gold™ and the Cygnus GlucoWatch® G2 Biographer (GWB) have been more rigorously assessed in clinical studies than other devices. The Diabetes Research in Children Network (DirecNet), a multi-center collaborative study group, has produced a number of non-randomised studies on the accuracy of both of these devices in children and adolescents with Type-1 diabetes. These studies found that both sensors were less accurate in measuring glucose levels during hypoglycaemia and that gender, ethnicity, Body Mass Index (BMI), or age (3-18 years) had no effect on the function of either sensor. The CGMS® sensors were equally accurate in measuring glucose levels on each of the three days of wear while the GWB was less accurate in the last 5-hours of wear. In comparing day and night-time accuracy the GWB showed no differences in accuracy whilst the CGMS® was less accurate with lower readings at night (Buckingham et al, 2005).

The diagnostic accuracy of the continuous glucose monitoring systems evaluated in randomised controlled trials

Diagnostic accuracy outcomes for CGM devices were reported in four RCT studies. These compared glucose level measurements derived from CGM sensors compared to those obtained from SMBG. These studies were graded as level 3b evidence according to the levels of evidence for grading diagnostic accuracy (refer to evidence grading hierarchy in the Appendix, Table 13).

The diagnostic accuracy of the STS™ Continuous Glucose Monitoring System

One RCT study by Garg et al (2006) (level 3b evidence) reported on the accuracy of real-time sensor values for the Dexcom STS™ Continuous Glucose Monitoring System compared with SMBG values. Overall 95.4% of paired glucose values were within Clarke error grid A and B zones with a correlation coefficient of 0.88. There were mean and median absolute differences but sensor values were within pre-specified accuracy limits with SMBG glucose values and no systematic bias was detected (Table 2).

Table 2 Diagnostic accuracy Dexcom STS™ Continuous Glucose Monitoring System

Study Features	Population	Outcomes
Garg et al (2006), USA Level 3b evidence RCT	47 Type-1 and Type-2 diabetic patients wearing DexCom STS for CGM (with display data provided only during 72-hr periods 2 and 3) 44 Type-1 and Type-2 diabetic control patients wearing DexCom STS for CGM (with data not provided during any 72-hour period) For the 91 subjects mean age 44± 13 years and 75 patients with Type-1 diabetes and 16 with Type-2 diabetes Study conducted in a clinic/home environment	Prospective real-time sensor values were compared with SMBG values, 95.4% of 6,767 paired glucose values within Clarke error grid A and B zones. Correlation coefficient was 0.88. Mean absolute difference 21.2% Median absolute difference 15.9% No systematic bias detected at pre-specified glucose levels (50, 80, 100, 150, 200 mg/dL)

The diagnostic accuracy of the Guardian® and the CGMS® systems

Three RCT studies reported diagnostic accuracy (level 3b evidence) in the Medtronic MiniMed Guardian® and the Medtronic MiniMed CGMS® glucose sensors. The study by Bode et al (2004) assessed an earlier version of the Guardian® continuous monitoring system that did not provide real time sensor glucose values. A later model has been developed with real-time functionality, the Guardian® RT Subcutaneous Glucose Monitoring System (SGMS). The accuracy of the Guardian® was measured using the absolute relative error (ARE) where a lower ARE indicates greater equivalency between sensor and home meter blood glucose readings.

The study by Tansey et al (2005) evaluated a modified CGMS® sensor. The overall median relative absolute difference (RAD) in readings was 12% and CGMS® accuracy was greater during periods of hyperglycaemia than hypoglycaemia and did not vary significantly by the number of calibrations entered.

The study by Fiallo-Scharer et al (2005) compared glucose monitoring with the CGMS® sensor and eight-point SMBG over 3-days. This study was part of the same trial for the studies by Chase et al (2005) and The Diabetes Research in Children Network (DirecNet) Study group (2006). Both monitoring regimes gave similar mean glucose profiles in terms of target ranges and associations with HbA1c but only 10% of subjects completed 3-days of eight-point home glucose testing. The CGMS® sensor tended to overestimate postprandial excursions (p<0.001) and underestimate mean overnight glucose levels (p<0.001) (Table 3).

Summary

In these studies the CGMS® sensors were less accurate than home sensors and less accurate during periods of hypoglycaemia compared to SMBG. The Guardian® was also less accurate during periods of hypoglycaemia with nearly half of all alerts being false alerts and consistently lower readings than concurrent home SMBG readings.

With the STS[®] monitoring device pairs of sensor and SMBG glucose values were well correlated and differences were within pre-specified accuracy limits with SMBG glucose values and no systematic bias was detected.

Table 3 Diagnostic accuracy of the CGMS[®] and Guardian[®] Monitoring Systems

Study Features	Population	Outcomes																					
<p>Bode et al (2004), USA</p> <p>Level 3b evidence</p> <p>RCT, accuracy assessed using single sample comparative study of all alert and non-alert data</p>	<p>35 type-1 diabetic patients with the Guardian CGMS with 2 alert sensors switched off followed by 2 sensors alerts switched on in the alert group</p> <p>Mean age 42.2 ± 10.3 years, range (24-68)</p> <p>36 type-1 diabetic controls with all 4 Guardian CGMS sensors alerts switched off</p> <p>Mean age 45.8 ± 12.2 years, range (24 -71)</p> <p>Study conducted in the home environment</p>	<p>Hypoglycemia alert for the Guardian</p> <p>≤ 70 mg/dL</p> <p>67% sensitivity, 90% specificity, 46% false alerts</p> <p>Hyperglycemia alert for the Guardian</p> <p>≥ 250 mg/dL</p> <p>63% sensitivity, 97% specificity, 19% false alerts</p> <p>Mean (median) absolute relative error between home SMBG and the Guardian was 21.3% (17,3%).</p> <p>Average readings for Guardian were 12.8 mg/dL below the concurrent home SMBG readings</p>																					
<p>Tansey et al (2005), USA</p> <p>Level 3b evidence</p> <p>As a part of an RCT, a cross-classification study</p>	<p>Two hundred children enrolled in an outpatient setting, 191 children included in analysis</p> <p>191 Type-1 diabetic patients wearing the CGMS over 2-3 days compared with reference home glucose meter</p> <p>Mean age 12.5±2.8 years,</p> <p>Study conducted in the home environment</p>	<p>1,899 CGMS-reference pairs, median pairs per subject 10. Mean calibrations per 24h of CGMS was 5.3.</p> <p>Median, 25%/75% percentiles</p> <p>Difference (mg/dL) -4 (-24,13)</p> <p>Absolute diff (mg/dL) 18 (8, 38)</p> <p>Relative difference -3% (-15%, 9%)</p> <p>RAD^a 12% (6%, 23%)*</p> <p>ISO^b criteria met 72% (69%, 74%)**</p> <p>(mean and 95%CI)</p> <p>* p<0.001; ** p<0.002</p>																					
<p>Fiallo-Scharer et al (2005), USA</p> <p>Level 3b evidence</p> <p>Cross-over RCT</p>	<p>Two hundred children enrolled</p> <p>161 Type-1 diabetic patients wearing CGMS over 3 days</p> <p>Mean age 12.4 years, range (7-17)</p> <p>161 Type-1 diabetic controls with 8-point testing using meters over 3 days</p> <p>Mean age 12.4 years, range (7-17)</p> <p>Study conducted in the home environment</p>	<p>Patients used CGMS an average of 70 h over 3 days</p> <p>Average readings per subject 859</p> <p>Eight-point testing per subject 19</p> <table border="1"> <thead> <tr> <th></th> <th>Eight-point</th> <th>CGMS</th> </tr> </thead> <tbody> <tr> <td>Mean glucose (mg/dL) (overnight)</td> <td>188 ± 41</td> <td>183± 37*</td> </tr> <tr> <td>In target range***</td> <td>50%</td> <td>49%</td> </tr> <tr> <td>Above target range</td> <td>47%</td> <td>46%</td> </tr> <tr> <td>Below target range</td> <td>3%</td> <td>5%</td> </tr> <tr> <td>Postprandial excursions (Mean mg/dL)</td> <td>17</td> <td>63**</td> </tr> <tr> <td>Correlation HbA1c and mean glucose (mg/dL)</td> <td>0.40**</td> <td>0.39**</td> </tr> </tbody> </table> <p>* p<0.009; ** p<0.001; *** 61-180 mg/dL</p>		Eight-point	CGMS	Mean glucose (mg/dL) (overnight)	188 ± 41	183± 37*	In target range***	50%	49%	Above target range	47%	46%	Below target range	3%	5%	Postprandial excursions (Mean mg/dL)	17	63**	Correlation HbA1c and mean glucose (mg/dL)	0.40**	0.39**
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^a Median relative absolute difference (difference divided by reference value*100) ^b International Organisation for Standardisation reference glucose values for ≤75 mg/dL, CGMS value ± 15 mg/dL for glucose values for 75 mg/dL, CGMS value ± 20 mg/dL

Effectiveness

The optimal method for assessing overall and long-term glycaemic control and the effectiveness of glucose monitoring with CGM devices or SMBG in the management of diabetes is the measurement of glycosylated haemoglobin (HbA1c). When plasma glucose is consistently elevated there is a corresponding increase in levels of HbA1c stored in erythrocytes. Due to the 120 day life span of erythrocytes, the levels of HbA1c will reflect the glycaemic history of the patient over the past 2-3 months. Levels of HbA1c should reflect to a certain extent glucose levels measured by SMBG and those measured by CGM.

Diabetic control and the GlucoWatch® G2 Biographer

Two RCTs (level II evidence) evaluated the effectiveness of the GlucoWatch® G2 Biographer blood glucose monitoring system on HbA1c levels in paediatric patients with Type-1 diabetes. A retrospective review by physicians of blood glucose profiles and a real-time alarm function for impending hypo- and hyperglycaemia from the GlucoWatch® G2 Biographer was used to adjust therapy regimes. Safety and effectiveness outcomes for the study by Chase et al (2003) was sourced from the ANZHSN report on the GlucoWatch® G2 Biographer (Australia and New Zealand Horizon Scanning Network, 2005) (Table 4).

An RCT by Chase et al (2003) (level II evidence) monitored the HbA1c levels of 20 paediatric patients wearing a GlucoWatch® G2 Biographer for three months and 20 patients using SMBG. This study reported that the HbA1c levels of the GlucoWatch® G2 Biographer patients were significantly lower (8.4%), which may indicate improved glycaemic control, than those patients using standard care alone (9.0%, $p < 0.05$), at the end of the three month intervention period.

Another RCT by Chase et al (2005) (level II evidence) compared the GlucoWatch® G2 Biographer with SMBG in 200 children and adolescents with Type-1 diabetes (also see studies by The Diabetes Research in Children Network (DirecNet) Study group 2006 and Fiallo-Scharer et al 2005 as part of same trial). There were no significant decreases in HbA1c at six months ($p = 0.15$) in either group. There was no significant difference between groups in the proportion of HbA1c decreases of $\geq 0.5\%$.

Diabetic control and the CGMS® continuous glucose monitor

Four RCTs (two with level II evidence and two with poorer quality study design with level III-1 evidence) evaluated the effectiveness of the CGMS® continuous glucose monitor plus SMBG on HbA1c levels in paediatric and adult patients with Type-1 diabetes. Therapy regimes were adjusted by physicians and patients based on retrospective review of glycaemic profiles from the CGMS in these four trials (Table 5).

A smaller pseudo-randomised RCT with eleven children with Type-1 diabetes by Chase et al (2001) (level III-1 evidence) compared the CGMS® with SMBG. After the first month all five subjects in the CGMS® group decreased their HbA1c levels by at least 0.2%. At 3-months there was no significant decrease in HbA1c in the CGMS® group ($p = 0.07$) or the control group ($p > 0.05$). This study was limited by the very small numbers of children included and did not compare monitoring groups.

The RCT by Ludvigsson and Hanas (2003) (level II evidence) compared subjects with CGMS[®] plus SMBG in an open trial arm with subjects using the CGMS[®] blinded to CGMS[®] monitoring profiles in 27 paediatric subjects with Type-1 diabetes. At 3-months HbA1c levels had significantly decreased in the open trial arm patients (p=0.013) but not the patients blinded to CGMS[®] profiles and there was a statistically significant difference in HbA1c levels between groups (p=0.011).

The study by Tannenburg et al (2004) (level II evidence) compared CGMS[®] in 128 adults with Type-1 diabetes with SMBG. At 3-months both the intervention and control groups of subjects showed statistically significant improvements in HbA1c levels (p<0.001). For between-group comparison there were similar improvements in HbA1c levels at 3-months. The CGMS[®] group had a significantly reduced duration of hypoglycaemia at the end of the study compared to baseline (p=0.009).

The pseudo-randomised RCT by Chico et al (2003) (level III-1 evidence) compared the CGMS[®] in 75 Type-1 adult diabetes patients with SMBG. At 3-months both the intervention and control subjects showed improvements in HbA1c levels that were statistically significant (p<0.01). A between-group comparison of improvements in HbA1c levels at 3-months was not done. A subgroup analysis of patients who underwent continuous subcutaneous insulin infusion (CSII) also showed greater decreases in HbA1c, regardless of monitoring method, (p<0.01) than those who underwent multiple insulin infusion (MII) (p<0.05).

Diabetic control and the Guardian[®] CGMS continuous monitoring system

One RCT, Bode et al (2004) (level II evidence), compared the Guardian[®] CGMS continuous monitoring system (sensor alert switched on) with the Guardian[®] CGMS (sensor alert switched off) in 71 adult patients with Type-1 diabetes. This Guardian[®] CGMS model did not provide real time sensor glucose values but provided alarms that activated when user excursions go below or above predetermined thresholds of hypo- and hyperglycaemia. The sensor alert group had significantly (p=0.03) reduced median hypoglycaemia excursion periods compared to the control group without sensor alert and there was no differences in the frequency of hypoglycaemia excursions (Table 6).

Diabetic control and the STS[™] Continuous Glucose Monitoring System

One RCT by Garg et al (2006) (level II evidence) evaluated the STS[™] continuous glucose monitoring system plus SMBG where 47 Type-1 and Type-2 diabetes patients over two 72-hour periods were provided with real-time glucose values, trend information, and received alerts and alarms compared with 44 controls who were not provided with any of this information. Patients in the display group spent significantly less time as hypoglycaemic (especially during night time) and hyperglycaemic, and significantly more time within blood glucose level targets (p<0.001) (Table 7).

Table 4 Diabetic control from the GlucoWatch® G2 Biographer

Study Features	Population	Outcomes															
<p>Chase et al (2003), USA</p> <p>Level II evidence</p> <p>RCT*</p> <p>*Some authors affiliated with Cygnus Inc, Redwood, CA</p>	<p>20 Type-1 diabetic patients wearing GlucoWatch G2 Biographer:</p> <p>Mean age 11.9 ± 3.1 years, range (7-16)</p> <p>20 Type-1 diabetic controls with SMBG:</p> <p>Mean age 11.9 ± 3.3 years, range (7 -17)</p> <p>Study conducted in the home environment</p>	<p>Patients used biographer an average of 3.5 times per week</p> <p>Total readings 11,925</p> <p>3.6% readings >300 mg/dL (16.7 mmol/L)</p> <p>15.5% readings <70 mg/dL (3.9 mmol/L)</p> <p>HbA1c% (median)</p> <table border="1" data-bbox="804 636 1136 824"> <thead> <tr> <th></th> <th>GlucoWatch® G2 Biographer</th> <th>Control</th> </tr> </thead> <tbody> <tr> <td>Baseline</td> <td>8.9</td> <td>8.6</td> </tr> <tr> <td>3 months</td> <td>8.4</td> <td>9.0</td> </tr> <tr> <td>6 months</td> <td>8.3</td> <td>8.5</td> </tr> <tr> <td>9 months</td> <td>8.4</td> <td>8.6</td> </tr> </tbody> </table> <p>At 3 months HbA1c was significantly lower in GlucoWatch® G2 Biographer compared to control groups (p< 0.05), Wilcoxon Rank Sum test.</p>		GlucoWatch® G2 Biographer	Control	Baseline	8.9	8.6	3 months	8.4	9.0	6 months	8.3	8.5	9 months	8.4	8.6
	GlucoWatch® G2 Biographer	Control															
Baseline	8.9	8.6															
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<p>Chase et al (2005), USA</p> <p>Level II evidence</p> <p>RCT</p>	<p>99 Type-1 diabetic patients wearing GlucoWatch G2 Biographer for CGM over 6 months:</p> <p>Mean age 12.3± 2.7 years, range (7-17)</p> <p>101 Type-1 diabetic controls having SMBG over 6 months:</p> <p>Mean age 12.7± 2.9 years, range (7 -17)</p> <p>Study conducted in the home environment</p>	<p>Patients with the biographer used an average of 1.2 ± 0.7 sensors per week with at least 8-hours of use, and 16% subjects at least 2.0 uses of 8≥ hours/week.</p> <p>Usage declined throughout the study from mean 2.1 times/week in 1st month to 1.5 times/week in the 6th month. Reasons for declining usage:</p> <table border="1" data-bbox="804 1218 1332 1370"> <thead> <tr> <th></th> <th>Usual care</th> <th>GW2B</th> </tr> </thead> <tbody> <tr> <td>Mean HbA1c (6 months)</td> <td>7.9%</td> <td>8.1%</td> </tr> <tr> <td>95% CI mean reduction</td> <td colspan="2">(-0.4% to 0.1%; p=0.15)</td> </tr> <tr> <td>Decrease on HbA1c ≥ 0.5%</td> <td>21%</td> <td>28%*</td> </tr> </tbody> </table> <p>*p=0.21</p>		Usual care	GW2B	Mean HbA1c (6 months)	7.9%	8.1%	95% CI mean reduction	(-0.4% to 0.1%; p=0.15)		Decrease on HbA1c ≥ 0.5%	21%	28%*			
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Table 5 Diabetic control from the CGMS®

Study Features	Population	Outcomes																																	
<p>Chase et al (2001), USA</p> <p>Level III-1 evidence</p> <p>RCT</p>	<p>5 Type-1 diabetic patients with the CGMS:</p> <p>Mean age 14.8 ± 2.2 years, range (10-17)</p> <p>6 Type-1 diabetic controls with SMBG:</p> <p>Mean age 12.6 ± 0.6 years, range (11 -13)</p> <p>Study conducted in the home environment</p>	<p>Patients using CGMS used 6 3-day sensors within a 30 day period. Both groups self-monitored at least 4-times daily.</p> <p>Sensor readings 421.4 (mean) 86.7 (sd)</p> <p>Sensor hours 35.1 (mean) 7.2 (sd)</p> <table border="0"> <tr> <td></td> <td style="text-align: center;">Controls</td> <td style="text-align: center;">CGMS</td> </tr> <tr> <td>Mean HbA1c levels %</td> <td></td> <td></td> </tr> <tr> <td>Baseline</td> <td style="text-align: center;">9.0± 1.2</td> <td style="text-align: center;">10.0± 0.7</td> </tr> <tr> <td>1-month</td> <td style="text-align: center;">8.8± 0.4</td> <td style="text-align: center;">9.5± 0.9*</td> </tr> <tr> <td>3-month</td> <td style="text-align: center;">8.4± 0.2</td> <td style="text-align: center;">8.8± 0.3</td> </tr> <tr> <td>Mean decrease in HbA1c %</td> <td></td> <td></td> </tr> <tr> <td>1-month</td> <td style="text-align: center;">0.2± 0.2</td> <td style="text-align: center;">0.36± 0.07</td> </tr> <tr> <td></td> <td style="text-align: center;">p=0.37</td> <td style="text-align: center;">p<0.01</td> </tr> <tr> <td>3-month</td> <td style="text-align: center;">0.62± 0.44</td> <td style="text-align: center;">1.04± 0.43</td> </tr> <tr> <td></td> <td style="text-align: center;">*p<0.01</td> <td style="text-align: center;">p>0.05</td> </tr> <tr> <td></td> <td></td> <td style="text-align: center;">p=0.07</td> </tr> </table>		Controls	CGMS	Mean HbA1c levels %			Baseline	9.0± 1.2	10.0± 0.7	1-month	8.8± 0.4	9.5± 0.9*	3-month	8.4± 0.2	8.8± 0.3	Mean decrease in HbA1c %			1-month	0.2± 0.2	0.36± 0.07		p=0.37	p<0.01	3-month	0.62± 0.44	1.04± 0.43		*p<0.01	p>0.05			p=0.07
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<p>Tanenberg et al (2004), USA</p> <p>Level II evidence</p> <p>RCT*</p> <p>*Sponsored by Medtronic MiniMed, Northridge CA</p>	<p>128 patients enrolled</p> <p>51 Type-1 & 2 diabetic patients with the CGMS:</p> <p>Mean age 44.0 ± 10.2 years</p> <p>58 (54 analysed) Type-1 & 2 diabetic controls with SMBG:</p> <p>Mean age 44.5 ± 12.6 years</p> <p>Study conducted in the home environment</p>	<p>Patients using CGMS used self-monitoring 4.0± 1.7 times daily and SMBG was 3.9± 1.6 times daily.</p> <table border="0"> <tr> <td></td> <td style="text-align: center;">SMBG</td> <td style="text-align: center;">CGMS</td> </tr> <tr> <td>Mean HbA1c levels (%)</td> <td></td> <td></td> </tr> <tr> <td>Baseline</td> <td style="text-align: center;">9.0± 1.0</td> <td style="text-align: center;">9.1± 1.1</td> </tr> <tr> <td>2-month</td> <td style="text-align: center;">8.3± 0.9*</td> <td style="text-align: center;">8.3± 0.9*</td> </tr> <tr> <td>3-month</td> <td style="text-align: center;">8.3± 0.9</td> <td style="text-align: center;">8.3± 0.9</td> </tr> </table> <p>*p<0.001 improvement from baseline for each group</p> <p>Similar improvement from baseline between groups p=0.95</p>		SMBG	CGMS	Mean HbA1c levels (%)			Baseline	9.0± 1.0	9.1± 1.1	2-month	8.3± 0.9*	8.3± 0.9*	3-month	8.3± 0.9	8.3± 0.9																		
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<p>Ludvigsson and Hanas (2003), USA</p> <p>Level II evidence</p> <p>Cross-over RCT*</p> <p>*Supported by grant from Medtronic MinMed, Northridge CA</p>	<p>32 patients enrolled and randomised, 27 participated.</p> <p>Mean age 12.5 ± 3.3 years, range 5-19 years</p> <p>16 type-1 diabetic patients with the CGMS in an open trial arm and insulin therapy adjusted accordingly by team/patient</p> <p>16 type-1 diabetic patients with the CGMS in a blinded study arm with insulin therapy adjusted based solely on SMBG</p> <p>Study conducted in the home environment</p>	<p>Patients using CGMS used self-monitoring 4.0± 1.7 times daily and SMBG was 3.9± 1.6 times daily.</p> <p>Average sensor life 2.1± 1.0 days</p> <p>298 sensor profiles in both arms</p> <table border="0"> <tr> <td></td> <td style="text-align: center;">CGMS</td> <td style="text-align: center;">CGMS</td> </tr> <tr> <td></td> <td style="text-align: center;">Open</td> <td style="text-align: center;">blinded (SMBG)</td> </tr> <tr> <td>Mean HbA1c levels (%)</td> <td></td> <td></td> </tr> <tr> <td>Baseline</td> <td style="text-align: center;">7.70</td> <td style="text-align: center;">7.75</td> </tr> <tr> <td>3-month</td> <td style="text-align: center;">7.31*</td> <td style="text-align: center;">7.65**</td> </tr> </table> <p>*p=0.013 improvement from baseline</p> <p>**p=0.011 difference between the two arms</p>		CGMS	CGMS		Open	blinded (SMBG)	Mean HbA1c levels (%)			Baseline	7.70	7.75	3-month	7.31*	7.65**																		
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Table 5 (continued) Diabetic control from the CGMS®

Study Features	Population	Outcomes												
Chico et al (2003), Spain	105 patients enrolled 40 Type-1 diabetic patients with the CGMS:	Mean number of readings with CGMS 816±179 and glucose meter 19±6 in 75 Type-1 diabetic patients.												
Level III-1 evidence	Mean age 36.5± 12 years 35 Type-1 diabetic controls SMBG	<table border="0"> <tr> <td></td> <td style="text-align: center;">SMBG</td> <td style="text-align: center;">CGMS</td> </tr> <tr> <td>Mean HbA1c levels (%)</td> <td></td> <td></td> </tr> <tr> <td>Baseline</td> <td style="text-align: center;">8.0± 1.4</td> <td style="text-align: center;">8.3± 1.6</td> </tr> <tr> <td>3-month</td> <td style="text-align: center;">7.5± 0.8*</td> <td style="text-align: center;">7.5± 1.2*</td> </tr> </table>		SMBG	CGMS	Mean HbA1c levels (%)			Baseline	8.0± 1.4	8.3± 1.6	3-month	7.5± 0.8*	7.5± 1.2*
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RCT	Mean age 41± 10 years Plus CGMS arm compared with 30 additional Type 2 diabetic patients for asymptomatic hypoglycemias: Mean age 58± 11 years Study conducted in the home environment	<p>*p<0.01 improvement from baseline</p> <p>Subgroup analysis of patients also showed decreases in HbA1c in both groups with continuous subcutaneous insulin infusion (CSII) (p<0.01) and multiple insulin infusion (MII) (p<0.05).</p>												

Table 6 Diabetic control from the Guardian® CGMS

Study Features	Population	Outcomes																		
Bode et al (2004), USA	35 type-1 diabetic patients with the Guardian CGMS with 2 alert sensors switched off followed by 2 sensors alerts switched on in the alert group:	Patients used 322 Guardian CGMS sensors over 699 cumulative days																		
Level II evidence	Mean age 42.2 ± 10.3 years, range (24-68)	<table border="0"> <tr> <td>Average home readings per day</td> <td style="text-align: center;">6.4</td> <td></td> </tr> <tr> <td>Average calibration values per day</td> <td style="text-align: center;">3.9</td> <td></td> </tr> <tr> <td>Average paired readings 7.0 per day the Alert group and 5.8 for the Control group</td> <td></td> <td></td> </tr> </table>	Average home readings per day	6.4		Average calibration values per day	3.9		Average paired readings 7.0 per day the Alert group and 5.8 for the Control group											
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RCT	36 type-1 diabetic controls with all 4 Guardian CGMS sensors alerts switched off: Mean age 45.8 ± 12.2 years, range (24 -71) Study conducted in the home environment	<table border="0"> <tr> <td></td> <td style="text-align: center;">Non-Alert Guardian (control)</td> <td style="text-align: center;">Alert Guardian</td> </tr> <tr> <td>Change from baseline (period 2-1)</td> <td></td> <td></td> </tr> <tr> <td>Hypoglycemia excursions (minutes) (Median change of time)</td> <td style="text-align: center;">-4.5</td> <td style="text-align: center;">-27.8*</td> </tr> <tr> <td>Hypoglycemia excursions (number) (frequency)</td> <td style="text-align: center;">+0.5</td> <td style="text-align: center;">+0.03</td> </tr> <tr> <td>Hyperglycemia excursions (minutes) (Median change of time)</td> <td style="text-align: center;">+9.9</td> <td style="text-align: center;">-9.6</td> </tr> <tr> <td>Hyperglycemia excursions (number) (frequency)</td> <td style="text-align: center;">+0.2</td> <td style="text-align: center;">+0.1</td> </tr> </table> <p>* p=0.03</p>		Non-Alert Guardian (control)	Alert Guardian	Change from baseline (period 2-1)			Hypoglycemia excursions (minutes) (Median change of time)	-4.5	-27.8*	Hypoglycemia excursions (number) (frequency)	+0.5	+0.03	Hyperglycemia excursions (minutes) (Median change of time)	+9.9	-9.6	Hyperglycemia excursions (number) (frequency)	+0.2	+0.1
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Table 7 Diabetic control in the DexCom STS™ Continuous Glucose Monitoring System

Study Features	Population	Outcomes
Garg et al (2006), USA Level II evidence RCT	47 Type-1 and Type-2 diabetic patients wearing STS for CGM (with display data provided only during 72-hr periods 2 and 3) 44 Type-1 and Type-2 diabetic control patients wearing STS for CGM (with data not provided during any 72-hour period) For the 91 subjects mean age 44± 13 years. 75 patients with Type-1 diabetes and 16 with Type-2 diabetes. Study conducted in a clinic/home environment	Compared with the control group, the display group spent 21% less time as hypoglycaemic (< 55 mg/dL)* 23% less time hyperglycaemic (≥ 240 mg/dL)* 26% more time on target (81-140 mg/dL)* *p<0.001 Nocturnal hypoglycemia (time~hours) -38% reduction (<55 mg/dL) -33% reduction (<55-80 mg/dL)

Summary

CGM devices were of limited effectiveness in assisting with glycaemic control in the short term (up to 3-months) as measured by HbA1c levels. The measurements of glucose levels with CGM devices were used to make adjustments and generally resulted in small improvements in HbA1c levels in monitored patients. However, the quality of the evidence in these studies was limited by a lack of between-group comparison with SMBG and the very select (mainly children and adolescents) and small patient samples assessed in the studies.

Quality of life

Three RCT studies (two level II and one with poorer quality study design with level III-1 evidence) reported quality of life outcomes derived from a range of validated and reliable psychometric questionnaires.

The RCT by Chase et al (2003) (level II evidence) reported on the quality of life of paediatric patients with Type-1 diabetes wearing the GlucoWatch® G2 Biographer compared to those with SMBG and found no difference between the two groups at the end of the three month intervention (Table 8).

An RCT by The Diabetes Research in Children Network (DirecNet) Study group (2006) (level II evidence) compared the GlucoWatch® G2 Biographer with SMBG in 200 children and adolescents with Type-1 diabetes (also see studies by Chase et al 2005 and Fiallo-Scharer et al 2005 as part of same trial). The validity and reliability of the Fear of Hypoglycaemia and Quality of Life questionnaires had been assessed. There were no significant differences or changes between parents and youths and glucose monitoring groups between baseline and at 6-months for the Diabetes Worry Scale. There was some indication of a small deterioration in diabetes self-management over the period as Management Profile scores significantly decreased for youths and parents for both monitoring groups (p<0.001) but there were no

differences between groups. The Paediatric Quality of Life scale (PedsQL) showed that parent's scores were significantly higher than youth's and both increased slightly over the period indicating deterioration in quality of life but there was no significant differences between monitoring groups.

One small RCT with eleven children with Type-1 diabetes by Chase et al (2001) (level III-1 evidence) compared the CGMS[®] with SMBG. The validity and reliability of the Fear of Hypoglycaemia and Quality of Life questionnaires were assessed. There were no significant differences between the two groups of subjects at baseline, 1-month and 3-months in the Fear of Hypoglycemia and Quality of Life survey questionnaire results. This study was limited by the very small number of children included.

Summary

There was a lack of clear evidence indicating significant improvements in quality of life for patients using CGM devices compared to SMBG as assessed by various psychometric measures.

Table 8 Quality of life

Study Features	Population	Outcomes
<p>Chase et al (2003), USA</p> <p>Level II evidence</p> <p>RCT*</p> <p>*Some authors affiliated with Cygnus Inc, Redwood, CA</p>	<p>20 Type-1 diabetic patients wearing GlucoWatch G2 Biographer:</p> <p>Mean age 11.9 ± 3.1 years, range (7-16)</p> <p>20 Type-1 diabetic controls with SMBG:</p> <p>Mean age 11.9 ± 3.3 years, range (7 -17)</p> <p>Study conducted in the home environment</p>	<p>Fear of hypoglycaemia scores ^a at 3 months</p> <p>GlucoWatch[®] G2 Biographer 59.0 ± 14.3</p> <p>Control 56.4 ± 9.6</p> <p>DCCT ^b Quality of Life score ^a at 3 months</p> <p>GlucoWatch[®] G2 Biographer 81.3 ± 11.7</p> <p>Control 79.8 ± 15.5</p>
<p>The Diabetes Research in Children Network (DirecNet) Study group (2006), USA</p> <p>Level II evidence</p> <p>RCT</p>	<p>99 Type-1 diabetic patients wearing GlucoWatch G2 Biographer over 6 months:</p> <p>Mean age 12.3 ± 2.7 years, range (7-17)</p> <p>101 Type-1 diabetic controls having SMBG over 6 months:</p> <p>Mean age 12.7 ± 2.9 years, range (7 -17)</p> <p>Study conducted in the home environment</p>	<p>Psychological measures^a at 6-months for parents and youths for GW2B and SC groups</p> <p>Diabetes Self-Management Profile Scores decreased over 6-months for both youths and parents for both groups ($p < 0.001$) but no differences between groups.</p> <p>Diabetes Worry Scale No significant changes or differences between groups over the 6-months</p> <p>PedsQL Diabetes Module Parents scores significantly higher than youth score.</p> <p>Scores increased over the 6-months among both groups ($p = 0.16$).</p> <p>No differences between GlucoWatch and SMBG groups.</p>
<p>Chase et al (2001), USA</p> <p>Level II evidence</p> <p>RCT</p>	<p>5 Type-1 diabetic patients with the CGMS:</p> <p>Mean age 14.8 ± 2.2 years, range (10-17)</p> <p>6 Type-1 diabetic controls with SMBG:</p> <p>Mean age 12.6 ± 0.6 years, range (11 -13)</p> <p>Study conducted in the home environment</p>	<p>No significant differences between the two groups of subjects in results for fear of Hypoglycemia and Quality of life survey questionnaires for baseline, 1-month and 3-months after.</p> <p>Fear of Hypoglycemia score decreased slightly in CGMS group from 61.8 to 56.6 at 3-months ($p > 0.05$).</p>

^a questionnaires are reliable and validated, ^b DCCT = Diabetes control and complications trial, RCT=randomised controlled trial

Safety

Outcomes considered in the studies assessed were the CGM alarm function in the detection of the frequency and duration of hypoglycaemia, and symptomatic and non-symptomatic hypoglycaemia during day and night time periods, adverse outcomes related to device malfunction and monitor-related adverse reactions such as skin rashes.

Hypoglycaemia and adverse events-The GlucoWatch® G2 Biographer

Two RCT studies (level II evidence) reported on hypoglycaemia and other adverse outcomes for the GlucoWatch® G2 Biographer device compared to a control group using SMBG (Table 9).

The study by Chase et al (2003) (level II evidence), reported that hypoglycaemic events were detected significantly more often in the GlucoWatch® G2 Biographer intervention group than the control group ($p < 0.005$), and those patients wearing the GlucoWatch® G2 Biographer intermittently were able to detect hypoglycaemic events more easily even when not wearing the device ($p < 0.03$), which may reflect increased patient awareness of nocturnal hypoglycaemia resulting from the experience of wearing the GlucoWatch® G2 Biographer device. However, GlucoWatch® G2 Biographer was not able to detect all hypoglycaemic events, missing approximately 21 per cent of those events that actually occurred and were confirmed by conventional finger-prick testing. In addition, the proportion of readings below 70 mg/dL (3.9 mmol/L), and therefore in the hypoglycaemic range, increased over the course of the three month intervention, from 14.2 to 16.5 per cent of readings ($p < 0.002$). The increase in hypoglycaemic readings may be due to a more aggressive approach to glycaemic management by the patients over the course of the intervention.

The RCT by Chase et al (2005) (level II evidence) compared the GlucoWatch® G2 Biographer with SMBG in children and adolescents with Type-1 diabetes (also see studies by The Diabetes Research in Children Network (DirecNet) Study group 2006 and Fiallo-Scharer et al 2005 as part of same trial). Sensor use declined during the study from a mean 2.1 times/week in the 1st month to 1.5 times/week in the 6th month. The reasons provided for declining usage were skin reactions with approximately half of patients experiencing moderate or acute skin problems and sensor technical difficulties. The addition of the GlucoWatch® G2 Biographer to standard blood glucose monitoring did not decrease severe hypoglycaemic events in that group of patients. These were at least three times greater in the GWB group than the SMBG group.

Table 9 Hypoglycaemic alarm and adverse outcomes with the GlucoWatch® G2 Biographer

Study Features	Population	Outcomes						
<p>Chase et al (2003), USA</p> <p>Level II evidence</p> <p>RCT*</p> <p>*Some authors affiliated with Cygnus Inc, Redwood, CA</p>	<p>20 Type-1 diabetic patients wearing GlucoWatch G2 Biographer:</p> <p>Mean age 11.9 ± 3.1 years, range (7-16)</p> <p>20 Type-1 diabetic controls with SMBG:</p> <p>Mean age 11.9 ± 3.3 years, range (7 -17)</p> <p>Study conducted in the home environment</p>	<p>Hypoglycaemia (≤70 mg/dL or 3.9 mmol/L)</p> <p>Detected more frequently in GlucoWatch® G2 Biographer compared to control group χ^2, p<0.0005</p> <p>There were 42 episodes of hypoglycaemia, 78.6% of these were registered by GlucoWatch® G2 Biographer</p> <p>Detected more frequently in GlucoWatch® G2 Biographer at night, compared to control group even when NOT wearing device χ^2, p<0.03</p> <p>Percent of GlucoWatch® G2 Biographer readings < 70mg/dL during intervention phase</p> <table> <tr> <td>Month 1</td> <td>14.2%</td> </tr> <tr> <td>Month 2</td> <td>16.6%</td> </tr> <tr> <td>Month 3</td> <td>16.5%</td> </tr> </table>	Month 1	14.2%	Month 2	16.6%	Month 3	16.5%
Month 1	14.2%							
Month 2	16.6%							
Month 3	16.5%							
<p>Chase et al (2005), USA</p> <p>Level II evidence</p> <p>RCT</p>	<p>99 Type-1 diabetic patients wearing GlucoWatch G2 Biographer for CGM over 6 months:</p> <p>Mean age 12.3± 2.7 years, range (7-17)</p> <p>101 Type-1 diabetic controls having SMBG over 6 months:</p> <p>Mean age 12.7± 2.9 years, range (7 -17)</p> <p>Study conducted in the home environment</p>	<p>Usage declined throughout the study from mean 2.1 times/week in 1st month to 1.5 times/week in the 6th month. Reasons for declining usage from questionnaire:</p> <p>Skin irritation (76%), frequent skips (56%), excessive alarms (47%), inaccurate readings (44%).</p> <table> <thead> <tr> <th></th> <th>Usual care</th> <th>GW2B</th> </tr> </thead> <tbody> <tr> <td>Severe hypoglycaemia events</td> <td>2%</td> <td>7%**</td> </tr> </tbody> </table> <p>**p=0.10</p> <p>Skin reactions from GW2B use: all subjects reported at least once over 6-months. One subject severe and 48 subjects (48%) moderate. At the 6-month follow-up 54 (55%) subjects had acute changes (mild 36%, moderate 19%, severe 0%). 50 (51%) subjects had non-acute changes such as scabbing, dry skin, hypo-hyperpigmentation or scarring.</p>		Usual care	GW2B	Severe hypoglycaemia events	2%	7%**
	Usual care	GW2B						
Severe hypoglycaemia events	2%	7%**						

Hypoglycaemia and adverse events-The CGMS® continuous glucose monitoring system

Four RCT studies (two level II and two with poorer quality study design with level III-1 evidence) reported on hypoglycaemia and adverse outcomes for the CGMS® continuous glucose monitoring system compared to a control group with SMBG. The CGMS® sensor monitoring was always in addition to SMBG in the intervention group (Table 10).

Chase et al (2001) (level III-1 evidence) compared the CGMS® with SMBG in children with Type-1 diabetes. There were significantly more mean hypoglycaemic episodes (<60 mg/dL) detected per subject in the first month in the CGMS® group, p=0.001. The majority of night time episodes were asymptomatic in the CGMS® group. No severe adverse events occurred during the study which may indicate that CGMS® monitoring occurred without an increase in the risk of severe hypoglycaemia.

The RCT by Tannenburg et al (2004) (level II evidence) compared the CGMS[®] with SMBG. At 3-months both groups of subjects showed no statistically significant differences in the frequency and duration of hypoglycaemia. There were two severe hypoglycaemic events and five monitor-related adverse reactions in the CGMS[®] group compared to one severe hypoglycaemic event in the SMBG group.

Ludvigsson and Hanas (2003) (level II evidence) compared subjects with CGMS[®] plus SMBG in an open trial arm with subjects using the CGMS[®] plus SMBG in a blinded study arm. At 3-months there was no statistical significant difference in the frequency of hypoglycaemic episodes between treatment arms. However, the duration of night-time hypoglycaemic episodes was over twice the duration of day time episodes. There was one case of severe hypoglycaemia in each study arm. Only one-third of subjects had a 3-day curve for sensor functionality data.

The study by Chico et al (2003) (level III-1 evidence) compared the CGMS[®] with SMBG in Type-1 and Type-2 diabetes patients. At 3-months Type-1 diabetes patients showed more asymptomatic hypoglycaemic episodes than Type-2 patients with night time episodes being more prevalent than during the day. Over half the patients monitored by CGMS[®] had unrecognised hypoglycaemic episodes detected.

Table 10 Hypoglycaemic alarm and adverse outcomes and the CGMS[®]

Study Features	Population	Outcomes		
		Controls	CGMS	
Chase et al (2001), USA Level III-1 evidence RCT	5 Type-1 diabetic patients with the CGMS: Mean age 14.8 ± 2.2 years, range (10-17)	Mean hypoglycaemic episodes (<60 mg/dL) per subject 1 st month	6.7 ± 1.1	12.8 ± 1.6*
	6 Type-1 diabetic controls with SMBG: Mean age 12.6 ± 0.6 years, range (11 -13)	Night time episodes Asymptomatic Symptomatic		17 3
	Study conducted in the home environment	No seizures, episode requiring help, or unconscious episodes in either group during study	4	3
		* p=0.001		

Table 10 (continued) Hypoglycaemia and adverse outcomes and the CGMS®

Study Features	Population	Outcomes	
		SMBG	CGMS
<p>Tanenberg et al (2004), USA</p> <p>Level II evidence</p> <p>RCT*</p> <p>*Sponsored by Medtronic MiniMed, Northridge California.</p>	<p>128 patients enrolled</p> <p>51 Type-1 & 2 diabetic patients with the CGMS:</p> <p>Mean age 44.0 ± 10.2 years</p> <p>58 (54 analysed) Type-1 & 2 diabetic controls with SMBG:</p> <p>Mean age 44.5 ± 12.6 years</p> <p>Study conducted in the home environment</p>	<p>Hypoglycaemia (n)*</p> <p>Events per week 2.3± 2.3</p> <p>At 3-months</p> <p>Night time 0.5± 0.5</p> <p>Daytime 1.2± 1.0</p> <p>Total 24h 1.7± 1.2</p> <p>Severe hypoglycaemic event 1</p> <p>Monitor-related adverse reactions 5</p> <p>*No statistically significant differences in frequency and duration</p>	<p>1.9± 1.6</p> <p>0.4± 0.4</p> <p>1.1± 0.8</p> <p>1.4± 1.1</p> <p>2</p> <p>5</p>
<p>Ludvigsson et al (2003), USA</p> <p>Level II evidence</p> <p>Cross-over RCT*</p> <p>*Supported by grant from Medtronic MinMed, Northridge CA</p>	<p>32 patients enrolled and randomised, 27 participated.</p> <p>Mean age 12.5 ± 3.3 years, range 5-19 years</p> <p>16 type-1 diabetic patients with the CGMS in an open trial arm and insulin therapy adjusted accordingly by team/patient</p> <p>16 type-1 diabetic patients with the CGMS in a blinded study arm with insulin therapy adjusted based solely on SMBG</p> <p>Study conducted in the home environment</p>	<p>There were 1.5 episodes per day of daytime high subcutaneous glucose (>15 mmol/L), duration 126± 33 minutes, 19.4% of total time.</p> <p>There were 0.6 episodes per day of night time high subcutaneous glucose (>15 mmol/L), duration 177± 83 minutes, 25.5% of total time</p> <p>Twenty-six of twenty-seven patients had 0.8 episodes per day of low daytime subcutaneous glucose (<3.0 mmol/L), duration 58± 29 minutes, 5.5% of total time</p> <p>All patients had at least one episode per day of low night time subcutaneous glucose (<3.0 mmol/L), duration 132± 81 minutes, 10.1% of total time</p> <p>1 case each of severe hypoglycaemia in each arm</p> <p>No statistical significant differences in low glucose frequency between treatment arms</p> <p>Sensor functionality curve</p> <p>3-day 34.9%, 1-2 day 51.7%, none 8.4%</p>	
<p>Chico et al (2003), Spain</p> <p>Level III-1 evidence</p> <p>RCT</p>	<p>105 patients enrolled</p> <p>40 Type-1 diabetic patients with the CGMS:</p> <p>Mean age 36.5± 12 years</p> <p>35 Type-1 diabetic controls with SMBG:</p> <p>Mean age 41± 10 years</p> <p>Plus CGMS arm compared with 30 Type 2 diabetic patients monitored with CGMS for asymptomatic hypoglycemias:</p> <p>Mean age 58± 11 years</p> <p>Study conducted in the home environment</p>	<p>Asymptomatic hypoglycaemic events (<60 mg/dl) recorded in subjects</p> <p>Mean duration 214±288 minutes</p> <p>Type 1 diabetic patients</p> <p>Frequency of hypoglycaemic episodes 62.5%</p> <p>16% during the day, 40% at night, 44% both</p> <p>Type-2 diabetic patients</p> <p>Frequency of hypoglycaemic episodes 46.6%</p> <p>42.8% during the day, 42.8% at night, 14.3% both periods</p> <p>Adverse events</p> <p>Misunderstanding instructions 5 patients</p> <p>Skin lesions none</p> <p>Discomfort 8 patients</p> <p>Sensor malfunction 6 patients</p>	<p>CGMS</p> <p>55.7%</p> <p>(81 events)</p>

Hypoglycaemia and adverse outcomes-The STS™ Continuous Glucose Monitoring System

One RCT by Garg et al (2006) evaluated the STS™ real-time continuous blood glucose monitor. Only mild adverse events related to skin complaints were reported and all resolved within one week and no patients with hypoglycaemic events required assistance (Table 11).

Table 11 Hypoglycaemic alarm and adverse events and the STS™ system

Study Features	Population	Outcomes
Garg et al (2006), USA Level II evidence RCT	47 Type-1 and Type-2 diabetic patients wearing DexCom STS for CGM (with display data provided only during 72-hr periods 2 and 3) plus SMBG 44 Type-1 and Type-2 diabetic control patients wearing DexCom STS for CGM (with data not provided during any 72-hour period) plus SMBG For the 91 subjects mean age 44± 13 years 75 patients with Type-1 diabetes and 16 with Type-2 diabetes Study conducted in a clinic/home environment	There were 21 mild adverse effects from device use reported in 16 patients. These were blister (n=1), bullae around site (n=1), edema (n=2), erythema (n=17). All resolved within seven days. No hypoglycaemic events required assistance in the display group. Three events (in two subjects) in control group.

Summary

Four RCTs reported on safety outcomes for the CGMS® continuous glucose monitoring system. One small RCT reported significantly more mean hypoglycaemic episodes detected per subject in the CGMS® group compared to controls and two other studies reported that asymptomatic hypoglycaemic episodes were commonly detected in the CGMS® group. Where compared with SMBG, studies showed no statistically significant differences in the frequency of hypoglycaemic episodes. One other RCT evaluated the STS™ real-time continuous glucose monitoring system and minor skin irritations were reported in the CGM device group a greater number of serious hypoglycaemic events were reported in the control group.

Two RCTs reported on safety outcomes for the GlucoWatch® G2 Biographer. In one RCT hypoglycaemic events were detected more often with the GlucoWatch® G2 Biographer but this was not able to detect all hypoglycaemic events confirmed by SMBG and in the other study there was declining usage due to skin reactions which were common in the GlucoWatch® G2 Biographer group and severe hypoglycaemic events were at least three times greater in the GlucoWatch® G2 Biographer group of patients than the SMBG group.

Cost Analysis

Findings from the ANZHSN report on the GlucoWatch® G2 Biographer are briefly repeated here (Australia and New Zealand Horizon Scanning Network, 2005). Eastman¹ et al (2003) (an affiliate of Cygnus international) used a Monte Carlo simulation model to study the cost-effectiveness of the GlucoWatch® G2 Biographer based on patients enrolled in the randomised controlled trial described by Chase et al (2003). This study was conducted in the United States and health costs to the patient will vary compared to those experienced by Australian and New Zealand patients. It was assumed that the same frequency of biographer usage would be required for the lifetime of the patient in order to achieve consistent lowering of HbA1c. The Monte Carlo model predicted that the use of GlucoWatch® G2 Biographer, if sustained for life, would delay the onset of the first serious complication of diabetes by 4.1 years. Treating 18 patients with GlucoWatch® G2 Biographer would prevent one case of blindness and 1.4 cases of renal failure. However, the validity of the model is questionable given that there are no long-term morbidity or mortality data reported in the study by Chase et al. The intervention costs US\$91,059 per year of life, US\$61,326 per quality adjust life year (QALY) and US\$9,930 per year free of major complication. If GlucoWatch® G2 Biographer ceased to be effective after 17 years of age, the cost per QALY would increase to US\$103,178 per QALY gained (Eastman et al 2003).

One other study evaluated the cost-effectiveness of the FreeStyle Navigator™ continuous glucose monitoring system (currently under review with the FDA) compared with SMBG to predict hypo- and hyper- glycaemic variation in pregnant women with Type-1 diabetes (Marangos and Papatheofanis, 2005). The study, partly sponsored by the manufacturer Abbott Laboratories, utilised a Markov model and the analysis showed that a trained user of the FreeStyle Navigator™ device was more cost-effective than SMBG, even though it had a higher overall cost (\$US) of treatment for a 36-month period (\$17,305 vs \$13,388). CGM use was associated with an improved quality of life profile compared with SMBG use (53.7 quality-adjusted life months (QALMs) vs 39.0 QALMs) resulting in a cost-effectiveness ratio of the FreeStyle Navigator™ of \$322/QALM compared with \$343 for SMBG. The incremental cost-effectiveness ratio (ICER) for the FreeStyle Navigator™ was \$267/QALM or (\$3,204/QALY) over SMBG. This was also expressed that for an extra 14.7 QALMs gained the additional cost over SMBG would be \$3,917 (Marangos and Papatheofanis, 2005). The extensive cost of the FreeStyle Navigator™ compared to SMBG was outweighed by its greater effectiveness. The ICER, and depending on the willingness-to-pay threshold adopted, the cost/QALY ratio would be extremely favourable for the FreeStyle Navigator™ over SMBG. The limitations with this study are that the study was conducted in the United States so health costs will be different to those experienced by Australian and New Zealand patients. The patient data used in the model was preliminary and sourced from on-going trials and the model itself had limitations in terms of representing patients with multiple diabetes complications,

¹ Dr Richard Eastman is affiliated with Cygnus Incorporated

and assuming complete patient compliance and effectiveness of treatments in returning patients to a stable euglycaemic state.

Simple costings

Medtronic Australasia Pty. Ltd markets the CGMS[®] and its successor the CGMS[®] System Gold[™] continuous glucose monitoring system. In Australia this system costs approximately A\$5,800 and a box of 4 or 10 sensors costs A\$300 – A\$700. A new AutoSensor is required for every 12 hours of monitoring. In addition the inserter required by the patient for device attachment costs A\$120 (Medtronic Australasia, personal communication). These are ineligible for a subsidy from the National Diabetic Supply Scheme (NDSS). In New Zealand CGMS[®] models are distributed through Medica Pacifica with a cost of approximately NZ\$8,000 for the system and NZ\$78 per sensor. No other continuous glucose monitoring systems are currently available in Australia or New Zealand. By contrast the GlucoWatch[®] G2 Biographer if purchased in either the United States or the United Kingdom would cost approximately A\$900 and a packet of 16 AutoSensors (one use only) is A\$130, or A\$8 each. A new AutoSensor is required for every 13 hours of monitoring (McGahan 2002).

Continuous blood monitoring systems are an adjunct to and do not replace standard finger-prick SMBG. Although continuous monitoring devices may reduce the number of finger-prick blood glucose tests patients will still be required to purchase a blood glucose monitor and strips. A blood glucose monitor such as the Roche Diagnostic Accu-Chek Advantage 3 currently costs A\$70 and has a lifetime guarantee (Roche Diagnostics Australia Pty Limited). Newly diagnosed diabetic patients are issued with a National Diabetic Supply Scheme (NDSS) card. The NDSS is an Australian Government registration scheme, which provides a subsidy for blood glucose testing strips, free insulin syringes and free needles for insulin delivery pens. The NDSS does not provide a subsidy for blood glucose meters, lancets or lancet devices. By quoting their unique NDSS number, patients may order testing strips from their local diabetic association. Testing strips and lancets currently cost approximately A\$13 (packet 100) and A\$16 (packet of 200), respectively and would cost a total of approximately 64 cents per day if patients tested three times daily (personal communication, Diabetes South Australia).

Ethical Considerations

Informed Consent

In the clinical studies reviewed patients (and the parents of patients where required) provided informed written consent to participate and study protocols underwent ethics approval. Subjects were informed of the device specifications, limitations and training in their use was provided. In clinical practice patients should be provided with this information for each CGM device. CGM is not a substitute for conventional point-in-time blood glucose testing but may be offered as an adjunct to assist with self-monitoring and glycaemic control and to reduce the number of daily conventional tests. These devices assist in achieving near normoglycaemia, while minimizing the risk of unexpected hypoglycaemia.

Access Issues

Commercial CGM devices are being produced by a growing number of companies and approved for clinical use, particularly in the U.S. Currently these devices are available on a prescription basis and patient use is closely monitored. There is only limited availability of these devices in Australia and New Zealand and their use is strictly controlled.

Companies will need to create more affordable and viable CGM products if there is to be greater acceptance and utilisation of CGM among clinicians and patients. Critical factors that may determine this include the development of systems with real-time capability and being comfortable to wear for patients. The development of performance standards that are diagnosis specific, combine accuracy for point and trend prediction, provide definitions for varying magnitudes of glycaemia, and device specific performance standards will provide target specifications that will ensure better CGM devices (Klonoff, 2005b). Other factors that will promote the development of CGM technologies in clinical practice are the provision of more outcomes data related to improvements in HbA1c, reductions in the frequency and severity of hypoglycaemic episodes, clinical guidelines for the use of CGM, and algorithms and performance assessment for real-time readings compared with retrospective analysis (Klonoff, 2005b).

The potential uptake of CGM in clinical practice is huge given the clinical need and burden of disease associated with diabetes mellitus worldwide and the benefits for patients requiring blood glucose monitoring, especially for those with unstable glycaemic control and for paediatric patients. At present the potential utilisation of CGM will remain as an adjunctive procedure and will not replace existing SMBG methods until limitations in non-invasive and minimally invasive CGM technologies are resolved.

Training and Accreditation

Training

Patients and the parents/care givers of patients require training in the use of continuous blood glucose monitoring systems. Within Australia and New Zealand these can only be used in controlled physician-supervised settings. Apart from product inserts containing instructions for using these systems company representatives are the main source of training. Physicians and diabetes nurse educators are the primary recipients of company training, who in turn, would train diabetes patients and their parents/care givers on device use. CGM systems are an adjunct to and do not replace standard finger-prick and home glucose meter testing.

Clinical Guidelines

Recent Australian clinical practice guidelines for children and adolescents with Type-1 diabetes have been published (Department of Health and Aging, 2005a). These guidelines address the diagnosis and clinical management of Type-1 diabetes in children of all ages, including adolescents up to the point of transition to adult care. Related to glycaemic control the guidelines recommend (1) that diabetes control

should be optimised as much as possible as improved glycaemic control reduces the risk of development and progression of microvascular and macrovascular complications in adolescents and adults. (2) Frequent daily blood glucose monitoring as part of a package of care has been shown to be associated with improved glycaemic control. (3) The frequency of blood glucose monitoring should be adapted to the insulin regimen, the age of the child and the stability of the diabetes. (4) HbA1c is the only measure of glycaemic control that has been shown to be associated with long-term complications of diabetes and best reflects glycaemic levels over the preceding 2-3 months. (5) The American Diabetes Association recommends measuring the HbA1c at least twice per year in patients who are meeting treatment goals, and more frequently (quarterly) in those whose treatment has changed or who are not meeting glycaemic goals.

In the guidelines minimally invasive continuous glucose monitoring systems are recognised as a useful tool for detecting asymptomatic hypoglycaemia and for providing detailed information on blood glucose trends during stabilisation of diabetes or during initiation and monitoring of insulin pump therapy. There is only limited introduction of the minimally invasive systems (e.g. the CGMS[®] system) within Australia and New Zealand currently and these are only available for short-term use in individual patients attending larger hospitals and clinics. Non-invasive devices (e.g. GlucoWatch[®] G2 Biographer) have not been released in Australia and New Zealand.

Recommended frequencies for SMBG to optimise or advance therapy range from a recommended 1 to 4 times daily depending upon the type of therapy, the degree of glycaemic control, risk of hypoglycaemia, the need for short term treatment adjustments and other special situations such as pregnancy (Bergenstal and Gavin, 2005).

The timing of SMBG should be at various times during the day, including preprandially and 1 to 2 hours postprandially. The value of SMBG for Type-2 diabetes patients not treated with insulin has been the subject of some debate in the literature but recent evidence supports its use in these patients (Bergenstal and Gavin, 2005).

There are also available recently published Australian evidence based guidelines for the primary prevention, case detection and diagnosis of Type 2 diabetes (Department of Health and Aging, 2005b).

Sources of Further Information

Two Horizon Scanning reports on CGM devices have been produced by the Spanish Agency for Health Technology Assessment in Andalusia (AETSA).

One assessment considered RCTs and CCTs on the Cygnus GlucoWatch[®] G2 Biographer (AETSA, 2005a). The key findings were that most studies were of low to poor quality, there was good correlation with standard monitoring, accuracy decreased with increasing glucose levels, and sensitivity for hypoglycaemia increased with pre-set detection levels but so did the false positive rate. There were contradictory results in terms of blood glucose control (measured by HbA1c levels), there was no

improvement in quality of life compared with SMBG and skin irritations were the main adverse event and resolved after discontinuation. One economic assessment study was found.

The other horizon scanning assessment considered RCTs and CCTs on the CGMS[®] and Glucoday[®] minimally invasive CGM systems (AETSA, 2005b). The key findings were that most studies were of low to poor quality, there was good correlation with standard monitoring, accuracy was satisfactory in the euglycaemic range but tended to overestimate the frequency and duration of hypoglycaemic events, contradictory results were seen in the improvement of blood glucose control (measured by HbA1c levels), there was no improvement in quality of life compared with SMBG and minor skin irritations were the main adverse event. No economic assessment studies or long-term data were found.

A number of non-randomised controlled studies were also identified on the GlucoWatch[®] G2 Biographer and the CGMS[®] Continuous Glucose Monitoring System. These were the first clinically approved and commercially available devices and have been studied more extensively in the medical literature than other devices.

Several RCTs investigating various continuous glucose monitoring devices are listed here. These trials are on-going or have recently been completed.

An ongoing U.K. based four-arm multi-centre RCT (Minimally Invasive Technology Role and Evaluation- MITRE trial) with a sample size of 600 subjects aged 18+ years looking at the Cygnus GlucoWatch[®] G2 Biographer, Medtronic MiniMed CGMS[®], attention control with a frequency of nurse feedback sessions the same as the CGM device groups, and conventional monitoring (one visit every six months) in the management of insulin treated diabetes mellitus (National Research Register Document – N0484119008).

An ongoing U.K. based multi-centre RCT evaluating the Medtronic MiniMed CGMS[®] for continuous monitoring in 120 subjects with pregnancies complicated by pre-existing diabetes. Subjects were allocated to either standard antenatal care or CGMS[®] in addition to standard care (National Research Register Document – N0254145814). One other U.K. based single-centre RCT similarly examining the CGMS[®] in 30 subjects with pregnancies complicated by pre-existing diabetes is on-going (National Research Register Document – N0547148012).

The Guardcontrol Trial is an international multi-centre RCT to assess whether insulin dependent Type-1 diabetes patients with poor glycaemic control can be improved by the utilisation of the Guardian[®] RT Telemetered Glucose Monitoring System compared with finger-stick based self testing (SMBG). Expected enrolment was 162 subjects and this trial was recently completed (ClinicalTrials.gov identifier NCT00111228).

Impact Summary

Due to the importance of optimizing glycaemic control in diabetes management and limitations with conventional SMBG methods there has been considerable investment and development in CGM technologies with more than 100 companies currently

involved in the research. At present there are no large-scale clinical studies supporting the use of non-invasive CGM technologies that use the interaction of electromagnetic radiation with tissue in glucose detection. Therefore, minimally invasive technologies that sample and monitor glucose concentrations in the ISF across the skin offer the greatest potential for practical CGM in clinical practice.

Seven CGMs have been approved by the FDA for clinical use in the U.S. or carry the CE marking for clinical use in Europe. The GlucoWatch[®] G2 Biographer and the original CGMS[®] Continuous Glucose Monitoring System and its second-generation replacement the CGMS[®] System Gold[™] were the first clinically approved and commercially available devices and have been studied more extensively in the medical literature than other devices. Only the CGMS[®] Continuous Monitoring System and its successor the CGMS[®] System Gold[™] are currently available in Australia and New Zealand and access is strictly controlled through physician-supervised use in the management of specialised diabetes cases. In Australia the devices are currently not approved by the TGA.

The potential uptake for CGM is huge given the clinical need and burden of disease associated with diabetes mellitus worldwide and because testing glucose levels is essential for children, adolescents and adults who suffer from Type-1 and Type-2 diabetes requiring treatment with insulin and for people taking oral hypoglycaemic agents. CGM is an adjunct to standard finger-prick SMBG and current CGM technology will not replace this. Currently there is a need to develop more affordable and viable CGM devices with sound performance standards and produce more evidence of efficacy and safety in clinical trials if there is to be greater acceptance and utilisation of CGM among clinicians and patients.

Conclusions

The importance of achieving optimal glycaemic control in diabetes management and limitations with conventional SMBG methods led to the development of continuous glucose monitoring (CGM) technologies with more than 100 companies currently involved in the research. At present there are no large-scale clinical studies supporting the efficacy, portability, and affordability of non-invasive technologies. Therefore, minimally invasive technologies are offering the greatest potential for practical continuous glucose monitoring devices for clinical use. At this stage only non-invasive impedance spectroscopy (the application of electromagnetic radiation through the skin to the blood vessels) and minimally invasive technologies (interstitial fluid (ISF) measurement in situ or extraction through the skin) are approved for clinical use.

CGM systems consist of a small monitor that reads and displays glucose values in real-time or retrospectively, a glucose sensor which is implanted subcutaneously in the abdomen (or externally to the wrist, arm or forearm), and a transmitter to relay information about glucose concentrations between the sensor and monitor. Typically, each device undergoes a warm-up period of 1-2 hours, a device specific calibration process of between 1 and 4 times per day and each device's sensor provides a blood glucose reading every 1-10 minutes for up to 72 hours and up to 3-months for newer non-invasive technology. The glucose level information is available to the patient and

clinician either in real time (a feature of more recently developed models) or retrospectively and many models have alarms that trigger if glucose levels fall outside of preset euglycaemic ranges.

Seven CGMs have been approved by the U.S. Food and Drug Administration (FDA) for clinical use in the U.S. or carry the CE marking for clinical use in Europe. The Cygnus GlucoWatch[®] G2 Biographer and the original Medtronic MiniMed CGMS[®] Continuous Glucose Monitoring System and its second-generation replacement the CGMS[®] System Gold[™] were the first clinically approved and commercially available devices. These devices have been studied more extensively in the literature than other devices. The RCT studies in this report mainly utilised the original CGMS[®], the GlucoWatch[®] G2 Biographer and in one RCT, the Guardian[®] RT Continuous Glucose Monitoring System and in another the STS[™] Continuous Glucose Monitoring System.

Only the CGMS[®] Continuous Monitoring System and its successor the CGMS[®] System Gold[™] are currently available for limited use in Australia and New Zealand (currently not approved by the TGA in Australia) but are only available in approved institutions for controlled physician-supervised use in the management of specialised diabetes cases.

The accuracy of the original CGMS[®] and its modified successor the CGMS[®] System Gold[™] and the GlucoWatch[®] G2 Biographer have been rigorously assessed in clinical studies. These studies found that both sensors were less accurate during hypoglycaemia and that gender, ethnicity, Body Mass Index (BMI), or age (3-18 years) had no effect on the function of either sensor. The CGMS[®] sensors were equally accurate on each of the three days of wear while the GlucoWatch[®] G2 Biographer was less accurate in the last 5-hours of wear. In comparing day and night-time accuracy the GlucoWatch[®] G2 Biographer showed no differences in accuracy whilst the CGMS[®] was less accurate with lower readings at night.

Diagnostic accuracy outcomes for CGM devices were reported in four RCT studies (level 3b evidence in the assessment of diagnostic accuracy hierarchy). Three RCTs reported diagnostic accuracy in the Medtronic MiniMed Guardian[®] and the CGMS[®] glucose sensors. In these studies the CGMS[®] sensors were less accurate than home sensors (SMBG) and less accurate during periods of hypoglycaemia. One RCT reported on the accuracy of real-time sensor values for the Dexcom STS[™] Continuous Glucose Monitoring System compared with SMBG values. Overall 95.4% of paired glucose values were within Clarke error grid A and B zones with a correlation coefficient of 0.88. There were mean and median absolute differences but sensor values were within pre-specified accuracy limits with SMBG glucose values and no systematic bias detected.

Effectiveness was evaluated in four RCTs (two level II and two with poorer quality study designs with level III-1 evidence) with glycaemic control outcomes using the CGMS[®] continuous glucose monitoring system compared with SMBG. In the two studies with paediatric patients therapy adjustments were made for patients on the basis of CGMS[®] and resulted in improvements in HbA1c levels. In the other two studies with adult patients there were significant improvements in HbA1c levels in both the CGMS[®] and control groups. Two of the RCTs did not provide between-group comparisons. Where these were compared in one study both groups had similar improvement while in the other the CGMS[®] group had greater improvement in HbA1c levels.

Effectiveness was also evaluated in two RCTs (level II evidence) with glycaemic control outcomes for patients with Type-1 diabetes using the GlucoWatch® G2 Biographer compared with SMBG. One study found a significant improvement in HbA1c levels in the CGM monitoring group at three months but not at six and nine months follow-up and the other study found no significant decreases or differences in either group in HbA1c at six months.

One RCT (level II evidence) evaluated the effectiveness of the Guardian® CGMS and found the glucose sensor alert group had significantly reduced median hypoglycaemia excursion periods compared to the control group without sensor alert. One other RCT (level II evidence) evaluated the STS™ continuous glucose monitoring system and found that real-time sensor monitoring assisted in significant reductions in periods of hypoglycaemia and hyperglycaemia.

In the three RCTs considered there was a lack of clear evidence indicating significant improvements in quality of life for patients using CGM devices compared to SMBG as assessed by various psychometric measures.

Four RCTs (two level II and two with poorer quality study designs with level III-1 evidence) reported on safety outcomes for the CGMS® continuous glucose monitoring system compared to a control group using SMBG. In one small RCT there were significantly more mean hypoglycaemic episodes detected per subject in the CGMS® group compared to controls and two studies reported that asymptomatic hypoglycaemic episodes were commonly detected in the CGMS® group. Where compared, two studies showed no statistically significant differences in the frequency of hypoglycaemic episodes between the two study arms. Asymptomatic hypoglycaemic episodes were reported in the CGMS® groups. One other RCT evaluated the STS™ real-time continuous glucose monitoring system and minor skin irritations were reported in the CGM device group. There were a greater number of serious hypoglycaemic events in the control group.

Two RCTs (level II evidence) reported on safety outcomes for the GlucoWatch® G2 Biographer compared to a control group using SMBG. In one RCT hypoglycaemic events were detected more often with the GlucoWatch® G2 Biographer but this was not able to detect all hypoglycaemic events confirmed by SMBG and in the other study there was declining usage due to skin reactions which were common in the GlucoWatch® G2 Biographer group and severe hypoglycaemic events were at least three times greater in the GlucoWatch® G2 Biographer group of patients than the SMBG group.

The quality of the evidence in these RCTs was limited by a lack of between-group comparison with patients in the SMBG group and the very select (mainly children and adolescents) and small patient samples assessed in the studies.

There were two cost-effectiveness studies identified, one evaluated the GlucoWatch® G2 Biographer, and the other evaluated the FreeStyle™ Navigator system. It was estimated from a Monte Carlo simulation that life time use of the GlucoWatch® G2 Biographer would delay the onset of serious diabetes complications by 4.1 years and treating 18 patients would prevent one case of blindness and 1.4 cases of renal failure. The intervention cost was US\$61,326 per QALY and US\$9,930 per year free of major complication. However the major limitation was that no long-term morbidity and mortality data were included in the model. The other study showed that the high cost of the FreeStyle™ Navigator compared to SMBG was outweighed by its greater effectiveness. The incremental cost-effectiveness ratio (ICER), and depending on the

willingness-to-pay threshold adopted, the cost/QALY ratio may be favourable for the FreeStyle Navigator™ over SMBG. However, there were limitations with this study as the model data were preliminary and broad assumptions were made about patient conditions and treatment effectiveness.

Testing blood glucose levels is essential for children, adolescents and adults who suffer from Type-1 and Type-2 diabetes requiring treatment with insulin and for people taking oral hypoglycaemic agents. The potential uptake of CGM in clinical practice is huge given the clinical need and burden of disease associated with diabetes mellitus worldwide and the benefits for patients requiring blood glucose monitoring, especially for those with unstable glycaemic control and for paediatric patients.

Current CGM systems are an adjunct to SMBG and do not replace standard finger-prick testing in SMBG. Although continuous monitoring devices may reduce the number of finger-prick blood glucose tests patients will still be required to purchase a blood glucose monitor and strips. There is a need to develop more affordable and viable CGM products with real-time capability and maximum comfort if there is to be greater acceptance and utilisation of CGM among clinicians and patients. Other factors that will promote the development of CGM technologies in clinical practice are the development of performance standards and the provision of more outcomes data related to improvements in HbA1c, reductions in the frequency and severity of hypoglycaemic episodes, clinical guidelines for the use of CGM, and algorithms and performance assessment for real-time readings compared with retrospective analysis.

HPACT Advisory:

There is significant potential for the uptake of continuous glucose monitoring (CGM) devices given the worldwide clinical need and burden of disease associated with diabetes mellitus. There is a need to develop more affordable and viable CGM devices with sound performance standards and to show more beneficial clinical effectiveness and safety outcomes if there is to be greater acceptance and utilisation of CGM devices. Evidence from RCTs, though somewhat contradictory and limited by small and select patient groups, indicates some effectiveness in glycaemic control and increased safety due to greater awareness of glycaemic variation but these devices are less accurate, particularly during hypoglycaemic episodes and can cause minor skin reactions, and do not improve diabetes related quality of life, compared with SMBG. CGM is useful as an adjunct to conventional (standard blood glucose self-monitoring) SMBG in selected patients with difficulties in maintaining glycaemic control. However, at this stage, CGM will not replace conventional SMBG in the majority of patients.

Appendix: Levels of Evidence

There were thirteen published studies included for assessment in this report. All studies were graded according to the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC, 1999) (Table 12) and/or levels of evidence for assessing diagnostic accuracy (Phillips et al 2001) (Table 13).

Four RCTs reported diagnostic accuracy outcomes (level 3b evidence). There were two level II evidence grade RCTs which reported safety, effectiveness outcomes related to glycaemic control for the GlucoWatch[®] G2 Biographer and one of these studies plus one other RCT reported on quality of life outcomes for paediatric patients. Four RCTs (two level II and two level III-1 evidence) reported effectiveness and safety outcomes related to glycaemic control in paediatric and adult patients utilising the CGMS[®] continuous glucose monitoring system. One of these RCTs reported on quality of life outcomes for the CGMS[®]. One further RCT reported effectiveness outcomes for the Guardian[®] CGMS. One RCT reported on effectiveness and safety outcomes in adult patients utilising the real-time STS[™] continuous monitoring system. Three studies, Fiallo-Scharer et al (2005), Chase et al (2005) and The Diabetes Research in Children Network (DirecNet) Study group (2006) were part of the same trial.

Two cost-effectiveness studies were also included with one RCT based analysis for the GlucoWatch[®] G2 Biographer and the other for FreeStyle Navigator[™] continuous glucose monitoring device.

Of the thirteen studies included, two studies were sponsored by and at least two authors were employees of Medtronic MiniMed manufacturing the CGMS device. In three other studies one author was an employee of Cygnus Inc and in one study an employee of Medtronic MiniMed. In four studies monitoring devices were provided free by the manufacturer. All studies, except one that was conducted in Sweden, were conducted within the USA.

Table 12 Designations of levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

Modified from: National Health and Medical Research Council (1999). *A guide to the development, implementation and evaluation of clinical practice guidelines*, Commonwealth of Australia, Canberra, ACT.

Table 13 Levels of evidence for assessing diagnostic accuracy^a

Level of evidence	Study design
1a	SR (with homogeneity*) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres
1b	Validating** cohort study with good† reference standards; or CDR tested within one clinical centre
1c	Absolute SpPins and SnNouts††
2a	SR (with homogeneity*) of Level ≥2 diagnostic studies
2b	Exploratory** cohort study with good† reference standards; CDR after derivation, or validated only on split-sample§ or databases
2c	n/a
3a	SR (with homogeneity*) of 3b and better studies
3b	Non-consecutive study; or without consistently applied reference standards
4	Case-control study, poor or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

^a (Phillips et al 2001). SR = systematic review; CDR = clinical decision rule - these are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category; RCT = randomised controlled trial; n/a = not applicable.

* Homogeneity means a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. Studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level. ** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'. † Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study. †† An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis. § Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

Search Strategy

The medical literature (Table 14) was searched utilising the search terms outlined (Table 15) to identify relevant studies and reviews, until 15th March 2006. In addition, major international health technology assessment databases were searched.

Table 14 Literature sources utilised in assessment

Source	Location
<i>Electronic databases</i>	
Cinahl	Ovid
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL)	Ovid
Current Contents	ISI
Embase	Ovid
Pre-Medline and Medline	Ovid
Medline (via PubMed last 60 days)	National Library of Medicine
International Pharmaceutical Abstracts	Ovid
Web of Science	ISI
The Health Technology Assessment Database, the NHS Economic Evaluation Databases	http://www.york.ac.uk/inst/crd/crddatabases.htm
<i>Internet</i>	

American Diabetes Association	www.diabetes.org
US Food & Drug Administration (FDA) Center for Devices & Radiological Health	http://www.fda.gov/cdrh
Australian Institute of Health and Welfare	http://www.aihw.gov.au/
Australian NH&MRC	http://www.nhmrc.gov.au/
Statistics New Zealand	http://www.stats.govt.nz/
New Zealand Ministry of Health	http://www.moh.govt.nz/
Canadian Coordinating Office for Health Technology Assessment Emerging Technology List	http://www.ccohta.ca
Blue Cross Blue Shield Technology Evaluation Center	http://www.bcbs.com/tec/tecassessments.html
Agencia de Evaluacion de Tecnologias Sanitarias de Andalusia	http://www.juntadeandalucia.es/salud/orgdep/aetsa/
Google Search Engine and Google Scholar Search	http://scholar.google.com

Table 15 Search terms utilised

Search terms
MeSH & EMBASE headings
N/A
Text words
(Continuous adj3 glucose), ((continuous adj3 monitor\$) and glucose), minimed, gluco watch, gluco watch, pendra, freestyle navigator, glucoday, guardian RT, (guardian and glucose), STS system
AND
Random\$, control\$, trial\$, (systematic\$ adj3 review\$)
Limits
No limits by date or language

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose compared to a comprehensive systematic review. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a ‘state of play’ assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of continuous glucose monitoring devices, their present and potential use in the Australian and New Zealand public health systems, and future implications for the use of this technology.

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