Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Rapid Health Technology Assessment of Continuous Glucose Monitoring in Adults with Type 1 Diabetes Mellitus

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Safer Better Care

About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

Foreword

Diabetes complications are associated with significant morbidity and mortality for individuals and can place a considerable economic burden on healthcare systems and society. Intensive treatment is required to in reduce the risk of developing complications. Monitoring glucose levels is an integral part of the management plan for individuals with diagnosed type 1 diabetes mellitus on intensive insulin therapy, as they are at risk of hypoglycaemia (when blood glucose is too low) and hyperglycaemia (when blood glucose is too high). Glucose readings are important to guide insulin treatment, maintain optimal glucose control, and reduce the occurrence of complications of diabetes. In common use since the 1980s, the standard method of glucose monitoring has been self-monitoring of blood glucose (SMBG) using capillary blood glucose. SMBG is commonly done through intermittent use of a finger-prick test (although blood may be drawn from other sites) with a lancet, using testing strips and electronic blood glucose meters to determine blood glucose concentration.

Continuous glucose monitoring (CGM) systems provide an alternative to SMBG, by measuring glucose levels in the interstitial fluid (a thin layer of fluid around the cells). CGM systems can provide current glucose levels as well as trend data (increasing, decreasing, stable, rate of change).

Information on glucose levels is used by the person with diabetes to inform decisions about their insulin regimen (such as schedule or dose) or interventions to minimize the risk of high and low glucose levels. CGM enables people with diabetes to monitor their blood glucose levels without the need for finger pricking. Numerous professional medical bodies worldwide now recommend the use of CGM in this population.

The HSE currently reimburses several CGM systems, but access rules differ by system and individual's age, and access can be limited by local health area budgets.

Work on the health technology assessment was undertaken by an evaluation team in HIQA. A multidisciplinary Expert Advisory Group was convened to advise the evaluation team during the course of the health technology assessment. HIQA would like to thank its evaluation team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy CEO & Director of Health Technology Assessment

Health Information and Quality Authority

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Particular thanks are due to the Expert Advisory Group (EAG) and the individuals within the organisations listed in the table below who provided advice and information.

Expert advisory group membership

Membership of the Expert Advisory Group involves review of evidence synthesis documents and contribution to a discussion which informs the advice from HIQA to the Minster for Health and HSE. It does not necessarily imply agreement with all aspects of the health technology assessment or the subsequent advice.

The membership of the EAG was as follows:

Dr Anne Dee	Specialist in Public Health Medicine - HSE Mid-West (Limerick, Clare and North Tipperary)
Dr Eibhlin Connolly	Deputy Chief Medical Officer, Department of Health
Dr Aislinn Conway#	Senior Health Technology Assessment Analyst, HIQA
Prof Seán Dinneen	Clinical Lead, National Clinical Programme for Diabetes, HSE (former*) and Consultant Diabetologist, Galway University Hospitals
Ms Linda Fitzharris	Head of Pharmacy Function, HSE Primary Care Reimbursement Service (PCRS)
Dr Hannah Forde	Irish Endocrine Society and Consultant Endocrinologist at Beaumont Hospital
Dr Kate Gajewska	Clinical Manager for Advocacy and Research, Diabetes Ireland (Patient Representative)
Dr David Hanlon	National Clinical Advisor and Group Lead (NCAGL), Primary Care
Dr Patricia Harrington	Deputy Director, Health Technology Assessment, HIQA
Dr Suzanne Kelly	Clinical Lead for Diabetes, Irish College of General Practitioners
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Prof Nuala Murphy	HSE National Lead for Paediatric Diabetes and Paediatric Endocrinologist, CHI Temple St
Ms Anne-Louise Neenan	A/Assistant Head of Sourcing & Contracts, Medical Surgical Pharma Portfolios, HSE Procurement
Prof Derek O' Keeffe	Clinical Lead, National Clinical Programme for Diabetes, HSE (Current) and Consultant Physician

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Ms Joan Quigley	Head of Assessment HTA, HIQA
Dr Máirín Ryan (Chair)	Director of Health Technology Assessment & Deputy Chief Executive Officer, HIQA
Dr Susan Spillane	Deputy Director, Health Technology Assessment, HIQA
Dr Conor Teljeur	Chief Scientist, Health Technology Assessment, HIQA
Dr Kieran Walsh	Deputy Director, Health Technology Assessment, HIQA

* Professor Seán Dinneen was the Clinical Lead for the National Clinical Programme for Diabetes until January 2023. Professor Derek O'Keeffe is the Clinical Lead since January 2023.
# Dr Aislinn Conway left HIQA in March 2023.

Members of the Evaluation Team

Ms Joan Quigley, Dr Aislinn Conway#, Dr Kieran Walsh, Dr Conor Teljeur, Dr Patricia Harrington, Dr Susan Spillane, Ms Michelle O'Neill and Dr Máirín Ryan.

#Dr Aislinn Conway left HIQA in March 2023.

Conflicts of interest

Dr Hannah Forde declared that she has received speaker fees for talks related to diabetes technology and was part of an expert panel at Dexcom Ireland advisory board meetings in March 2022 and July 2023.

Dr Kate Gajewska declared that she is employed by a charity (Diabetes Ireland), which is supported by companies, including those that produce glucose monitoring systems available in Ireland (Medtronic, Abbott, Dexcom), as part of the corporate partnerships and grants. In the latest annual audited accounts to 30 June 2022, 5% of Diabetes Ireland's total income was through its corporate partnership programme and a further 10% was received via corporate grants.

No other conflicts were declared.

Advice to the Health Service Executive

Following a request from the office of the Chief Clinical Officer at the Health Service Executive (HSE), the Health Information and Quality Authority (HIQA) agreed to undertake a rapid health technology assessment (HTA) of continuous glucose monitoring (CGM), with an exclusive focus on adult populations with type 1 diabetes mellitus (T1DM). The current Irish National Clinical Guideline for T1DM is based on a contextualisation of 2015 guideline from NICE in the UK. This NICE guideline was updated in 2022.

The key findings of this HTA, which informed HIQA's advice, were:

- There is substantial uncertainty regarding the prevalence of T1DM in adults aged 18 years or older in Ireland. Estimates of the prevalence have ranged from 17,053 (based on an analysis of Irish pharmacy claims data and current to 2016), to 24,480 (based on prevalence estimates from the Scotland Diabetes Survey 2018 applied to 2016 Irish census data).

- Self-monitoring of glucose levels is a crucial part of the management plan for individuals with diagnosed T1DM on intensive insulin therapy, as they are at risk of hypoglycaemia (when blood glucose is too low) and hyperglycaemia (when blood glucose is too high). Glucose readings can be used to guide insulin treatment, so as to maintain optimal glucose control and reduce the occurrence of complications of diabetes.

- Self-monitoring of blood glucose (SMBG) has traditionally been performed by capillary blood glucose monitoring, using a drop of blood from a finger prick to provide point-in-time information on current blood glucose levels. Continuous glucose monitoring (CGM) systems provide an alternative approach to SMBG by frequently measuring glucose levels in the interstitial fluid (a thin layer of fluid around the cells) using a small disposable sensor inserted by the user under the skin.

- CGM systems have the following features:
    - They comprise sensors (which are self-administered subcutaneously, typically in the upper arm and replaced every seven to 14 days depending on the system), transmitters (or combined sensors and transmitters) and a mechanism to display the results (readers/receivers or smart device apps).
    - In addition to current glucose levels, CGM systems provide trend data (increasing, decreasing, stable, rate of change).
    - Those using CGM may still require SMBG, for example, when readings conflict with symptoms or expectations.

- Two types of CGM are considered in this rapid HTA:
  - **Real-time continuous glucose monitoring (rtCGM)**
    Readings are automatically sent at set intervals (for example, every five minutes). As of July 2023, multiple rtCGM systems are reimbursed by the HSE, including both Dexcom G7 and Medtronic Guardian Connect 4. All reimbursed systems allow the user to set alerts for high and low glucose levels and for rapid changes in glucose levels.
  - **Intermittently scanned continuous glucose monitoring (isCGM)**
    Commonly referred to as 'flash glucose monitoring', isCGM sensors currently available in Ireland measure glucose levels at one-minute intervals with readings stored every 15 minutes and retained for eight hours. Data can be obtained by scanning the sensor with a mobile phone or a reader. As of July 2023, one isCGM system is reimbursed by the HSE, the Abbott Freestyle Libre®; this version does not allow for alerts.

- CGM is also an essential part of automated insulin delivery (AID) systems such as sensor-augmented pump therapies, in which the CGM data are combined with a dosing control algorithm and an insulin pump. This rapid HTA focuses on CGM systems regardless of whether or not they are part of an AID system.

- The day-to-day burden of managing T1DM includes frequent glucose monitoring (meaning regular SMBG with finger prick tests or continuous glucose monitoring), insulin dosing and adjustment of insulin dosing, monitoring of diet, timing of exercise and physical activity. There can also be an emotional impact to living with diabetes, including distress associated with treatment regimens, food or eating, living with the fear of hypoglycaemia, consideration of the future and or of complications.

- In addition to having a negative impact on individuals with diabetes, complications also have significant implications for health service resources, use and costs. Approximately €129 million was spent in Ireland in 2018 on costs associated with T1DM. Direct healthcare costs were estimated at €81.5 million. Indirect costs such as working time lost due to morbidity and mortality were found to account for the remaining €47.5 million.

- Clinical evidence included in guidance from the UK was reviewed. A targeted update search was conducted by HIQA to find the most recent randomised controlled trial (RCT) data on glycaemic outcomes and observational data on quality of life (QoL) and other patient reported outcomes.

  - There was some evidence to suggest that rtCGM or isCGM improves glycaemic control and reduces hypoglycaemic events relative to SMBG.

- For HbA1c outcomes there were conflicting findings for rtCGM and for isCGM compared with SMBG; some studies showed benefit to CGM use while others found no evidence of a difference.
- For hypoglycaemic and hyperglycaemic outcomes, the findings were mixed for isCGM and rtCGM compared with SMBG.
- RtCGM usage resulted in increased time in range versus SMBG, although there was very low certainty in this estimate. There were mixed findings for isCGM compared with SMBG for time in range.

- There was limited evidence to suggest that rtCGM improved glycaemic control and reduced hypoglycaemic events relative to isCGM.
  - At follow-up periods up to six months, rtCGM was associated with a significantly higher likelihood of achieving an HbA1c target less than 7.0% compared with isCGM. However, when considering mean HbA1c levels, no clinically meaningful difference was observed over the same follow-up period.
  - For rtCGM, nocturnal hypoglycaemia and the risk of severe hypoglycaemic events were lower compared with isCGM.
  - The available study data provided limited evidence of a benefit to rtCGM over isCGM. There was some evidence that rtCGM use leads to longer time in range than isCGM, but further comparative data are needed.
- A range of general, disease-specific and complication/symptom-specific QoL and other patient-reported outcome measures were used across studies and were not universally applied to both types of device. This limited comparisons of these outcomes across systems.
  - For rtCGM there was some evidence of increased well-being at 12 months. There was also evidence that use of rtCGM led to reduced fear or worry about hypoglycaemia over time.
  - For isCGM there was some evidence of improved QoL up to 12 months. There was conflicting evidence for anxiety and distress measures; median anxiety and depression scores increased in isCGM user after starting isCGM monitoring, but users also reported reduced diabetes distress.
- CGM is a rapidly developing field with iterative development of devices. The evidence base and associated recommendations are therefore likely to evolve over the coming years. The available trial evidence partly relates to earlier generations of devices, and so the understanding of relative effectiveness and the differences between isCGM and rtCGM may not be applicable to the current generation of devices.
- Routes of access to the technologies approved for reimbursement by the HSE differ by CGM system type and component:

- Sensors are accessed through community pharmacies, with reimbursement managed through the Primary Care Reimbursement Service (PCRS). Medical equipment (for example, transmitters and readers) are managed by the HSE Community Funded Schemes administered by the Local Health Office of the area in which the person with diabetes resides.
- For rtCGM systems, if equipment is required (for example, the system requires a separate transmitter or if the person with diabetes requires a reader), an application must be made by a consultant endocrinologist or diabetes nurse specialist to the Local Health Office, where it is subject to administrative and clinical review. Where no medical equipment is required (for example, a person with diabetes using the Dexcom G7 system which has a combined sensor transmitter and who chooses to access their readings through a smart device app), this prior authorisation step is not required - a person can have reimbursed access once they are eligible under a Community Drug Scheme and have a valid prescription.
- Access to the isCGM FreeStyle Libre® system is managed through a dedicated online portal. Reimbursement is limited to individuals with T1DM who meet strict clinical criteria and is linked to the age at which reimbursement is first sought. For those meeting the clinical criteria, access is automatic for those aged four to 21 years, but is only granted in 'very exceptional circumstances' to those aged 22 years and older, when first seeking access. Individuals who were first granted access to CGM prior to 22 years of age continue to be eligible.
- There are differences in costs in rtCGM systems, but currently the annual costs per person for all reimbursed rtCGM systems are considerably more expensive than the costs per person for the listed isCGM system.

- The number of adults for whom rtCGM has been reimbursed has increased markedly, particularly for Dexcom, increasing from just over 250 users in 2018 to almost 8,000 users in 2022. The associated expenditure on rtCGM increased from approximately €1 million in 2016 to over €27 million in 2022. The corresponding number of adults in receipt of isCGM devices has grown from almost 400 in 2018 to over 2,000 in 2022, with expenditure increasing from €0.19 million to €2.42 million over the same period. The different pathways to accessing rtCGM and isCGM and substantial difference in costs between technologies have considerable implications for the cost effectiveness and overall budget impact of CGM for the HSE.
- A literature search to identify economic evaluations was conducted, supplemented by a targeted search of specific HTA agency outputs. A number of international cost-effectiveness analyses were identified, and these provided some evidence that CGM systems can be cost effective. However, it is unclear to

what extent this evidence applies to currently available CGM systems in the Irish healthcare system.

- A budget impact analysis (BIA) was undertaken to estimate the cost to the HSE of expanding access to CGM for adults with T1DM. The budget impact reflects the cost over and above that currently being spent on CGM. Given the nature of this rapid HTA, a simplified model was used. Input parameters comprised population size, uptake rates, SMBG daily test frequency, reimbursement prices, value added tax (VAT) and pharmacy fees.
    - Relative to SMBG, the annual incremental cost per person in the base case was estimated to be €811 for isCGM and €2,771 for rtCGM.
    - As there is substantial uncertainty regarding the prevalence of T1DM in adults in Ireland, an upper estimate (n=24,480) was used. Given this and current usage, it is estimated that 50.5% of the adult population with T1DM is already in receipt of CGM.
    - It is estimated that if uptake increases to 85.5% of the total adult population with T1DM (that is an additional 35% access CGM), over the next five years this would cost the HSE an additional:
        - €24.8 million if all new uptake relates to isCGM
        - €84.4 million if all new uptake relates to rtCGM
        - €24.8 million to €84.8 million should new uptake include a mix of rtCGM and isCGM systems, as is likely.
    - If uptake increases at a faster rate or were to be closer to full coverage then the budget impact would be considerably higher.
    - The BIA assumed that once initiated on a particular system, individuals remained on the same CGM system for the remaining duration of the five year period. It also does not account for those who are currently using CGM, switching systems. Switching to an economically advantageous system, when clinically appropriate to do so, may result in cost savings for the HSE.
    - The use of HSE tendering and procurement processes would also provide an opportunity to maximise value for money.
- As noted, the current Irish National Clinical Guideline for T1DM is based on a contextualisation of 2015 guideline from NICE in the UK. The following recommendations with respect to CGM have been made in the UK:
    - NICE in 2022 issued an update to the relevant guideline and recommended that adults with T1DM be offered a choice of rtCGM or (isCGM, based on their individual preferences, needs, characteristics, and the functionality of the devices available.
    - Health Improvement Scotland has issued specific guidance with respect to FreeStyle Libre® (an isCGM system) recommending that it is available for individuals with diabetes who are actively engaged in the management of

their diabetes and who intensively manage their condition with multiple daily insulin injections or insulin pump therapy. This was a single technology appraisal and did not assess rtCGM.
    - Health Technology Wales has also issued specific recommendations with respect to FreeStyle Libre® noting that it should be routinely available for people with diabetes (of any type) who require treatment with insulin.
- As highlighted in international guidelines, improvements in glycaemic control may only be achieved if the user and providers take appropriate action on the basis of the data provided. Therefore, for people with T1DM, CGM should be provided in the context of the existing model of care which includes oversight by specialist diabetes services and empowerment of the person with diabetes through access to structured diabetes self-management education.
- The limited data on the number of adults with T1DM in Ireland creates uncertainty over the likely budget impact and service demand. Consideration should be given to the establishment of a national registry for people with diabetes to support healthcare service planning for that population.

HIQA's advice to the HSE is as follows:

- Continuous glucose monitoring (CGM) is an alternative to self-monitoring using capillary blood glucose (SMBG) in individuals with diabetes. CGM is a sensor-based technology that reduces the need for finger-prick testing and provides additional information about trends in glucose levels. There are two types of CGM: intermittently scanned (isCGM) and real-time (rtCGM).
- The current Irish National Clinical Guideline for type 1 diabetes mellitus (T1DM) is based on a contextualisation of the corresponding 2015 guideline from NICE. In 2022, the NICE guideline was updated to recommend CGM for all adults with T1DM. Given this update, the Irish National Clinical Guideline should be revisited.
- There is some evidence to suggest that CGM improves glycaemic outcomes compared with SMBG, particularly time in range. There is limited head-to-head evidence to distinguish between CGM types in terms of effectiveness.
- In Ireland, routes of access to the technologies approved for reimbursement differ by CGM system type and component. Current reimbursement protocols mean that access to isCGM is highly restricted for those aged over 21 years when first seeking access. However, reimbursed access to rtCGM is not restricted to the same degree.
- Annual HSE expenditure on CGM increased from €0.9 million in 2016 to €30 million in 2022; over 90% of the expenditure in 2022 related to rtCGM. There

are differences in costs in rtCGM systems, but currently all reimbursed rtCGM systems are considerably more expensive than the reimbursed isCGM system.

- The different pathways to reimbursed access to rtCGM and isCGM, and the substantial difference in costs between technologies have considerable implications for the cost effectiveness and overall budget impact of CGM for the HSE.
- There is substantial uncertainty regarding the prevalence of T1DM in adults in Ireland. Considering a potential total adult population with T1DM of 24,480:
  - If uptake increases to 85.5% (that is an additional 35% access CGM), this would cost the HSE an additional €24.8 million over the next five years if all new uptake relates to isCGM and €84.4 million if all new uptake relates to rtCGM.
  - If uptake increases at a faster rate or were to be closer to full coverage then the budget impact would be considerably higher.
  - These costs are in addition to existing annual expenditure on CGM.
  - The BIA assumes that once initiated on a particular system, individuals remain on the same CGM system for the duration of the five year period. It also does not account for those who are currently using CGM, switching systems.
  - Switching to an economically advantageous system, when clinically appropriate to do so, may result in cost savings for the HSE.
- Consideration should be given to the:
  - Provision of CGM in the context of the existing model of care for people with T1DM which includes oversight by specialist diabetes services and empowerment of the person with diabetes through access to structured diabetes self-management education.
  - Establishment of a single managed access programme for all CGM systems for all individuals with T1DM regardless of age. Such a system would need clearly defined criteria for access.
  - Establishment of a national registry for people with diabetes, within the context of ongoing national and European policy and legislative developments regarding health information, to support healthcare service planning for this population.

Executive Summary

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided.

1. Background

Following a request from the office of the Chief Clinical Officer at the Health Service Executive (HSE), the Health Information and Quality Authority (HIQA) agreed to undertake a HTA of continuous glucose monitoring (CGM) focused exclusively on adult populations with type 1 diabetes mellitus (T1DM).

2. Description of the technology

Monitoring glucose levels is an integral part of the management plan for individuals with diagnosed T1DM on intensive insulin therapy, as they are at risk of hypoglycaemia (when blood glucose is too low) and hyperglycaemia (when blood glucose is too high). Glucose readings are important for the person with diabetes to inform decisions about their insulin dosing schedule, to enable optimal glucose control, and reduce the occurrence of severe and long-term complications of diabetes. In common use since the 1980s, the standard method of glucose monitoring was self-monitoring of blood glucose (SMBG) using capillary blood glucose. SMBG is commonly done through intermittent use of a finger-prick test (although blood may be drawn from other sites) with a lancet, using testing strips and electronic blood glucose meters to determine blood glucose concentration.

Continuous glucose monitoring (CGM) systems provide an alternative approach to SMBG, by measuring glucose levels in the interstitial fluid (a thin layer of fluid around the cells). They comprise sensors (self-administered subcutaneously, typically in the upper arm and replaced every seven to 14 days depending on the system), transmitters (or combined sensors and transmitters), and a mechanism to display the results (readers/receivers or smart device app). In addition to current glucose levels, CGM systems can provide trend data (increasing, decreasing, stable, rate of change). Those using CGM may still require SMBG, for example, when readings conflict with symptoms or expectations.

Two types of CGM are considered in this rapid HTA:

- Real-time continuous glucose monitoring (rtCGM): Readings are automatically sent at set intervals (for example, every five minutes). As of July 2023, multiple

rtCGM systems are reimbursed by the HSE including both Dexcom G7 and Medtronic Guardian Connect 4; older systems currently reimbursed for existing individuals with diabetes are being phased out. All reimbursed systems allow the user to set alerts for high and low glucose levels and for rapid changes in glucose levels.

- Intermittently scanned continuous glucose monitoring (isCGM): Commonly referred to as flash glucose monitoring, the sensor measures glucose levels at one-minute intervals with readings stored every 15 minutes and retained for eight hours. Data can be obtained by scanning the sensor with a mobile phone or a reader. As of July 2023, one isCGM system is reimbursed by the HSE, the Abbott Freestyle Libre®; this version is not capable of providing alerts. Newer iterations of Freestyle Libre® available internationally include Freestyle Libre® 2 (incorporates optional alarms) and Freestyle Libre® 3 (a full rtCGM system which incorporates alarms and allows for automatic streaming of real time glucose readings).

Routes of access to the technologies approved for reimbursement differ by CGM system type and component. Sensors are accessed through community pharmacies, with reimbursement managed through the Primary Care Reimbursement Service (PCRS). Medical equipment (for example, transmitters and readers) are managed by the HSE Community Funded Schemes administered by the Local Health Office of the area in which the person with diabetes resides. For rtCGM systems, if equipment is required (for example the system requires a separate transmitter or if the individual requires a reader), an application must be made by a consultant endocrinologist or diabetes nurse specialist to the Local Health Office, where it is subject to administrative and clinical review. Where no medical equipment is required (for example, a person with diabetes using a system which has a combined sensor transmitter and who chooses to access their readings through a smart device app), this prior authorisation step is not required - a person with T1DM can have reimbursed access once they are part of any Community Drug Scheme, including the long-term illness scheme for which all those with T1DM are eligible, and have a valid prescription. Access to the FreeStyle Libre® system, on the other hand, is managed through a dedicated online portal. Reimbursement is limited to people with T1DM aged 4 to 21 years that meet strict clinical criteria. For those seeking access for the first time aged 22 years and older, reimbursement is only granted in 'very exceptional circumstances'.

HSE expenditure on CGM has increased substantially since 2016. For adults (aged greater than 21 years), rtCGM use has increased from 435 individuals in 2016 to over 10,000 in 2022. The associated annual expenditure increased from €0.9 million to €27.5 million for the same time period. For isCGM, use has grown from almost 400 individuals in 2018 to over 2,000 in 2022, with annual expenditure increasing

from €0.19 million to €2.42 million over the same period.

The different pathways to accessing rtCGM and isCGM and substantial price difference between technologies have considerable implications for the cost effectiveness and overall budget impact of CGM for the HSE.

3. Epidemiology and burden of disease

There is substantial uncertainty regarding the epidemiology of T1DM in adults in Ireland due to the lack of a national diabetes register to collect and provide population-level data. Estimates of the prevalence of T1DM in Ireland, for adults aged 18 years or older, have ranged from 17,053 (based on an analysis of 2016 Irish pharmacy claims data) to 24,480 (based on prevalence estimates from the Scotland Diabetes Survey 2018 applied to 2016 Irish census data). The day-to-day burden of managing T1DM includes glucose monitoring (including regular SMBG with finger prick tests, for those using this method), adjustment of insulin dosing, and restrictions with respect to carbohydrate intake and timing of physical activity.

The management of diabetes can be associated with emotional impacts. Specifically, diabetes distress refers to the emotional impact of living with diabetes, and can include distress associated with treatment regimens, food or eating, living with the fear of hypoglycaemia, consideration of the future and or of complications, social or interpersonal relationships, and reliance on healthcare professionals (for example, the person with diabetes feeling as though the professional cannot help them).

Complications of T1DM can broadly be divided into two categories; microvascular complications and macrovascular complications. Microvascular complications are caused by damage to small blood vessels, and can affect the eyes, kidneys and peripheral nervous system and may manifest as retinopathy, nephropathy and neuropathy, respectively. Macrovascular complications are caused by damage to large blood vessels, and can affect the heart, brain and large arteries supplying the lower limbs. Such damage can place the individual at increased risk of, for example, stroke and myocardial infarction.

Complications of T1DM are associated with significant mortality. International data show that people with T1DM have a two to five times higher risk of death compared with those without diabetes. The loss of lifetime in T1DM is estimated to be approximately 30% greater than that observed in T2DM (for example, at 60 years lifetime lost to T2DM was 3.8 years and to T1DM was 5.6 years); this reflects the earlier diagnosis and hence the longer exposure to risk factors for acute and chronic microvascular and macrovascular complications. Irish data show age-related differences in mortality rates; rates typically increased with age with higher mortality observed in those aged 85 years and older.

In addition to having a negative impact on individuals with diabetes, complications

also have significant implications for health service resources, use and costs. Based on 2019 Hospital In-patient Enquiry (HIPE) data, the Department of Health reported that the national age-sex standardised hospitalisation rate for diabetes was 95.1 hospitalisations per 100,000 population. While comparing favourably with the OECD average (129 per 100,000), substantial variation was noted by county of residence.

4. Clinical effectiveness evidence

A rapid review approach was taken for this chapter. Guidance documents and supporting evidence reviews from the National Institute of Health and Care Excellence (NICE) were used as index documents, supplemented with data derived from evidence review documents from Health Technology Wales (HTW), the Scottish Health Technologies Group (SHTG) and targeted searches by HIQA.

Type 1 diabetes in adults

In the comparison of rtCGM and SMBG, there was evidence of a beneficial effect for rtCGM for three out of nine measures of HbA1c. The evidence was graded as being of low and very low certainty. For the other six measures there was no clinically meaningful difference between the two interventions. Three RCTs were identified comparing isCGM and SMBG for HbA1c outcomes; two found no clinically meaningful difference, but the third favoured isCGM. No clinically meaningful difference in mean HbA1c levels was observed between rtCGM and isCGM for a follow-up period up to six months. However, over the same follow-up period, rtCGM was associated with a significantly higher likelihood than isCGM of achieving an HbA1c target less than 7.0%.

For hypoglycaemic and hyperglycaemic outcomes, the findings were mixed for isCGM and rtCGM compared with SMBG. Nocturnal hypoglycaemia and the risk of severe hypoglycaemic events were lower for rtCGM compared with isCGM.

RtCGM usage resulted in increased time in range versus SMBG, although there was very low certainty in this estimate. There were mixed findings for isCGM compared with SMBG for time in range. There was some evidence that rtCGM use led to increased time in range compared with isCGM, but further comparative data with the same duration of follow-up is needed.

A range of general, disease-specific and complication/symptom-specific quality of life (QoL) and other patient-reported outcome measures were used across studies and these were not universally applied to both types of device. Additionally, identified observational studies were non-comparative, limiting comparisons of QoL. For rtCGM there was some evidence of increased well-being at 12 months compared to baseline. There was also evidence that rtCGM reduced fear or worry over time about hypoglycaemia. For isCGM there was some evidence of improved QoL up to 12 months compared to baseline. There was conflicting evidence for anxiety and

distress measures; isCGM users showed increased median anxiety and depression scores since starting isCGM monitoring but users also reported reduced diabetes distress.

Diabetes in pregnancy

There is some benefit to the use of rtCGM compared with SMBG for maternal and neonatal outcomes. There was very limited data for isCGM and no conclusion can be drawn for use of this intervention in pregnancy.

5. Cost effectiveness and budget impact

A literature search to identify economic evaluations was conducted, supplemented by a targeted search of publications from specific HTA agencies. The review included 16 studies with 23 analyses from eight countries. For rtCGM compared with SMBG results were mixed with some analyses reporting ICERs for rtCGM that would be considered cost effective at €20,000 per QALY, some at €45,000 per QALY, and some concluding it was not cost-effective. One analysis reported that SMBG dominated rtCGM (that is, SMBG was more effective and less expensive). Of the eight analyses identified for isCGM compared with SMBG, most concluded that isCGM was cost effective compared with SMBG. A non-industry analysis focused on pregnant women with T1DM found isCGM dominated SMBG. Only two analyses directly compared rtCGM and isCGM. An industry-funded study found isCGM to be cost effective relative to rtCGM while one study found isCGM to be more effective and less costly that rtCGM for a population of pregnant women. None of the included studies was considered directly applicable to the Irish setting due to modelling assumptions and the data used to populate the models.

A budget impact analysis (BIA) focusing on the reimbursement of CGM devices to adults with T1DM in Ireland was undertaken. Given the nature of this rapid HTA, a simplified model was used. Input parameters comprised population size, uptake rates, SMBG daily test frequency, and costs of CGM and SMBG to the HSE. The BIA base case assumed a total population with T1DM of 24,480. It was assumed that uptake is an additional 15% in the first year, rising to an additional 35% by the fifth year, and that all individuals switch to the same type of CGM system (that is, either isCGM or rtCGM), and not a mix of the two.

In the base case analysis compared with SMBG the estimated five year incremental cost to the HSE (over and above what the HSE currently spends on CGM) was €24.8 million for isCGM and €84.8 million for rtCGM. The estimated five year incremental cost to the HSE would fall between €24.8 million and €84.8 million should a mix of rtCGM and isCGM systems be rolled out. The annual incremental cost per person was estimated to be €811 for isCGM and €2,771 for rtCGM.

The cost estimates vary substantially depending on the uptake rate and the level of

testing in the SMBG comparator. Five year incremental cost estimates range from €16.9 million for isCGM and €76.9 million for rtCGM for a scenario of low uptake and high baseline SMBG test rates, up to €49.5 million for isCGM and €145.2 million for rtCGM for a scenario of high uptake and low baseline SMBG test rates.

The BIA assumed that once initiated on a particular system, individuals remained on the same CGM system for the duration of the five year period. It also does not account for switching systems in those who are currently using CGM. Switching to an economically advantageous system, when clinically appropriate to do so, may result in cost savings for the HSE.

There are several important limitations associated with this BIA primarily relating to the limited availability of data and the requirement to make assumptions in the model. Of particular importance is the substantial uncertainty regarding the total numbers in the eligible T1DM adult population in Ireland.

The analysis presented here is based on the CGM systems available at the time of assessment. There has been iterative development of CGM technologies, with the potential that new systems that incorporate additional or different functionality could be associated with increased costs and would have implications for the budget impact of CGM.

6. Published recommendations for CGM from the UK

Current Irish National Clinical Guidelines for type 1 diabetes mellitus (T1DM) are based on a contextualisation of 2015 guidelines from the UK's National Institute for Health and Care Excellence (NICE). A targeted search was undertaken for updated UK recommendations and guidelines on the use of continuous glucose monitoring (CGM) in individuals with T1DM.

T1DM in adults

NICE recommends that adults with T1DM be offered a choice of real-time continuous glucose monitoring (rtCGM) or intermittently scanned continuous glucose monitoring (isCGM), based on their individual preferences, needs, characteristics, and the functionality of the devices available. The NICE guideline also recommends that CGM should be provided by teams experienced in its use, as part of structured education so that users are empowered to interpret the results and to take appropriate action, and that use should be monitored and reviewed as part of the individual's diabetes care plan. Health Improvement Scotland has issued specific guidance with respect to isCGM using FreeStyle Libre®, recommending that it be made available for individuals with diabetes who are actively engaged in the management of their diabetes and who intensively manage their condition with multiple daily insulin injections or insulin pump therapy. With respect to rtCGM, no update was identified to the 2017 guidelines (which note that CGM should not be used routinely in individuals with diabetes).

Health Technology Wales has also issued specific recommendations with respect to isCGM with FreeStyle Libre®, noting that it should be made routinely available for people with diabetes (of any type) who require treatment with insulin.

T1DM in pregnancy

For pregnant women, guidance on CGM has been issued by NICE, Healthcare Improvement Scotland, and Health Technology Wales, with all three recommending the use of rtCGM.

NICE guidance in 2020 stated that rtCGM should be offered to all pregnant women with T1DM with the goal of meeting pregnancy blood glucose targets and improving neonatal outcomes. However, for women who are unable to use rtCGM, or where a clear preference for isCGM is expressed, NICE recommended that isCGM is to be offered.

7. Conclusions

CGM is an alternative to SMBG in individuals with diabetes. CGM is a sensor-based technology that reduces the need for finger-prick testing. The current Irish clinical guideline for managing adults with T1DM was developed through a contextualisation of the 2015 NICE clinical guideline. Since then, the evidence base for CGM has increased and is reflected in the updated 2022 NICE guideline. Given the 2022 update to the NICE guideline in relation to CGM, the Irish National Clinical Guideline should be revisited.

There are two types of CGM; intermittently scanned (isCGM) and real-time (rtCGM). There is some evidence to suggest that CGM, compared with SMBG, improves glycaemic outcomes, particularly time in range. There is limited head to head evidence to distinguish between CGM types in terms of effectiveness.

Routes of access to the technologies approved for reimbursement differ by CGM system type and component. Current reimbursement protocols mean that those aged over 21 have highly restricted access to isCGM in Ireland. However, reimbursed access to rtCGM is not restricted to the same degree. Annual HSE expenditure on CGM increased from €0.9 million in 2016 to €30 million in 2022. There are differences in costs in rtCGM systems, but currently all reimbursed rtCGM systems are considerably more expensive than the isCGM system. Should access to CGM be expanded, the five year incremental budget impact to the HSE of CGM compared with SMBG (over and above what the HSE currently spends on CGM) is estimated as €24.8 million for isCGM and €84.8 million for rtCGM. These estimates assumed increasing uptake from an additional 15% in the first year to an additional 35% in the fifth year. If uptake were to be close to full coverage then the budget impact would be considerably higher. The BIA assumed that once initiated on a particular system, individuals remained on the same CGM system for the duration of the five

year period. It also does not account for those who are currently using CGM, switching systems. Switching to an economically advantageous system, when clinically appropriate to do so, may result in cost savings for the HSE.

In light of the substantial uncertainty regarding the prevalence of T1DM in adults in Ireland, consideration should be given to the establishment of a national registry for people with diabetes to support healthcare service planning for that population. A registry would have to be established within the context of ongoing national and European policy and legislative developments regarding health information.

The different pathways to reimbursed access rtCGM and isCGM, and the substantial difference in costs between technologies have considerable implications for the cost effectiveness and overall budget impact of CGM for the HSE. Assuming the HSE continues to reimburse CGM systems, consideration should be given to a single managed access programme for all CGM systems for all individuals with T1DM regardless of age. Such a system would need clearly defined criteria for access. For people with T1DM, CGM should be provided in the context of the existing model of care which includes oversight by specialist diabetes services and empowerment of people with diabetes through access to structured diabetes self-management education.

Plain language summary

HIQA (the Health Information and Quality Authority) has assessed whether continuous glucose monitoring systems should be extended to additional adult populations with type 1 diabetes (T1DM) who may benefit from this technology.

T1DM is a condition that may affect multiple parts of the body, including the blood vessels. It is caused when the pancreas can no longer make enough or any insulin. Insulin is a hormone that allows glucose (blood sugar) to enter the body's cells after we eat and leads to the production of energy. When there is not enough insulin, glucose levels become too high and can cause damage to the body. People with type 1 diabetes can experience complications such as eye problems (retinopathy), kidney problems (nephropathy), foot problems potentially leading to amputation, nerve damage (neuropathy), heart attack and stroke.

People with diabetes can monitor their glucose in multiple ways. Finger-prick testing is when a person pricks their finger to produce a drop of blood and uses a machine to measure the glucose in it. This presents one-off information about the person's current glucose level. Continuous glucose monitoring is a relatively newer method which uses a sensor attached to your skin. There are two types of continuous monitoring: real-time and intermittently scanned (commonly known as flash monitoring). With real-time, the sensor sends results to your phone every few minutes and can alert the user when glucose levels are rising or dropping. With intermittently scanned, you need to scan the sensor with your phone to see the results.

We wanted to find out if the literature says continuous glucose monitoring is better than self-monitoring of blood glucose or if either real-time or intermittent scanning improves outcomes for people living with T1DM. We also wanted to find out the cost if more adults in Ireland switched from monitoring their glucose with finger-prick to continuous monitoring.

HIQA found some evidence that both types of continuous monitoring improve average blood sugar levels for people with T1DM. Compared to self-monitoring, people using either type of continuous monitoring saw an increase in time spent in the right blood sugar range. There was some evidence that people using real-time spent longer in the correct blood glucose range than those using intermittently scanned, but further evidence is needed to prove this. The risk of severe hypoglycaemic events and hypoglycaemia at night time was lower in those using real-time compared with intermittently scanned.

We estimated the likely cost to the HSE of making continuous monitoring more widely available to adults with T1DM. The costs to the HSE of extending access to continuous monitoring were about €24.8 million for intermittently scanned and €84.8 million for real-time. This means an extra cost each year to the HSE for each person with T1DM that starts using continuous monitoring would be €811 for intermittently scanned and €2,771 for real-time. Switching to a less expensive type of CGM system, if safe to do so, could yield cost savings for the HSE.

Conclusion

There is some evidence to suggest that continuous monitoring, compared with finger-prick, improves control of blood glucose. There is not a clear difference between continuous monitoring types in terms of effectiveness. At the moment access to intermittently scanned is mostly only for those under 21 years of age, while access to real-time is not as restricted. The HSE has increased spending on continuous monitoring in recent years. There are differences in costs in real-time systems, but currently all real-time systems are considerably more expensive than the intermittently scanned system. If access to continuous monitoring is expanded, the HSE will need a large increase in their budget to cover costs. The HSE should consider having one system to manage access for both types of continuous monitoring for everyone with T1DM, whatever their age. It is important that people with T1DM using continuous monitoring continue to attend specialist diabetes services.

List of abbreviations

BGMSRQ	Blood Glucose Monitoring System Rating Questionnaire
CEA	cost-effectiveness analysis
CFRD	cystic fibrosis-related diabetes
CGM	continuous glucose monitoring
CI	confidence interval
CSII	continuous subcutaneous insulin infusion
CSO	Central Statistics Office
CUA	cost-utility analysis
DKA	diabetic ketoacidosis
DQOL	Diabetes Quality of Life
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EQ-5D	EuroQol five-Dimension
EUnetHTA	European Network for Health Technology Assessment
EAG	expert advisory group
EPICC	Evidence for Policies to Prevent Chronic Conditions (study)
FGM	flash glucose monitoring (FreeStyle Libre®)
GDM	gestational diabetes mellitus
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	glycated haemoglobin
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
HSE-PCRS	Health Service Executive Primary Care Reimbursement Service
HTA	health technology assessment
HTW	Health Technology Wales
HFS-II	Hypoglycaemia Fear Survey- II
IAH	impaired awareness of hypoglycaemia
ICDNR	Irish Childhood Diabetes National Register
ICER	incremental cost-effectiveness ratio
IDF	International Diabetes Federation

INAHTA	International Network of Agencies for Health Technology Assessment
isCGM	intermittently scanned continuous glucose monitoring
IV	inverse variance
JDRF	Juvenile Diabetes Research Foundation
LADA	latent autoimmune diabetes in adults
LTI	Long Term Illness (scheme)
MDI	multiple daily injections (insulin)
MID	minimally important difference
MODY	maturity onset diabetes of the young
NCG	National Clinical Guideline
NDM	neonatal diabetes mellitus
NG	national guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAID	Problem Areas in Diabetes
PICO	population(s), intervention(s), comparator(s), outcome(s)
POCT	point-of-care testing
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QALY	quality-adjusted life year
RCT	randomised controlled trial
RWE	real world evidence
rtCGM	real-time continuous glucose monitoring
SD	standard deviation
SE	standard error
SHTG	Scottish Health Technologies Group
SIGN	Scottish Intercollegiate Guidelines Network
SMBG	self-monitoring of blood glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
WHO	World Health Organization
WTP	willingness-to-pay

1 Introduction

1.1 Background to the request

Following a request from the office of the Chief Clinical Officer at the Health Service Executive (HSE), the Health Information and Quality Authority (HIQA) agreed to undertake a rapid health technology assessment (HTA) of continuous glucose monitoring (CGM) focused exclusively on adult populations with type 1 diabetes mellitus (T1DM). The request was submitted following recent changes to recommendations relating to CGM in the National Institute for Health and Care Excellence (NICE) guidelines for England and Wales[1-4] and in recognition of strong demand for CGM from people with diabetes and healthcare providers, escalating costs for the HSE and concerns regarding equity of access.[5] Monitoring glucose levels is an integral part of diabetes management for individuals with diagnosed T1DM on insulin therapy. Glucose readings can be used to guide insulin treatment to avoid incidences of hypoglycaemia (when blood glucose is too low) or hyperglycaemia (when blood glucose is too high). Maintaining optimal glucose control is also a preventative measure to reduce complications of diabetes such as diabetic retinopathy, stroke, heart failure or chronic kidney disease.

Clinical guidelines recommend that people with T1DM should be empowered to self-monitor their glucose levels, and be educated about how to interpret the results. Historically, this self-monitoring has typically been done using a finger-prick capillary blood sample taken at intermittent intervals during the day. Within this report, this form of self-monitoring of blood glucose is known by the acronym SMBG. Continuous glucose monitoring (CGM) is a relatively recent development in diabetes management that enables glucose monitoring with a reduced need for finger-prick testing. In contrast to SMBG which measures blood glucose levels, CGM measures glucose levels in the interstitial fluid (fluid found outside blood vessels in the spaces around cells). It has been presented as an innovative technology in diabetes care; internationally its use has been increasing and in several countries it has replaced SMBG as the standard of care.[6]

There are two types of CGM considered in this rapid HTA:

- *real-time continuous glucose monitoring (rtCGM)* - provides real-time numerical and graphical information about the current glucose level, glucose trends, the direction and or rate of change of glucose level. These monitoring systems provide alarms and alerts when glucose levels reach a pre-set threshold.[7] These monitoring systems automatically transmit glucose readings to a device where the information can be accessed.

- *intermittently scanned continuous glucose monitoring (isCGM)* also known as *flash monitoring* – requires the sensor to be 'scanned' using another device, such as a reader or smartphone, in order to access the information regarding glucose levels. This form of monitoring provides the glucose level at the time of scanning plus retrospective glucose data for a specified time period.[7] Depending on the model, isCGM monitoring systems may also include alarms and alerts.

In the literature, the term 'CGM' is often used to represent rtCGM specifically; the term 'flash glucose monitoring' (FGM) is frequently used to represent isCGM. In this rapid HTA, the terms rtCGM and isCGM will be used to distinguish between the two CGM modalities. Exceptions were made if using a direct quotation from another source or the title of a document, in which case a footnote or explicit statement provides clarification. CGM is an essential part of automated insulin delivery (AID) systems such as sensor-augmented insulin pumps (that can integrate with the CGM monitoring system) and hybrid closed-loop systems (in which the CGM data are integrated with a dosing control algorithm and an insulin pump).[8] This rapid HTA focuses on the use of CGM regardless of whether it is being used in conjunction with an insulin pump as part of an AID system. However, the BIA is limited to the CGM components and exclude the insulin pump and proprietary dosing algorithms.

Current guidance on use of CGM in Ireland

In Ireland, there are two national-level guidelines that make recommendations regarding glucose monitoring in adults with T1DM. Firstly, the *National Clinical Guideline 17: Adult type 1 diabetes mellitus* published by the National Clinical Effectiveness Committee in 2018 includes recommendations for CGM in adults in specific circumstances (See Appendix 1).[9] This guideline was developed through a formal contextualisation of the National Institute for Health and Care Excellence (NICE) guideline published in 2015: *NG 17 Type 1 Diabetes in adults: diagnosis and management*.[10] The 2018 Irish guideline recommends that rtCGM should not be offered routinely to adults with T1DM, but suggests that it may be considered for a limited subgroup of adults. No recommendation was made with respect to isCGM as its clinical and cost effectiveness were not formally evaluated by NICE in its 2015 guideline. Pregnant women were not included in the scope of the Department of Health guideline and the user is instead referred to the HSE guideline below and to the NICE guideline published in 2015: *NG3 Diabetes in pregnancy: management from preconception to the postnatal period* (recommendations 1.3.17 to 1.3.20). Following a HTA by the HSE Health Technology Assessment Group, the HSE approved access to an isCGM system, FreeStyle Libre®, for people with T1DM aged between four and 21 years that meet strict eligibility criteria.[11] A dedicated online portal for FreeStyle Libre applications was established and became operational in April 2018.[12]

The second national-level guideline of relevance to this rapid HTA is the HSE's *Guidelines for the Management of Pre-gestational and Gestational Diabetes Mellitus from Pre-conception to the Postnatal Period*. This document, published in 2010, refers to glucose monitoring in women with T1DM who are pregnant or planning to become pregnant.[13]

It is important to highlight that:

- The 2010 HSE guideline does not mention CGM (rtCGM or isCGM) though it recommends SMBG if blood sugar monitoring is indicated in this population. This may be attributable to the limited evidence base and use of CGM prior to the publication of this guideline in 2010.[13]
- Since the publication of the Department of Health guideline in 2018, updated evidence reviews have been produced for both NICE guidelines (NG3 and NG17) and this has led to new or updated recommendations extending CGM use for pregnant and non-pregnant adults with T1DM.[10, 14]

1.2 Terms of reference

The purpose of this document is to provide an overview of the evidence in relation to CGM systems in the form of a rapid HTA. This overview is provided in order to inform decision-making by the HSE as to whether reimbursement for CGM systems in the Irish healthcare system should be extended to additional adult populations with T1DM who may benefit from this technology.

Given the comprehensive evidence reviews carried out by the National Institute of Health and Care Excellence (NICE) in 2020 and 2021, a rapid rather than full HTA approach was used. A full HTA would typically involve a systematic review of the evidence and de novo economic evaluation. This rapid HTA presents a rapid review of clinical effectiveness and cost-effectiveness evidence and an estimate of the budget impact. For the rapid review of clinical effectiveness, recent HTAs were identified, with priority placed on UK data. Guidance documents from NICE were used as index documents, supplemented with data from Health Technology Wales (HTW), the Scottish Health Technologies Group (HTG) and targeted searches by HIQA. Targeted update searches were also undertaken, following advice from the EAG, to identify the latest clinical effectiveness and health-related quality of life evidence for the general adult population with T1DM.

The focus of this rapid HTA was the general adult population with T1DM. While consideration of the use of CGM in specific subpopulations was outside the scope of the rapid HTA, the clinical effectiveness of CGM in pregnant women with T1DM, as described in the guidance documents from NICE, is briefly summarised.

This rapid HTA also includes a review of the epidemiology and burden of disease of type 1 diabetes as well as a summary of the recommendations on CGM from UK HTA bodies.

The terms of reference of this rapid HTA, agreed with the HSE National Clinical Programme for Diabetes, are to:

- Describe the CGM systems available for use in adults with T1DM.
- Summarise the recommendations in UK guidance regarding CGM for adults with T1DM.
- Review the evidence of the impact of CGM on outcomes in adults with T1DM.
- Determine which groups have been shown to benefit from CGM.
- Review the current evidence of cost effectiveness of CGM for adults with T1DM.
- Assess the potential budget impact for the Irish healthcare system with respect to different CGM strategies.
- Based on the evidence in this assessment, provide advice to the HSE on CGM to inform decision-making in relation to whether reimbursement for CGM systems should be extended to additional adult populations with T1DM in Ireland.

1.3 Overall approach

HIQA appointed an evaluation team comprising staff working in the HTA Directorate to conduct the rapid HTA. An expert advisory group (EAG) comprising representation from key stakeholders was convened to inform and guide the process, and to provide expert advice and information. This EAG includes representation from the HSE, clinicians with specialist expertise in the management of diabetes, endocrinology and public health medicine, national organisations representing general practitioners, and a patient representative from Diabetes Ireland. The membership of the EAG is provided in the Acknowledgements section of this report.

The terms of reference of the Expert Advisory Group are to:

- Contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate.
- Support the Evaluation Team led by HIQA during the assessment process by providing expert opinion and access to pertinent data, as appropriate.
- Review draft versions of the report from the Evaluation Team and recommend amendments, as appropriate.

This rapid HTA was drafted by an evaluation team at HIQA and disseminated to the EAG for review prior to their meeting. At the meeting, the EAG reviewed the Terms of Reference of the HTA and discussed the draft evidence of the clinical effectiveness, cost effectiveness, and budget impact analysis. All feedback was reviewed and incorporated as appropriate, and additional searches and evidence synthesis were undertaken, with the final draft being sent for review to the EAG. Following further amendments the report was approved by HIQA's Executive Management Team. The completed assessment has been submitted as advice to the HSE to inform decision-making, and published on the HIQA website.

2 Description of the technology

Key points

- Monitoring glucose levels is an integral part of the management plan for individuals with diagnosed T1DM on intensive insulin therapy, as they are at risk of hypoglycaemia (when blood glucose is too low) and hyperglycaemia (when blood glucose is too high). Glucose readings are used to guide insulin treatment, so to support optimal glucose control and reduce the occurrence of complications of diabetes.
- In common use since the 1980s, the standard method of glucose monitoring was self-monitoring of blood glucose (SMBG) using capillary blood glucose. This is typically done through intermittent use of a finger-prick test (although blood may be drawn from other sites) with a lancet, using testing strips and electronic blood glucose meters to determine current blood glucose concentration.
- Continuous glucose monitoring (CGM) systems provide an alternative approach to SMBG, by measuring glucose levels in the interstitial fluid (a thin layer of fluid around the cells).
    - They comprise sensors (self-administered subcutaneously, typically in the upper arm and replaced every seven to 14 days depending on the system), transmitters (or combined sensors and transmitters) and a mechanism to display the results (readers/receivers or smart device app).
        - In addition to providing current glucose levels, CGM systems provide trend data (increasing, decreasing, stable, rate of change) and alerts (some systems) when levels change rapidly or fall above or below specified limits. These data can be used by the person with diabetes to make changes to their insulin dosing schedule.
        - Those using CGM may still require SMBG, for example, when readings conflict with symptoms or expectations or to calibrate the device. Some devices do not require calibration.
- Two types of CGM were considered in this rapid HTA:
    - **Real-time continuous glucose monitoring (rtCGM)**
      Readings are automatically sent at set intervals (for example, every five minutes). As of July 2023, multiple rtCGM systems are reimbursed by the HSE including both Dexcom G7 and Medtronic Guardian Connect 4; older systems currently reimbursed for existing people with diabetes are being

phased out. All reimbursed systems allow the user to set alerts for high and low glucose levels and for rapid changes in glucose levels.

- **Intermittently scanned continuous glucose monitoring (isCGM)** Commonly referred to as flash glucose monitoring, the sensor measures glucose levels at one-minute intervals with readings stored every 15 minutes and retained for eight hours. Data can be obtained by scanning the sensor with a mobile phone or a reader. As of July 2023, one isCGM system is reimbursed by the HSE, the Abbott Freestyle Libre®; this version is not capable of providing alerts. Newer iterations of Freestyle Libre® available internationally include Freestyle Libre® 2 (incorporates optional alarms) and Freestyle Libre® 3 (a full rtCGM system).

- Routes of access to the technologies approved for reimbursement differ by CGM system type and component:
  - Sensors are accessed through community pharmacies, with reimbursement managed through the Primary Care Reimbursement Service (PCRS). Medical equipment (for example, transmitters and readers) are managed by the HSE Community Funded Schemes administered by the Local Health Office of the area in which the individual resides.
  - For rtCGM systems, if equipment is required (for example the system requires a separate transmitter or if the individual requires a reader), an application must be made by a consultant endocrinologist or diabetes nurse specialist to the Local Health Office, where it is subject to administrative and clinical review. Where no medical equipment is required (for example, an individual using a system which has a combined sensor transmitter and who chooses to access their readings through a smart device app), this prior authorisation step is not required - individuals can have reimbursed access once they are part of any PCRS community scheme, and have a valid prescription.
  - Access to the FreeStyle Libre® system is managed by through a dedicated online portal. Reimbursement is limited to people with T1DM aged 4 to 21 years that meet strict clinical criteria. Access for those aged 22 years and older, when first seeking access, is only granted in 'very exceptional circumstances'.

- HSE expenditure on CGM has increased substantially since 2016. For adults (aged >21 years):
  - rtCGM use has increased from 435 individuals in 2016 to over 10,000 in 2022. The associated annual expenditure increased from €0.9 million to over €27 million for the same time period.

- isCGM use has grown from almost 400 individuals in 2018 to over 2,000 in 2022, with annual expenditure increasing from €0.19 million to €2.42 million over the same period.

- The absence of a single managed access programme for CGM has resulted in different pathways for accessing rtCGM and isCGM which, combined with a substantial difference in costs between technologies, has considerable implications for the cost effectiveness and overall budget impact of CGM for the HSE.

2.1 Introduction

The aim of this chapter is to describe the use and importance of glucose monitoring as a disease management strategy in adults with T1DM. To facilitate understanding, a brief description of the disease is provided along with a description of target values. An outline of the various CGM systems is provided along with a review of their current availability in Ireland.

2.2 Diabetes

Diabetes mellitus is defined by the World Health Organization (WHO) as:

> a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves.[15] It is a treatable condition and diet, exercise, monitoring and medication can help to delay and prevent complications.[16]

There are several different kinds of diabetes, described as follows.

Type 1 diabetes mellitus (T1DM) commonly develops in childhood or adolescence (although it can occur at any age) when the pancreas makes insufficient or no insulin to help the body regulate glucose levels.[17, 18] People with diabetes therefore require exogenous insulin which may be delivered either as multiple daily injections (MDI) or by an insulin pump. T1DM is the focus of this rapid HTA.

Type 2 diabetes mellitus (T2DM) usually develops in adults over the age of 45 years, although it can develop at any age. In people with T2DM, the cells become insulin resistant causing the pancreas to respond by making more insulin. Eventually the demand on the pancreas becomes unmanageable and glucose levels rise leading to prediabetes and T2DM.[19]

Gestational diabetes mellitus (GDM) is hyperglycaemia which is diagnosed for the first time during pregnancy.[20] During pregnancy, changes in the body, such as those associated with hormones and weight gain, can cause cells to become insulin resistant, leading to GDM.[21]

Other less common types of diabetes include:

- *monogenic forms of diabetes* caused by changes or mutations to a single gene; these include maturity-onset diabetes of the young or neonatal diabetes mellitus,[22] Wolfram syndrome,[23] Alström syndrome,[24] and cystic fibrosis-related diabetes[25]
- *latent autoimmune diabetes in adults*
- *type 3c diabetes*
- *steroid-induced diabetes.*[26]

Diabetes results in extensive morbidity and mortality. In 2021 alone, diabetes was attributed as the cause of 6.7 million deaths worldwide.[27]

Monitoring of current glucose levels is an integral part of diabetes management for individuals diagnosed with T1DM on insulin therapy. Intensive therapy including frequent glucose monitoring (i.e., glucose readings taken at regular intervals, before and after events such as exercise) is used to guide insulin treatment to avoid incidences of hypoglycaemia (when blood glucose is too low) or hyperglycaemia (when blood glucose is too high). Glucose monitoring is also essential to recognise and confirm those events, and inform action (carbohydrate intake or insulin correction). Several options for monitoring glucose levels are discussed in sections 2.4 and 2.5.

Glycaemic control in individuals with diabetes is also measured through glycated haemoglobin (HbA1c) levels. HbA1c is the internationally recognised established marker for evaluating glucose levels at an intermediate term, as it reflects average plasma glucose over the preceding eight to 12 weeks. In individuals with T1DM, there is evidence that maintaining glycaemic levels as close to the non-diabetes range as possible is an effective preventive measure associated with substantial reduction in the risk of microvascular and macrovascular complications.[10] Clinical guidelines recommend that HbA1c levels should be measured every three to six months in adults with T1DM.[9, 10] Typically this testing is undertaken by the GP or diabetes care team.

2.3 Target values

National clinical guidelines for Ireland, England and Wales recommend that adults with T1DM should aim for HbA1c levels of 48 mmol/mol (6.5%) or less to reduce the risk of long-term vascular complications. Each individual is advised to work with their healthcare professional or team to formulate a plan to reach this target, taking into

account their health status and lifestyle factors.[9, 10] Without national audits or a register, it is not possible to say how many adults with T1DM in Ireland achieve this target. However, evidence of sub-optimal control is available from a number of studies, some of which report Irish data. One such study comprised a multinational comparison of glycaemic control data from people with T1DM, which collected data from a clinic in Galway, Ireland between January 2012 and December 2013. From these Irish data, the median HbA1c value was 77 mmol/mol for people aged 15 to 24 years (n=198) and 67 mmol/mol for people aged 25 years or older (n=927).[28] Similarly, an international cross-sectional study of people with T1DM included data from 1,341 adults aged 25 years or older who were attending clinics in Ireland. These data indicated less than optimal control in the majority of those attending; it was reported that 75.6% of this population had an HbA1c level of 58 mmol/mol (7.5%) or greater and 30.5% had an HbA1c level of greater than or equal to 75mmol/mol (9.0%).[29]

Time in range may also be considered as a clinical target for people using continuous glucose monitoring technology. The International Consensus in Time in Range (TIR) was published in 2019 and defined the concept of the time spent in the target range between 70 and 180 mg/dL while reducing time in hypoglycaemia, for people using continuous glucose monitoring.[30] It is recommended that adults with diabetes should aim to be in the target range at least 70% of the time.

2.4 Intermittent capillary blood glucose monitoring

Self-monitoring of blood glucose (SMBG) using capillary blood glucose testing became the standard of care for glucose monitoring for individuals with T1DM during the 1980s.[31] This is commonly done through intermittent use of a finger-prick test (although blood may be drawn from other sites) with a lancet, using testing strips and electronic blood glucose meters. SMBG allows the individual to determine their current, point in time blood glucose concentration. Meters frequently include a memory function allowing the storage of readings and may allow for upload of the data to a personal computer or secure website.

2.5 Continuous glucose monitoring

An alternative to SMBG is continuous glucose monitoring (CGM), which involves using a device to measure glucose levels in the interstitial fluid (a thin layer of fluid found outside blood vessels in the spaces around cells). CGM systems feature the following components:

- sensors
- transmitters (or combined sensors and transmitters)

- mechanism to display the results (readers/receivers or smart device apps, or both options provided with the option selected based on user preference).

The sensor is inserted under the skin and serves to measure the interstitial glucose levels; sensors can be self-administered subcutaneously using an applicator, typically into the upper arm or abdomen. The transmitter, where required for the system, wirelessly sends the information to a device featuring a display (such as a handheld data receiver/reader or compatible smart phone with a dedicated app), where the results can be viewed. Systems may be adjunctive, that is, they should be used in conjunction with SMBG before making a treatment decision, or non-adjunctive, that is, no SMBG is required.

There have been substantial developments in terms of CGM. Currently, there are three broad types of CGM system: real-time continuous glucose monitoring (rtCGM), intermittently scanned continuous glucose monitoring (isCGM), and professional CGM systems. While the professional CGM systems are outside the scope of this rapid HTA, all three types are described below. Table 2.1 presents the key features of selected CGM systems manufactured or distributed by Dexcom, Inc., Medtronic, Abbott Diabetes Care, and Windzor Pharmaceuticals Ltd.[7] These companies were invited to complete a factual accuracy check of this information. The systems and system components that are currently reimbursed in Ireland are outlined in section 2.6.

Table 2.1 Key features of a selection of continuous glucose monitoring systems

Manufacturer	Abbott Diabetes Care[32]			Dexcom, Inc.[33]		Medtronic[34]	Windzor Pharmaceutical Ltd.[35]
System Name	**FreeStyle Libre® Flash Glucose Monitoring System**	**FreeStyle Libre® 2 system**	**FreeStyle Libre® 3 system**	**Dexcom® G6 CGM System**	**Dexcom® G7 CGM System**	**Guardian™ 4 CGM System**	**GlucoRx AiDEX™ (CGM) System**
Type of CGM	isCGM	isCGM	rtCGM	rtCGM	rtCGM	rtCGM	rtCGM
Class	FreeStyle Libre® FGM System (Reader kit): IIb FreeStyle Libre® FGM System (Sensor kit): IIb	Reader kit: IIb Sensor kit: IIb	Reader kit: IIb Sensor kit: IIb	System: IIb	System: IIb	Guardian™ 4 Sensor: Class IIb Guardian 4 Transmitter Class IIa Guardian Connect App Class IIa	System: IIa.
Adjunctive*	No	No	No	No	No	No	Yes
Sensor duration (days)	14	14	14	10	10 (+12 hr grace period)	Up to 7 days	14
Alarm and/or alert function	No	Yes	Yes	Yes	Yes	Yes	Yes
Reader/receiver, smart-device compatible app, or both options	Both options	Both options	App only	Both options	Both options	App only	App only

Manufacturer	Abbott Diabetes Care[32]			Dexcom, Inc.[33]		Medtronic[34]	Windzor Pharmaceutical Ltd.[35]
System Name	**FreeStyle Libre® Flash Glucose Monitoring System**	**FreeStyle Libre® 2 system**	**FreeStyle Libre® 3 system**	**Dexcom® G6 CGM System**	**Dexcom® G7 CGM System**	**Guardian™ 4 CGM System**	**GlucoRx AiDEX™ (CGM) System**
Combined or separate sensor and transmitter components	No transmitter, it is embedded in the sensor	No transmitter, it is embedded in the sensor	No transmitter, it is embedded in the sensor	Separate	Combined	Separate	Separate
Currently available in Ireland**	Yes	No (based on correspondence received 11 November 2022)	No immediate plans for availability	Yes	Yes	Yes	Yes, although not reimbursed

* Adjunctive = used with self-monitoring of blood glucose before making a treatment decision.
** Due to the evolving nature of this technology, it is possible that there are additional CGM systems currently available in Ireland.
Key: CGM – continuous glucose monitoring; rtCGM – real time continuous glucose monitoring; isCGM – intermittently scanned continuous glucose monitoring.

Real-time continuous glucose monitoring (rtCGM)

Real-time continuous glucose monitoring (rtCGM) systems available in Ireland include those produced by Dexcom and Medtronic, with various generations of devices having become available over time. These systems involve disposable sensors which have a lifespan of between seven and 14 days depending on the version, after which time the sensor must be removed and replaced. At set intervals, such as every one or five minutes, the sensor (with or without the aid of a separate transmitter) automatically sends data to a device featuring a display (such as a handheld reader or smart phone with a dedicated app). These data can be used by the person with diabetes in real-time to make changes to their insulin dosing schedule. The data can also be shared with others such as family members or healthcare professionals and used retrospectively by clinicians to inform changes in the individual's diabetes management. In addition to the automatic data feed, many systems allow the user to set alerts for high and low glucose levels and for rapid changes in glucose levels.[36-38] Both adjunctive and non-adjunctive systems are marketed.

While systems may be indicated as non-adjunctive (that is no SMBG is required), individuals with diabetes are typically cautioned to use a blood glucose meter to make treatment decisions if the alerts and readings from their CGM system do no match their symptoms or expectations. Systems identified in Table 2.1 are all factory calibrated and do not require user calibration.

Intermittently scanned continuous glucose monitoring (isCGM)

Intermittently scanned continuous glucose monitoring (isCGM), also known as 'intermittently viewed continuous glucose monitoring' (iCGM), is commonly referred to as flash glucose monitoring (FGM). The Abbott FreeStyle Libre® system is an example of isCGM which is available in Ireland. This system features a disposable sensor with a thin fibre inserted subcutaneously, usually into the upper arm. The sensor may be worn for up to 14 days and then removed from the skin by the user and replaced. At one-minute intervals, the fibre sends interstitial fluid from the muscles into the sensor to allow glucose levels to be measured.[39] Readings are stored every 15 minutes and retained for eight hours.[39] These readings can be accessed by scanning the sensor for one second with a device such as a smartphone or a reusable, rechargeable reader; scanning can be accomplished through clothing.[39] The readings can include real-time data (current glucose levels), retrospective data (levels from the previous eight hours) and trends (ascending or descending levels, and associated rate of change). The FreeStyle Libre® systems are factory calibrated and do not require user calibration. However, SMBG is still necessary when people are unwell, at high risk of hypoglycaemia, or scanned readings conflict with symptoms or expectations.[39-41]

In the original FreeStyle Libre® system, alerts for high and low glucose levels are shown only when scanned, which increases the possibility of missing hypo- or hyperglycaemic events. Newer versions of the FreeStyle Libre system launched internationally by Abbott include the FreeStyle Libre® 2 and FreeStyle Libre® 3 systems. The FreeStyle Libre® 2 system gives the option to set alarms when the wearer has low or high glucose levels, or when the alarm signal is lost, making it more similar to the alert feature of rtCGM. Abbott's most recently launched CGM system, the FreeStyle Libre® 3 system, is an rtCGM system which allows for automatic streaming of real time glucose readings.

Professional continuous glucose monitoring

Professional CGM systems, also known as masked continuous glucose monitoring (mCGM) systems, are used by healthcare professionals. These systems capture glucose levels in real-time with data saved, so that they can be viewed in the future. The systems allow for unblinded or blinded monitoring, that is, where the glucose levels are visible or not visible to the person with diabetes.[42, 43] They are used intermittently to monitor diabetes and to help inform decision making. The American Diabetes Association (ADA) recommends that readings are shared with the person with diabetes, and that education is provided and tailored management options are implemented.[44] Professional systems are not included in the scope of this rapid HTA.

2.6 Current availability and reimbursement of CGM in Ireland

Currently, a number of rtCGM systems[45] as well as the Abbott FreeStyle Libre® Flash Glucose Monitoring System (isCGM) are available for use in Ireland. Other isCGM systems, including the FreeStyle Libre® 2 and FreeStyle Libre®3 systems which have been launched internationally by Abbott, are currently either not yet marketed, or approved for reimbursement by the HSE (as of July 2023). The rtCGM GlucoRx AiDEX™ is not yet approved for reimbursement by the HSE (as of July 2023).

As noted, CGM systems feature the following components: sensors; transmitters (or combined sensors and transmitters); and a mechanism to review the results (readers/receivers or smart device apps, or both). Routes of access to the reimbursed technologies differ by system type and system component. Table 2.2 outlines the CGM system components that are currently reimbursed by the HSE with the access routes described in detail below.

Table 2.2 CGM components currently reimbursable by the HSE and associated reimbursement pathway

	Reimbursed via HSE PCRS	**Reimbursed via HSE Community Funded Schemes (application through Local Health Office)**	
CGM systems by type and manufacturer	**System components**		
	Sensor *(replacement interval)*	**Separate transmitter required** *(replacement interval)*	**Receiver/App** *(replacement interval)*
rtCGM - Medtronic			
Guardian Connect CGM System*	Glucose Enlite Sensor *(6 days)*	✔ *(12 months)*	App only
Guardian Connect CGM System*	Guardian Sensor 3 *(7 days)*	✔ *(12 months)*	App only
Guardian 4 CGM System	Guardian Sensor 4 *(7 days)*	✔ *(12 months)*	App only
rtCGM - Dexcom			
Dexcom G6 CGM System	Dexcom G6 Sensor *(10 days)*	✔ *(3 months)*	Receiver or app *12 month warranty for receiver*
Dexcom G7 CGM System	Dexcom G7 CGM Sensor *(10 days +12 hour grace period)*	✘	Receiver or app *12 month warranty for receiver*
isCGM - Abbott			
FreeStyle Libre CGM system	Freestyle Libre *(14 days)*	✘	Receiver or app *2 year warranty for reader*

Key: CGM – continuous glucose monitoring; rtCGM – real time continuous glucose monitoring; isCGM – intermittently scanned continuous glucose monitoring; PCRS - Primary Care Reimbursement Service.

*Glucose Enlite Sensors and Guardian Sensors 3 are both listed on the most current reimbursement list (July 2023); therefore, it is possible that these sensors are used by some individuals, though the majority of use is expected to be for the Guardian 4.

The HSE operates a suite of schemes through which it delivers a significant proportion of primary care to the public. These include:

- Community Funded Schemes for medical equipment and appliances which are administered by Local Health Offices
- Schemes operated by the Primary Care Reimbursement Service (PCRS), which include a number of community drug schemes through which the HSE reimburses approved prescribed pharmaceuticals and non-pharmaceuticals (for example, dressings, test strips, sensors), but not medical equipment.

Suppliers must apply for their product to be included on the approved reimbursement lists with separate mechanisms applying for pharmaceuticals and non-pharmaceuticals (for example, dressings, test strips, sensors). The process whereby personal diagnostic monitoring and delivery systems can be added to the HSE reimbursement list is outlined in guidelines issued by the HSE.[46] Following receipt of an application by HSE PCRS and completion of an initial review, the file is assessed by their National Expert Group for Diabetic Ancillaries from a clinical and technical perspective with consideration also given to the proposed price, the potential budget impact and the resources available to the HSE. This National Expert Group for Diabetic Ancillaries makes a recommendation to the appropriate delegated authority within the HSE whether the product should be added to the list. The final decision may be informed by a HTA.

In line with the HSE's National Corporate Procurement Plan,[47] procurement contracts may be organised though a Dynamic Purchasing System (DPS) which offers a degree of flexibility in terms of when new suppliers and products can join or be added.[48] A DPS tender may then be run in order to put a contract in place. Where a range of options are available, contracts may be awarded on the basis of a Most Economically Advantageous Tender. Such tenders are for a defined period and allow the HSE to take account of a range of criteria, including price. The final selection of a preferred product is agreed by the National Advisory Group for Diabetes Technology for each procurement process, with a requirement that the preferred product is used except where exemptions are sought on an exceptional basis.[49] Use of such tenders can drive price reductions enabling cost savings to be achieved. The use of tendering may therefore provide an opportunity to maximise value for money. At the time of writing, procurement of rtCGM systems through the HSE Diabetes Technology subgroup is on the basis of a commercial agreement. The agreement is applicable to all suppliers who can supply a suitable product (transmitters/readers) that meets HSE quality standards and that meet HSE requirements in terms of service support including training and after sales support. Mechanisms by which individuals with diabetes can access reimbursed components of their CGM system, such as readers and transmitters are described in the following sections.

As noted, the HSE's Primary Care Reimbursement Service (PCRS) oversees a number of community drug schemes through which it reimburses community pharmacies which provide free or reduced-cost pharmaceuticals and non-pharmaceuticals (for example, dressings, test strips, sensors) to the public. One such scheme is the Long Term Illness (LTI) scheme.[50] This is a non-means tested, condition-specific community pharmacy scheme through which eligible participants receive prescription medications, medical products, and medical and surgical appliances associated with their qualifying condition free of charge.[50] While diabetes is an eligible condition,

individuals must first register to avail of the scheme. With respect to SMBG and CGM, individuals with diabetes can access approved items, such as sensors and test strips, that have been prescribed by a clinician through their community pharmacy.[51]

Reimbursement of real-time continuous glucose monitoring (rtCGM) systems

As of August 2023, the HSE does not have a centralised prior authorisation scheme through which applications for reimbursement of rtCGM systems are received. As the PCRS does not reimburse medical equipment, typically, reimbursement of the rtCGM systems has involved two separate budget holders within the HSE:

- Local Health Offices: responsible for authorisation, reimbursement and distribution of approved non-consumable components (that is, readers (where required) and transmitters)
- PCRS: responsible for reimbursement of the approved consumable components, that is the disposable sensors which are distributed through community pharmacies.

Until October 2022, all generations of rtCGM systems approved for use by the HSE required a separate transmitter.[52] As outlined in Table 2.2, these transmitters needed replacement at intervals of either three or 12 months depending on the brand. A prior authorisation process is in place for reimbursement of these devices through the HSE. Briefly, an application is made by a consultant endocrinologist (or diabetes specialist nurse attached to their service) to the Local Health Office (LHO) for the area in which the patient resides.[53] Following administrative review and clinical review by the Area Medical Officer, reimbursement may be authorised. As there is no centralised list of qualifying clinical criteria and reimbursement may be subject to available LHO budgets, there may be regional differences in the degree to which funding applications are successful. Distribution is initially coordinated through the LHO with replacement transmitters sent directly by the company to the person with diabetes.

While the majority of individuals with diabetes using rtCGM rely solely on free dedicated user apps compatible with specific smart devices to display their glucose values, a small proportion continue to rely on separate reader / receiver devices. As outlined in Table 2.2, the option of a separate reader is limited to certain rtCGM systems; for example, current Medtronic systems approved for use by the HSE are all app-based only. The readers have a 12-month warranty, with reports that they typically need to be replaced every four years.[54] As with the process for accessing the transmitter devices outlined above, reimbursement of readers is subject to approval by the LHO following receipt of an application from a consultant endocrinologist or diabetes nurse specialist. For those who require both transmitters

and a reader / receiver, this can be done as part of a single application. Smart devices (for example, smart phones) are not reimbursed by the HSE.

Individuals with diabetes access the ancillary disposable sensor devices necessary for the operation of their rtCGM system through their community pharmacies. These must be prescribed and are reimbursed by the PCRS for eligible individuals (that is, medical card holders or those with LTI scheme eligibility).

In October 2022, the Dexcom G7 sensor, compatible with the G7 CGM system, was added to the PCRS list of reimbursable items.[55] This is a combined sensor and transmitter. It is indicated to be worn for up to 10 days (plus a 12-hour grace period at the end) after which it must be removed and replaced with a new sensor. For those who also choose to use the dedicated app rather than relying on a separate reader, this means that it is no longer necessary to apply to the LHO as no equipment is required. Instead, any person with diabetes registered for any PCRS community drug scheme can have the sensors reimbursed subject to a valid prescription. As there is no prior authorisation mechanism, the criteria that have typically applied for reimbursement of CGM (application by a consultant endocrinologist and meeting defined clinical criteria) no longer apply.

While a range of rtCGM systems and components listed in Table 2.2 are approved for reimbursement, it is noted that those newly commencing on standalone rtCGM are likely to receive the following devices (July 2023):

- Dexcom G7 CGM sensor (no separate transmitter required) +/- reader (if smartphone app not accessible)
- Medtronic Guardian Sensor 4 + Guardian 4 Smart CGM System Transmitter +/- reader (if smartphone app not accessible).

Reimbursement of intermittently scanned continuous glucose monitoring (isCGM) systems

In Ireland, since April 2018, the FreeStyle Libre® system has been reimbursed by the HSE for individuals with T1DM aged four to 21 years who satisfy the following additional eligibility criteria:

- are not pregnant
- use multiple daily injections (MDI) of insulin or insulin pump therapy
- have a need to test eight or more times daily
- have experienced frequent episodes of diabetic ketoacidosis (DKA) or hypoglycaemia which included hospital admissions.[56]

This decision was informed by a report by the HSE's Health Technology Assessment Expert Group which was operational at the time.

A consultant endocrinologist (or diabetes nurse specialist attached to their service) makes an application on behalf of their patient through a dedicated portal managed by the PCRS.[12, 57] For approved individuals, subject to ongoing clinical need, reimbursement is allowed to continue after they exceed the age of 21 years. While adults with T1DM who are older than 21 years at the time of first application are not currently entitled to reimbursement for FreeStyle Libre®, reimbursement may be granted 'in very exceptional circumstances'. This has led to a large number of reimbursement applications for adults. Between 2018 and 2021, the HSE received 2,755 applications for reimbursement support of FreeStyle Libre® for persons aged 22 years and older with T1DM; a total of 1,662 of these applications were subsequently approved based on the clinical information provided, while 1,093 applications were rejected.[58]

Individuals for whom reimbursement has been approved can obtain their sensors by presenting their prescription to their local pharmacy.

Current CGM utilisation estimates

Analysis was undertaken by the evaluation team to estimate current usage of CGM by adults (aged > 21 years) within the publicly funded healthcare system (that is, reimbursed by the HSE); this analysis used data provided by HSE PCRS alongside publicly available information outlined in parliamentary questions (PQs).[58-62]

Figure 2.1 shows the number of individuals aged over 21 years in receipt of CGM devices from 2016 to April 2023. Since the introduction of reimbursement of FreeStyle Libre®, there has been a gradual increase in the number of isCGM users, from almost 400 individuals in 2018 to over 2,000 in 2023. The rise in the number of rtCGM users has been much more rapid, particularly for Dexcom, with the number of Dexcom users increasing from just over 250 individuals in 2018 to over 10,000 in 2023. By April 2023, there were over 12,000 adults reimbursed for any CGM system.

Disaggregated utilisation data by type of diabetes are not available. While noting that criteria for the use of FreeStyle Libre® are limited to individuals with T1DM, it is not known if approval has been granted for individuals with T2DM under exceptional circumstances. While expert feedback suggest that the majority of use relates to individuals with T1DM, utilisation data for rtCGM may also include individuals with T2DM (for example those on multiple daily doses of insulin) given that there is no centralised list of qualifying clinical criteria.

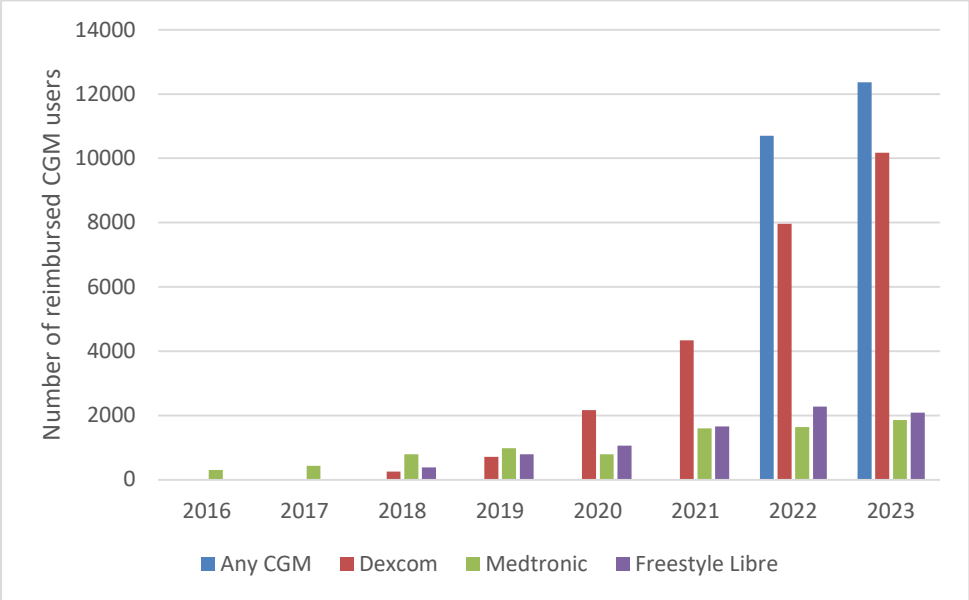
Figure 2.2 shows the expenditure by the HSE on CGM for adults (aged >21 years) from 2016 to 2022. Expenditure has increased from €0.9 million in 2016 to €30 million in 2022. The majority of this increase has been driven by increased expenditure on rtCGM, with €27.5 million spent in 2022. This is a rapidly evolving area; in the years between 2016 and 2020, expenditure on rtCGM for adults

increased by factors between 55% and 99%, while between 2020 and 2021, expenditure more than doubled (122% increase).

Based on PCRS data to the end of April 2023, the projected spend on CGM sensors through PCRS to the end of 2023 will be approximately €32.5 million on rtCGM and €2.6 million on isCGM. That does not take into account the additional spend on transmitters, receivers and readers that comes through the HSE Diabetes Technology subgroup.

In addition to expenditure on CGM systems, there is also ongoing high levels of expenditure on blood glucose test strips to support SMBG. In 2021, blood glucose testing strips accounted for a total expenditure of approximately €31 million on the community drug schemes.[63] Expenditure data on lancets and blood glucose testing strips are not disaggregated by diabetes type; estimation of expenditure on materials for SMBG for those accessing CGM was beyond the scope of this rapid HTA.

Figure 2.1 HSE reimbursed usage of CGM (adults aged >21 years) by CGM type from 2016 to 2023*

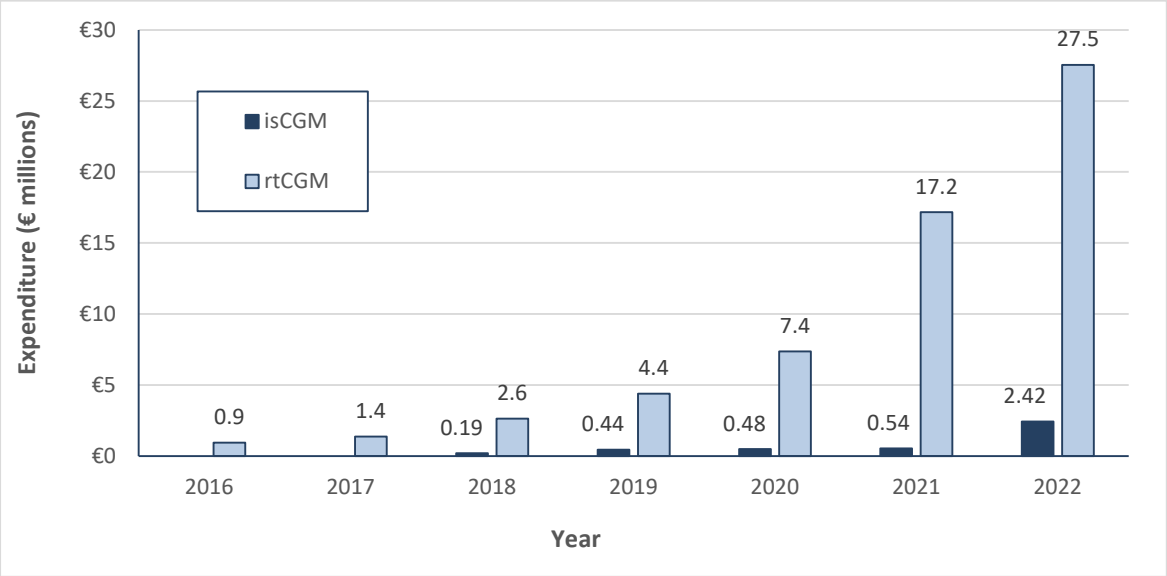


Source: PCRS[64] and PQs[58-62]

Key: CGM – continuous glucose monitoring.

Notes: First addition of an isCGM system to the PCRS list of approved products was in April 2018. As an individual can switch CGM systems within a calendar year, the sum of reimbursed users per system may exceed the total number of unique individuals reimbursed for any CGM. *Utilisation estimates for 2023 are based on data from January to April.

Figure 2.2 HSE expenditure on CGM for adults (aged > 21 years) by CGM type from 2016 to 2022



Source: PCRS[64] and HSE[54]

Key: CGM – continuous glucose monitoring; isCGM - intermittently scanned continuous glucose monitoring; rtCGM – real time continuous glucose monitoring

Notes: First addition of an isCGM system to the PCRS list of approved products was in April 2018. Data from HSE Aids & Appliances were split into adult and child expenditure using the proportions observed in the PCRS data, which was approximately 75% adult in 2021.

2.7 Accessibility and equity of access

International clinical guidelines and literature highlight a range of issues in relation to the accessibility of and equity of access to CGM for individuals with T1DM, with evidence to suggest poorer access in underserved communities, including populations living in remote or socio-economically disadvantaged areas.[65, 66] This is identified to be important given that some populations are at greater risk of diabetic complications, and may therefore stand to benefit more from tight monitoring. While not limited to T1DM, a 2022 report on the burden of chronic disease in Ireland (the EPICC study) estimated that the prevalence of diabetes (type 1 and 2) tripled in the extremely disadvantaged population when compared to people deemed extremely affluent as defined by the Pobal HP Deprivation Index.[67] Internationally, there is also evidence that low socioeconomic status is associated with higher levels of morbidity and mortality for adults with T1DM, even when individuals have access to a universal healthcare system, with mixed evidence in relation to the relationship between low socioeconomic status and disease management (for example, being on an intensive insulin regimen, use of glucose monitoring or access to specialist diabetes services).[68, 69] The burden of disease associated with T1DM is discussed further in Chapter 3.

Factors that may influence accessibility and equity of access include:

- Socioeconomic status: Given that individuals of lower socioeconomic status with T1DM are at increased risk of complications and mortality, they may stand to gain more through use of CGM. However, members of this group who do not qualify for reimbursement (for example, due to age) may be unable to afford CGM system costs.
- Capacity to monitor: Some people with diabetes may experience issues associated with disabilities and cognitive functioning which can impact on the ease of glucose monitoring and need for support. For some individuals, the use of CGM may enable some extent of glucose monitoring without the help of a care-worker.
- Health literacy: The level of health literacy and technological understanding may impact on the ability of some individuals to adopt CGM, or may create a need for educational support.
- Language: There could be potential language barriers for non-English speaking members of the population. This could be impacted by the availability of manufacturer instructions and associated education in a range of languages.
- Place of residence: For people with diabetes living in rural areas of Ireland, the use of CGM may facilitate sharing of monitoring data with a healthcare professional and or family members and carers. However, poor internet coverage may hinder the communication of glucose levels, limiting some of the potential benefits of CGM.
- Older adults: Older individuals may have lower digital, internet or online information literacy skills, which could create challenges for adopting CGM systems in this population. This could create needs for suitable educational or training supports.
- Religion: Traditions such as fasting during the holy month of Ramadan for Muslim populations may increase the risk of hypoglycaemic and hyperglycaemic complications. Therefore, the need for careful monitoring is of increased importance.

Given this array of factors, the potential for benefit or harm with CGM in individuals with T1DM may be misrepresented for subgroups of the population if they are under-represented in the underpinning trials or if they are not explicitly considered in the clinical guidelines.

2.8 Discussion

Monitoring glucose levels is an integral part of diabetes management for individuals with diagnosed T1DM on insulin therapy. Glucose readings taken at intervals during the day can be used to guide insulin treatment to avoid incidences of hypoglycaemia or hyperglycaemia. Monitoring also supports the aim of maintaining optimal glycaemic control, thereby reducing the longer-term risk of diabetes-related microvascular and macrovascular complications.

Two types of CGM were considered in the rapid HTA: real-time continuous glucose monitoring (rtCGM) and intermittently scanned continuous glucose monitoring (isCGM). With rtCGM, data are automatically transmitted to a data display device; with isCGM, the transmitter must be scanned by the user to obtain the data. There has been iterative development of CGM systems over the last decade with changes in the specifications of the systems and the range of features they offer. Earlier versions of devices may no longer available; however it is also the case that newer, enhanced versions of some devices, which have been launched and are available for use in other jurisdictions, are not yet accessible to individuals with diabetes in Ireland, either because they have not yet been marketed here or because they are not listed for reimbursement. As of July 2023, one isCGM system is reimbursed as part of the publicly funded healthcare system in Ireland, Abbott's Freestyle Libre®. Newer versions of this system not yet available in Ireland incorporate an alarm option (FreeStyle Libre® 2) or represent an rtCGM device (FreeStyle Libre® 3). Multiple rtCGM systems are reimbursed, including both Dexcom G7 and Medtronic Guardian Connect 4; older systems currently reimbursed for existing patients are being phased out.

The HSE manages access to the range of CGM systems that are available for use in the community through their inclusion on approved lists of reimbursed items. At the individual patient level, approval for reimbursement of CGM has to date been largely predicated on a requirement for prior authorisation following a request from a consultant endocrinologist and subject to meeting clinical eligibility criteria. However, routes of access to the reimbursed technologies differ by system type and system component, raising issues in relation to equity of access and the cost effective use of resources. Furthermore, as discussed below, the HSE's ability to restrict access through prior authorisation is no longer possible with the existing mechanisms for one of the approved rtCGM systems.

Following a HTA by the HSE Health Technology Assessment Group,[(11)] the HSE approved access to an isCGM system, FreeStyle Libre, for people with T1DM aged between four and 21 years that meet strict eligibility criteria. A dedicated online portal for FreeStyle Libre® applications was established and became operational in April 2018. This system, which is operated by the PCRS, has provided an efficient

means of managing and supporting access to this particular form of isCGM, with authorised patients obtaining supplies of their sensors on prescription through their local pharmacy. However, concerns have been raised regarding equity of access to FreeStyle Libre®. Specifically, while individuals with diabetes approved for reimbursement prior to turning 22 years of age can continue with their access, consistent with the defined eligibility criteria, there are restrictions for those seeking reimbursement for the first time after this age. The HSE notes that access for those who do not meet the age eligibility criteria may be obtained in very exceptional circumstances. Demand for such exceptional access to FreeStyle Libre® has, however, been substantial, with over 2,700 applications received between 2018 and 2021 for persons aged 22 years and older with T1DM; 60% of these applications were subsequently approved for reimbursement based on the clinical information provided. It is noted also that the HTA that informed the 2018 decision to reimburse FreeStyle Libre® recommended that the decision should be evaluated after one year in light of both the cost analysis (to ensure incurred costs were in line with expectations) and the potential for additional evidence of clinical effectiveness, particularly in relation to longer term outcomes. It was originally anticipated that the review of the FreeStyle Libre® Flash Glucose Monitoring System would be finalised at the end of Q1 2020. However, the Health Technology Assessment Group (HTAG) which was responsible for conducting this review was disbanded prior to conducting the review. The group has not been re-established. A full HTA on Freestyle Libre® was not undertaken.[70] In the absence of a full value assessment of the product, additional funding for the provision of Freestyle Libre® to other cohorts was not included in the National Service Plan 2022.

As discussed in Section 2.6, no dedicated portal is currently in place for processing applications for approved rtCGM systems for individual patients; however, given the requirement to supply those commencing rtCGM with equipment (transmitters and readers / receivers) in addition to the consumable components (sensors), mechanisms have been in place that have facilitated a system of prior authorisation. As for FreeStyle Libre®, this has entailed an application by a consultant endocrinologist (or diabetes specialist nurse attached to their service) to the Local Health Office for the area in which the person with diabetes resides. In the case of rtCGM, while the national clinical guideline indicates a list of criteria to indicate in whom rtCGM should be considered[9] (see Appendix 1 of this document), unlike FreeStyle Libre®, there is no centralised list of reimbursement criteria for rtCGM; this therefore creates the potential for regional differences in access. Moreover, given sharply increasing growth in the use of rtCGM, with the number of adults for which rtCGM is being reimbursed by the HSE more than doubling between 2020 and 2021, it is likely that there are differences in the interpretation and application of criteria. Furthermore, as noted in Section 2.6, a new issue has arisen with the addition to the PCRS list of reimbursable items, in October 2022, of a combined sensor and

transmitter for one of the rtCGM systems (Dexcom G7 sensor). The application for Dexcom G7 was submitted to PCRS by the company as a replacement for Dexcom G6 which is currently on the Reimbursement List at the same price. The application was reviewed by the HSE National Advisory Group for Diabetes Technology. For individuals with diabetes who choose to use the dedicated app to accompany this combined sensor and transmitter, rather than relying on a separate reader (that is, individuals who therefore do not have a requirement for equipment to accompany the sensor), there is now no existing mechanism by which prior authorisation criteria can be applied. Instead, as noted, any individual registered for any community drug scheme may access the sensors (subject to varying levels of co-payment, depending on the scheme) subject to a prescription from a medical doctor registered with the PCRS, with the dispensing pharmacy being reimbursed for their provision by the PCRS. This now limits the ability of the HSE to restrict the use of rtCGM to specific groups (for example T1DM or T2DM) or subgroups (T1DM meeting specific clinical criteria) of patients. Access is also outside the scope of tender processes undertaken by the HSE Diabetes Technology subgroup.

The issues here identified have considerable implications for the cost effectiveness and overall budget impact of CGM for the HSE, a situation which may be exacerbated by the current significant price difference between CGM systems, and in particular for rtCGM relative to isCGM. For adults (age >21 years), expenditure on CGM has increased substantially since 2016, rising from €0.9 million in 2016 to €30 million in 2022, with the majority of this increase (>90%) driven by increased expenditure on rtCGM. Furthermore, while not yet available in Ireland, as highlighted in Section 2.5, newer versions of FreeStyle Libre® have been launched internationally, the most recent of which, the FreeStyle Libre® 3 system, is an rtCGM system rather than an isCGM system. A switch to this system could result in a scenario whereby there is restricted access to one rtCGM system through a dedicated application portal, variable access to other rtCGM systems through LHOs, and no mechanism by which access can be restricted for rtCGM systems that incorporate a combined sensor and transmitter.

Of note, continued access to SMBG is required for those using CGM, for example, when readings conflict with symptoms or expectations. The extent to which CGM users continue to require and or use SMBG also has implications for the cost effectiveness of care and overall budget impact. Pharmacy reimbursement claims data, provided to HIQA by PCRS, indicate ongoing high levels of expenditure on blood glucose test strips, a proportion of which will relate to individuals also reimbursed for CGM. While it may be anticipated that widespread adoption of CGM may directly lead to a substantial reduction in expenditure on blood glucose test strips, it is challenging to measure as there are other ongoing national initiatives

which aim to reduce expenditure on test strips. However, it was beyond the scope of this rapid HTA to evaluate the impact of CGM usage on SMBG expenditure.(63)

Issues in relation to equity of access to CGM have been identified in clinical guidelines and the international literature. There are also factors such as health and digital literacy that may impact the accessibility of CGM for subgroups of the population. Any decision to expand access to CGM should also consider ways to maximise equity of access within eligible groups and to ensure that individuals with diabetes are empowered to use CGM effectively as part of their diabetes self-management.

In summary, there has been substantial growth in the reimbursement of CGM for adults by the HSE since 2016 and since the first reimbursement of isCGM in 2018, access to which is managed through a dedicated online portal. While growth in use of CGM may reflect international trends in terms of clinical guideline recommendations, it is also possible that some of the growth may have been driven by the recognised challenges presented by the COVID-19 pandemic and the need to optimise self-management given restrictions in accessing primary and secondary care. While CGM represents a new and disruptive technology, with iterative development of devices, it presents a significant challenge for the HSE in terms of the efficient use of finite healthcare resources. The absence of a single manged access programme for CGM has impacted the relative diffusion of the technologies. The epidemiology and burden of disease are presented in Chapter 3. Evidence of the clinical effectiveness and cost effectiveness of CGM, including the relative effectiveness of rtCGM and isCGM is discussed in Chapters 4 and 5, respectively; budget impact is presented in Chapter 5. Published international recommendations are presented in Chapter 6.

3 Epidemiology and burden of disease

Key points

- There is substantial uncertainty regarding the epidemiology of T1DM in adults in Ireland due to the lack of a national diabetes register to collect and provide population-level data.
- Estimates of the prevalence of T1DM in Ireland in adults aged 18 years or older have ranged from 17,053 (based on an analysis of 2016 Irish pharmacy claims data) to 24,480 (based on prevalence estimates from the Scotland Diabetes Survey 2018 applied to 2016 Irish census data).
- The day-to-day burden of managing T1DM includes glucose monitoring (including regular SMBG with finger prick tests, for those using this method), adjustment of insulin dosing, and restrictions with respect to carbohydrate intake and timing of physical activity.
- The management of diabetes can be associated with emotional impacts. Diabetes distress refers to the emotional impact of living with diabetes. Sources can include distress associated with treatment regimens, food or eating, living with the fear of hypoglycaemia, consideration of the future and or of complications, as well as distress associated with interpersonal relationships and social supports, and interactions with healthcare professionals (for example, a perceived lack of support).
- Complications of T1DM can broadly be divided into two categories:
    - Microvascular complications caused by damage to small blood vessels, which can affect the eyes, kidneys and peripheral nervous system and may manifest as retinopathy, nephropathy and neuropathy, respectively.
    - Macrovascular complications caused by damage to large blood vessels, which can affect the heart, brain and large arteries supplying the lower limbs. Such damage can place the individual at increased risk of, for example, stroke and myocardial infarction.
- Complications of T1DM are associated with significant mortality. International data show that people with T1DM have a two to five times higher risk of death compared with those without diabetes. The loss of lifetime in T1DM is greater than that observed in T2DM reflecting the earlier diagnosis and hence the longer exposure to risk factors for acute and chronic microvascular and macrovascular complications. Irish data show age-related differences in

mortality rates; rates typically increased with age, with higher mortality observed in those aged 85 years and older.

- In addition to having a negative impact on individuals with diabetes, complications also have significant implications for health service resources, use and costs. Approximately €129 million was spent in Ireland in 2018 on costs associated with T1DM. Direct healthcare costs were estimated at €81.5 million. Indirect costs such as working time lost due to morbidity and mortality were found to account for the remaining €47.5 million.

3.1 Introduction

This chapter describes the epidemiology and burden of disease of diabetes, with a focus on the target population of adults with T1DM in Ireland. There is currently no national register that collects data on the prevalence and incidence of diabetes and its complications in this age group. In the absence of such a register, data from a number of sources are summarised. A high-level description of information sources is provided rather than a systematic approach to identifying studies.

3.2 International prevalence of diabetes

According to the International Diabetes Federation (IDF), in 2021 there were 537 million adults aged 20 to 79 years worldwide living with diabetes.[27] The IDF notes an estimated adult (aged 20-79 years) prevalence in high-income countries of 11.1% in 2021, but that this is expected to increase to 12.4% in 2045. Specifically in Europe, the IDF estimated that one in 11 adults are living with diabetes, with over one in three of these (36%) undiagnosed.[27] T2DM is noted to be the most common type of diabetes, estimated to account for over 90% of all diabetes cases worldwide.[27] Specifically in relation to T1DM, the IDF estimated that in 2022 there were 8.75 million people with T1DM globally and that of these, 83.9% were aged 20 years or older.[18]

3.3 Incidence and prevalence of diabetes in Ireland

It is challenging to estimate the incidence and prevalence of adults with diabetes in Ireland, given the lack of a national diabetes register. The following aims to provide an indication of incidence and prevalence in adults by summarising available information from the paediatric population, for which a registry is in place in Ireland, and from studies which aimed to estimate incidence and prevalence using other observational data sources.

Paediatric population data

Established in 2008, the Irish Childhood Diabetes National Register (ICDNR) collects data on children and young people with T1DM, aged fifteen years or younger in the Republic of Ireland.[71] Based on ICDNR data from 2014 to 2018, Ireland was identified as a country with a high incidence of T1DM in children.[72] Standardised incidence rates for T1DM showed mild annual variation, ranging from 27.0 to 30.9 cases per 100,000 per year, and an overall fall in the standardised incidence rate of 3.35% was observed over the 2014 to 2018 period. For context, a robust national study undertaken in 1997 had observed that Ireland had a high incidence of type 1 diabetes at 16.3 cases per 100,000 per year.[73] Subsequently, the first report from the ICDNR found that, by 2008, incidence of T1DM in the Irish paediatric population had increased substantially since the 1997 estimate.[74] Following this, a stabilisation in rates was observed between 2008 and 2013.[72] In the most recent ICDNR publication (above, data from 2014 to 2018), the observed stabilisation and fall in the incidence of T1DM was noted as being similar to that observed in other high incidence countries.[72]

Adult population estimates – diabetes overall

The Healthy Ireland Survey is an annual interviewer-administered face-to-face survey commissioned by the Department of Health. The most recent data are derived from the eighth wave of the survey, which was conducted between November 2021 and July 2022.[75] The survey achieved an overall response rate of 40% and included data from 7,455 interviews with a representative sample of those living in Ireland. Respondents were asked whether they had been medically diagnosed with any of a list of 25 common long-term conditions, including diabetes, though this was not disaggregated by diabetes type. The survey results reported that 5% of respondents have been diagnosed with diabetes (male: 6%; female: 4%), with prevalence increasing with age. In males, the prevalence of diabetes in the age-groups 15-24, 25-34, 35-44, 45-54, 55-64 and 65+, was reported as 0%, 0%, 3%, 7%, 10% and 16%, respectively. The corresponding reported prevalence in female age-groups were 1%, 1%, 1%, 2%, 6% and 10%.

The Evidence for Policies to Prevent Chronic Conditions (EPICC) study, which analysed survey data from the fifth wave of the Healthy Ireland Survey (conducted between September 2018 and September 2019), additionally considered prevalence of diabetes as stratified by deprivation status, based on the Pobal HP Deprivation Index.[67] Overall, data from wave five showed a similar prevalence of diabetes to that observed from wave eight, above; the prevalence of diabetes was reported as 4.6% (95% CI: 4.1 to 5.2), with a male prevalence of 3.4% (95% CI: 2.8 to 4.1), a female prevalence of 5.9% (95% CI: 4.9 to 6.8), and prevalence increasing with age. When stratified by deprivation status, the estimated prevalence in 'extremely

affluent' people (defined as people in the 9th and 10th deciles of the deprivation index) was 2.0% (95% CI: 0.8 to 3.1) while the prevalence in those categorised as 'extremely disadvantaged' (those in the 1st and 2nd deciles of the index) was 6.0% (95% CI: 3.7 to 8.4).[67, 76]

There is substantial uncertainty about the degree of undiagnosed diabetes and the extent to which it applies to people with T1DM. The IDF, as part of the Diabetes Atlas, aims to provide estimates of the numbers of individuals with undiagnosed diabetes. These estimates are based on published studies of the prevalence of undiagnosed diabetes whereby a pooled average is calculated for countries that reported data on estimates of undiagnosed diabetes. For countries such as Ireland which do not have such in-country data sources, the undiagnosed prevalence is approximated from averages of countries within the same IDF region and World Bank Income group. Based on this approach, the IDF in their 2021 Diabetes Atlas report estimated that there are approximately 46,600 (95% CI: 41,400 to 52,400) adults aged 20–79 years living with undiagnosed diabetes in Ireland; these estimates are not disaggregated by type of diabetes.[27]

Adult population estimates – T1DM

In recent years several studies have attempted to estimate the prevalence and incidence specifically for T1DM in Ireland; these include a 2020 publication by Gajewska et al. based on electronic pharmacy claims data,[77] a survey conducted by the National Clinical Programme for Diabetes of diabetes care delivery in acute hospitals,[78] a crude analysis of data from the Scotland Diabetes Survey 2018,[79] and a global modelling study funded by the Juvenile Diabetes Research Foundation (JDRF) International.[80]

Gajewska et al.[77] analysed HSE Primary Care Reimbursement Service pharmacy claims data from 2011 to 2016; specifically, data from individuals who were dispensed diabetes medication under the GMS and LTI schemes were included and were assumed to represent the entire population with diabetes who have been dispensed diabetes-related medication in Ireland. For the purposes of the analysis, prevalent cases of T1DM were assumed to be individuals who had in 2016 been dispensed at least one insulin prescription and at least one blood glucose test strip prescription. Data for individuals were excluded from prevalence estimates if they had been dispensed treatments indicative of T2DM (at least three prescriptions for oral hypoglycaemic agents or injectable hypoglycaemic agents other than insulin within the 12 months before initiating insulin in 2011-2016) or if they had been dispensed only long-acting insulin without any prescription for short or fast-acting insulin. For the purposes of estimating incidence of T1DM, data for individuals in receipt of insulin continuously before 2016 were further removed and only data for those individuals who received the first insulin dispensing in 2016 were retained.

This analysis found that 20,081 individuals met the definition for prevalent T1DM in 2016, of which 17,053 (85%) were aged 18 years or over. These figures correspond to an estimated prevalence of T1DM of 0.22% (95% CI: 0.21 to 0.23) in those aged below 18 years and 0.48% (95% CI: 0.47 to 0.48) in those aged 18 years or above. A significant increase in the prevalence of T1DM was observed with increasing age; for example, a prevalence of 0.38% was observed in those aged 15 to 24 years while this rose to 0.74% in those aged 75 years or above.[77] In terms of incidence, an estimated 1,527 cases were estimated as newly incident in 2016, corresponding to a crude incidence rate of 32.1 (95% CI: 30.5 to 33.7) per 100,000 persons per year based on 2016 Irish census figures.[77]

Notably, the findings of Gajewska et al. were included in a recent systematic review of the incidence of adult-onset T1DM across 32 countries and regions.[81] This systematic review failed to identify health surveys from Ireland with published data on T1DM in adults and identified the Gajewska et al. study as the only relevant data source for Ireland. The authors of the systematic review performed quality assessment, using a modified version of the Newcastle-Ottawa Scale, on all studies included in the review, to assess the representativeness of the study population, the sample size, the method of assessing diabetes status, and the quality of the diagnostic criteria used to assess diabetes status. Quality assessment scores across the studies in the review ranged from five (scores of five to seven considered to represent 'moderate' quality) to 11 (scores of eight to the maximum of eleven represent 'high' quality); amongst these, the study by Gajewska et al. was attributed a score of nine. Nonetheless, in the absence of other national data sources, it is challenging to confirm the reliability of the estimates in the study; Gajewska et al. observe that their data for younger age groups appear consistent with findings from other international evidence and registries, but note the possibility that their methodology may overestimate the overall number of individuals with T1DM, and particularly the number of older persons.[77] However, it is also noted that the estimated prevalence rates were lower than those observed in the Scottish Diabetes Survey.[77]

As reported in an analysis conducted to inform the National Clinical Guideline No. 17 (Adult Type 1 Diabetes Mellitus), the National Survey of Acute Hospital Diabetes Services and Resources initially estimated, in 2017, a total of 19,745 adults with T1DM as being under the care of acute services.[78] However, this was considered to be an underestimate because the patient populations of three hospitals were not estimated and the provided data were deemed inaccurate for 20 of the 28 hospitals.[82] The survey did not make adjustments for this uncertainty or adjustments in respect of the three hospitals which could not return data. Notably, authors of the survey have not included these figures in their official final report.[83]

As part of a 2021 response to a parliamentary question, estimates for the prevalence of T1DM in Ireland were calculated crudely based on Scottish T1DM prevalence, as identified from the Scotland Diabetes Survey 2018 and applied to 2016 Irish census data. The Scottish prevalence estimate equated to 28,800 persons in Ireland with T1DM.[79] Assuming that the proportion of the T1DM population aged 18 years and older is as per the findings of Gajewska et al., that is, that the adult population represents 85% of all persons with T1DM, this would equate to an adult population with T1DM of approximately 24,480.

A global modelling study funded by the Juvenile Diabetes Research Foundation (JDRF) International, published in 2022[80] and made available publicly as The Type 1 Diabetes Index model,[84] aims to provide data for the prevalence, incidence, mortality and life expectancy associated with T1DM in each of 201 countries. The Type 1 Diabetes Index, a data simulation tool based on a Markov model, represents a collaboration between a number of organisations including the International Diabetes Foundation (IDF), the JDRF International and the International Society for Paediatric and Adolescent Diabetes.[84] The model estimated that in 2022 there were 26,412 people (of all ages) with T1DM in Ireland, of which 22,847 were aged 20 years or older.[18, 85] Irish data within the model for the population aged 20 years or older appear to be derived from the study by Gajewska et al.[77]; the authors note that the primary data source informing the model of adult T1DM was the systematic review[81] (described above) which included this study.

In summary, estimates of the prevalence of T1DM in Ireland in adults aged 18 years or older, have ranged from 17,053 (based on an analysis of Irish pharmacy claims data by Gajewska et al.) in 2016[77], to 24,480 (based on prevalence estimates from the Scotland Diabetes Survey 2018 applied to 2016 Irish census data).

3.4 Burden on individuals with T1DM

The National Clinical Guideline No. 17 ‘Adult type 1 diabetes mellitus’ describes the burden on individuals with T1DM resulting from their disease.[9] Due to the loss (or substantial reduction) of endogenous insulin production, individuals with T1DM are required to administer insulin subcutaneously either by intermittent injection or using an insulin pump. In addition to this, glucose concentrations must be monitored and insulin doses adjusted with care also taken in relation to intake of carbohydrates and levels of physical activity; the objective is to maximise the time spent with near normal glucose concentrations, while avoiding episodes of hypoglycaemia. As noted by the national guideline, the complexity of maintaining tight glucose control means that outcomes depend heavily on full engagement of the adult with T1DM in lifelong daily self-management. Such self-management, and the general experience of being diagnosed with and living life with T1DM, can result in a significant physical and emotional burden on the individual.

Physical burden

Beyond the symptoms associated with hyperglycaemia (for example, increased thirst, increased frequency of urination, fatigue, blurred vision, recurrent infections), hypoglycaemia (for example, sweating, fatigue, feeling dizzy) and complications of T1DM, people with T1DM incur a physical burden as a result of self-management. Those who use SMBG (as described in section 2.4) as their main method of glucose monitoring use a finger prick test several times a day. Finger prick tests can result in finger lesions including haematoma, induration, keratosis, or scarring, which have been associated with longer duration of SMBG and higher frequency of conducting finger prick tests.[86]

Emotional burden

The concept of 'diabetes distress' was described in the mid-1990s to capture the emotional impact of living with diabetes, and is common in both people who have diabetes and in their partners or caregivers.[87] Diabetes distress can include distress associated with treatment regimens, food or eating, consideration of the future and or of complications, hypoglycaemia, as well as distress associated with interpersonal relationships and social supports, and interactions with healthcare professionals (for example, perceived lack of support).[87] Specifically in T1DM, major sources of diabetes distress have been described as per Table 3.1.

Anxiety associated with conducting finger prick tests is an important concern; in a UK study, finger prick anxiety was observed in 30% of individuals with diabetes, and general anxiety in 33%, with finger prick anxiety and avoidance of testing being correlated with general anxiety.[88] People with T1DM who were asked about daily disruptions to life also reported these as being largely due to managing hypoglycaemia, hyperglycaemia, and various forms of diabetes technology all at the same time.[89]

As noted above, fear of hypoglycaemia is an identified source of diabetes distress and can serve as a barrier to activities such as exercise and travel.[89] In a cross-sectional study of individuals with T1DM, factors most reported as either positively or negatively affecting their quality of life included the severity of hypoglycaemia, presence of complications, efficacy of self-management of diabetes, and acceptance of the disease.[90]

Activities of daily living may be restricted for those with T1DM. Medical Fitness to Drive Guidelines issued by the Road Safety Authority outline requirements for those seeking to obtain or maintain a driving license and include specific criteria for those diagnosed with diabetes mellitus. These include restrictions in relation to individuals treated with a medication which carries a risk of inducing hypoglycaemia (for example, insulin), for those with severe recurrent hypoglycaemia or impaired

awareness of hypoglycaemia, and for those who have experienced complications as a result of their diabetes (for example, neuropathy or visual impairment). Those treated with insulin must monitor their glucose levels at times relevant to driving to enable the detection of hypoglycaemia Criteria differ depending on the driving license held. The July 2020 guidelines specify that for those with a Group 1 license (car, motorcycle, tractor) CGM systems may be used, but individuals must also carry capillary glucose testing equipment for driving purposes as the blood glucose level must be confirmed with SMBG when the glucose level is 4.0 mmol/L or below, when symptoms of hypoglycaemia are being experienced, and when the glucose monitoring system gives a reading that is not consistent with the symptoms being experienced (for example, symptoms of hypoglycaemia and the system reading does not indicate this).[91] For those with a Group 2 driving licence (buses and trucks), there are additional legal requirements to monitor and document glycaemic control for medical licensing reviews. The guidelines specify that CGM is not a permitted method of glucose monitoring; individuals who use CGM devices must continue to monitor capillary blood glucose levels (that is, to use SMBG) and to capture readings using a glucose meter with a memory function, so that these can be reviewed at the annual examination by a consultant endocrinologist (three months blood glucose readings must be available).

Table 3.1: Sources of diabetes distress

Source of distress	Description
Powerlessness	For example, perceptions of not successfully managing diabetes and difficulty in navigating blood glucose measurements
Management distress and eating distress	Frustrations and worries associated with, for example, not monitoring blood glucose enough
Hypoglycaemia distress	Lack of confidence in ability to identify and address hypoglycaemic symptoms (and concerns regarding associated danger, for example, with driving)
Social distress	Concerns about the reactions of others and being treated differently
Family/friend distress	Concerns of the person with diabetes that they will be treated as overly fragile
Physician distress	Concerns about not receiving sufficient help, support and understanding from the healthcare team.

Source: Fisher et al. (2015)[92]

3.5 Prevalence of T1DM complications in Ireland

Complications secondary to T1DM can broadly be divided into two categories:

- Microvascular complications caused by damage to small blood vessels, which can affect the eyes, kidneys and peripheral nervous system[93] and may manifest as retinopathy, nephropathy and neuropathy, respectively.
- Macrovascular complications caused by damage to large blood vessels, which can affect the heart, brain and large arteries supplying the lower limbs. Such damage can place the individual at increased risk of, for example, stroke and myocardial infarction.[94]

A systematic review undertaken by Tracey et al. analysed data from 15 studies reporting data collected between 1998 and 2015 on the epidemiology of diabetes and diabetes-related complications among adults in Ireland.[95] Disaggregated data by diabetes type were not reported, with studies focussed solely on T1DM and gestational diabetes excluded from the review. There was substantial variation in the prevalence of diabetes complications, with estimates ranging widely depending on the study population and methodology used (Table 3.2). The authors concluded that there is an urgent need for a comprehensive national diabetes register in Ireland to provide reliable baseline data and to facilitate monitoring of improvements in care over time at a national level.

Table 3.2 Prevalence of microvascular and macrovascular complications in individuals with diabetes in the Republic of Ireland

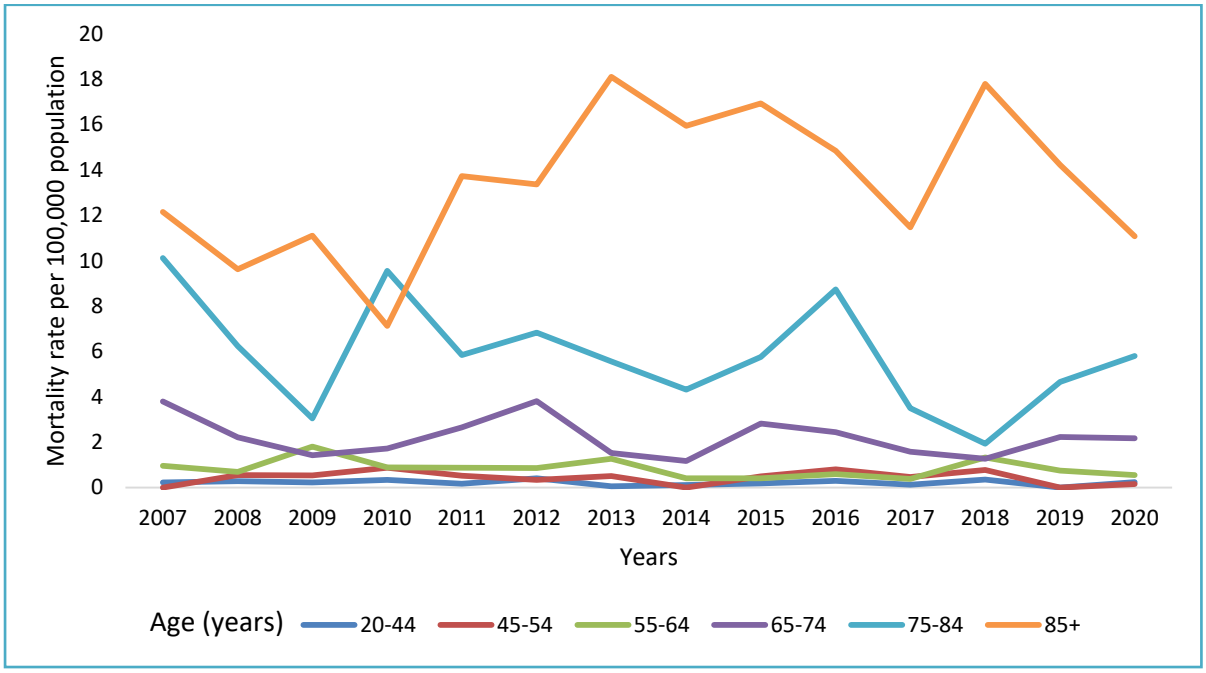
Type of complication	Prevalence (%) total
Diabetic retinopathy	6.5 to 25.6
Blindness due to diabetic retinopathy	4.7
Neuropathy	3.0 to 14.6
Neuropathy symptoms at examination	32.0
Foot ulceration	2.5 to 3.7
Leg ulceration	4.2
Cerebrovascular disease	5.2
Chronic kidney disease	5.5
Heart Failure	0.3
Microalbuminuria	32.1
Myocardial Infarction	0.4
Nephropathy	5.1
Non-traumatic lower leg amputation	0.2
Past amputation	1.7
Peripheral vascular disease	12.9
Proteinuria	6.0 to 6.1
Stroke	0.5
Transient Ischemic Attack	1.5
Total macrovascular	3.5 to 15.1

Source: Tracey et al. 2016[95]

The impact of diabetes complications is stark; in addition to the morbidity experienced by the individual, complications are associated with significant mortality. A recent Danish population-level study aimed to model the difference in expected lifetime between persons with T1DM, T2DM and persons without diabetes.[96] This study found that, at the beginning of 2017, the lifetime lost to T1DM was 8.3 years at age 20 years and 5.6 years at age 60 years. The loss of lifetime in T1DM was found to be approximately 30% greater than that observed in T2DM (for example, at 60 years lifetime lost to T2DM was 3.8 years and to T1DM was 5.6 years); the authors observed that this reflects the earlier diagnosis and hence longer duration of diabetes at a given age for T1DM as compared with T2DM, and, consequently, the longer exposure to risk factors for acute and chronic microvascular and macrovascular complications. Similarly, an analysis of six population-based cohorts (Australia, Denmark, Latvia, Scotland, Catalonia, and the US Kaiser Permanente Northwest) identified that people with T1DM have a two to five times higher risk of death compared with those without diabetes.[97] However, considering temporal changes, the standardised mortality ratio (reflecting excess mortality in those with T1DM relative to those without diabetes) declined from 2000 to 2016 in half (Denmark, Scotland and Spain) of the six data sources, with the other half remaining stable.

Considering the overall burden of mortality, the International Diabetes Federation attributed 182,000 worldwide deaths in 2022 to T1DM.[18] It is difficult, however, to accurately quantify the exact burden of T1DM-related mortality. While there is a higher likelihood that capture of causes of death that may be clearly related back to an underlying diagnosis of T1DM (for example, deaths due to hypoglycaemic coma), it is unlikely that the cause of death reported on death certificates reflects the full burden of mortality associated with T1DM given the many complications arising from T1DM.[98] The Central Statistics Office provides national vital statistics data for Ireland with deaths broken down by underlying cause of death; this measure is defined as ‘the disease or injury which initiated the train of morbid events leading directly to death’ or ‘the circumstances of the accident or violence which produced the fatal injury’.[99] From these data, deaths attributed to T1DM can be identified using the E10 ICD-10 code. Such data, for deaths of adults in Ireland over the period 2007 to 2020, are presented in Figure 3.1 in terms of age-specific trends in T1DM-related mortality, This figure shows age-related differences in mortality rates; rates typically increased with age with higher mortality observed in those aged 85 years and older. As noted, these data reflect only those deaths in which T1DM was noted as the ‘underlying cause’, and are therefore likely to underestimate the full burden of mortality in Ireland associated with T1DM.[100]

Figure 3.1 Age-specific mortality rate in adults in Ireland 2007 to 2020: deaths in which T1DM was noted as being the underlying cause



Key: T1DM – type 1 diabetes mellitus.

Source: Central Statistics Office 2022, Deaths Occurring Files, ICD-10 cause of death code: E10[101-103]

3.6 Burden of T1DM on the healthcare system

In addition to having a negative impact on the lives of individuals with diabetes, complications also have significant implications for health service resources and costs. The Department of Health reported that in 2019, based on Hospital In-patient Enquiry (HIPE) data, the national age-sex standardised hospitalisation rate for diabetes (all forms) was 95.1 hospitalisations per 100,000 population (population aged 15 years or older), with substantial variation by county of residence. This figure compared favourably with international data as reflected by an OECD average of 129 hospitalisations per 100,000.[104]

A retrospective audit of diabetes-related admissions data from a public hospital in Ireland estimated hospitalisation costs for the period 2013-2017 using the Australian Diagnosis Related Groups costing methodology.[105] The mean hospitalisation cost per admission for individuals with T1DM was estimated as €4,027 (standard deviation: €3,604). For admissions with a primary diagnosis of T1DM, sex, admission type, and length of stay were significantly associated with hospitalisation costs, with each additional day spent in hospital being associated with an increase in costs of €260. Women's admissions were less costly than men's admissions by €866 ($p < 0.001$). Admissions with a primary diagnosis of T1DM were associated with higher costs of €654 ($p = 0.007$) relative to an alternative diagnosis, and unscheduled

admissions were associated with lower costs of €1,578 (p = 0.035) relative to elective admissions.

A cost of illness study reported that approximately €129 million was spent in Ireland in 2018 on costs associated with T1DM. Direct healthcare costs such as primary and emergency care, medications such as insulin, and costs associated with glucose monitoring were estimated at €81.5 million.[106] Indirect costs such as working time lost due to morbidity and mortality were found to account for the remaining €47.5 million.[106]

3.7 Discussion

This chapter aimed to provide an indication of the epidemiology and burden of disease of diabetes, with a focus on the target population of adults with T1DM in Ireland. In the absence of a national patient registry or database to systematically capture and make available reliable data, estimates of the incidence and prevalence of diabetes in Ireland are subject to substantial uncertainty. The estimates identified in this chapter are based on studies that use healthcare utilisation data (prescription records for those obtaining treatment in the community or records of patients registered with hospital endocrinology services) and or applied validated international prevalence estimates to Irish census data. Challenges with these estimates include the limitations of the methodological approaches used and or that the underpinning data are not nationally representative. While nationally representative data are available from the 2021/2022 Healthy Ireland Survey, these data are based on self-report and are not disaggregated by diabetes type. In all instances, estimates refer to individuals with diagnosed diabetes only.

Using the Healthy Ireland survey data collected in 2021 and 2022, the overall prevalence of diagnosed diabetes is estimated as 5%. This would equate to 256,177 people living with diabetes (all forms) in Ireland, based on the latest 2022 census data.[107] The EPICC study analysis of earlier Healthy Ireland survey data showed that overall diabetes prevalence increases with population age and disproportionately affects those who are socially disadvantaged.[67] Concerning the prevalence of T1DM in Ireland in adults aged 18 years or older, estimates have ranged from 17,053 (based on an analysis of Irish pharmacy claims data by Gajewska et al.) in 2016[77] to 24,480 (based on prevalence estimates from the Scotland Diabetes Survey 2018 applied to 2016 Irish census data). These estimates should be interpreted with the methodological caveats described in this chapter, and noting that exact prevalence could only be derived from a national patient registry or database of all people with T1DM in Ireland.

A significant burden of disease is placed on adults with T1DM and their families or carers, both in the daily management of the condition and when microvascular and

macrovascular complications lead to considerable morbidity and premature mortality. Day-to-day burden includes regular SMBG with finger prick tests, for those using this method, and living with the fear of hyperglycaemia and hypoglycaemia.[89] With respect to premature mortality, diabetes has been associated with significantly reduced lifespan, with a greater impact on those with T1DM than those with T2DM; this has been attributed to the earlier onset of T1DM as compared with T2DM, and, consequently, the longer exposure to risk factors for acute and chronic microvascular and macrovascular complications. Irish data for deaths attributed to T1DM as the underlying cause show age-related differences in mortality rates; rates typically increased with age with higher mortality rates in those aged 85 years and older.

From a health system perspective, T1DM results in high healthcare resource utilisation costs due to diabetes-related hospitalisations and other healthcare spending, which places significant pressure on national health budgets. The identification of effective complication prevention strategies is crucial to reducing the burden associated with T1DM and to enabling people with T1DM to live long, healthy lives.

4 Clinical effectiveness evidence

Key points

- A rapid review approach was taken for this chapter. Guidance documents and supporting evidence reviews from the National Institute of Health and Care Excellence (NICE) were used as index documents, supplemented with data derived from evidence review documents from Health Technology Wales (HTW), the Scottish Health Technologies Group (SHTG) and targeted searches by HIQA.

Type 1 diabetes in adults

- In the comparison of rtCGM and SMBG, there was evidence of a beneficial effect for rtCGM for three out of nine measures of HbA1c. The evidence was graded as being of low and very low certainty. For the other six measures there was no clinically meaningful difference between the two interventions. Three RCTs were identified comparing isCGM and SMBG for HbA1c outcomes; two found no clinically meaningful difference, but the third favoured isCGM. No clinically meaningful difference in mean HbA1c levels was observed between rtCGM and isCGM for a follow-up period up to six months. However, over the same follow-up period, rtCGM was associated with a significantly higher likelihood than isCGM of achieving an HbA1c target less than 7.0%.
- For hypoglycaemic and hyperglycaemic outcomes, the findings were mixed for isCGM and rtCGM compared with SMBG. Nocturnal hypoglycaemia and the risk of severe hypoglycaemic events were lower for rtCGM compared with isCGM.
- RtCGM usage resulted in increased time in range versus SMBG, although there was very low certainty in this estimate. There were mixed findings for isCGM compared with SMBG for time in range. There was some evidence that rtCGM use led to increased time in range compared with isCGM, but further comparative data with the same duration of follow-up is needed.
- A range of general, disease-specific and complication/symptom-specific quality of life (QoL) and other patient-reported outcome measures were used across studies and these were not universally applied to both types of device. Additionally, identified observational studies were non-comparative. This limited comparisons of QoL.
- For rtCGM there was some evidence of increased well-being at 12 months compared to baseline. There was also evidence that rtCGM reduced fear or worry over time about hypoglycaemia.

- For isCGM there was some evidence of improved QoL up to 12 months compared to baseline. There was conflicting evidence for anxiety and distress measures; isCGM users showed increased median anxiety and depression scores since starting isCGM monitoring but users also reported reduced diabetes distress.

Diabetes in pregnancy

- There is some benefit to the use of rtCGM compared with SMBG for maternal and neonatal outcomes.
- There was very limited data for isCGM and no conclusion can be drawn for this intervention.

4.1 Introduction

The aim of this chapter is to present a review of existing evidence on the clinical effectiveness of continuous glucose monitoring (CGM) systems for adults with type one diabetes mellitus (T1DM). For the purpose of this rapid HTA, synthesised evidence from HTAs, systematic reviews and national guidelines were prioritised. In particular, priority was placed on UK guidance from the National Institute of Health and Care Excellence (NICE), Health Technology Wales (HTW) and the Scottish Health Technologies Group (SHTG) at Healthcare Improvement Scotland, because of known recent changes to NICE guidelines which were referred to in the HTA request from the HSE, and because of similarities in population between Ireland and the UK.

The focus of this rapid HTA was the general adult population with T1DM. While consideration of the use of CGM in specific subpopulations was outside the scope of the rapid HTA, the clinical effectiveness of CGM in pregnant women with T1DM, as described in the guidance documents from NICE and HTW, is briefly summarised.

4.2 Methods

Research Question:

> What does the literature say about the effectiveness of CGM for adults with T1DM?

The inclusion criteria for clinical effectiveness evidence were developed using an adapted PICO framework (Table 4.1).

As outlined in Chapter 2, CGM systems are evolving rapidly with iterative development of devices. The focus of this rapid HTA was to compare CGM (either

rtCGM or isCGM) with SMBG using capillary blood. Also of interest were head-to-head comparisons of rtCGM and isCGM systems. Comparisons within these classes (for example, head-to-head comparisons of two rtCGM systems) were considered outside the scope of the rapid HTA.

Table 4.1 Inclusion criteria for sources of clinical effectiveness evidence using an adapted PICO framework

Population:	Adults ≥18 years with T1DM, Subgroup of interest: pregnant women with pre-existing T1DM
Interventions & comparators:	▪ rtCGM compared with intermittent self-monitoring using capillary blood samples (SMBG) ▪ isCGM compared with SMBG ▪ rtCGM compared with isCGM. Comparisons within classes (for example, comparisons of two rtCGM systems) were considered outside scope.
Outcomes:	Due to the exploratory nature of this rapid HTA, outcomes were not pre-specified.
Information sources:	Include: national guidance or guidelines, HTAs, systematic reviews Exclude: all other information sources

Key: CGM – continuous glucose monitoring; HTA – health technology assessment; isCGM – intermittently scanned continuous glucose monitoring; PICO – population, intervention, control and outcome; rtCGM – real time continuous glucose monitoring; SMBG – self-monitoring of blood glucose; T1DM – type 1 diabetes mellitus.

Literature search strategy

Sources searched to identify national guidelines or guidance and HTAs included the following:

- NICE guidance (https://www.nice.org.uk/guidance/)
- Health Improvement Scotland - Scottish Health Technologies Group (https://shtg.scot/)
- Technoleg Iechyd Cymru / Health Technology Wales (https://healthtechnology.wales/)
- The International Health Technology Assessment Database (https://database.inahta.org/)
- The European Network for Health Technology Assessment (EUnetHTA) (https://www.eunethta.eu/).

In order to identify relevant systematic reviews separate to those identified from the above sources, a targeted search using the PubMed Clinical Queries tool (https://pubmed.ncbi.nlm.nih.gov/clinical/) was also conducted using the following search terms: ("continuous glucose monitor*") AND (Diagnosis/Broad[filter]). Results were limited to systematic reviews on humans, published in English within the last 10 years. The Cochrane Library https://www.cochranelibrary.com/advanced-search was also searched applying the following broad search terms to the title, abstract and keyword fields: ((flash or continuous) glucose monitor*) and (diabet*), and word variations were searched; results were limited to Cochrane reviews and protocols only. All searches for such systematic reviews were completed in May 2022. Scoping methodology was used for this search and included sources should not be considered a comprehensive list of all relevant sources.

As noted above, guidance documents identified from NICE were used as index documents, and were supplemented with data from Health Technology Wales (HTW), the Scottish Health Technologies Group (HTG) and targeted searches by HIQA. It was noted that searches performed by NICE that informed the current NICE recommendations for CGM in adults with T1DM (NG17) were conducted in May 2021.[2] Given that relevant data may have been published since this time, additional searches were undertaken by HIQA for the purposes of this rapid HTA. An update search was conducted in October 2022 using the search strategies and methods originally used by NICE. Additional searches for ongoing clinical trials were also performed by searching trials registers. MEDLINE was searched in October 2022 to identify studies specifically measuring quality of life and other patient-reported outcome measures (PROMs). As the focus of this rapid HTA was the general adult population with T1DM, update searches for evidence on diabetes in pregnancy were not considered. The search strategies used in the update search are provided in Appendix 2.

Data extraction

Considering the reviews identified which made recommendations on the use of CGM in the UK (to which this rapid HTA gave preference), it was identified that there was significant overlap in the data sources used to inform all recommendations from the UK. Furthermore, it was noted that the evidence reviews from NICE were both the most recent and the most comprehensive as they also incorporated evidence for rtCGM whereas others (for example, those from Health Technology Wales and the Scottish Health Technologies Group) focused solely on isCGM. Therefore, the evidence reviews on CGM underpinning two NICE guidelines, NG17: Type 1 diabetes in adults: diagnosis and management and NG3: Diabetes in pregnancy: management from preconception to the postnatal period were treated as index documents for this chapter.[1, 2]

Data were extracted from the evidence review underpinning NICE guidelines in the first instance. Where additional data, beyond that reported in the NICE documentation, was provided in other recommendation reports, these were also extracted. Sources are indicated in all tables. Data from studies identified in the update search (see above) were extracted into tables aligning with the summary tables provided in the NICE evidence review documents. All data tables are presented in Appendix 3. Data are presented separately by population group, first for T1DM in adults (section 4.3) and then for diabetes in pregnancy (section 4.4).

4.3 Results: Type 1 diabetes in adults

For adults with T1DM, the following outcomes were prioritised for this rapid HTA:

- HbA1c
- time in range: this refers to the amount of time an individual spends within a measured, specified glucose range (for example, time with glucose in range 3.9–10.0 mmol/L (70–180 mg/dL)
- hypo- and hyperglycaemic events
- diabetic ketoacidosis and hospitalisation
- quality of life and related PROMs.

Full data tables and additional outcomes such as glycaemic variability and time above range are reported in Appendix 3, but they are not discussed further in the main body of this rapid HTA.

Consistent with the PICO outlined in Table 4.1, outcome data are presented for the following comparisons:

- rtCGM compared with intermittent self-monitoring using capillary blood samples (SMBG)
- isCGM compared with SMBG
- rtCGM compared with isCGM.

For each outcome, an estimate of the effect size and the number of trial participants are presented along with conclusions on the overall certainty of the evidence using GRADE methodology; these were extracted from the information source (for example, NICE guidelines). To facilitate interpretation, an explanation of the GRADE certainty ratings is provided in Table 4.2.

Table 4.2 GRADE certainty ratings

Certainty	What it means
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimate effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect

Source: Balshem 2011[108]

4.3.1 Clinical outcomes

Data for this section are presented for each of the outcomes prioritised for this rapid HTA, for each of the relevant comparisons. As noted above, findings of the NICE evidence review informing the NG17 guideline are given precedence in this description, alongside findings of the update search performed by HIQA.

The NG17 guideline evidence review was limited to a synthesis of RCT data comprising 28 papers reporting 17 RCTs. These included 18 papers covering 12 parallel RCTs, three papers covering one factorial RCT, and seven papers covering four crossover RCTs. The following studies presented data appropriate for meta-analysis:

- rtCGM compared with SMBG – 13 trials
- isCGM compared with SMBG - one trial
- rtCGM compared with isCGM – three trials.

The review by the Scottish Health Technologies Group (SHTG) included one RCT of isCGM compared with SMBG, which was also included in the NICE review. No additional RCT data were identified in the review by Health Technology Wales.

The update search by HIQA identified two additional RCTs comparing isCGM with SMBG[109, 110] and one additional RCT for the comparison of rtCGM with isCGM.[111] Evidence relating to these studies are summarised below.

HbA1c

See Appendix 3, tables A3.1 and A3.2 for additional data on HbA1c outcomes by comparison type from NICE, the Scottish Health Technologies Group (SHTG) and other RCTs.

rtCGM versus SMBG

The NICE evidence review for NG17 (Type 1 diabetes in adults: diagnosis and management) compared rtCGM and SMBG across nine outcome categories for HbA1c. The evidence review team found no meaningful difference or could not differentiate between the two interventions for six of the nine measures, based on low or very low certainty evidence. For the three measures for which there was an effect, this favoured rtCGM. Specifically, based on very low certainty evidence, rtCGM was associated with a significantly higher percentage change from baseline HbA1c (mean difference (MD) -0.52, 95% confidence interval (CI): -0.80 to -0.24) at follow-up greater than six months compared with SMBG. Similarly, at follow-up at six months or greater, based on low certainty evidence, rtCGM was associated with a significant increase in the likelihood of achieving HbA1c targets of <7.5% (relative risk (RR) 2.02, 95% CI: 1.18 to 3.46) and <7.0% (RR 1.80, 95% CI: 1.00 to 3.22), compared with SMBG.

No new data were identified in the update search for this comparison.

isCGM versus SMBG

The NICE evidence review for NG17 found that there were no meaningful differences between isCGM and SMBG for the HbA1c outcomes reported based on moderate certainty evidence. The SHTG review came to the same conclusion having identified the same single study for this comparison.[112]

Two new RCTs were identified in the update search for this comparison.[109, 110] One of these studies (n=81) did not find a meaningful difference between isCGM and SMBG for percentage change from baseline HbA1c.[109] However, the second study (n=141) involving participants with high baseline HbA1C levels (7.5% to 11.0%) found a statistically significant, clinically meaningful difference in all six reported HbA1c measures (change from baseline HbA1c; reduction from baseline ≥ 0.5% points and ≥1.0% points; percentage HbA1c; odds of achieving HbA1c ≤ 7.5% and ≤7.0%) at six months, favouring isCGM.[110]

rtCGM versus isCGM

The NICE evidence review for NG17 identified one head-to-head comparison of CGM modalities (n=254) which considered different measures relating to HbA1c; these included the likelihood of achieving a HbA1c target less than 7%, and differences in HbA1c levels.[113] At follow-up periods up to six months, rtCGM was associated with a significantly higher likelihood of achieving an HbA1c target less than 7.0% (RR 1.50 95% CI: 1.09 to 2.06), based on moderate certainty evidence. However, for the outcome of HbA1c levels, no meaningful difference was observed between the modalities over a follow-up period up to six months; this was based on high certainty evidence.

A second RCT comparing rtCGM with isCGM (n=90) in individuals with T1DM prone to hypoglycaemia (glucose values < 70mg/dL ($TBR^{<70}$) >1.5hr / day during the previous 28 days while wearing an isCGM sensor) was identified in the update search.[111] At 120 days follow-up there was no difference (aMD: -0.1; 95% CI: -0.3-0.1; p=0.048) between rtCGM and isCGM for HbA1c levels.

Subgroup of users above treatment targets at baseline

The included RCTs differed in their inclusion and exclusion criteria, with studies variably including or excluding individuals based on their HbA1C at baseline and or a history of severe hypoglycaemia. Seven RCTs identified by NICE and one from the update search (all for the comparison rtCGM vs. SMBG) preselected for participants who were above treatment target at study enrolment.[110, 114-123] The reported outcomes for these trials therefore all reflect the efficacy of rtCGM in those with sub-optimal control at baseline. Across all identified RCTs, mean HbA1c at baseline ranged from 6.7% in the IMPACT trial[124] (which limited enrolment to those with HbA1C <7.5% at baseline) to 9.1% in the rtCGM arm of Tanenberg et al. (trial enrolment limited to those with baseline HbA1C >7.9%).[121] Eight of the included trials also specified a maximum HbA1c at baseline as an exclusion criterion (range: <9.5% to <11%). Analyses associated with four trials relating to rtCGM use aimed to examine the impact of baseline HbA1c on outcomes, with mixed findings between trials and by outcome. These findings are detailed in Appendix 4.

Additional measures of glycaemic control and glycaemic events

See Appendix 3, tables A3.3 and A3.4 for data on glycaemic outcomes by comparison type from NICE, the SHTG and other trials.

rtCGM versus SMBG

RCTs included in the NICE NG17 evidence review reported the impact of rtCGM on a range of hypoglycaemia outcome measures, however, the range of outcomes considered and the time point at which they were measured differed between studies. NICE reported that rtCGM led to a reduction in the duration of hypoglycaemic events relative to SMBG based on follow up periods up to three months (MD -31.60, 95% CI: -50.90 to -12.30); very low certainty evidence), and six months (MD -37.80, 95% CI: -44.60 to -31.00); high certainty evidence). Data were inconsistent with respect to the risk of severe hypoglycaemic events with evidence favouring rtCGM at less than six months follow-up (RR 0.65, 95% CI: 0.44 to 0.97; low certainty evidence) and favouring SMBG at greater than six months follow-up (RR 2.46, 95% CI: 1.02 to 5.92; very low certainty evidence). No meaningful difference between rtCGM and SMBG was noted in terms of the frequency of hypoglycaemic events (per day or per week) at follow-up periods up to six months, with differences in the certainty of the evidence noted (range: very low

to high). Based on very low certainty evidence, rtCGM was associated with a reduction in the percentage of time spent in nocturnal hypoglycaemia relative to SMBG (MD -3.97, 95% CI: -6.95 to -0.98) with no meaningful difference noted in terms of the frequency of these events (high certainty evidence).

No new RCT data were identified in the update search for this comparison.

isCGM versus SMBG

A single RCT with six month follow-up informed both the NICE evidence review for NG17 and the SHTG evidence note for this comparison.[124] A range of measures relating to glycaemic control with different cut-points were reported with mixed findings. Based on moderate certainty evidence, the NICE evidence review reported that isCGM led to reduced time (in hours) spent in nocturnal hypoglycaemia (<3.1mmol/L; MD -0.30 (-0.32, -0.28)). However, no meaningful difference was observed in relation to the risk of hypoglycaemia or of severe hypoglycaemia based on very low certainty evidence. Using the same study, the SHTG evidence note reported that isCGM use led to a statistically significant reduction in time in hypoglycaemia (<3.9mmol/L) per 24 hours and in nocturnal hypoglycaemia (<3.9mmol/L) as well as in the incidence of hypoglycaemic and nocturnal hypoglycaemic events when compared with SMBG. They also reported evidence of a 19.1% reduction in time (in hours) spent in hyperglycaemia (>13.3mmol/L (240mg/dL) per 24 hours) relative to SMBG (difference in adjusted means: -0.37 (0.163) p=0.0247).

Two RCTs for this comparison were identified in the update search. One RCT (n=81) reported no difference in time spent in hypoglycaemia or in time spent in hyperglycaemia (>10 mmol/L) based on six months follow-up data.[109] The second RCT reported fewer episodes of severe hypoglycaemia with isCGM than SMBG (0% vs. 3%); however, no formal test of comparative efficacy was conducted.[110]

rtCGM versus isCGM

The NICE evidence review for NG17 identified two RCTs for this comparison.[2] Based on moderate certainty evidence from one RCT (n=60), rtCGM use for three months or longer was associated with a reduction in the percentage of time spent in nocturnal hypoglycaemia (≤3.9mmol/L: MD -3.96 (-7.30, -0.62); ≤ 3.0mmol/L: MD -2.79 (-4.90, -0.68)).[125] From the second RCT (n=254), there was high certainty evidence that use of rtCGM led to a significant reduction in the risk of severe hypoglycaemic events compared with isCGM (RR 0.08, 95% CI: 0.03 to 0.25) at follow-up of up to six months.[113]

No new data were identified in the update search for this comparison.

Time in range

Time in range (TIR) reflects the amount of time glucose levels fall within a target range (typically 3.9-10.0 mmol/L, that is, 70-180mg/dL) with evidence that each 10% increase in TIR approximates a 0.5% reduction in HbA1c.[30] There is also evidence that each incremental 5% increase in TIR is associated with clinically significant benefits in individuals with T1DM.[30] See Appendix 3, tables A3.5 and A3.6 for data on time in range outcomes by comparison type from NICE and other RCTs. Other related metrics include time above range (TAR), that is the percentage of readings and time above a certain value (Level 1: 181–250 mg/dL (10.1–13.9 mmol/L); Level 2: >250 mg/dL (>13.9 mmol/L) and time below range (TBR), that is the percentage of readings time spent below a set value (Level 1: 54-69mg/DL (3.0-3.8mmol/L); Level 2: <54mg/DL (<3.0mmolL)). While not explicitly labelled as TBR and TAR, these metrics were discussed in the preceding section in terms of time in, or episodes of, hypoglycaemia and hyperglycaemia, respectively.

rtCGM versus SMBG

A meta-analysis, comprising six RCTs,[114, 119, 126-129] by NICE of rtCGM compared with SMBG found that rtCGM led to significantly increased TIR at follow-up periods of up to six months (MD 7.03 (4.88, 9.19). Using GRADE, this estimate was considered as being of very low certainty due to issues with risk of bias, inconsistency and imprecision.

No new RCTs informing this comparison were found by the update search.

isCGM versus SMBG

The NICE evidence review for NG17 identified one RCT reporting TIR for isCGM compared with SMBG with a statistically significant benefit found in favour of isCGM use at six month follow-up (MD 4.16 (3.84, 4.48) (moderate certainty evidence).[2]

There was mixed findings from the two RCTs identified in the update search, with one study reporting an increase in TIR with isCGM use at six months follow up (aMD: 9.0 (4.7 to 13.3) and one study reporting no difference (MD: 3.9 (-12 to 23).[109, 110]

rtCGM versus isCGM

The NICE evidence review for NG17 identified three RCTs reporting time in range outcomes for rtCGM compared with isCGM. A significant improvement in favour or rtCGM was noted for follow-up periods of up to three months (MD: 5.56 (0.31 to 10.81), 2 RCT, low certainty evidence) and up to six months (MD 6.85 (4.36 to 9.34), 1 RCT, moderate certainty evidence).

One RCT identified in the update search relating to individuals with T1DM prone to

hypoglycaemia (glucose values < 70mg/dL ($TBR^{<70}$) >1.5hr / day during the previous 28 days while wearing an isCGM sensor) found that use of rtCGM led to significantly longer TIR for the 90 to 120 day follow-up period (aMD: 4.7% (95%CI: 1.0 to 8.4).[111]

Diabetic ketoacidosis and hospitalisations

See Appendix 3, table A3.7 for data on diabetic ketoacidosis (DKA) and hospitalisation outcomes by comparison type from NICE, Health Technology Wales and one other trial.

rtCGM versus SMBG

Based on very low certainty evidence, NICE concluded that it was not possible to differentiate between rtCGM and SMBG with respect to the relative risk of DKA at follow-up periods of up to and greater than six months or the relative risk of hospitalisation for a follow-up period up to six months.

isCGM versus SMBG

No RCT data for the outcomes of DKA or hospitalisation were reported in the NICE evidence review. One trial identified in the update search reported a single hospitalisation due to DKA in the group using isCGM (n=78) and no hospitalisations in the SMBG group (n=78), while two participants in the SMBG group and no participants in the isCGM reported a clinically significant ketosis event without hospitalisation.[110]

rtCGM versus isCGM

No RCT data for the outcomes of DKA or hospitalisation were reported in the NICE evidence review or were identified in the update search.

4.3.2 Quality of life and other patient-reported outcome measures

The evidence for quality of life (QoL) outcomes and other patient-reported outcome measures (PROMs) for each of the three comparisons as identified in the systematic review undertaken to inform the NICE clinical guidance and from the trials identified from the update search, are presented in Appendix 5 Tables A5.1 and A5.2, respectively. The identified evidence was all based on randomised controlled trial (RCT) data and included generic and disease-specific PROMs that capture QoL including health-related quality of life (HRQoL), emotional well-being, diabetes distress, treatment satisfaction, the impact of hypoglycaemia on quality of life as well as the individual's awareness of hypoglycaemia.

rtCGM versus SMBG

The NICE guidance reported summary RCT data for 12 different QoL and PROM metrics. Across all measures, it was concluded that there was no meaningful difference between rtCGM and SMBG or that it was not possible to differentiate between the interventions. The certainty of the evidence ranged from very low (two metrics) to high (three metrics).[2]

No additional RCT data for this comparison were identified in the update of the NICE NG17 search.

isCGM versus SMBG

NICE did not identify any studies reporting QoL outcomes for this comparison.

The update search identified two RCTs that compared isCGM with SMBG with follow-up periods of 24 and 26 weeks.[109, 110] Both trials reported significant improvements in overall treatment satisfaction with isCGM use when compared with SMBG, with one trial also noting an improvement in glucose monitoring satisfaction. There was mixed evidence in relation to range of other HRQoL and PROMs. While no difference was noted in a range PROMs (diabetes distress, fear of self-injection, diabetes eating problem survey) in an RCT by Leelarathna et al. at 24 weeks follow up, a statistically significant increase in fear of self-testing was reported with isCGM use (aMD: 1.5 (95% CI: 0.1 to 3.0), although this was noted by the authors to not be substantive.[110] Meanwhile, Secher et al. reported that total diabetes quality of life worsened in the isCGM group at 26 week follow-up.[109]

rtCGM versus isCGM

NICE reported evidence in relation to a range of QoL measures from two RCTs with follow up ranging from up to three months and up to six months for the comparison isCGM with rtCGM. Based on moderate certainty evidence, they concluded that it was not possible to differentiate between the two CGM modalities for four different QoL domains at follow-up of up to three months. For two other metrics, fear of hypoglycaemia and treatment satisfaction, the difference in effect observed was noted to be less than the minimally important difference.

No additional RCT data for this comparison were identified in the update of the NICE NG17 search.

An evidence note from Health Improvement Scotland identified patient and social aspects for isCGM versus SMBG from a survey, focus groups and reported experiences by Diabetes Scotland.[112] The included populations with diabetes were not limited to T1DM. The isCGM was reported to have a positive effect on quality of life measures for people with diabetes, carers and family members by easing stress

and anxiety linked to the management of diabetes. Respondents felt that benefits from diabetes management with the isCGM could decrease long-term complications and costs.[112] Some people with diabetes had jobs that made SMBG using finger-prick testing difficult or inconvenient; in these cases, isCGM was reported to be a suitable option.[112]

To supplement the RCT data on quality of life outcomes presented in tables A6.1 and A6.2, cross checking of systematic reviews and an additional targeted search of Medline was undertaken to identify studies measuring QoL outcomes and other PROMs with one additional eligible study identified from an evidence submission to HIQA by one of the pharmaceutical companies. A total of 11 studies were included (see Tables 4.3 and 4.4). All studies were observational and were published between 2018 and 2022. In nine of the 11 studies a single glucose monitoring method (either isCGM (n=7) or rtCGM (n=2)) was used with HRQoL measured at multiple time points. Two studies compared QoL outcomes for a CGM system with SMBG (isCGM versus SMBG[130] and rtCGM versus SMBG.[131] Across the studies a range of disease-specific and generic QoL instruments and validated questionnaires were used with differences also in the duration of follow-up. Between-study comparison is often difficult when assessing QoL given the variety of metrics and metric-specific outcomes.[132]

Tables 4.3 presents the observational studies which assessed QoL outcomes for rtCGM. In three studies looking at time points pre- and post-initiation of rtCGM use, small to medium improvements in multiple HRQoL concepts (for example, worry, diabetes-related stress, social functioning, mental health, hypoglycaemic concerns) were consistently reported.[131, 133, 134] In the one study that compared outcomes for rtCGM relative to SMBG, use of rtCGM led to increases in overall wellbeing and satisfaction, improved participant confidence in managing hypoglycaemia issues, reduced worry and distress, with no difference noted in a range of other metrics (physical activity, problem areas in diabetes).[131]

Table 4.3 Summary of additional rtCGM studies with QoL outcomes

Study	Study type & Country	Population	Number of Participants	CGM system + comparator (if applicable)	Time points tested/follow up	QoL metric	Conclusions	Industry funded
Charleer 2018[135]	Prospective, observational, multicenter, cohort study The RESCUE Trial Belgium	Adults diagnosed with T1DM more than 1 year ago using CSII therapy for longer than 6 months, difficult glycaemic control (un-defined), motivated to use rtCGM, starting in the Belgian rtCGM reimbursement programme.	515 of which 417 (81%) adults with T1DM used rtCGM for at least 12 months.	**rtCGM** Medtronic MiniMed® Enlite® Sensor, Dexcom G4® PLATINUM, and FreeStyle Navigator®	Baseline and after 12 months	SF-36	Small significant increases in all 8 SF-36 health concepts*were reported after 12 months of rtCGM reimbursement when compared with pre-reimbursement data.	No
						PAID-SF	After 12 months of rtCGM reimbursement, a small and significant improvement in QoL in the total population and a medium (defined as an effect size of 0.3–0.5) and significant improvement was noted in those of which had hypoglycaemia as their indication to start rtCGM. No improvement was seen in participants with insufficient or variable glycaemic control.	
						HFS - worry subscale	A significant medium effect size (defined as 0.3 – 0.5) indicated reduced worry after one year of rtCGM use in the total study population and in a sub-group with hypoglycaemia at baseline.	
Charleer 2020a[136]	Prospective, 24-month observational cohort study The RESCUE Trial Belgium	Adults with T1DM on insulin pumps receiving full reimbursement for rtCGM, of which 42% had IAH	441 included in analysis (515 initially but for some data collection stopped after 12 months). 360 in final analysis at 24 months.	**rtCGM** Medtronic Enlite, Dexcom G4 Platinum, Dexcom G5	Pre-reimbursement/ baseline and 4, 8, 12 and 24 months after start of reimbursement	SF-36	Small increases in all SF-36 concepts* were observed when comparing data for rtCGM users at baseline to 12 months and at baseline to 24 months; however, not all score differences were statistically significant.	No
						PAID-SF	RtCGM use was found to significantly improve QoL scores in the total population and also separately in IAH (42% of participants) and non-IAH participants at 12 months and at 24 months. Greater improvements in participants with IAH may be explained by poorer QoL scores at baseline.	
						HFS - worry subscale	Participants experienced decreased levels of worry between baseline and after 12 months and again at 24 months of rtCGM reimbursement.	
Gilbert 2021,[134]	Real-world prospective study US	Adults aged 25–65 years,T1DM or T2DM on intensive insulin therapy (IIT),	182/248 who provided data were adults with T1DM, the rest were T2DM	**rtCGM** Dexcom G6	Baseline and at 12+ weeks after G6 initiation	DDS (17-item)	Significantly lower overall DDS scores indicated lower diabetes-related stress, after 12 weeks of rtCGM use compared to baseline.	Yes Dexcom Inc.

Study	Study type & Country	Population	Number of Participants	CGM system + comparator (if applicable)	Time points tested/follow up	QoL metric	Conclusions	Industry funded
		and no prior CGM use, identified when they contacted Dexcom for their first order of G6				HABS (14-item)	This metric is used to measure hypoglycaemia-related anxiety, avoidance, and confidence in adults with T1DM and T2DM. When total and sub-item scores at baseline were compared with scores taken after 12 weeks of rtCGM use in the T1DM group, a significant improvement (P< 0.001) in hypoglycaemic concerns was reported.	
Lind 2021[131]	The SILVER study (an extension to a randomised crossover trial - the GOLD Trial) Sweden	People with T1DM treated with MDI	107	**rtCGM** either Dexcom G4 or G5 vs. **SMBG**	Baseline (after conventional therapy in GOLD study) and 1 year (at the end of the SILVER study). Total follow up = 2.5 years.	WHO-5	There was an increase in overall well-being scores between baseline (after SMBG was used in the GOLD study) and by the end of the extension study at which point rtCGM had been used by participants for 1 year.	Yes Dexcom Inc.
						DTSQ	There was an increase in treatment satisfaction a) between baseline (after SMBG was used in the GOLD study) and by the end of the extension study at which point rtCGM had been used by participants for 1 year and b) over the 2.5 year period from the start of the GOLD trial to the end of the SILVER trial.	
						HCS	There was a significant increase in the confidence of participants in their own ability to effectively prevent and respond to hypoglycaemia issues between baseline (after SMBG was used in the GOLD study) and by the end of the extension study at which point rtCGM had been used by participants for 1 year and b) over the 2.5 year period from the start of the GOLD trial to the end of the SILVER trial.	
						HFS-II	Swe-HFS (HFS-II) mean scores for worry decreased significantly between baseline (after SMBG was used in the GOLD study) and by the end of the extension study at which point rtCGM had been used by participants for 1 year. The mean score for behaviour /avoidance also decreased, but not significantly.	
						SWE-PAID-20	The improvement in Swe-PAID-20 scores was not significant when rtCGM was compared to SMBG.	
						IPAQ	Changes in IPAQ score in the Silver study were not significant, indicating that rtCGM did not improve physical activity when compared to SMBG.	

***** The eight SF-36 health concepts are: (1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems, and 8) mental health (psychological distress and psychological well-being).

Key: CGM – continuous glucose monitoring; CSII – continuous subcutaneous insulin infusion; DTSQ - Diabetes Treatment Satisfaction Questionnaire; HABS - Hypoglycemia Attitudes and Behavior Scale; HCS -Hypoglycemic Confidence Scale; HFS - Hypoglycemia Fear Survey; HFS-II - Hypoglycemia Fear Survey-II; IAH - impaired awareness of hypoglycaemia; IPAQ - International Physical Activity Questionnaire; MDI - multiple daily injections; PAID-SF - Problem Areas in Diabetes Short Form; QoL – quality of life; T1DM – type 1 diabetes mellitus; rtCGM – real-time continuous glucose monitoring; SF-36 - 36-Item Short Form Health Survey; SWE-PAID-20 - Swedish Problem Areas in Diabetes-20 scale; WHO-5 - World Health Organization 5-item well-being index.

Table 4.4 presents the findings from observational studies which reported QoL outcomes and other PROMs for isCGM. There were six studies comparing time points pre- and post-initiation of isCGM use at a range of time points and one study that compared use of isCGM to SMBG.[130] A variety of validated disease-specific and generic QoL tools were used with one de novo tool also used to capture diabetes burden and metrics related to glucose monitoring.

In two studies comparing outcomes pre- and post-initiation of isCGM, there was evidence that satisfaction levels increased.[130, 137] While two studies reported increases in health-related QoL, the authors of the first study noted that the small increases noted may not be clinically relevant[138] and in the second an increased risk of bias was noted by the authors due to a poor response rate.[139] In a third study, evidence of improvements in total quality of life scores at three months were reported, but only for participants with good glucose control and participants using multiple daily insulin injections and not those on continuous subcutaneous insulin infusion (CSII).[140] No improvement in fear of hypoglycaemia or diabetes-related emotional distress were noted in another study at six or 12 months follow-up.[137]

There was conflicting evidence regarding the impact of isCGM use on diabetes-related distress. In one study,[133] participants' feelings of being overwhelmed and failure in managing their diabetes regimen were significantly reduced with isCGM use and in another study,[141] there was an improvement in total distress scores for 90% of participants who had commenced NHS-funded isCGM. However, a third study found no difference in diabetes distress after three months although it was noted that outcomes differed based on the level of glycaemic control at baseline (with a significant reduction in distress observed in those with better control) and the mode of insulin administration (greater distress in those on continuous subcutaneous insulin infusion compared with those using multiple daily injections).[140]

There was mixed evidence also in relation to a range of mental health scores. One study noted increases in median anxiety and depressions scores after starting isCGM use.[133] Newly-elevated anxiety scores seen in 8.2% of participants, was associated with previous self-funding, younger age and shorter duration of diabetes and with mode of insulin administration, specifically CSII.[133] Newly-elevated depression scores seen in 12.3% of participants was associated with level of deprivation.[133] Three studies which used the Short Form Health Survey reported varying results. Significantly lower general health, vitality and mental health outcome measures were reported in one study,[137] while an improvement in the mental health component at 12 months was noted in another study.[138] In the third study, while no improvement in mental health scores was noted at 12 months, the scores were noted to be significantly higher than for those who stopped isCGM with inconsistent results also noted in relation to physical health scores[139].

In the study that compared isCGM use to SMBG, after 5 to 11 months of isCGM use, there was a significant increase in satisfaction that was correlated with decreased HbA1c levels particularly in participants younger than 43 years and in those with poor glycaemic control at inclusion.[130] This study also found that isCGM use significantly reduced participant behaviours aimed at preventing hypoglycaemia.

Table 4.4 Summary of additional isCGM studies with QoL outcomes

Study	Study type & Country	Population	Number of Participants	CGM system + comparator (if applicable)	Time points tested/follow up	QoL metric	Conclusions	Industry funded
Charleer 2020b[137]	Prospective, 12-month Observational Real World Cohort Study (The FUTURE Trial) Belgium	Adults with T1DM for > 3 months who planned to start isCGM	1,913, of which, 1,711 (89%) participants had ≥ 12 months follow-up, 47 (3%) < 12 months follow-up, and 155 (8%) participants stopped participating	**isCGM** FreeStyle Libre	Baseline and 12 months after start of isCGM. Different questionnaires were used at baseline, 6 months, and 12 months	1. SF-36	Participants receiving reimbursement for isCGM had high baseline SF-36 scores. In 6 of the 8 concepts, scores were slightly lower at 12 months although only general health, vitality and mental health were significantly lower.	No
						2. PAID-SF	There was no improvement in diabetes-related emotional distress at 6 months and a slight improvement at 12 months that was not significant.	
						3. HFS-II–worry subscale	This study failed to show a significant decrease in the worry score of the HFS-II.	
						4. DTSQ - status and change	After reimbursement of isCGM, there was a significant increase in DTSQ status satisfaction and DTSQ change satisfaction at one year.	
Deshmukh 2020[133]	Nationwide audit UK	Adult FreeStyle Libre users from 102 UK (NHS) hospitals. At follow up, 3126 (98%) had T1DM.	Number with follow up data: Gold score n=2,801 DDS n=2,532	**isCGM** FreeStyle Libre	Baseline and after 12 months	1. DDS2	In a nationwide audit by the Association of British Clinical Diabetologists (ABCD), follow up data were available for 2,532 participants. Feelings of being overwhelmed and failure in managing their diabetes regimen were significantly reduced after 12 months of isCGM use.	Yes Abbott Laboratories
Fokkert 2019[138]	Prospective nationwide registry study (FLARE-NL4) The Netherlands	Adults (≥18 years) with T1DM, T2DM or other type of diabetes, using insulin	1054/1365 (77.2%) had T1DM of which 537 (52%) had follow up data at 12 months.	**isCGM** FreeStyle Libre	Baseline, 6 months and 12 months	1. SF-12v2	The SF-12v2 showed a significant increase from baseline to 12 months in the mental health component for adults with T1DM and showed no change in the physical health component.	No
						2. EQ-5D-3L	Users of isCGM reported a significant increase in health-related QoL. Given the small size of these differences, the authors questioned whether it would be better to focus on their clinical relevance rather than significance, however they did not comment on whether they found the differences clinically significant.	
						3. DVN-PROM	This metric was co-developed by Fokkert et al. to assess the disease burden for people with diabetes and the requirement for, use of and usefulness of glucose monitoring. They report a selected number of results from this unvalidated metric and it is not clear how some of them translate into QoL outcomes.	
	Prospective observational study	Adults with T1DM who started	114	**isCGM** FreeStyle	Baseline (measured 2 weeks	1. EsDTSQ	After starting isCGM, satisfaction improved significantly. In 2 stratified analyses, 1 based on blood glucose control and 1 based	No

Study	Study type & Country	Population	Number of Participants	CGM system + comparator (if applicable)	Time points tested/follow up	QoL metric	Conclusions	Industry funded
Jimenez-Sahagun 2022[140]	Spain	treatment with isCGM for the first time, met requirements for the financing of flash GM according to the NHS and committed to completing 3 educational sessions. Women wishing to become pregnant or pregnant during the study period were excluded.		Libre	after applying and activating the sensor) and 3 months after applying and activating the sensor		on insulin treatment modality (CSII + MDI), all groups self-reported a significant increase in satisfaction at 3 months.	
						2. EsDQOL	This questionnaire was used to evaluate 1) satisfaction, 2) impact, 3) social and vocational concerns and 4) diabetes-related concerns. A significant improvement in total quality of life score was seen in participants 3 months after starting isCGM. In a stratified analysis, a significant improvement in DQoL scores was seen in participants with better blood glucose control and no difference was seen in participants with poor blood glucose control. In another stratified analysis, participants using MDI experienced a significant improvement, while there was no difference reported by those using CSII.	
						3. EsDDS	There was no significant difference in diabetes distress at 3 months follow up after isCGM use. In a stratified analysis, the group with better glucose control at baseline had a significantly reduced score when compared to participants with poor glucose controlled (defined as HbA1c greater than 8%). In another stratified analysis, participants who used CSII had a significant increase in distress score, when compared to participants using MDI.	
Lameijer 2021[139]	Prospective, observational design (FLARE-NL-6 - follow-up study of the FLARE-NL4) The Netherlands	People with T1DM (76% of total), T2DM or other type of diabetes who participated in the 1-year FLARE-NL-4 study and continued to use isCGM for a minimum of 1 year	272/342 (76%) had T1DM of which 214 had data to be analysed at the 2 year time point	**isCGM** Freestyle Libre	Baseline, 1 year and 2 years. QoL in the previous year was assessed	1. EQ-5D-3L	The lack of response from many of the FLARE-NL4 study participants increased the risk of selection bias. Those who continued isCGM use over the study duration had a significant increase in health-related QoL according to the EQ-5D Dutch tariff score, compared to participants who discontinued their use of isCGM.	No
						2. SF-12v2	Participants with T1DM who continued isCGM showed no change in mental component scores measured by the SF-12v2 from baseline to two years and participants who stopped isCGM reported lower mental component scores, the difference between groups was significant. For the physical component, both those who continued isCGM and those who stopped it had increased scores when comparing baseline to two years. There was no significant difference between groups.	
						3. DVN-PROM	The authors report a selected number of results from this unvalidated metric and it is not clear how some of them translate into QoL outcomes.	

Study	Study type & Country	Population	Number of Participants	CGM system + comparator (if applicable)	Time points tested/follow up	QoL metric	Conclusions	Industry funded
Rouhard 2020[130]	Prospective observational study Belgium	Adults with T1DM (98%) diabetes secondary to pancreatectomy (2%)	257 recruited, of which 248 were analysed	**isCGM** FreeStyle Libre vs. **SMBG**	At inclusion, after 2-4 months and after 5-11 months	1. DTSQ	DTSQ was used to assess satisfaction. There was a significant increase between baseline and the second time point (5-11 months). There was a significant correlation between this increase in satisfaction and decreased HbA1c levels particularly in participants younger than 43 years and in those with poor glycaemic control at inclusion.	NR
						2. HFS	Between the time of inclusion and after 5-11 months, there was a non-significant decrease in HFS worry score and a significant decrease in the behaviour score, meaning fewer avoidant behaviours to prevent hypoglycaemia.	
Tyndall 2019[141]	Prospective observational study UK	The first 900 individuals with T1DM started on NHS-funded isCGM in 2 hospital clinics. People with T1DM were eligible for NHS funding if: (1) they were an intensive insulin therapy user (2) were willing to attend an isCGM education session; (3) agreed to scan glucose levels a minimum of 6 times daily (4) agreed to share glucose data with their clinic (5) attended a diabetes education programme or	589/900 (subgroup that attended the Royal Infirmary of Edinburgh)	**isCGM** FreeStyle Libre	Pre- and post- flash monitoring. At each attendance at the Royal Infirmary of Edinburgh (Gold, modified Clarke and HADS) 1 month after attendance only (DDS modified)	1. HADS	Data from isCGM users showed increased median anxiety and depression scores after commencing isCGM monitoring compared to before it was started. In the 12.3% of participants who developed higher anxiety scores after starting isCGM, younger age, shorter duration of T1DM, prior self-funding and continuous subcutaneous insulin infusion (CSII) were associated factors. A lower ranking on the Scottish Index of Multiple Deprivation was the only associated factor for the 8.2% of participants with increased depression scores after starting isCGM.	No
						2.Modified DDS	There was a net improvement in total DDS scores for 90% of participants who had commenced NHS-funded isCGM 1 month after attending an isCGM educational session.	

Study	Study type & Country	Population	Number of Participants	CGM system + comparator (if applicable)	Time points tested/follow up	QoL metric	Conclusions	Industry funded
		demonstrated equivalent diabetes self-management knowledge.						

***** The eight SF-36 health concepts are: (1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems, and 8) mental health (psychological distress and psychological well-being).

Key: CGM – continuous glucose monitoring; DDS - Diabetes Distress Scale; DDS2 -Diabetes Distress Scale version 2; DTSQ - Diabetes Treatment Satisfaction Questionnaire; DVN-PROM - Diabetes Vereniging Nederland, Patient-Reported Outcome Measures; EQ-5D-3L - EuroQol Five Dimension the 3-level version; EsDDS - Diabetes Distress Scale in its Spanish version; EsDQOL - Diabetes Quality of Life questionnaire in its Spanish version; EsDTSQ - DTSQ in its Spanish version; HADS - Hospital Anxiety and Depression Scale; HFS - Hypoglycemia Fear Survey; HFS-II - Hypoglycemia Fear Survey-II; isCGM – intermittently-scanned continuous glucose monitoring; NHS - National Health Service; NR – not reported; PAID-SF - Problem Areas in Diabetes Short Form; QoL – quality of life; SF-12v2 - 12-Item Short Form Health Survey v2; SF-36 - 36-Item Short Form Health Survey; T1DM – type 1 diabetes mellitus; T2DM – type 2 diabetes mellitus; UK – United Kingdom.

4.4 Diabetes in pregnancy

Outcomes relating to CGM in pregnancy for adults with T1DM were extracted from the NICE and HTW reports for the interventions (rtCGM and isCGM) of interest to this HTA. Table 4.5 presents data for both maternal and infant outcomes by comparison and, by time period (pre-conception period and during pregnancy). Additional outcomes are reported in Table A4.9.

rtCGM versus SMBG

NICE identified two RCTs for this comparison.[1] In one of these RCTs by Secher et al.[142] also included by HTW,[143] the population included pregnant women with T1DM (n=123) and T2DM (n=31). Results were reported separately for the T1DM subgroup for some, but not all outcomes.

In the preconception period, for women who were planning to become pregnant, NICE concluded that based on moderate to high certainty evidence that it was not possible to differentiate between the monitoring systems with respect to HbA1C, time in glucose target range, risk of severe hypoglycaemia or diabetic ketoacidosis. There was inconsistent evidence with respect to QoL and other patient-reported outcome measures, with rtCGM associated with improvements in QoL for three subscales (impact, obstruction, worry) based on moderate certainty evidence, but with no difference noted for other measures.[1] During pregnancy, NICE concluded that while the overall evidence base was small and ranged in quality, there was high to moderate certainty evidence for a number of important outcomes (HbA1C, neonatal hypoglycaemia, neonatal ICU, time spent in target glucose range) that favoured rtCGM.[143, 144]

isCGM versus SMBG

No RCTs relevant to this comparison were identified in the UK guidance documents.

rtCGM versus isCGM

No RCTs relevant to this comparison were identified in the UK guidance documents, with evidence limited to one retrospective cohort study.[1, 143] The study which could not differentiate between rtCGM and isCGM for a number of important outcomes was noted to be at high risk of bias with the conclusion that it could not be used to inform decision making.

Table 4.5 Maternal and infant outcomes

Outcome	Effect estimate	Participants	GRADE	Source
rtCGM vs SMBG				
Preconception period (women who are planning to become pregnant) Maternal outcomes at follow up ≤ 6 months				
Quality of life-Blood Glucose Monitoring System Rating Questionnaire (BGMSRQ)- Impact subscale	MD 5.10 (2.31, 7.89) (Favours rtCGM)	110[144]	Moderate	NICE
Quality of life- BGMSRQ – Obstruction subscale	MD -2.80 (-4.71, -0.89) (Favours rtCGM)	110[144]	Moderate	NICE
Quality of life- Hypoglycaemia Fear Survey- II (HFS-II)– Worry subscale	MD -6.80 (-11.62, -1.98) (Favours rtCGM)	110[144]	Moderate	NICE
Adverse event- local reaction (skin changes during trial)	RR 5.04 (2.07, 12.29) (Favours SMBG)	109[144]	High	NICE
It was not possible to differentiate between monitoring systems for other relevant assessed outcomes: HbA1c; achieved HbA1c target; time spent in glucose target range; time spent in glucose target range – whole population; time spent in glucose target range – insulin pump users; time spent in glucose target range – multiple daily injection users; severe hypoglycaemia; serious adverse events; adverse event – diabetic ketoacidosis; Quality of life- BGMSRQ- Satisfaction subscale; Quality of life- HFS-II – Behaviour subscale; Quality of life- Short form; Diabetes related distress – Problem Areas in Diabetes (PAID) score.				NICE
During pregnancy - Maternal and infant outcomes at follow up ≤ 6 months				
It was not possible to differentiate between monitoring systems for the relevant assessed outcome: HbA1c (%)				NICE
During pregnancy - Maternal and infant outcomes at follow up greater than 6 months				
HbA1c (%)	MD -0.18 (-0.36, 0.00) (Favours rtCGM)	187[144]	High	NICE
Achieved HbA1c target ≤6.5% (48 mmol/mol)	MD 1.27 (1.00, 1.62) (Favours rtCGM)	187[144]	High	NICE
Time spent in glucose target range (%) – whole population	MD 7.00 (2.57, 11.43) (Favours rtCGM)	154[144]	Moderate	NICE
Time spent in glucose target range (%) – multiple daily injection users	MD 8.00 (1.43, 14.57) (Favours rtCGM)	24[144]	Moderate	NICE
Adverse event- local reaction due to CGM monitor (skin changes during trial)	RR 6.18 (3.08, 12.40) (Favours SMBG)	207[144]	High	NICE
Mode of birth – Caesarean section	RR 0.82 (0.69, 0.99) (Favours rtCGM)	325[142, 144]	High	NICE
Quality of life- BGMSRQ – Impact subscale	MD 4.80 (2.98, 6.62) (Favours rtCGM)	214[144]	Moderate	NICE
Quality of life- BGMSRQ – Obstruction subscale	MD -1.90 (-3.09, -0.71) (Favours rtCGM)	214[144]	Moderate	NICE
Neonatal hypoglycaemia	RR 0.67 (0.47, 0.95) (Favours rtCGM)	317[142, 144]	Moderate	NICE

Outcome	Effect estimate	Participants	GRADE	Source
During pregnancy – women who conceived during 24-week planning pregnancy trial				
Very small sample size for outcomes (range 24 – 31 participants). It was not possible to differentiate between monitoring systems or the treatment effect could not be estimated for all maternal and infant outcomes at ≤ 6 months and maternal and infant outcomes at > 6 months (HbA1c (maternal), HbA1c (neonatal), achieved HbA1c target, severe hypoglycaemia, serious adverse events, adverse event – diabetic ketoacidosis, pre-eclampsia, mode of birth – caesarean section, preterm birth < 37 weeks, still birth, congenital anomaly, small for gestational age, large for gestational age, macrosomia, neonatal hypoglycaemia, high level neonatal care > 24 hours).				NICE
isCGM vs SMBG				
NICE did not identify any RCTs that compared isCGM to SMBG[1] and HTW did not address this comparison.[143]				-
rtCGM vs isCGM				
NICE did not identify any RCTs that compared rtCGM to isCGM[1] and HTW did not address this comparison.[143]				-
High level neonatal care (NICU) greater than 24 hours	RR 0.63 (0.42, 0.93) (Favours rtCGM)	200[144]	High	NICE
It was not possible to differentiate between monitoring systems for all the additional other assessed outcomes (time spent in glucose target range – insulin pump users; adverse event – diabetic ketoacidosis; adverse event- diabetes related hospitalisation).				

Key: BGMSRQ - Blood Glucose Monitoring System Rating Questionnaire; HbA1c - glycated haemoglobin; HFS-II - Hypoglycaemia Fear Survey- II; HTW – Health Technology Wales; isCGM – intermittently scanned continuous glucose monitoring; NICE – National Institute for Health and Care Excellence; NICU – neonatal intensive care unit; rtCGM – real-time continuous glucose monitoring; SMBG – self-monitoring of blood glucose.

4.5 Safety

A study by Ulriksdotter *et al.* (2020) reported cases of allergic contact dermatitis in the general T1DM population attributed to use of the FreeStyle Libre isCGM system.[145] A joint consensus report by the American Diabetes Association and the European Association for the Study of Diabetes, includes advice that adults with T1DM should be warned about the potential for CGM system sensors to cause irritant and allergic contact dermatitis.[146] At least one RCT (the CONCEPTT trial)[144] comparing rtCGM to SMBG for women with T1DM who were planning pregnancy or who were pregnant, reported adverse events related to skin reactions to rtCGM subcutaneous sensors. The reported skin changes included acute erythema, acute oedema, chronic scabbing, chronic dry skin, chronic hypopigmentation and chronic

hyperpigmentation. This trial was included in the NICE clinical evidence review where it was concluded that based on high certainty evidence, isCGM was associated with an increased risk of local skin reactions both in the pre-conception period (RR: 5.04 (95% CI: 2.07 to 12.29) and during pregnancy (RR: 6.18 (95% CI: 3.08 to 12.40). No difference in the risk of serious adverse events was noted for either period.[1]

4.6 Discussion

Glucose monitoring as part of a diabetes management strategy is aimed at reducing micro- and macrovascular complications. This chapter sought to review the existing evidence of the clinical effectiveness of continuous glucose monitoring systems for adults with T1DM. The focus of the review was on HTAs and national guidelines or guidance from the UK, supplemented by targeted searches for new randomised controlled trials.

Evidence was available for all three comparisons, but in some cases only for limited outcomes.

Adults with T1DM

In terms of impact on HbA1c, for the comparison of rtCGM and SMBG, for three out of nine measures of HbA1c there was evidence of a beneficial effect for rtCGM, although the evidence was graded as low and very low certainty. For the other six measures, the evidence review team found no meaningful difference or could not differentiate between the two interventions. Three RCTs were identified comparing isCGM and SMBG for HbA1c outcomes, two found no meaningful difference, but the third favoured isCGM. Comparing rtCGM with isCGM; at follow-up periods up to six months, rtCGM was associated with a significantly higher likelihood of achieving an HbA1c target less than 7.0%. However, when considering mean HbA1c levels, no clinically meaningful difference was observed over the same follow-up period.

For hypoglycaemic and hyperglycaemic outcomes, there was low certainty evidence that the use of rtCGM improved hypoglycaemic event duration and severe hypoglycaemia relative to SMBG NICE reported that rtCGM led to a reduction in the duration of hypoglycaemic events relative to SMBG. Data were inconsistent with respect to the risk of severe hypoglycaemic events with evidence favouring rtCGM at less than six months follow-up and favouring SMBG at greater than six months follow-up. No meaningful difference between rtCGM and SMBG was noted in terms of the frequency of hypoglycaemic events. Based on very low certainty evidence, rtCGM was associated with a reduction in the percentage of time spent in nocturnal hypoglycaemia but with no meaningful difference noted in terms of the frequency of these events. The findings for hypoglycaemic events were mixed for isCGM compared to SMBG. A single RCT with six month follow-up informed both the NICE

evidence review for NG17 and the SHTG evidence note for this comparison. A range of measures relating to glycaemic control with different cut-points were reported with mixed findings; some reported measures favouring isCGM, but for others there was no meaningful difference. For rtCGM compared with isCGM, nocturnal hypoglycaemia and the risk of severe hypoglycaemic events were more favourable in rtCGM users.

RtCGM use led to increased time in range versus SMBG, although there was very low certainty in this estimate. There were mixed findings for isCGM compared with SMBG for time in range. There was some evidence that rtCGM used lead to longer time in range than isCGM, but further comparative data with the same duration of follow-up of analysis is needed.

There was no statistically significant difference in diabetic ketoacidosis or hospitalisations between isCGM, rtCGM, and SMBG in the RCTs identified by NICE and the updated search reported here. This was likely attributable to the low number of events overall, and the short duration of trials, typically six months of follow-up. The included RCTs did not generally consider resource use as an outcome, although one before and after study with a median follow-up of 14 months, identified by Health Technology Wales, found overall hospital admissions to internal medicine wards were significantly reduced after use of isCGM for six months or more, compared to the six months before purchase of their first isCGM system.[147] Deshmukh et al conducted a large, real-world study of isCGM users by analysing data from 10,370 users of which 97% were adults with T1DM.[133] They reported significant reductions in paramedic callouts and hospital admissions for hyperglycaemic, DKA or hypoglycaemia. Long-term comparative data are needed to verify this finding.

In the updated search reported here, four systematic reviews of clinical effectiveness published between 2020 and 2022 were identified.[148-151] These reviews included the same studies identified in the evidence review for NICE NG17. The findings of these systematic reviews broadly align with our findings.

As distinct from glycaemic control, patient-reported outcomes including quality of life are clearly important for individuals with diabetes. However, data on these outcomes were limited and inconclusive. This report considered both RCT and observational data. A range of general, disease-specific and complication/symptom-specific quality of Life (QoL) measures or other patient-reported outcome measures were used across studies and were not universally applied to both types of device. Additionally, identified observational studies mostly were non-comparative. This limited comparisons of QoL. For rtCGM there was some evidence of increased well-being at 12 months compared to baseline. There was also evidence that rtCGM reduced fear or worry over time about hypoglycaemia. For isCGM there was some evidence of

improved QoL up to 12 months compared to baseline. There was conflicting evidence for anxiety and distress measures; isCGM users showed increased median anxiety and depression scores since starting isCGM monitoring but users also reported reduced diabetes distress. Two systematic reviews focusing on HRQoL were identified in the updated search.[152, 153] The reviews included limited observational data, however, the findings of these reviews align with our findings for HRQoL. It is possible that the available QoL and PROM instruments do not adequately capture the perceived benefits of CGM in those living with diabetes.

A search for ongoing trials in the ClinicalTrials.gov registry and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) identified eight trials and one protocol that may publish results relevant to this rapid HTA.

Diabetes in pregnancy

There is was limited evidence for use of CGM in pregnant women with T1DM. There is some benefit to the use of rtCGM compared to SMBG for maternal and neonatal outcomes. Evidence for isCGM compared with SMBG was completely lacking.

For rtCGM compared with isCGM, only a single retrospective study was identified. It was not possible to differentiate between monitoring systems for assessed outcomes.

Safety

Overall, continuous glucose monitoring appears to be safe with no reported mortality. Healthcare professionals are advised to warn potential CGM users of the risk of CGM sensor-related skin reactions.

Strengths and limitations

The method used to inform this chapter was a rapid review of the evidence using the NICE evidence reviews as index documents. It is possible that additional relevant literature has been missed with the chosen approach, however, given the systematic methods applied in the NICE evidence reviews and in the update search conducted by HIQA, this is unlikely to be the case. With the exception of the additional searches undertaken by HIQA for QoL data and other PROMs, the evidence considered was largely limited to RCT data for adults with T1DM. Observational data on clinical effectiveness were not included in the NICE evidence review, but could also be considered relevant. It is worth noting that as the clinical data are not definitive, other HTAs and guidelines may have used the same data, alongside clinical guideline group input, to come to different recommendations. For example Diabetes Canada reported that with respect to isCGM, RCTs did not consistently demonstrate differences in HbA1C compared with SMBG, but that other glucose

measures have been shown to improve. These included time in range, less time in high glucose range and less glucose variability. In head-to-head studies, the superiority of rtCGM to protect against hypoglycaemia (significant reduction in time below range) in individuals with impaired awareness of hypoglycaemia or recent severe hypoglycaemia was noted.

The numbers of study participants for most comparisons was low, being less than 300 for almost all outcomes. Data were typically limited to short-term follow-up, with no disaggregated data provided for follow-up greater than six months. The certainty of the evidence was primarily considered low or very low for the comparisons of rtCGM and SMBG, very low to moderate for isCGM versus SMBG, and moderate to high for rtCGM versus isCGM. A rating of low certainty evidence means that the authors believe that the true effect might be markedly different from the estimated effect, whereas a rating of moderate certainty means that they believe the true effect is probably close to the estimated effect.

For diabetes in pregnancy, there was evidence that rtCGM resulted in improved maternal HbA1c and some neonatal outcomes relative to SMBG. There were no data comparing isCGM and SMBG, and no difference between rtCGM and isCGM, based on a single study.

The review of evidence of clinical effectiveness focused on glycaemic outcomes and health-related quality of life. These are endpoints that demonstrate direct or indirect benefits for individuals with diabetes. However, the identified measures did not capture issues such as acceptability and preference. While these may not translate into measurable reductions in complications, they can improve the experience of individuals in managing their diabetes.

The use of CGM can, for example, enable people with diabetes to gain a sense of empowerment over glucose management by improving the ability to quickly identify and respond to dysglycaemia.[154] While criteria for testing may differ depending on diabetes type, evidence on obstacles to self-monitoring from the broader population with diabetes may be applicable to those with T1DM. Key obstacles to self-monitoring of blood glucose identified in a study involving individuals with T2DM included forgetting to test, being too busy and not wanting to test in front of others.[155] The use of CGM may address some of these obstacles by automating the testing, although individuals still need to access the data and act on the readings. There is substantial variation in compliance with SMBG, but it is low in some countries.[156] Compliance may be higher with CGM devices[157] with potential benefits for diabetes management, although this has not been clearly demonstrated in terms of impact on clinical outcomes. The ability to remotely share data with a physician means that CGM can also support care for remote or difficult to reach populations, with the potential to reduce inequities.[158] It is also worth noting that,

compared with SMBG, CGM enables the generation of additional glucose metrics, including time in range, time above range, time below range and glycaemic variability.[159] As the use of CGM increases, additional evidence will likely emerge to support the interpretation of these glucose metrics and to identify potential target areas for intervention.

The potential disadvantages to CGM for the user include the risk of information overload and alarm fatigue.[154, 160] The implications are that some users of CGM may disengage or cease using it because of the continuous flow of information and warnings. It should be noted that an individual can stop using CGM and revert to SMBG at any point if they find it preferable. However, from a healthcare perspective that may represent a poor use of resources. It would therefore be important to provide appropriate education to individuals prior to using CGM to ensure that they are empowered to make decisions about whether CGM or SMBG is a more acceptable system to help them manage their diabetes.

5 Cost effectiveness and budget impact

Key points

- A literature search to identify economic evaluations was conducted, supplemented by a targeted search of publications from specific HTA agencies. The review included 16 studies with 23 analyses from eight countries.
  - **rtCGM compared with SMBG:** results were mixed with some reporting ICERs for rtCGM that would be considered cost effective at €20,000 per QALY, some at €45,000 per QALY, and some concluding it was not cost effective. One reported that SMBG dominated rtCGM (that is, SMBG was more effective and less expensive)
  - **isCGM compared with SMBG:** of the eight analyses identified, most concluded that isCGM was cost effective compared with SMBG. A non-industry analysis focused on pregnant women with T1DM found isCGM dominated SMBG.
  - **isCGM compared with rtCGM:** only two analyses directly compared rtCGM and isCGM. An industry-funded study found isCGM to be cost effective relative to rtCGM while one study found isCGM to be more effective and less costly that rtCGM for a population of pregnant women.
  - None of the included studies was considered directly applicable to the Irish setting due to modelling assumptions and the data used to populate the models. The methodological quality of the studies varied, with five of the sixteen considered of high quality, and five as low quality.
- A budget impact analysis (BIA) focusing on the expanded reimbursement of CGM devices to adults with T1DM in Ireland was undertaken. Given the nature of this rapid HTA, a simplified model was used. Input parameters comprised population size, uptake rates, SMBG daily test frequency and costs of CGM and SMBG to the HSE.
  - There is substantial uncertainty regarding the prevalence of T1DM in adults in Ireland. The base case assumed a total adult population of 24,480 with T1DM.
  - It was assumed that 50.5% of all adults with T1DM are already reimbursed for CGM, that uptake is an additional 15% in the first year, rising to an additional 35% by the fifth year, and that all individuals switch to the same type of CGM system (that is, either isCGM or rtCGM), and not a mix of the two.

- In the base case analysis compared with SMBG:
  - The estimated five year incremental cost to the HSE (over and above what the HSE currently spends on CGM) was €24.8 million for isCGM and €84.8 million for rtCGM.
  - The estimated five year incremental cost to the HSE would fall between €24.8 million and €84.8 million should a mix of rtCGM and isCGM systems be adopted as part of expanded access.
  - The annual incremental cost per person was estimated to be €811 for isCGM and €2,771 for rtCGM.
- The cost estimates vary substantially depending on the uptake rate and the level of testing in the SMBG comparator. Five year incremental cost estimates range from €16.9 million for isCGM and €76.9 million rtCGM (for a scenario of low uptake and high baseline SMBG test rates), up to €49.5 million for isCGM and €145.2 million for rtCGM (for a scenario of high uptake and low baseline SMBG test rates).
- There are several important limitations associated with this BIA primarily relating to the limited availability of data and the requirement to make assumptions in the model. Of particular importance is the substantial uncertainty regarding the total numbers in the eligible T1DM adult population in Ireland.
- The BIA assumed that once initiated on a particular system, individuals remained on the same CGM system for the duration of the five year period. It also does not account for those who are currently using CGM, switching systems. Switching to an economically advantageous system, when clinically appropriate to do so, may result in cost savings for the HSE.
- The analysis presented here is based on the CGM systems available at the time of assessment. There has been iterative development of CGM technologies, with the potential that new systems that incorporate additional or different functionality could be associated with increased costs and would have implications for the budget impact of CGM.

5.1 Introduction

This chapter provides a rapid review of published international evidence on the cost effectiveness of continuous glucose monitoring (CGM) systems for adults with type 1 diabetes mellitus (T1DM). This chapter also describes a budget impact analysis to

estimate the potential costs associated with CGM reimbursement for adults with T1DM in Ireland.

5.2 Review of cost-effectiveness evidence

For the review of cost-effectiveness evidence, the research question (RQ) was developed using an adapted PICO framework (Table 5.1). A literature search to identify economic evaluations was conducted and this was supplemented by a targeted search of specific HTA agencies. These agencies were selected based on prior scoping work by the evaluation team. The findings of this review are described below.

RQ: In adults with type 1 diabetes mellitus (T1DM) what is the cost effectiveness of:

- rtCGM compared with SMBG?
- isCGM compared with SMBG?
- rtCGM compared with isCGM?

Table 5.1 Inclusion criteria for cost-effectiveness evidence using a PICOS framework

Population:	Adults ≥18 years with T1DM, including pregnant women with pre-existing T1DM
Interventions:	rtCGM isCGM
Comparisons:	▪ SMBG (usual care) ▪ Other type of CGM
Outcomes:	Any relevant incremental ratio of costs and benefits (such as ICERs)
Study design:	Include: economic evaluations (CEA or CUA) Exclude: all other information sources

Key: CEA – cost-effectiveness analysis; CUA – cost-utility analysis; ICERs – incremental cost effectiveness ratios; isCGM – intermittently scanned continuous glucose monitoring; rtCGM – real time continuous glucose monitoring; SMBG – self monitoring of blood glucose; T1DM – type 1 diabetes mellitus

5.1.1 Methods

Search strategy

A scoping search strategy was designed, and conducted on PubMed (National Library of Medicine, National Center for Biotechnology Information) on 20 June 2022. The full search strategy is available in Appendix 6. This pragmatic strategy search was

designed to identify a sample of studies with cost-effectiveness evidence and was not a comprehensive and systematic search to identify all available evidence.

The population and intervention search terms were informed by the search strategy from a Cochrane systematic review[161] and the study design search terms were those used in a previous HIQA publication.[162] The PubMed search was supplemented by a review of websites of a select number of HTA agencies from England, Scotland, Wales, Canada and Norway, as a scoping review identified that these agencies had assessed the use of CGM.

Selection of studies

Search strategy results were uploaded to EndNote X8 software and then to Covidence® for screening. One person conducted title and abstract and full text screening. A second person reviewed the list of records that were shortlisted and excluded additional records.

Data extraction and management

Two people discussed and agreed on data fields to extract. One person extracted data into an Excel 2013 spreadsheet.

Quality appraisal of cost-effectiveness studies

The quality of included studies was assessed by one person using the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) questionnaire to assess the relevance and credibility, and the Consensus on Health Economic Criteria (CHEC) CHEC-list to assess the methodological quality. Due to the subjective nature of the instruments, a second individual reviewed the assessments, made suggestions for improvement and clarified uncertainties.

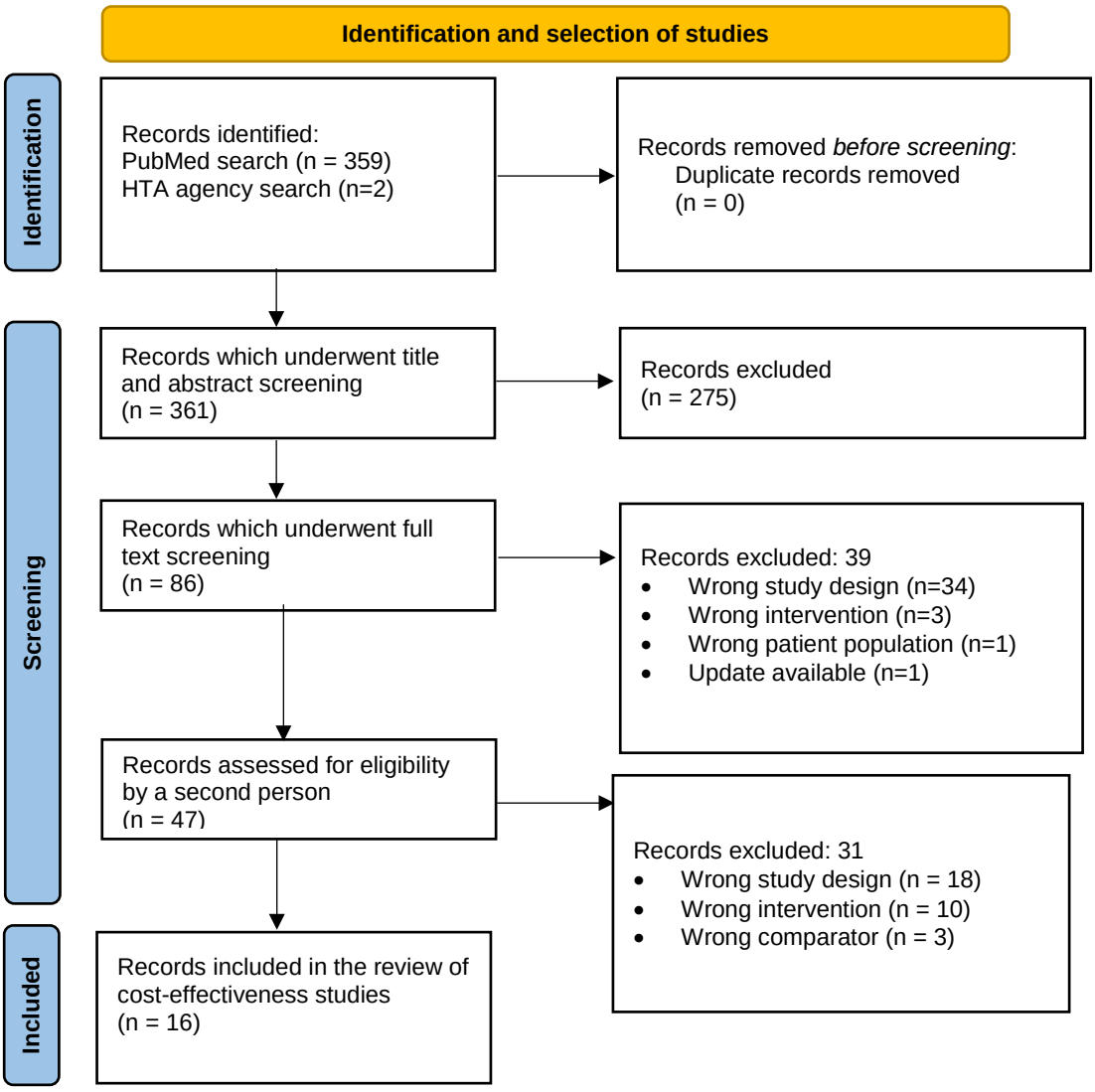
Data synthesis

Costs are presented in the 2021 Irish Euro following adjustment for inflation and purchasing power parity in accordance with national HTA guidelines.[163] For records where authors did not report the unit cost year, it was assumed that the unit costs were from two years prior to study publication (based on the average lag from analysis to publication estimated from included studies which reported the unit cost year).[164] Cost effectiveness was reported relative to reference willingness-to-pay (WTP) thresholds of €20,000 and €45,000 per quality-adjusted life year (QALY) gained. While there is no fixed threshold in Ireland below which interventions are routinely considered to be cost effective, WTP thresholds of €20,000 and €45,000 per QALY gained are typically used as reference points for decision-making regarding the reimbursement of medicines.[163] Results are therefore discussed in this context.

5.1.2 Results

The PubMed search identified 359 records, with two additional studies identified from the HTA agency search. Since the search was run on a single database there was no need for deduplication. One person completed title and abstract screening and 275 records were excluded, a further 39 records were excluded though full text screening. A second person reviewed the shortlisted 47 records and excluded 31 records. A total of 16 studies were identified for inclusion. The adapted PRISMA 2020 flow diagram[165] (Figure 5.1) presents the number of records in the search and selection process and the final number of records included.

Figure 5.1 Adapted PRISMA 2020 flow diagram



Key: PRISMA – Preferred Reporting Items for Systematic Review and Meta-Analysis; n – number of records.

The 16 included studies with 23 analyses were published between 2010 and 2022 and came from UK (n=5),[1, 2, 112, 166, 167] Canada (n=3),[168-170] US (n=3),[171-173]

Australia (n=1),[174] China (n=1),[175] France (n=1),[176] Spain (n=1),[177] and Sweden (n=1),[178] Spain (n=1),[177] US (n=3),[171-173] Australia (n=1),[174] France (n=1)[176] and China (n=1).[175] Studies are presented according to the interventions being compared. To identify studies at an increased risk of publication bias, they are reported below according to their source of funding. To facilitate comparisons between studies, ICERs are presented in 2021 Irish Euro for all 16 included records found in the search. Appendix 7 provides a more detailed description of the individual studies and results which are summarised below.

5.1.2.1 rtCGM compared with SMBG

Eleven studies with thirteen analyses compared rtCGM with SMBG (Table 5.2). Five analyses were not industry supported. Of these, three reported ICERs which would be considered not cost effective in Ireland relative to a WTP threshold of €45,000 per QALY gained,[2, 168, 172, 177] with rtCGM considered cost effective in one analysis at this threshold.[2] In the fifth evaluation by NICE which included utility benefits associated with a reduced fear of hypoglycaemia in addition to the utility benefits associated with improved glycaemic control, the reported ICER would be considered cost effective at the lower WTP threshold of €20,000 per QALY gained.[2] Overall, there was substantial variation in the reported ICERs, with adjusted ICERs ranging from approx. €18,000 to €3.292 million.

The seven industry-supported records reporting eight analyses also produced mixed results, ranging from rtCGM being dominated to an adjusted ICER of €112,049. Of these, two reported ICERs that would be considered not cost-effective relative to a WTP threshold of €45,000 per QALY gained,[171, 173] with rtCGM considered cost effective at this threshold based on the reported ICER in one analysis.[169] Four analyses reported ICERs that would be considered cost effective in Ireland at the €20,000 per QALY WTP threshold.[166, 170, 174, 176] In a within-trial analysis, SMBG was reported to dominate rtCGM (that is, SMBG was found to be more effective and less expensive).[173] It should be noted that a finding of rtCGM being cost effective in these industry-supported studies is associated with more recent studies, potentially reflecting the evolving evidence base regarding costs and effectiveness.

5.1.2.2 isCGM compared with SMBG

Six studies with eight analyses were identified comparing isCGM with SMBG (Table 5.3). Four non-industry funded analyses reported ICERs that would be considered cost effective in Ireland at a WTP threshold of €20,000 per QALY gained.[1, 2, 112, 167] The remaining non-industry funded analysis focused on pregnant individuals; isCGM dominated SMBG, that is, it was considered to be more effective and less expensive.[1]

Of the two industry-funded records reporting three analyses for the general population, one reported ICERs that suggest that isCGM is cost effective at the lower WTP threshold of €20,000 per QALY;[175] another reported an ICER which would only be cost effective at the higher WTP threshold of €45,000 per QALY.[178] In the remaining analysis, which focused on a real-world evidence scenario, isCGM dominated SMBG, that is, it was more effective and less expensive.[175]

Table 5.2 Reports of the cost effectiveness of rtCGM compared with SMBG presented in 2021 Irish Euro

Study	Country	Comparison	Adjusted ICER (€/QALY)*
Non-industry funded			
Health Quality Ontario 2018 (population on multiple daily insulin injections)[168]	Canada	rtCGM vs. SMBG	706,576
NICE 2022 (general adult population with T1DM)[2]	UK	rtCGM vs. SMBG (potential utility benefits associated with reduced fear of hypoglycaemia excluded)	27,627
		rtCGM vs. SMBG (potential utility benefits associated with reduced fear of hypoglycaemia included)	18,486
García-Lorenzo 2018[177]	Spain	rtCGM vs. SMBG	3,292,186
McQueen 2011[172]	United States	rtCGM vs. SMBG	53,030
Industry funded			
Chaugule 2017[169]	Canada	rtCGM vs. SMBG	21,765
Huang 2010 (cohort with baseline ≥A1C 7.0%)[171]	United States	rtCGM vs. SMBG	112,049
Isitt 2022[174]	Australia	rtCGM vs. SMBG	10,250
Roze 2020[166]	UK	rtCGM vs. SMBG	11,396
Roze 2021a[170]	Canada	rtCGM vs. SMBG	10,745
Roze 2021b[176]	France	rtCGM vs. SMBG	16,391

Wan 2018[173]	US	rtCGM vs. SMBG within-trial CEA	Intervention was dominated
		rtCGM vs. SMBG long-term CEA	90,782

Key: A1C – glycated haemoglobin; CEA – cost-effectiveness analysis; ICER – incremental cost-effectiveness ratios; QALY – quality–adjusted life year; rtCGM – real time continuous glucose monitor; SMBG - self-monitoring of blood glucose.
*Results were adjusted to 2021 Irish Euro using purchasing power parity and consumer price indices.

Table 5.3 Reports of the cost effectiveness of isCGM compared with SMBG presented in 2021 Irish Euro

Study	Country	Comparison	Adjusted ICER (€/QALY)*
Non-industry funded			
NICE 2020 (pregnant population with T1DM)[1]	UK	isCGM vs. SMBG	Dominant
NICE 2022 (general adult population with T1DM)[2]	UK	isCGM vs. SMBG - potential utility benefits associated with reduced fear of hypoglycaemia excluded	11,483
Health Improvement Scotland 2018[179]	UK	isCGM vs. SMBG – full analysis	3,049
		isCGM vs. SMBG – restricted analysis	15,303
Health Technology Wales 2021[167]	UK	isCGM vs. SMBG	5,492
Industry funded			
Bilir 2018[178]	Sweden	isCGM vs. SMBG	26,710
Zhao 2021[175]	China	isCGM vs. SMBG - RCT scenario	9,042
		isCGM vs. SMBG - RWE scenario	Dominant

Key: ICER – incremental cost-effectiveness ratio; isCGM – intermittently scanned continuous glucose monitoring; QALY – quality–adjusted life year; RCT – randomised controlled trial; RWE – real world evidence; SMBG - self-monitoring of blood glucose;.
*Results were adjusted to 2021 Irish Euro using purchasing power parity and consumer price indices.

5.1.2.3 rtCGM compared with isCGM

Two analyses from two studies directly compared rtCGM and isCGM (Table 5.4). The non-industry funded analysis by NICE, which modelled pregnant women with T1DM, found isCGM to be the dominant option, that is, isCGM was more effective and less costly that rtCGM.[1] The industry-funded analysis by Isitt *et al.* reported an ICER that indicated isCGM to be cost effective relative to rtCGM.[174]

Table 5.4 Reports of the cost effectiveness of rtCGM compared with isCGM presented in 2021 Irish Euro

Study	Country	Intervention	Adjusted ICER (€/QALY)*
Non-industry funded			
NICE 2020 (pregnant population with T1DM)[1]	UK	rtCGM vs. isCGM	Intervention was dominated
Industry funded			
Isitt 2022[174]	Australia	rtCGM vs. isCGM	11,066

Key: ICER – incremental cost-effectiveness ratios; isCGM – intermittently scanned continuous glucose monitoring; QALY – quality–adjusted life year; rtCGM – real time continuous glucose monitoring.
*Results were adjusted to 2021 Irish Euro using purchasing power parity and consumer price indices.

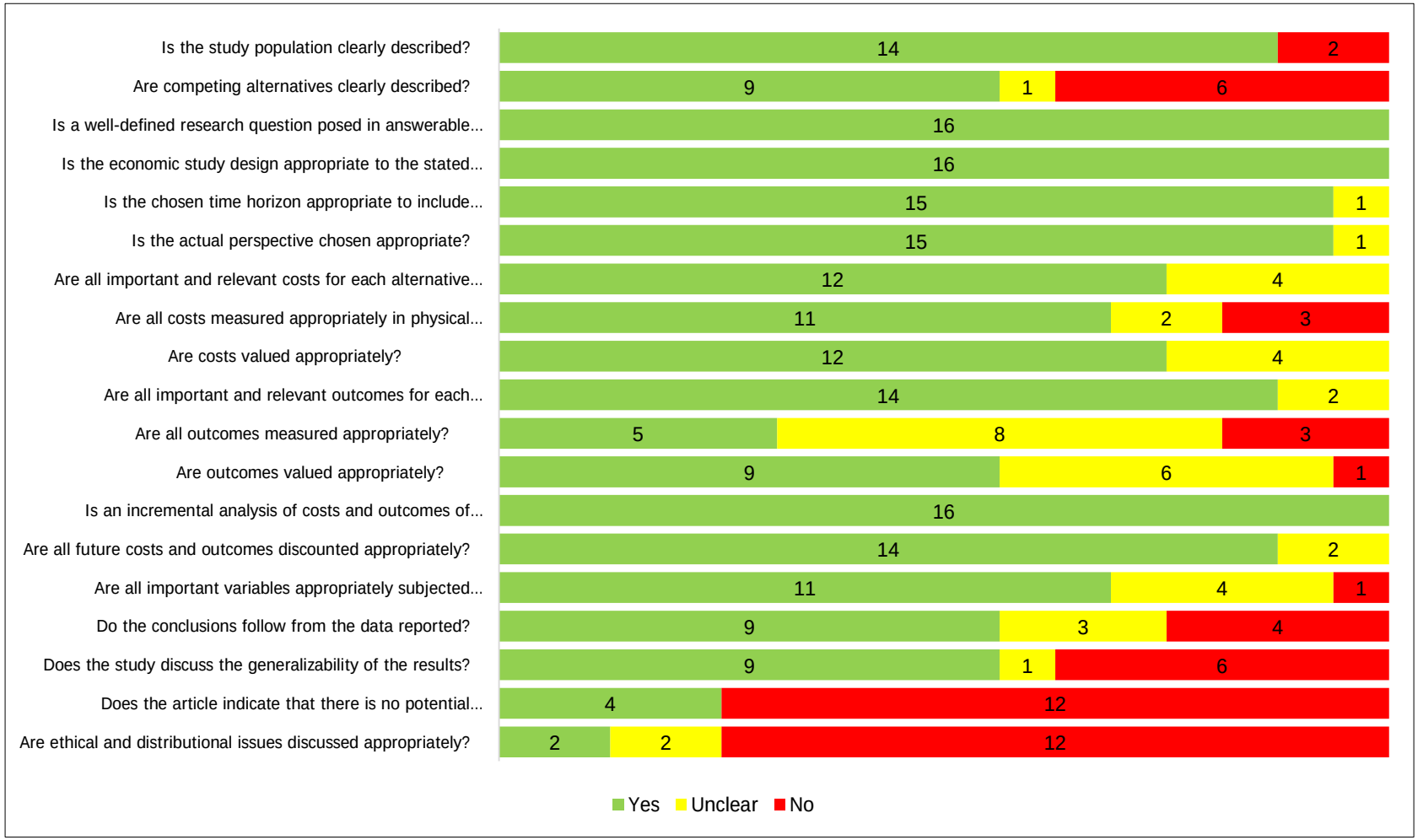
5.1.2.4 Assessment of study methodological quality and applicability

Studies were categorised as high,[1, 2, 112, 168, 169] moderate[167, 171, 173, 175, 177, 178] or low[166, 170, 172, 174, 176] methodological quality according to the CHEC-list questionnaire based on the information provided (Figure 5.2). The accuracy of results is more questionable for lower quality studies.

In a number of studies, the alternative was poorly described. While the alternative was almost always SMBG and therefore, theoretically well understood, from a cost perspective, it is important to know the average number of daily finger prick tests. Studies did not always provide a sufficiently detailed description to know whether the modelled costs for SMBG were reflective of the real-world experience.

Multiple studies did not discuss the generalisability of the results. None of the included studies were set in Ireland, so consideration should be given to the impact of varying health systems, population demographics, and associated differences in costs and outcomes.

Figure 5.2 Methodological quality assessment of economic evaluations using CHEC-list



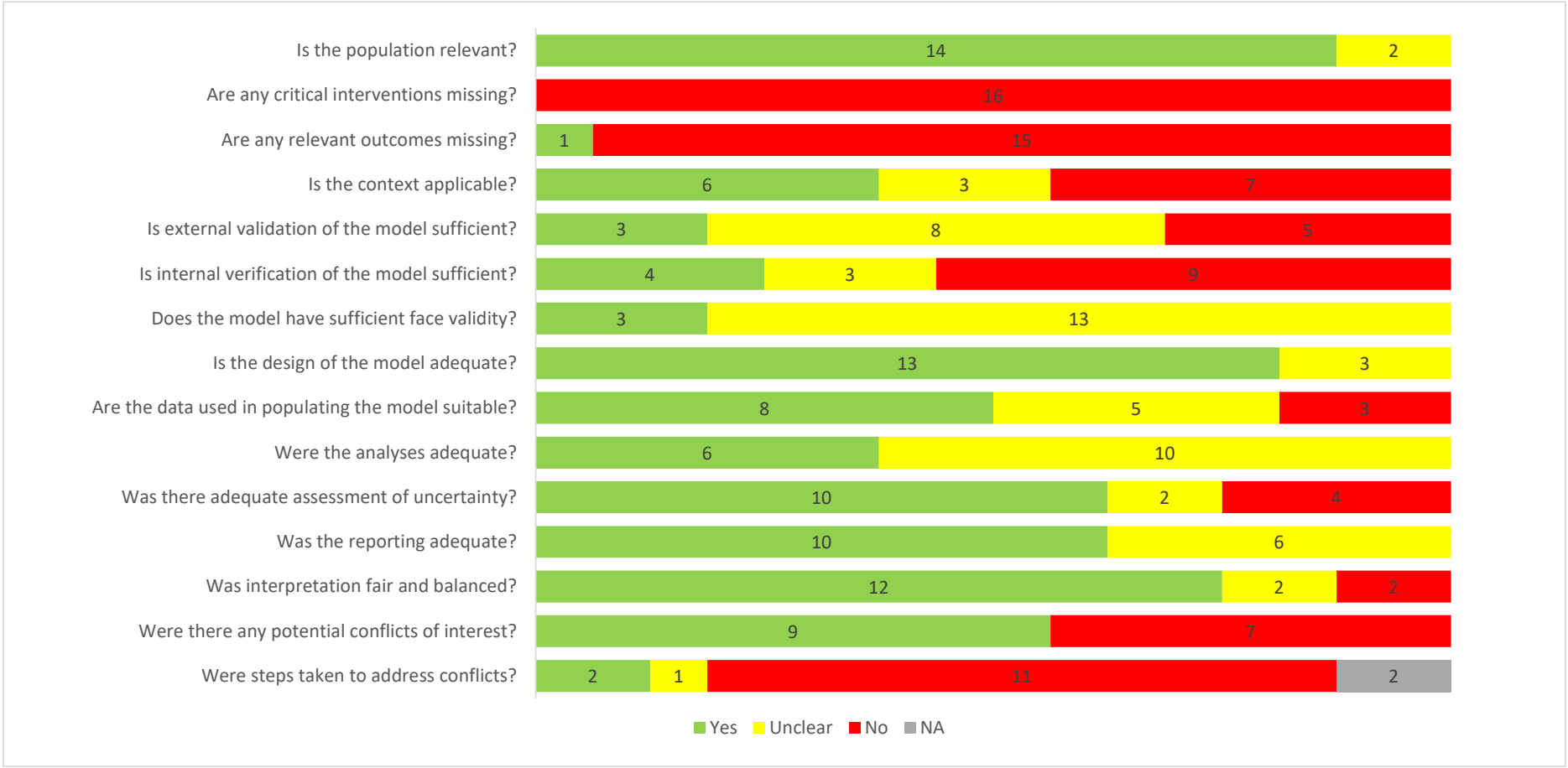
Applicability of the evidence

The ISPOR assessment highlighted several potential areas of concern for the applicability of the evaluations to the Irish context (Figure 5.3). None of the included studies were deemed directly applicable to the Irish setting. Six studies[1, 2, 112, 167, 168, 177] were deemed partially applicable, and ten studies[166, 169-176, 178] were not considered applicable to the context in Ireland for reasons related to industry sponsorship, cost differences, and older studies which do not include interventions that reflect the rapid advancements in CGM functionality.

A large number of the studies, nine of the sixteen, involved industry funding or authors that were either employed by or supported by manufacturers of CGM devices. In most of these studies, the authors did not outline methods they used to address potential conflicts. Industry-supported evaluations are more likely to conclude that an intervention is cost-effective and therefore, the findings of these studies are at risk of bias.[180] There is variable consistency in the findings across the non-industry sponsored studies by agencies for rtCGM when compared to SMBG. Analyses from agencies in Ontario[168] and Spain[177] showed that rtCGM was not cost-effective while NICE[2] showed that it could be cost-effective depending on the WTP threshold used, and those results may be more broadly reflective of what an Irish-specific analysis would find. Generally, across comparisons of CGM with SMBG, more recent studies were more likely to find CGM cost-effective, likely due to the evolving evidence base and costs.

Another common issue across evaluations was a lack of clarity around the outcomes included and the extent to which the modelled values reflected what was seen in practice and in trials. Some studies used recognised or well-established models for disease progression and complications in people with diabetes. These models can project long-term benefits (for example, reduced incidence of complications) through intermediate or surrogate outcomes such as reduced HbA1c. This raises questions about the long-term sustainability of benefits observed in trials with short-term follow-up.

Figure 5.3 Transferability assessment of economic evaluations to the Irish context using the ISPOR questionnaire



5.3 Budget impact estimate

For the purpose of this rapid HTA, an estimate of the budget impact of introducing CGM to all adults with T1DM in Ireland was undertaken. The research question was as follows:

> What is the possible budget impact on the Irish publicly-funded healthcare system for different CGM strategies over the next five years?

This rapid HTA focuses on CGM systems regardless of whether or not they are part of an AID system. The provision of hybrid closed loop systems that combine an insulin pump with CGM was however excluded from the BIA.

5.2.1 Methods

Data sources

Published budget impact analyses, epidemiological data and various costing data sources identified through the course of this rapid HTA were used for the purpose of this budget impact analysis (BIA). This was supplemented by CGM dispensing data provided in confidence by the HSE Primary Care Reimbursement Service (PCRS) and HSE Procurement, as well as publicly available information outlined in Parliamentary Questions (PQs). The source for each parameter is reported below.

The BIA focuses on the three main CGM systems reimbursed in Ireland as of July 2023. In terms of isCGM systems, this specifically relates to Abbott Freestyle Libre®. In terms of rtCGM, this comprises both Dexcom G7 and Medtronic Guardian 4. While other CGM systems are reimbursed (notably, Dexcom G6, Medtronic Enlite and Medtronic Guardian 3), these systems are no longer likely to be recommended for new users, and so were not costed as part of this BIA. However, usage data up until April 2023, inclusive for all reimbursed sensors, helped inform population usage parameters.

Current Irish guidance and reimbursement status

As detailed in Chapter 2.6, since 3 April 2018 the FreeStyle Libre® system has been reimbursed in Ireland for people with T1DM, aged between 4 and 21 years, who meet all of the following eligibility criteria:[181]

- are using multiple daily injections of insulin or insulin pump therapy
- have increased blood glucose testing requirements (≥8 times daily)

- have frequent episodes of diabetic ketoacidosis (DKA) or hypoglycaemia which have included hospital admissions
- are not pregnant.

Of note, the application process does cater for a consultant endocrinologist (or diabetes nurse specialist attached to their service) to make an application for adults with T1DM outside of this group in very exceptional circumstances.[53]

The National Clinical Guideline for adults with type 1 diabetes recommends rtCGM for adults with T1DM who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following, despite optimised use of insulin therapy and conventional blood glucose monitoring:[9]

- More than one episode a year of severe hypoglycaemia with no obviously preventable precipitating cause.
- Complete loss of awareness of hypoglycaemia.
- Frequent (more than two episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities.
- Extreme fear of hypoglycaemia.
- Hyperglycaemia (HbA1c level of 75 mmol/litre [9%] or higher) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of 27 mmol/mol (2.5%) or more.

As detailed in Chapter 2.6, rtCGM is not currently routinely offered to everyone with T1DM but may be reimbursed by the HSE for eligible individuals with diabetes, following an application from a consultant endocrinologist (or diabetes specialist nurse attached to their service).[182] Approval for funding is issued at a local HSE CHO area level rather than centrally.[53] However, in October 2022 the Dexcom G7 sensor compatible with the G7 CGM system, which does not require a separate transmitter, was added to the PCRS list of reimbursable items.[55] Therefore, any patient registered for any PCRS community drug scheme can have the sensors reimbursed subject to a valid prescription. As there is no prior authorisation mechanism, the criteria that have typically applied for reimbursement of CGM (application by a consultant endocrinologist and meeting defined clinical criteria) no longer apply.

Epidemiology

As outlined in Section 3.2, there is currently no national registry of adults living with diabetes in Ireland. Therefore, there is substantial uncertainty surrounding national prevalence and incidence estimates. In a cross-sectional study, Gajewska *et al.* estimated that in 2016, 20,081 people were living with T1DM in Ireland, of which 17,053 (84.9%) were 18 years and older.[77] In the absence of detailed Irish data, the HSE used Scottish Diabetes Register data to estimate that there were 28,800 people living with T1DM in Ireland (with no breakdown by age).[79] Assuming that the proportion of the T1DM population aged 18 years and older is as per the findings of Gajewska et al.[77], that is, that the adult population represents 85% of all persons with T1DM, this would equate to an adult population of approximately 24,480. Given the challenges in estimating the prevalence of T1DM in Ireland, the estimate used here is indicative of the likely population, but may reflect the upper end of the scale and is subject to substantial uncertainty.

For this BIA, it is assumed that all adults aged 18 years and older with T1DM are eligible for either isCGM or rtCGM, with the comparator being SMBG using lancets and test strips. The incremental budget impact is based on the assumption that the increased costs associated with CGM systems is partially offset by a sustained reduction of test strip and lancet usage among CGM users.

Consistent with a conservative approach, the higher population prevalence estimate as provided by the HSE was used given uncertainty around the true national prevalence. Therefore the total eligible population used for the purpose of this BIA was as follows:

- T1DM 18 years and older: ~85% of 28,800 = 24,480

Given the limited comparative data and the fact that current standard of care in adults is SMBG, the different CGM modalities, isCGM and rtCGM, are not directly compared.

It was assumed that the prevalence of T1DM will not change over the course of the five years.

Test strip utilisation

There is substantial variability reported in the literature regarding the average number of daily SMBG tests undertaken by people with T1DM.[167, 183] For the purpose of the base case, data from the IMPACT trial was used, which found that the control group participants used an average of 5.6 SMBG tests per day.[184] Data from this study were selected as it was the first RCT to assess the effect of isCGM on hypoglycaemia in adults with well-controlled T1DM as a replacement for SMBG.

However, as SMBG usage patterns may differ between those with sub-optimally managed T1DM and those who have well-controlled T1DM, it is unclear how representative this figure is of the general adult T1DM population in Ireland. For the purpose of sensitivity analysis, higher (eight per day) and lower (four per day) test rates were modelled.

Current CGM utilisation estimates

Analysis was undertaken by the evaluation team using data provided by the HSE PCRS alongside publicly available information outlined in a PQ, to estimate the number of adults with T1DM using each type of CGM in 2021.[57] As of 30 April 2023, a total of 12,364 unique adults with T1DM aged over 21 years were reimbursed for a CGM system. Considering the adult T1DM population in Ireland to be 24,480, it was estimated that this represents 50.5% of the eligible population. Therefore, it was estimated that 12,116 (49.5%) of the adult T1DM population were not reimbursed for any CGM at this point in time.

Between January and April 2023, among adults 21 years and older for both T1DM and T2DM (data not disaggregated), the number of reimbursed CGM sensors that were dispensed was as follows:

- Dexcom: 10,174 (72% of all reimbursed CGM sensors dispensed)
- Freestyle Libre: 2,082 (15% of all reimbursed CGM sensors dispensed)
- Medtronic: 1,861 (13% of all reimbursed CGM sensors dispensed).

There are some important limitations associated with these data and resulting estimates. Of note, an individual may have been dispensed more than one sensor in the time period. Therefore, these data relate to the number of individual products dispensed rather than the number of unique persons with diabetes in receipt of a CGM sensor. The information provided is based on claims data which have been received by the PCRS from community pharmacists and includes items reimbursed by the PCRS only. In addition, the PCRS does not capture data in relation to diagnosis or indication. With regards to the included data for Dexcom and Medtronic systems, there is no distinction between users who have T1DM or T2DM. However, for the purpose of this BIA, it is assumed based on expert clinical opinion that the number of individuals with T2DM who are using these devices, within this particular dataset, is negligible.[64] In contrast, only individuals with T1DM are eligible for reimbursement for isCGM and so these data relate specifically to this cohort. Given these limitations, in the context of uncertainty regarding the eligible population size, it is important that these reimbursement estimates are viewed with some caution.

Uptake rates

There is uncertainty around how quickly and to what extent those who are not currently reimbursed for CGM will avail of it in the event that eligibility is extended. A BIA published by Health Quality Ontario in 2018 assumed an uptake rate of 15% for isCGM in year one for T1DM, increasing incrementally by 5% each year until it reached 35% by year five.[168] A similar assumption for the uptake of rtCGM was made for this BIA in the base case, starting from a baseline of 50.5% uptake, increasing by an additional 15% in year one and an additional 5% each year thereafter up to a maximum of 85.5% of the total T1DM adult population.

In another assessment, SHTG assumed a 30% uptake in year one, rising incrementally to 50% by year five.[179] Given the uncertainty regarding potential uptake of isCGM and or rtCGM, it is prudent to consider a scenario where there is very high uptake among the eligible Irish population (that is, the adult T1DM population who were not reimbursed for any CGM device as of 30 April 2023). As discussed above, it was estimated that potentially up to 49.5% of all adults with T1DM (n=12,116) were not reimbursed for any CGM system, representing the maximum available additional population as of 30 April 2023. Therefore, the upper limit was capped at an additional 49.5%, as it was not possible to convert anymore individuals from SMBG to CGM at that particular point in time. In scenario analyses, one higher uptake rate was considered. The uptake parameters for isCGM or rtCGM by year are presented in Table 5.5. For simplicity, it was assumed that those who are reimbursed for a particular CGM system do not switch to an alternative CGM system or revert to SMBG for the remaining duration of the five-year period.

Table 5.5 Estimated incremental uptake of isCGM or rtCGM in years 1 to 5

Uptake per year	Year 1	Year 2	Year 3	Year 4	Year 5
Base case: **Moderate** uptake (N=24,480)	3,672 (15%)	4,896 (20%)	6,120 (25%)	7,344 (30%)	8,568 (35%)
Scenario analysis: **Full** uptake (N=24,480)	7,344 (30%)	8,568 (35%)	9,792 (40%)	11,016 (45%)	12,116 (49.5%)

†Upper limit is 49.5% as it is estimated that 50.5% were already reimbursed for a CGM system prior to Year 1

Cost data

Cost data for approved sensors are publicly available through the HSE PCRS website, with additional costs obtained from HSE Procurement.[54, 185] The cost of the FreeStyle Libre® flash sensor to pharmacies is currently €45 (excluding VAT and pharmacy fees), and each sensor lasts for 14 days.[186] As outlined in section 2.5, users of the FreeStyle Libre® system must use the associated reader or the dedicated app on a compatible smart device to view their data, with expert opinion suggesting that almost all CGM users avail of the dedicated app.[54] Therefore it was assumed that the cost to the HSE of readers for FreeStyle Libre® was negligible. Inclusive of pharmacy fees and 23% VAT, the estimated annual cost to the HSE per person of FreeStyle Libre® flash sensors is €1,531.

Of note, pharmacy fees in Ireland vary depending on the volume of dispensing in the individual pharmacy. The pharmacy dispensing fee structure is based on a sliding scale as follows: €5 for the first 1,667 items, €4.50 for the next 833 items, and €3.50 for the remaining items per month. In certain circumstances, when a drug is dispensed on a phased basis, phased dispensing fees may also be claimed. In these cases, a phased dispensing fee of €3.27 per drug item for each dispensing phase other than the first dispensing phase is also payable in addition to the normal dispensing fee. Based on an analysis of published PCRS fee data from January to April 2018, it is currently recommended to apply an average dispensing fee of €5.48 per item on the community drug schemes, and this is what was done for this BIA.[187]

The reimbursement price of Dexcom G7 Sensor is €225 for a pack of three sensors (excluding VAT and pharmacy fees) and each sensor lasts 10 days. There is no

additional cost for a transmitter for Dexcom G7 as it is combined with the sensor.[38] The reimbursement price of Medtronic Guardian Sensor 4 is €495 for a pack of 10 sensors (excluding VAT and pharmacy fees) and each sensor lasts seven days. The transmitter for the Medtronic Guardian 4 needs to be replaced every year, at an additional cost to the HSE. However, this cost is commercially sensitive so it not reported as an individual cost here. As with the situation for the FreeStyle Libre® system outlined above, users of the approved rtCGM systems require the associated reader or the dedicated app on a compatible smart device to view their data. Based on data provided by HSE Procurement, the supply of readers was noted to be negligible, so for simplicity, no additional costs for readers were included in the model.

A HTA previously conducted by HIQA on metabolic surgery for comorbid type 2 diabetes and obesity in 2022 estimated the average costs for test strips and lancets in Ireland, and these data were used in this BIA.[188] Based on an average reimbursement price of €10.95 for a box of 50 test strips, and €6 for a box of 200 lancets, it was estimated that inclusive of pharmacy fees and 23% VAT, an SMBG strategy of 5.6 tests per day would cost the HSE €764 per person per year.

In sensitivity analyses, an SMBG strategy of four and eight tests per day would cost the HSE €562 and €1,023 per person per year in strips and lancets, respectively. As outlined in Chapter 2, those using CGM may still require SMBG, for example, when readings conflict with symptoms or expectations. Clinical guidelines therefore recommend that individuals should be provided with enough test strips to undertake SMBG as needed.[10] No data were available to provide quantitative estimates of co-usage. Therefore, a practical assumption was made by the evaluation team that each CGM user availed of two boxes of 50 test strips and a box of 100 lancets every year, costing the HSE an additional €44.11 per person per year. Of the preferred blood glucose test strips currently recommended by the Medicines Management Programme, most have an open pack expiry of 12 months or more.[63] Specifically, as of February 2023, only one of the 13 preferred blood glucose test strips (Accu-Chek Mobile test cassette) has an open pack expiry of less than six months. However, this particular brand of test strips is considered preferred (or a 'list A product') for existing users only, and as such, use of this particular test strip was assumed to be negligible for the purpose of this BIA.[189] Therefore, it was assumed that two boxes of test strips could last at least a year in those who do not use test strips frequently.

Inclusive of pharmacy fees and 23% VAT, the annual costs to the HSE per person for Dexcom G7 and Medtronic Guardian Sensor 4 are €3,451 and €3,213 (exclusive of transmitter), respectively. As indicated above, based on PCRS data (30 April 2023), there is substantially higher use of Dexcom systems than Medtronic systems

in Ireland (10,174 compared with 1,861) and so a weighted average annual cost per rtCGM system per person (€3,459) inclusive of supplementary blood glucose testing, was used to inform the model. Given that 15.5% of rtCGM sensors dispensed between January and April 2023 used Medtronic systems and so were in need of transmitters, at an additional cost to the HSE, it was assumed that the proportion of rtCGM users requiring an annual transmitter remained constant in the model.

For analyses presented here, given that no additional cost for a dedicated reader was included in the model for the isCGM or rtCGM systems, the incremental cost per person per year stays the same throughout the five-year time period.

Outcome data

Health Technology Wales (HTW) discussed the evidence from RCTs and observational studies regarding the impact of isCGM on patient-related outcomes that affect resource use (for example, reduced incidence of non-severe hypoglycaemic events leading to reduced paramedic callouts and hospital admissions).[167] The HTW assessment team noted that this evidence was inconsistent between RCTs (which found no reduction) and observational studies (which found a reduction). Similarly, for rtCGM, there may be some resource utilisation benefits in certain populations (for example, pregnant women with T1DM), but it is unclear if these benefits (or harms) are realised in all T1DM populations. Importantly, many of the CGM trials permitted participants to use insulin pumps alongside CGM devices. It is not known if this included the use of hybrid closed-loop systems, which combine an insulin pump with CGM, which may have augmented clinical effectiveness outcomes. As stated previously, the provision of hybrid closed loop systems was excluded from the BIA. Therefore for the purpose of this BIA, it is assumed that the efficacy and safety in terms of outcomes that affect resource utilisation are comparable between isCGM, rtCGM and SMBG. The total costs may reflect a conservative estimate of the effectiveness of these devices.

The parameter values for this BIA are outlined in Table 5.6.

Table 5.6 Base case parameter values

Parameter	Value	Source
Target population (≥ 18 years old with T1DM)	24,480 (85% of 28,800)	HSE based on Scottish Diabetes Register, [79] Gajewska et al.[77]
Uptake rates of CGM in years one to five – base case	Additional 15% - 20% - 25% - 30% - 35%	Health Quality Ontario HTA[168]
SMBG daily test frequency in comparator	5.6	IMPACT trial[184]
Daily supplementary test strip use in CGM users	0.27	Assumed
Average reimbursement price for 1 pack of SMBG (50 strips) (ex. 23% VAT and pharmacy fees)	€10.95	PCRS data, HIQA HTA on metabolic surgery[188]
Average reimbursement price for 1 pack of lancets (100 pack/200 pack) (ex. 23% VAT and pharmacy fees)	€3/€6	PCRS data, HIQA HTA on metabolic surgery[188]
Cost to Pharmacy for 1 FreeStyle Libre flash sensor (ex. 23% VAT and pharmacy fees)	€45	FreeStyle Libre Online Portal[186]
Reimbursement price for 3 Dexcom 7 Sensors (ex. 23% VAT and pharmacy fees)	€225	PCRS
Reimbursement price for 10 Medtronic Guardian Sensors 4 (ex. 23% VAT and pharmacy fees)	€495	PCRS
Average pharmacy (dispensing) fee	€5.48	NCPE guidance[187]
Estimated number of adults with T1DM reimbursed by the PCRS for a CGM sensor in 2021	12,364	PCRS data

Key: CGM – continuous glucose monitoring; HIQA – Health Information and Quality Authority; HSE – Health Service Executive, NCPE – National Centre for Pharmacoeconomics, PCRS – Primary Care Reimbursement Service; VAT – value added tax.

5.2.2 Results

In the base case, the five-year incremental cost to the HSE (that is, the cost of extending use of CGM for adults with T1DM) was estimated to be €24.8 million if all of those who newly adopt CGM adopt isCGM and €84.8 million for rtCGM if instead, all those newly adopting CGM adopt rtCGM (Table 5.7). The estimates are based on the assumption that uptake is an additional 15% of the total adult population with T1DM (n = 24,480) in the first year, rising to an additional 35% by the fifth year. It is important to note that these estimates are based on uptake relative to the total estimated adult population with T1DM (n=24,480). As noted in Section 5.2.1, based on PCRS data current as of April 2023, 50.5% of this cohort are already reimbursed for CGM. Therefore, the uptake figures of an additional 15% in year one rising to an additional 35% by year five would reflect a situation in which 65.5% of all individuals with T1DM would have access to CGM in year one rising to 85.5% in year five.

The annual incremental budget impact of isCGM increases from €3 million in year one to €6.95 million in year five. Similarly, the annual incremental budget impact of rtCGM increases from €10.2 million in year one to €23.7 million in year five. As noted, the above estimates are based on the assumption that 100% of those who newly adopt CGM all adopt isCGM or that 100% all adopt to rtCGM. The five-year incremental cost to the HSE would fall somewhere between €24.8 million and €84.8 million should a mix of rtCGM and isCGM systems be adopted.

The annual incremental cost per person in the base case was estimated to be €811 for isCGM and €2,771 for rtCGM. These estimates were based on the assumption that almost all users download the dedicated app for their CGM system on a personal smart device to view their glucose levels; that is, the cost of a reader (which typically would need to be replaced at four-yearly intervals) was excluded from the cost estimate. Given this assumption, the incremental cost per person to the HSE remains the same for each year of use.

Scenario analyses

Where uptake was assumed to increase from an additional 30% in year one to an additional 49.5% in year five (that is, full uptake), the incremental costs to the HSE per population across all five years in the base case were estimated to be €39.6 million for isCGM and €135.3 million for rtCGM (Table 5.8). Given that 50.5% of the cohort are assumed to already be receipt of CGM, this uptake scenario would represent a situation in which 80.5% of adults with T1DM would be in receipt of CGM in year one rising to 100% by year five.

Given the assumptions regarding the requirement for a standalone reader for systems that offer this option, changes in uptake do not impact the incremental cost per person.

The data on rates of SMBG testing are subject to uncertainty, as little is known about the actual rates of testing in the target population. Alternative rates of four and eight times daily were tested. Assuming these higher and lower rates of SMBG testing, the incremental costs were estimated to be:

- isCGM vs. SMBG four times daily: €31 million
- isCGM vs. SMBG eight times daily: €16.9 million
- rtCGM vs. SMBG four times daily: €91 million
- rtCGM vs SMBG eight times daily: €76.9 million.

The annual incremental cost per person in the base case was estimated to be €811 for isCGM and €2,771 for rtCGM. Assuming higher and lower rates of SMBG testing, the annual incremental costs per patient were estimated to be:

- isCGM vs. SMBG four times daily: €1,013
- isCGM vs. SMBG eight times daily: €552
- rtCGM vs. SMBG four times daily: €2,973
- rtCGM vs. SMBG eight times daily: €2,512

The impact of rates of daily testing on the scenario analyses of increased uptake were also explored. For full uptake (increasing from an additional 30% in year one to an additional 49.5% in year five), the incremental costs to the HSE per population across all five years were estimated to be:

- isCGM vs. SMBG four times daily: €49.6 million
- isCGM vs. SMBG eight times daily: €27 million
- rtCGM vs. SMBG four times daily: €145.2 million
- rtCGM vs SMBG eight times daily: €122.7 million

Table 5.7 Estimated incremental costs per testing strategy, for total population (low uptake - ranging from an additional 15% in year 1 to an additional 35% in year 5)

Incremental cost per total population	Year 1 (€)	Year 2 (€)	Year 3 (€)	Year 4 (€)	Year 5 (€)	Total: years 1-5 (€)
isCGM vs. SMBG (5.6 times daily) (base case)	2,978,792	3,971,722	4,964,653	5,957,584	6,950,514	24,823,265
rtCGM vs. SMBG (5.6 times daily) (base case)	10,173,458	13,564,611	16,955,764	20,346,917	23,738,069	84,778,819

Key: isCGM, intermittently scanned continuous blood glucose; rtCGM, real-time continuous blood glucose; SMBG, self-monitored blood glucose.

Table 5.8 Scenario analysis 1: Full uptake (ranging from an additional 30% in year 1 to an additional 49.5% in year 5).
Estimated incremental costs per testing strategy, for total population

Incremental cost per total population	Year 1 (€)	Year 2 (€)	Year 3 (€)	Year 4 (€)	Year 5 (€)	Total: years 1-5 (€)
isCGM vs. SMBG (5.6 times daily) (base case)	5,957,584	6,950,514	7,943,445	8,936,375	9,828,715	39,616,633
rtCGM vs. SMBG (5.6 times daily) (base case)	20,346,917	23,738,069	27,129,222	30,520,375	33,567,979	135,302,562

Key: isCGM, intermittently scanned continuous blood glucose; rtCGM, real-time continuous blood glucose; SMBG, self-monitored blood glucose.

Table 5.9 Scenario analysis 2: alternative rates of test strip usage in SMBG (4 times daily, 8 times daily; low uptake - ranging from an additional 15% in year 1 to an additional 35% in year 5). Estimated incremental costs per testing strategy, for total population

Incremental cost per total population	Year 1 (€)	Year 2 (€)	Year 3 (€)	Year 4 (€)	Year 5 (€)	Total: years 1-5 (€)
isCGM vs. SMBG (4 times daily)	3,720,397	4,960,529	6,200,662	7,440,794	8,680,926	31,003,309
isCGM vs. SMBG (8 times daily)	2,028,564	2,704,752	3,380,939	4,057,127	4,733,315	16,904,697
rtCGM vs. SMBG (4 times daily)	10,915,064	14,553,418	18,191,773	21,830,127	25,468,482	90,958,863
rtCGM vs. SMBG (8 times daily)	9,223,230	12,297,640	15,372,050	18,446,460	21,520,870	76,860,251

Key: isCGM, intermittently scanned continuous blood glucose; rtCGM, real-time continuous blood glucose; SMBG, self-monitored blood glucose.

5.4 Discussion

This chapter sought to review the international published evidence of the cost-effectiveness of CGM systems and to estimate the potential incremental budget impact of reimbursing CGM systems for adults with T1DM in Ireland.

5.3.1 Review of cost-effectiveness studies

The review of economic evidence included 16 evaluations from a variety of countries. Among industry and non-industry funded evaluations, there was a relatively consistent finding of isCGM being cost-effective relative to SMBG. The evidence relating to rtCGM was less consistent, with several studies suggesting that it is not cost-effective relative to SMBG. Two evaluations that considered the comparison of isCGM and rtCGM found that isCGM is the cost-effective option.

The NICE model published in 2022 is the most recent non-industry supported evaluation and thus may include the most recently available evidence of clinical effectiveness. The benefits accruing to the CGM over SMBG in that report are driven by reduced rates of severe and non-severe hypoglycaemic events and also lower HbA1c levels in people using rtCGM. Long-term benefits are modelled through a combination of direct utility gains (through reduced incidence of hypoglycaemic events) and indirect gains through reduced complications (for example, stroke, myocardial infarction, amputation, and diabetic retinopathy) over the longer-term. The longer-term benefits are modelled based on the understanding of the association between HbA1c levels and future risk of complications. The NICE evaluation used the IQVIA CD model to conduct the economic modelling, which is well-established and has been used widely.[190] However, modelling long-term benefits based on short-term, intermediate outcomes increases uncertainty and also requires implicit assumptions about the sustainability of those benefits. In this case, sustained reductions in HbA1c with rtCGM were assumed relative to SMBG. The evaluation included sensitivity analyses that explored the impact of changing this assumption, and a reduced period of effectiveness resulted in an increased ICER that would make the intervention no longer cost-effective.

There was heterogeneity across the studies in terms of the input parameters, assumptions and model structures. Some of the heterogeneity may be explained by the timing of the studies and the evidence base that was available at that time. The studies encompass a wide range of countries with differing healthcare systems and typical unit costs. The relative consistency in findings across studies regarding isCGM may give some confidence that the intervention may be cost-effective for people with T1DM in an Irish setting. However, based on the NICE model, the benefits accruing to isCGM are limited to the impact of a reduced incidence in hypoglycaemic events. Another parameter that impacted on cost-effectiveness was the rate of

SMBG use: scenarios where SMBG use is high are more likely to find CGM systems cost-effective. Of note, it has not been possible to accurately estimate typical SMBG usage in Ireland, so it is not possible to determine the applicability of the findings to Ireland.

5.3.2 Budget impact analysis

This BIA estimated that introduction of isCGM or rtCGM to an additional 35% of eligible adults with T1DM would cost the HSE an additional €24.8 million and €84.8 million, respectively, over the next five years, under the assumption that approximately 50.5% of the T1DM population were already in receipt of CGM as of 30 April 2023. The incremental cost to the HSE would fall somewhere between €24.8 million and €84.8 million should a mix of rtCGM and isCGM systems be rolled out. However, the cost estimates vary substantially depending on the uptake rate and the level of testing in the SMBG comparator. For the base case, it was assumed that those in the SMBG comparator group used an average of 5.6 SMBG tests per day, while scenario analyses considered low (four tests daily) and high (eight times daily) testing alternatives. Higher rates of testing in the SMBG comparator group reduces the incremental cost of CGM. Incremental cost estimates range from €16.9 million and €76.9 million respectively for isCGM and rtCGM, for scenarios of low uptake and high baseline SMBG test rates, up to €49.5 million and €145.2 million for isCGM and rtCGM, respectively for scenarios of high uptake and low baseline SMBG test rates.

Diabetes Ireland submitted a 2023 pre-budget submission to the Government on September 2022.[191] In their submission they call for the extension of the "eligibility for Flash glucose monitoring to all people with diabetes, based on clinical need." In its submission, Diabetes Ireland argues that "this technology allows people using insulin to more effectively manage their blood sugar levels and has been clinically demonstrated to reduce diabetes-related hospital admission."

There are some important limitations associated with this BIA.

- First, it was assumed that the use of CGM did not impact (positively or negatively) on healthcare resource use. Evidence of increased or decreased resource use associated with either isCGM or for rtCGM would change the total and incremental costs.

- Second, given the lack of a national diabetes registry in Ireland, it is not possible to provide an exact estimate of T1DM prevalence. For the budget impact presented here, the figures are consistent with what has been reported elsewhere by the HSE in response to a parliamentary question.[79] In the absence of recent applicable Irish data, there is substantial uncertainty regarding the prevalence of T1DM in adults in Ireland. The estimates used for

this analysis are based on Scottish data, which provide a higher prevalence estimate than has been previously reported for Ireland and therefore reflect a worst case scenario approach to estimating the potential budget impact. While the data on currently reimbursed devices are available, the critical gap is in the estimate of adults with T1DM not currently reimbursed for CGM. A ten percent error in the T1DM population estimate leads to an approximately 15% error in the absolute budget impact. It was also assumed that the population with T1DM would remain static over the course of the five years which may not be the case given the increasing population of Ireland as a whole.

- Third, the budget impact assumes that the cost of a proprietary CGM device (reader) does not accrue to the HSE, while the costs to the HSE are limited to the costs of the consumables (sensors) and transmitter, where needed. If the cost of the readers accrues to the HSE, overall costs would increase reflecting an increased upfront cost for individuals commencing on CGM and also a cost to replace readers over time. Individuals may already have access to a compatible smartphone and can use this to scan and access their data after downloading the relevant company app; expert opinion is that CGM users rarely need to avail of a reader.[54] Current reimbursement costs of the sensors to the HSE per patient per annum (inclusive of VAT and pharmacy fees) and supplementary blood glucose test strips and lancets are €1,576 for isCGM and a weighted average of €3,415 for rtCGM (exclusive of transmitter costs). The analysis presented here is based on the CGM systems available at the time of assessment. The technologies are under constant development and subject to change. New systems that incorporate additional or different functionality, such as hybrid systems, were not considered here and could be associated with increased costs that would have implications for the budget impact of CGM.

- Fourth, minimal supplementary blood glucose testing among GGM users was also assumed given the intention that these CGM systems replace SMBG. However, if there are greater levels of supplementary blood glucose testing than assumed, then overall costs to the HSE would increase reflecting additional costs due to greater usage of test strips and lancets.

- Fifth, the CGM utilisation data do not differentiate between T1DM and T2DM users, so it is possible that the number of adults with T1DM already reimbursed for CGM may be slightly lower than the figure used for the purpose of the BIA (n=12,364).

- Sixth, the BIA did not model the impact of changing from one CGM system to another (or from CGM back to SMBG). Given the cost differentials, switching to an economically advantageous CGM system, where clinically appropriate, may result in cost savings for the HSE.

- Finally, given the exploratory nature of this rapid HTA, limited scenario or sensitivity analyses were conducted. In the context of a full HTA, scenario analyses for a range of plausible scenarios and sensitivity analysis may be employed to systematically evaluate the level of uncertainty in the budget estimates, due to uncertainty associated with the model and the key parameters that inform it.[192]

6 Published recommendations for CGM from the UK

Key points

- The current Irish National Clinical Guideline for adults with type 1 diabetes mellitus (T1DM) are based on a contextualisation of 2015 guidelines from the UK's National Institute for Health and Care Excellence (NICE). A targeted search was undertaken for updated UK recommendations and guidelines on the use of continuous glucose monitoring (CGM) in individuals with T1DM.
- **T1DM in adults**
  - NICE recommends that adults with T1DM be offered a choice of real-time continuous glucose monitoring (rtCGM) or intermittently scanned continuous glucose monitoring (isCGM), based on their individual preferences, needs, characteristics, and the functionality of the devices available. Where multiple devices meet their needs or preferences, the cheapest device should be used. rtCGM is recommended as an option for those with impaired hypoglycaemia awareness.
  - The NICE guideline also recommends that CGM:
    - should be provided by a team with expertise in its use, as part of supporting people to self-manage their diabetes
    - is included as part of a structured education programme to be provided to all adults with T1DM, and to ensure that people are empowered to use CGM devices
    - use by the individual should be monitored and reviewed as part of reviewing their diabetes care plan (plan reviewed annually).
  - Health Improvement Scotland has issued specific guidance with respect to isCGM using FreeStyle Libre®, recommending that it be made available for individuals with diabetes who are actively engaged in the management of their diabetes and who intensively manage their condition with multiple daily insulin injections or insulin pump therapy. With respect to rtCGM, no update was identified to the 2017 guidelines (which note that CGM should not be used routinely in individuals with diabetes).
  - Health Technology Wales has also issued specific recommendations with respect to isCGM with FreeStyle Libre®, noting that it should be made routinely available for people with diabetes (of any type) who require treatment with insulin.

- **T1DM in pregnancy**
  - For pregnant women, guidance on CGM has been issued by NICE, Healthcare Improvement Scotland, and Health Technology Wales, with all three recommending the use of rtCGM.
  - NICE guidance in 2020 stated that rtCGM should be offered to all pregnant women with T1DM with the goal of meeting pregnancy blood glucose targets and improving neonatal outcomes. However, for women who are unable to use rtCGM, or where a clear preference for isCGM is expressed, NICE recommended that isCGM is to be offered.

6.1 Introduction

As outlined in the terms of reference, in this chapter we summarise the recommendations in UK guidance regarding continuous glucose monitoring (CGM) for adults with type 1 diabetes (T1DM). Guidelines and recommendations on the use of CGM in adults with T1DM were identified from several UK institutions, comprising recommendations from the National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland and associated bodies, and guidance from Health Technology Wales. This chapter provides a brief overview of advice and or recommendations in these reports in relation to both real time CGM (rtCGM) and intermittently scanned CGM (isCGM) and, where available, the rationale underpinning same. As per the other chapters of this rapid HTA, a systematic search was not performed.

The following sources of recommendations in the UK on the topic of CGM (rtCGM, isCGM) in T1DM were identified:

- two national clinical guidelines from NICE: NG17 and NG3
- a national clinical guideline from the Scottish Intercollegiate Guidelines Network (SIGN), a recommendation document, and an advice statement from the Scottish Health Technologies Group (SHTG) at Healthcare Improvement Scotland
- guidance from Health Technology Wales (HTW).

These documents are summarised in Table 6.1 and as follows.

6.2 NICE guidelines

- A **NICE guideline (NG17)** on the diagnosis and management of T1DM in adults was first published in August 2015.[10] At this time, the guideline stated that rtCGM should not be offered routinely to adults with T1DM. Rather, rtCGM was to

be considered for adults with T1DM who were willing to commit to using it at least 70% of the time and to calibrate it as needed, and in the context of any of a series of factors being present despite optimised insulin therapy and conventional self-monitoring of blood glucose (SMBG) using capillary blood glucose measurements.

Furthermore, the guideline highlighted that rtCGM should be continued only if HbA1c could be sustained at or below 53 mmol/mol (7%) and or there had been a fall in HbA1c of 27 mmol/mol (2.5%) or more. Specific recommendations were also given with respect to individuals with impaired hypoglycaemia awareness given its association with a significantly increased risk of severe hypoglycaemia; use of rtCGM was identified as one of the options to avoid hypoglycaemia in this cohort.

This guideline was updated in March 2022 with several recommendations on CGM being made within this update; this followed a review of evidence on diagnosis of T1DM and on CGM. More recent updates of the guideline took place in June 2022 and August 2022 and included recommendations that are outside of the scope of the present rapid HTA (recommendations pertaining to periodontitis and updates relating to control of blood pressure). The relevant March 2022 guideline sections are recommendations 1.6.10 to 1.6.18 of the guideline. Specifically in relation to what is to be offered, the recommendations state:

- Adults with T1DM are to be offered a choice of rtCGM or isCGM, based on their individual preferences, needs, characteristics, and the functionality of the devices available.
- If a person cannot or does not want rtCGM or isCGM, they are to be offered SMBG.

In choosing a CGM device, the 2022 recommendations specify that where multiple devices meet their needs and preferences, they should be offered the device with the lowest cost.

The specific recommendation regarding potential use of rtCGM in individuals with impaired glycaemic awareness was retained in the March 2022 update.

The 2022 NICE guideline updates also recommend that CGM:

- should be provided by a team with expertise in its use, as part of supporting people to self-manage their diabetes
- is included as part of a structured education programme to be provided to all adults with T1DM, and to ensure that people are empowered to use CGM devices
- use by the individual should be monitored and reviewed as part of reviewing their diabetes care plan (plan reviewed annually).

The 2022 updates reiterate the recommendation that adults using CGM will still need undertake capillary blood glucose measurements (SMBG) although this can be done less frequently. With respect to blood glucose management generally, the guideline notes that adults with T1DM should be taught how to measure their blood glucose level, interpret the results and take appropriate action (with these skills to be reviewed at least annually) and supported through structured education in how to make the best use of data from self-monitoring of blood glucose. (193)

The **NICE guideline (NG3)** on management of diabetes in pregnancy from preconception to the postnatal period was first published in February 2015 and last updated in December 2020.(14) In relation to CGM, the guideline states that rtCGM should be offered to all pregnant women with T1DM to help them meet their pregnancy blood glucose targets and to improve neonatal outcomes. For women with T1DM who are unable to use rtCGM, or where a clear preference for isCGM is expressed, isCGM is to be offered.

Rationale for recommendations

The rationale for the decision-making by the NICE guideline committees is summarised for each of NG17(2) and NG3(194) within the associated evidence reviews.

In the case of **NG17**, overall, the committee considered that the clinical evidence base for rtCGM and isCGM could have been greater and of a higher quality. The committee concluded that the evidence of clinical effectiveness on key outcomes, when combined with the positive health economic results, was sufficient to justify the recommendations. The guideline committee stated that there was agreement that there was enough evidence in relation to key outcomes (including glycated haemoglobin (HbA1c), time in range, and severe or nocturnal hypoglycaemia) to demonstrate that both rtCGM and isCGM were clinically beneficial over SMBG. The evidence was noted to be lacking for isCGM and, given the rapid advances in the technology, the NICE guideline committee made a research recommendation to investigate using routinely collected real-world data to examine the effectiveness and cost effectiveness of CGM. The evidence for rtCGM versus isCGM was not considered sufficient to demonstrate a benefit of one of these technology classes over the other. Also, CGM technologies were changing rapidly at the time of the evidence review and there was found to be notably increasing overlap between rtCGM and isCGM, for example, with the addition of predictive alerts to newer isCGM devices. Considering cost effectiveness, both technologies were identified as being cost effective for the full population of adults with T1DM compared with SMBG when the benefit of reduced fear of hypoglycaemia was also considered. Based on these factors and their review of the evidence, the committee agreed that there was no advantage to recommending a specific device compared with SMBG, and that the specific functionality of isCGM versus rtCGM should be discussed as part of shared decision-making. It was also considered that there are benefits of providing a choice

of different CGM devices as the most suitable device is unique to an individual and their specific circumstances. Providing choice was considered important as it was expected that adherence is likely to be higher if the device is matched to the person's needs and preferences. With respect to the impact of the recommendations, NICE noted that the recommendations would likely result in broader access to isCGM and rtCGM devices, as opposed to 'a binary decision on access based on stringent criteria'. The 2015 recommendation with respect to the use of rtCGM in adults with impaired glycaemic awareness, which was retained in the 2022 update, was based at the time on limited low quality evidence from two case series of an improvement in the rate of severe hypoglycaemia and inconsistent evidence of improved hypoglycaemia awareness.

In the case of **NG3**, the guideline committee considered comparisons of rtCGM with isCGM and with SMBG for pregnant women with T1DM.[14] When compared with SMBG, rtCGM was noted to result in improved control of blood glucose, fewer caesarean sections and fewer neonatal intensive care unit admissions. There were no studies identified that compared isCGM with SMBG. Only one retrospective study was found which compared rtCGM and isCGM. The NICE evidence review group found that they could not differentiate between the two monitoring systems based on this evidence. Considering isCGM, economic evaluation demonstrated that this was the least costly of the three glucose monitoring options, but was associated with lower certainty of relative benefit compared with rtCGM. Notably, there was a high level of certainty that SMBG is associated with the highest cost and lowest incremental quality-adjusted life years (QALYs) gained in all scenarios, due to associated higher delivery costs (greater proportion of pregnant women requiring caesarean sections) and higher neonatal care costs. Additionally, the committee had concerns regarding the accuracy of isCGM and the requirement for multiple finger-pricks for safe use of isCGM. Due to the uncertainties in the evidence, the committee concluded that isCGM could not be recommended for use in pregnancy and instead favoured rtCGM.

6.3 Healthcare Improvement Scotland

Healthcare Improvement Scotland first published the Scottish Intercollegiate Guidelines Network guideline **SIGN 116** ('Management of diabetes: A national clinical guideline') in 2010, which was updated most recently in 2017.[195] The updated guideline stated that CGM may be a useful adjuvant to conventional SMBG in selected adults with T1DM as an aid to improve glycaemic control. However, the evidence on the value of CGM in people with T1DM was noted to be conflicting and it was stated that further research was required to identify the groups who would gain most benefit. As such, the guideline concluded that CGM should not be used routinely in people with diabetes.

Subsequently, in July 2018, Healthcare Improvement Scotland published an **advice statement on the clinical and cost effectiveness of FreeStyle Libre®** isCGM. The advice recommended that isCGM with FreeStyle Libre® be available for individuals with diabetes who are actively engaged in the management of their diabetes and who intensively manage their condition with multiple daily insulin injections or insulin pump therapy. It was stated that the use of this technology was not intended to completely replace SMBG; for example, it was noted that the technology is not indicated for individuals whose condition requires continuous monitoring of blood glucose. The advice document considered clinical effectiveness, safety, cost effectiveness, a patient group submission from Diabetes Scotland, and organisational issues.

With respect to use of CGM in pregnancy, the **Scottish Health Technologies Group** of Healthcare Improvement Scotland made, in November 2020, a recommendation for NHS Scotland on the topic of rtCGM (described within the document using the term 'CGM') in pregnant women with T1DM. This recommendation was based on an adaptation of guidance published by Health Technology Wales in 2019 (see below). Pregnant women with T1DM were noted as being considered among the highest priority for rtCGM, for which the Scottish Government had provided policy support for use in diabetes. The SHTG recommendation stated that rtCGM should be offered to all pregnant women with T1DM, and that this was supported by the clinical evidence (based on the 2019 Health Technology Wales guidance).

6.4 Health Technology Wales

In September 2019, Health Technology Wales issued guidance (guidance no. 012) on the use of rtCGM in pregnant women with T1DM.[196] Following an evidence appraisal, it was concluded that the case for adopting rtCGM in this population was supported by the evidence.

In July 2021, Health Technology Wales issued guidance (guidance no. 004-2) on the use of the FreeStyle Libre® isCGM technology to guide blood glucose regulation in people with diabetes who require treatment with insulin. Following an evidence appraisal, the panel concluded that the clinical and cost-effectiveness evidence supported the routine adoption of this technology for people with diabetes (of any type) who require treatment with insulin. It was noted by the panel that there are a range of additional specific scenarios in which this technology may also potentially offer benefit. These were stated as including:

- 'people who cannot use current forms of glucose monitoring, or for whom use may be distressing, such as those with dementia, learning disabilities or needle phobias

- people who need extra care or assistance with glucose monitoring, such as children or the elderly
- people who need a course of intensive glucose monitoring in order to assist treatment decisions'.

Table 6.1 UK recommendations and guidance on glucose monitoring

	T1DM Population Groups	
Institution and relevant documents	**Guidance for adults**	**Guidance for pregnant individuals**
NICE • NG17: Type 1 diabetes in adults (March 2022 update)[10] • NG3:Diabetes in pregnancy (December 2020 update)[14] Note: while outside the remit of this HTA, NICE guidance on insulin pumps is in the process of being updated [197]	Offer rtCGM or isCGM, based on individual preferences, needs, characteristics, and the functionality of the devices available or Offer SMBG if person cannot use, or does not want rtCGM or isCGM. When choosing a CGM device: • Use shared decision making to identify the person's needs and preferences and offer them an appropriate device • If multiple devices meet their needs and preferences, offer the device with the lowest cost. Ways to avoid hypoglycaemia in adults with impaired hypoglycaemia awareness should be prioritised including the offering of rtCGM.	rtCGM for all or isCGM if preferred or if unable to use rtCGM
Healthcare Improvement Scotland: SIGN • NCG116 Management of diabetes (2010 updated 2017)[195] Note: glucose monitoring content is currently under review and it is estimated that new guidelines on type 1 diabetes will be published in Autumn 2024.[198]	rtCGM should not be used routinely in people with diabetes. SMBG is recommended for people with diabetes using insulin where individuals have been educated in appropriate alterations in insulin dose	rtCGM may be considered

	T1DM Population Groups	
Institution and relevant documents	**Guidance for adults**	**Guidance for pregnant individuals**
Healthcare Improvement Scotland: Scottish Health Technologies Group • Advice statement 009-18: FreeStyle Libre flash glucose monitoring (July 2018)*[179]	"It is recommended that flash glucose monitoring with FreeStyle Libre® is available for individuals with diabetes who are actively engaged in the management of their diabetes and who intensively manage their condition with multiple daily insulin injections or insulin pump therapy… …FreeStyle Libre® is not indicated for patients whose condition requires continuous monitoring of blood glucose."	
Healthcare Improvement Scotland: Scottish Health Technologies Group • SHTG Adaptation 01: Continuous glucose monitoring in pregnant women with type 1 diabetes (November 2020)[199]	N/A	rtCGM should be offered to all. "The case for adopting CGM in pregnant women with T1DM is supported by the clinical evidence." (Adapted from Health Technology Wales guidance 012)
Health Technology Wales • Guidance 012: CGM in pregnant women with T1DM (September 2019)[196]	N/A	The case for adopting rtCGM is supported by the evidence.
Health Technology Wales • Guidance 004-2: FreeStyle Libre flash glucose monitoring (FLGFM) (July 2021)*[200]	The evidence supports the adoption of FreeStyle Libre® isCGM "to guide blood glucose regulation in people with diabetes who require treatment with insulin". The Appraisal panel noted that there are a range of additional specific scenarios in which this technology may also potentially offer benefit, such as: - "people who cannot use current forms of glucose monitoring, or for whom use may be distressing, such as those with dementia, learning disabilities or needle phobias; - people who need extra care or assistance with glucose monitoring, such as children or the elderly; - people who need a course of intensive glucose monitoring in order to assist treatment decisions."	

Key: CGM - continuous glucose monitoring; HTW – Health Technology Wales; isCGM – intermittently scanned continuous glucose monitoring; NCG – national clinical guideline; NG – national guideline; NICE – National Institute for Health and Care Excellence; rtCGM – real time continuous glucose monitoring; SIGN - Scottish Intercollegiate Guidelines Network; SMBG – self-monitoring of blood glucose; SHTG - Scottish Health Technologies Group; T1DM – type 1 diabetes mellitus.
*Not limited to T1DM.

6.5 Discussion

This chapter briefly summarises recent guidance from the UK with respect to the use of CGM in people with T1DM. In the context of this rapid HTA, a systematic review was not undertaken; rather, an emphasis was placed on describing guidelines and recommendations from the UK and the rationale underpinning same. This choice was made due to current Irish guidelines for the management of people with T1DM being based on a contextualisation of NICE guidance issued in 2015. NICE guidelines, and guidance from Healthcare Improvement Scotland and Health Technology Wales, distinguish between the use of CGM in the general population with T1DM versus use in pregnant women with T1DM.

For the general population with T1DM, the most recently updated guidance from the UK comprises that issued by NICE in March 2022, which recommends that adults with T1DM be offered a choice of rtCGM or isCGM, based on their individual preferences, needs, characteristics, and the functionality of the devices available. The associated committee considered that the evidence demonstrated that both rtCGM and isCGM were clinically beneficial over SMBG, but that the evidence for rtCGM versus isCGM was not considered sufficient to demonstrate a benefit of one of these technology classes over the other. It is noted however that recommendations specific to individuals with impaired awareness of hypoglycaemia specify rtCGM as a potential option to support the individual in avoiding hypoglycaemia.

Other previous guidance from the UK for the general population of adults with T1DM has issued recommendations on rtCGM and isCGM separately. Considering isCGM, guidance on the use of the FreeStyle Libre® device was issued in 2018 by Healthcare Improvement Scotland, and in 2021 by Health Technology Wales. The SIGN guideline issued in 2018 concluded that rtCGM may be a useful adjuvant to conventional SMBG in selected adults with T1DM but that the evidence was conflicting and that further research was required to identify the groups of individuals who would gain most benefit.

For pregnant women, guidance on CGM has been published by NICE, Healthcare Improvement Scotland, and Health Technology Wales. NICE guidelines in 2020 stated that rtCGM should be offered to all pregnant women with T1DM with the goal of meeting pregnancy blood glucose targets and improving neonatal outcomes. For women with T1DM who are unable to use rtCGM, or where a clear preference for isCGM is expressed, NICE recommended that isCGM is to be offered. Similarly, Health Technology Wales concluded that the case for adopting rtCGM in this population was supported by the evidence, a position which was echoed by the Scottish Health Technologies Group in 2020.

Approaches to decision-making for guidance on the topic of CGM have differed between agencies and over time. For example, the most recent recommendations published by NICE, which include a broad recommendation for use of either rtCGM or isCGM by all people with T1DM, was noted by the committee as being likely to result in broader access to isCGM and rtCGM devices, as opposed to 'a binary decision on access based on stringent criteria'. This guidance contrasts with that issued previously; the 2015 iteration of the NICE guidelines on CGM recommended that rtCGM not be issued routinely and be considered instead for people with T1DM who meet specific criteria. Similarly, guidance from Scotland in 2018 found that the evidence on the value of CGM in people with T1DM was conflicting and that further research was required to identify the groups of people who would gain most benefit before a positive recommendation could be made. In this sense, the most recent update to the NICE guideline represents a departure, which may be influenced by the advent of more recent clinical effectiveness evidence and increased similarity of some of the features of isCGM versus rtCGM (as highlighted by the NICE committee) alongside concerns regarding access to CGM technologies, including considerations relating to equity. It is noted in particular in the NICE guideline that there are benefits of providing a choice of different CGM devices, with a view to improving adherence, as the most suitable device for an individual is likely to depend on a range of factors. However, additional considerations for decision-makers include feasibility and budget impact.

It may be of interest to compare the above recommendations by health authorities with those positions adopted by professional societies involved in the management of T1DM. A consensus report on the management of T1DM in adults was published by the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) in 2021.[201] CGM was noted as being the standard for glucose monitoring for most adults with T1DM. The report notes that rtCGM is effective for adults with T1DM (both those using insulin pumps or those using multiple daily injections) in improving HbA1c (particularly when high) and in reducing hypoglycaemia, and that, while RCTs of the original isCGM devices show more mixed results, observational data suggest it is effective. In addition to consideration of effectiveness data, the consensus report states that the choice of the device should be based on individual preferences and circumstances. Furthermore, it is noted that some people may feel that they do not require CGM or find the device stressful for a variety of reasons (feeling 'attached to a device', perceiving a constant reminder of their diabetes, or fatigue resulting from the device alarms) and that cost considerations can also play a role.

Considering other recent international guidance, in 2021, the Diabetes Canada Clinical Practice Guidelines Group issued an update of their 'Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada' specifically

with respect to monitoring glycaemic control.[202] The guidelines recommend that individuals with T1DM using basal-bolus insulin therapy (or insulin pump technology), who are willing and able to use these devices on a nearly daily basis, should use rtCGM to reduce A1C and increase time in range, reduce duration and incidence of hypoglycaemia, improve aspects of diabetes-specific quality of life, and increase treatment satisfaction. The guidelines also advise that isCGM may be used to increase time in range, reduce frequency and duration of hypoglycaemia, and increase treatment satisfaction. In adults with type 1 diabetes with impaired awareness of hypoglycaemia or recent severe hypoglycaemia, rtCGM is recommended.

These Canadian guidelines recognised the ability of new additional glucose metrics to be generated through CGM including time in range, time above range, time below range and glycaemic variability (standard deviation or coefficient of variation).[202] Noting that these metrics provide additional complementary glycaemic data to assess glycaemic control and to identify potential areas for improvement, the guidelines recognised that clinicians need to become more comfortable with their interpretation. The guidelines also highlighted that, as for any form of monitoring, the potential for improvements in glycaemic control will only be achieved if the user and providers take action on the basis of the data provided.[202] This highlights the underlying importance of providing CGM in association with structured diabetes self-management education and therapeutic programmes. This is consistent with recommendations regarding CGM in NG17 from NICE which emphasise that it should be provided by teams with expertise in its use, in the context of structured education, and with its use monitored and reviewed as part of the individual's annual diabetes care plan review.

7 Discussion

This rapid HTA has been conducted to support evidence-informed decision making relating to the reimbursement for continuous glucose monitoring in adults with T1DM in Ireland.

7.1 Interpretation of the evidence

Monitoring glucose levels is a key part of the management plan for individuals with T1DM, who may be at risk of hypoglycaemia or hyperglycaemia. An alternative to self-monitoring of blood glucose (SMBG) with regular finger prick tests each day is to use a continuous glucose monitoring system (CGM). These include intermittent scan CGM (isCGM) and real time CGM (rtCGM) systems. These systems feature a sensor that is generally placed on the upper arm and which needs to be replaced every seven to 14 days, depending on the product. In the case of rtCGM systems, sensors take automatic readings of blood glucose levels which are relayed directly to a compatible smart device (such as a handheld reader or smart phone with the dedicated app) at set intervals. For isCGM systems, the user must first scan the sensor using the compatible smart device to see the reading. While there are currently distinctions between the reimbursed isCGM and rtCGM systems, the differences in functionality are becoming smaller. Specifically, newer iterations of Freestyle Libre® available internationally include Freestyle Libre® 2 (incorporates optional alarms) and Freestyle Libre® 3 (a full rtCGM system which incorporates alarms and allows for automatic streaming of real time glucose readings).

The route of access to reimbursed isCGM is tightly controlled. A consultant endocrinologist or (diabetes nurse specialist attached to their service) makes an application on behalf of the patient, who meets pre-specified eligibility criteria, through a dedicated portal managed by the HSE Primary Care Reimbursement Service (PCRS).[12, 57] For approved patients, subject to ongoing clinical need, reimbursement may be allowed to continue after they exceed the age of 21 years. While adults with T1DM who are older than 21 years at the time of first application are not currently entitled to reimbursement for FreeStyle Libre, reimbursement may be granted ‘in very exceptional circumstances’. This has led to a large number of reimbursement applications for adults, with about 60% approved between 2018 and 2021.[58]

Historically, as rtCGM systems all required a hardware component, access to rtCGM systems was on basis of an initial application from a specialist diabetes service to the patient’s Local Health Office (LHO) for local approval. Since the addition of the Dexcom G7 CGM sensor to the HSE Primary Care Reimbursement Service (PCRS) list of reimbursable items in October 2022, there is streamlined access to a reimbursed

rtCGM system. No separate transmitter is required with this system, meaning no application to a Local Health Office (LHO) is necessary, and a person with T1DM will just require a prescription from any medical doctor to access a reimbursed sensor through any of the PCRS community schemes.

It should be noted that there is a significant price difference for isCGM compared with rtCGM. The current routes of access to these technologies may be creating a situation whereby there are fewer barriers to recommending the more expensive technology. The number of adults for whom rtCGM has been reimbursed has increased markedly, particularly for Dexcom increasing from just over 250 users in 2018 to almost 8,000 in 2022. The associated expenditure on rtCGM increased from approximately €1 million in 2016 to over €27 million in 2022. The corresponding number of adults in receipt of isCGM devices has grown from almost 400 in 2018 to over 2,000 in 2022, with expenditure increasing from €0.19 million to €2.42 million over the same period. The different pathways to accessing rtCGM and isCGM and substantial difference in costs between technologies have considerable implications for the cost effectiveness and overall budget impact of CGM for the HSE.

The rapid diffusion of the technologies in Ireland despite the restrictions on access indicates there is a strong demand for CGM amongst people with T1DM; user acceptability of CGM was reflected in a survey undertaken by Diabetes Ireland in 2021.[5]

There is substantial uncertainty regarding the epidemiology of T1DM in adults in Ireland due to the lack of a national diabetes register to collect and provide population-level data. Estimates of the prevalence of T1DM in Ireland in adults aged 18 years or older, have ranged from 17,053 (based on an analysis of Irish pharmacy claims data), in 2016 to 24,500 (based on prevalence estimates from the Scotland Diabetes Survey 2018 applied to 2016 Irish census data).

Complications of T1DM are associated with significant mortality. International data shows that people with T1DM have a two to five times higher risk of death compared with those without diabetes. Danish data shows that the loss of lifetime in T1DM was approximately 30% greater than that observed in T2DM; reflecting the earlier diagnosis and hence the longer exposure to risk factors for acute and chronic microvascular and macrovascular complications. Irish data shows age-related differences in mortality rates; rates typically increased with age with higher mortality observed in those aged 85 years and older.

In addition to having a negative impact on individuals with diabetes, complications also have significant implications for health service resources, use and costs. The Department of Health reported that in 2019, the national age-sex standardised hospitalisation rate for diabetes was 95.1 hospitalisations per 100,000 population

based on Hospital In-patient Enquiry data, which is lower than the OECD average of 129 per 100,000.

We reviewed clinical evidence based on evidence reviews for UK guidance and recommendations. The evidence included across the identified documents largely overlapped. A targeted update search was conducted by HIQA to find the most recent RCT data. There was limited evidence to suggest that rtCGM or isCGM improved glycaemic control relative to SMBG. Comparing rtCGM with isCGM; at follow-up periods up to six months, rtCGM was associated with a significantly higher likelihood of achieving an HbA1c target less than 7.0%. However, no meaningful difference was observed in HbA1c levels for a follow-up period up to six months. For hypoglycaemic and hyperglycaemic outcomes, the findings were mixed for isCGM and rtCGM compared to SMBG. For rtCGM compared to isCGM, nocturnal hypoglycaemia and the risk of severe hypoglycaemic events were more favourable in rtCGM users. rtCGM usage led to a longer time in range than SMBG, however there was mixed findings for isCGM and time in range. There is uncertainty in these data. The available study data provided limited evidence of a benefit to rtCGM over isCGM. There was some evidence that rtCGM use lead to longer time in range than isCGM, but further comparative data with the same duration of follow-up is needed.

A range of general, disease-specific, and complication/symptom-specific quality of life (QoL) and other patient-reported outcome measures were used across studies and were not universally applied to both types of device. Additionally, identified observational studies were non-comparative. This limited comparisons of QoL. For both rtCGM and isCGM there was some evidence of improved wellbeing and improved QoL. The available studies were not designed to capture the differences in the full range of day-to-day benefits CGM users may experience. Addressing these issues would require pragmatic RCTs or high-quality comparative observational studies that are designed to measure differences in QoL.

A literature search to identify economic evaluations was conducted, supplemented by a targeted search of specific HTA agencies. A number of international cost-effectiveness models were identified, and these provided some evidence that CGM systems can be cost-effective. However, it is unclear to what extent this applies to currently available CGM systems in the Irish healthcare system. This BIA estimated that introduction of isCGM would cost the HSE an additional €24.8 million, over the next five years assuming a gradual increase in uptake ranging from an additional 15% of all adults with T1DM in year one to an additional 35% in year five. Under the same uptake assumptions, introduction of rtCGM would cost the HSE an additional €84.8 million over five years.

The cost estimates vary substantially depending on the uptake rate and the level of testing in the SMBG comparator. Both the uptake rate and the level of testing are

not known with any certainty, although there may be scope to estimate indicative figures, for example using a survey approach amongst adults with T1DM in Ireland. It is possible that people with diabetes who are interested in CGM are those with higher rates of testing. The point estimate 5.6 times per day used for the budget impact assessment was derived from a CGM trial,[184] and hence should be broadly applicable to the patient cohort. However, it is also possible that under trial conditions individuals may have adhered more closely to guidelines about the recommended daily numbers of tests.

Scenario analyses considered low (four times daily) and high (eight times daily) testing alternatives. Higher rates of testing in the SMBG comparator group reduces the incremental cost of CGM. Incremental cost estimates range from €16.9 million and €76.9 million respectively for isCGM and rtCGM, for scenarios of low uptake and high baseline SMBG test rates, up to €49.5 million and €145.2 million for isCGM and rtCGM, respectively for scenarios of high uptake and low baseline SMBG test rates. In the BIA, it was assumed that the cost of a proprietary CGM device (reader) does not accrue to the HSE, while the costs to the HSE are limited to the costs of the consumables (sensors) and transmitter, where needed. Minimal supplementary blood glucose testing among GGM users was also assumed. If the cost of the readers accrues to the HSE and or there are greater levels of supplementary blood glucose testing than assumed, then overall costs would increase reflecting an increased upfront cost for individuals commencing on CGM, and a cost to replace readers over time, and also additional costs due to greater usage of test strips and lancets. Individuals may already have access to a compatible smartphone and can use this to scan and access their data after downloading the relevant company app; expert opinion is that people with diabetes rarely need to avail of a reader.

The analysis presented here was based on the CGM systems available at the time of assessment. New systems that incorporate additional or different functionality could be associated with increased costs and would have implications for the budget impact of CGM. Further, with additional competition in the market and potential innovations, the cost of the sensors may decrease overtime, and separate transmitters and readers may become redundant.

A final point to note is that the budget impact analyses were founded on the assumption that people with diabetes adopting CGM would all use the same type of device (i.e., isCGM or rtCGM). That is, the HSE would choose to reimburse only one kind of device for all adults with T1DM. The reality at present is that a mix of CGM devices are in use: predominantly isCGM devices in those that began using them before the age of 22 years, and rtCGM in those that were provided devices for the first time after the age of 21 years. Unless there was strict provision of only one type of device, there will continue to be a mix of devices in use and there may be a

variety of reasons why one type of devices may be considered favourable because of an individual person's context. As a consequence, the isCGM scenario may underestimate costs while the rtCGM scenario may overestimate costs. As indicated by information provided by PCRS, rtCGM devices are currently much more commonly used in this population to-date (approximately 85% vs 15% of all reimbursed CGM sensors), possibly due to different reimbursement procedures favouring the approval of rtCGM over isCGM devices. However, should these procedures change, then it is possible that isCGM may become the predominant CGM type in this population. Therefore, it is important that any policy change is this area carefully monitors changes in usage and cost relating not only to CGM devices, but also to test strips and lancets. As discussed, the BIA assumed that once initiated with a particular system, individuals remained on the same CGM system for the duration of the five year period. It also does not account for those who are currently using CGM, switching systems. Switching to an economically advantageous CGM system, when clinically appropriate to do so, may result in cost savings for the HSE.

International guidelines and recommendations on the use of CGM in people with T1DM have evolved in recent years in the context of this rapidly-changing field. For the general population with T1DM, the most updated guidance from the UK comprises that issued by NICE in March 2022; adults with T1DM are offered a choice of rtCGM or isCGM, based on their individual preferences, needs, characteristics, and the functionality of the devices available. The NICE guideline also recommends that CGM should be provided by teams experienced in its use, as part of structured education so that users are empowered to interpret the results and to take appropriate action, and that use should be monitored and reviewed as part of the individual's diabetes care plan. In the context of T1DM in pregnancy, NICE's 2020 clinical guideline NG3 applies; here, rtCGM is to be offered to all pregnant women with T1DM in order to help them meet their pregnancy blood glucose targets and to improve neonatal outcomes. For women with T1DM who are unable to use rtCGM, or where a clear preference for isCGM is expressed, isCGM is to be offered.

Elsewhere in the UK, adoption of isCGM (FreeStyle Libre® device) has been viewed favourably in guidance issued by Health Technology Wales (2018) and Healthcare Improvement Scotland (2019). However, rtCGM has not been reviewed by either agency for the general T1DM population.

As noted, this is a rapidly developing field and it is expected that recommendations are likely to evolve. It is noteworthy that the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) in 2021 stated that CGM is the standard for glucose monitoring for most adults with T1DM.[146]

In 2021, the Diabetes Canada Clinical Practice Guidelines Group issued an update of their Clinical Practice Guidelines for the Prevention and Management of Diabetes in

Canada guidelines specifically with respect to monitoring glycaemic control.[42] The guidelines recommend that rtCGM should be used, and that isCGM may be used, for people with T1DM to increase time in range and other glycaemic outcomes, to improve aspects of diabetes-specific quality of life, and to increase treatment satisfaction. Specifically rtCGM is recommended in adults with T1DM with impaired awareness of hypoglycaemia or recent severe hypoglycaemia. The Canadian guidelines highlighted, that as for any form of monitoring, improvements in glycaemic control may only be achieved if the user and providers take action on the basis of the data provided. This highlights the underlying importance of providing CGM in associated with structured diabetes self-management education and therapeutic programmes.

7.2 Other considerations

As noted previously, the current Irish clinical guideline for managing adults with T1DM was developed through a contextualisation of NICE's 2015 clinical guideline (NG17; Type 1 diabetes in adults: diagnosis and management). At that time, there were limited data available on CGM devices, particularly for isCGM. The evidence base has increased since then and is reflected in the updated 2022 NICE guideline. It is important to acknowledge that if the contextualisation process were to be repeated now, it would likely have implications for the content of the Irish guidelines.

Evolution of devices and evidence base

With respect to CGM, this is noted to be a rapidly developing field with iterative development of devices. The evidence base and associated recommendations are therefore likely to evolve over the coming years. Innovations include the addition of alerts in isCGM devices so that they approximate more closely to rtCGM devices, and the potential for increased connectivity between sensors and other devices, including connected insulin pens. The available trial evidence may relate to earlier generations of devices, and so the understanding of relative effectiveness and the differences between isCGM and rtCGM may not be applicable to the current generation of devices. As glucose concentration is measured indirectly, earlier generations of rtCGM devices required frequent calibration; however, due to refining of calibration models this has been improved in subsequent generations.[203] The highly dynamic development process is a common issue faced in the assessment of medical devices.[204] The earlier trials of CGM may also capture data related to people adjusting to the use of a novel technology. In their 2022 guidelines, the NICE guideline committee made a research recommendation to investigate using routinely collected real-world data to examine the effectiveness and cost effectiveness of CGM given the rapid advances in the technology.

It is noted that CGM generates significant amounts of data that can be used for remote monitoring, and which may support HTA to inform decision-making.[2, 146]

A CGM device on its own provides data on blood glucose levels, but to impact on treatment the person with diabetes or a clinician must act on foot of the data collected by the device. A well-functioning device will be of limited use if the person with diabetes or clinician does not respond when the device sounds alerts due to high or low blood glucose levels. Most of the trials that underpin the review of clinical effectiveness included some people with diabetes that used CGM in combination with insulin pumps. It was not always clear whether they were linked (hybrid closed loop) systems, whereby the insulin pump responded automatically to data from the CGM device. A linked system might be expected to achieve greater effectiveness than a CGM device on its own, as it reduces the need for action or decision making by the person with diabetes. As such, trials including linked CGM and insulin pump systems may over-estimate the effectiveness of a CGM device on its own.

Equity of access

The current approach to reimbursement has led to explicit inequities. An individual with T1DM who begins using an isCGM device before the age of 22 will continue to have access provided by the HSE after the age of 21. An individual who only seeks to avail of the device at the age of 22 will only have it funded in very exceptional circumstances by the HSE.[53] The decision is not based on clinical need or evidence of clinical effectiveness and safety, but simply on the age of first use of the device. Basing the decision for reimbursement on the grounds of clinical need and evidence of the clinical effectiveness of isCGM devices would remove this inequity.

Individuals with T1DM who are not eligible for isCGM but are deemed to have a clinical need may alternatively be provided with an rtCGM system by the HSE. Given the higher cost of the rtCGM systems and limited evidence to demonstrate their benefit over and above isCGM devices, this approach to managing adults with T1DM is potentially inefficient. In the event that a decision was made to reimburse isCGM in adults, a consideration would be whether those currently on rtCGM systems be switched to isCGM. Given that the clinical effectiveness and safety are not based on the age at which a person with diabetes begins using the device, the decision to reimburse and the type of device provided should also not be based on age of first use.

The absence of a single managed access programme for CGM has impacted the relative diffusion of the technologies. A single managed access system for all CGM systems, regardless of the age of individuals, could be considered as a measure to address the inequity.

Establishment of a national disease registry

Ireland does not have a national register for diabetes. Without accurate information on the proportion of the population with T1DM, healthcare service planning is challenging. Consideration should be given to the establishment of a national diabetes registry, within the context of ongoing national and European policy and legislative developments regarding health information, to support healthcare services planning and monitoring of epidemiological trends. Consideration should also be given to how such a national diabetes registry could integrate with existing infrastructures, such as the Diabetic RetinaScreen IT infrastructure. Should a national managed access programme for CGM be established, consideration should be given to the monitoring of clinical outcomes, usage, and costs in order to support and inform the efficient use of healthcare resources.

7.3 Strengths and limitations

This rapid HTA has a number of strengths. The evidence review has leveraged off recently published updates to UK guidance on the topic, so as to limit the resources needed and duplication of effort. In addition, a dedicated Expert Advisory Group has been convened to support the process by reviewing the report and providing valued stakeholder feedback.

There are a number of limitations which should also be considered when interpreting the findings of this rapid HTA. As discussed in chapter 3 on epidemiology, the lack of a national diabetes register means that the size of the population reported is an estimate rather than a verifiable figure. A full systematic review approach was not adopted for the clinical effectiveness and safety review, the cost-effectiveness review or for the identification of international guidance. The implications are a risk that relevant sources of data may have been missed in the search and hence that the conclusions may be based on a partial understanding of the evidence base. To counter this, we have reviewed documents that did apply a systematic search approach, and carried out an update search to identify recently published randomised controlled trials (RCTs); as such there is a low risk that relevant studies were overlooked.

Importantly, when reporting clinical effectiveness outcomes this review provides a brief overview of evidence from RCTs only. Observational studies were only included in the targeted review of QoL outcomes.

During the writing of this rapid HTA, a number of observational studies were brought to our attention.[141, 205-208] Some showed evidence of potential benefit for isCGM and rtCGM although this is not consistent across the literature, highlighting the need for cautious interpretation.

Furthermore, with respect to the underlying evidence base, multiple studies which have met our inclusion criteria have been funded by, or have declared conflicts of interest with, the manufacturers of CGM systems; Abbott, Dexcom, Inc. and Medtronic. Regarding international guidance, we have focused on UK guidance given similarities in the healthcare systems and the demography of people with T1DM, the approach used to evaluating the evidence base, and the timeliness of their updates. It should also be borne in mind that international guidance will predominantly be based on the same evidence base and therefore should have similar findings.

7.4 Conclusions

CGM is an alternative to SMBG in individuals with diabetes. CGM is a sensor-based technology that reduces the need for finger-prick testing. The current Irish clinical guideline for managing adults with T1DM was developed through a contextualisation of the 2015 NICE clinical guideline. Since then, the evidence base for CGM has increased and is reflected in the updated 2022 NICE guideline. Given the 2022 update to the NICE guideline in relation to CGM, the Irish National Clinical Guideline should be revisited.

There are two types of CGM; intermittently scanned (isCGM) and real-time (rtCGM). There is some evidence to suggest that CGM, compared with SMBG, improves glycaemic outcomes, particularly time in range. There is limited head to head evidence to distinguish between CGM types in terms of effectiveness. Routes of access to the technologies approved for reimbursement differ by CGM system type and component. Current reimbursement protocols mean that those aged over 21 have highly restricted access to isCGM in Ireland. However, reimbursed access to rtCGM is not restricted to the same degree. Annual HSE expenditure on CGM increased from €0.9 million in 2016 to €30 million in 2022; over 90% of the expenditure in 2022 related to rtCGM. There are differences in costs in rtCGM systems, but currently all reimbursed rtCGM systems are considerably more expensive than the isCGM system. Should access to CGM be expanded, the five year incremental budget impact to the HSE of CGM compared with SMBG (over and above what the HSE currently spends on CGM) is estimated as €24.8 million for isCGM and €84.8 million for rtCGM. These estimates assumed increasing uptake from an additional 15% in the first year to an additional 35% in the fifth year. If uptake were to be close to full coverage then the budget impact would be considerably higher. The BIA assumed that once initiated with CGM, individuals remained on the same CGM system for the duration of the five year period. It also does not account for those who are currently using CGM switching systems. Switching to an economically advantageous CGM system, when clinically appropriate to do so, may result in cost savings for the HSE.

The different pathways to reimbursed access rtCGM and isCGM, and the substantial difference in costs between technologies have considerable implications for the cost effectiveness and overall budget impact of CGM for the HSE. Consideration should be given to a single managed access programme for all CGM systems for all individuals with T1DM regardless of age. Such a system would need clearly defined criteria for access. For people with T1DM, CGM should be provided in the context of the existing model of care which includes oversight by specialist diabetes services and empowerment of the person with diabetes through access to structured diabetes self-management education.

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Appendix 1. Department of Health National Clinical Guideline 17: Adult type 1 diabetes mellitus (2018)

The recommendations in this guideline[9] relevant to CGM are:

3.6.21 Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes.

3.6.22 Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimised use of insulin therapy and conventional blood glucose monitoring:

- More than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause.
- Complete loss of awareness of hypoglycaemia.
- Frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities.
- Extreme fear of hypoglycaemia.
- Hyperglycaemia (HbA1c level of 75 mmol/litre [9%] or higher) that persists despite testing at least 10 times a day (see recommendations 3.6.11 and 3.6.12). Continue real-time continuous glucose monitoring only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of 27 mmol/mol (2.5%) or more.

3.6.23 For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy.

3.6.24 Real-time continuous glucose monitoring should be provided by a centre with expertise in its use, as part of strategies to optimise a person's HbA1c levels and reduce the frequency of hypoglycaemic episodes.

3.6.25 Flash glucose monitoring is becoming available, but NICE has not formally evaluated its clinical and cost effectiveness. In the interim, NICE has issued a briefing, available at https://www.nice.org.uk/advice/mib110/chapter/Summary. It is noted that this technology does not completely replace capillary blood

glucose monitoring. Patients will continue to require SMBG in addition to flash monitoring.

3.6.26 Refer to local guidelines and protocols for patients who are using flash glucose monitoring or real time continuous glucose monitoring as they will require education on the onset and duration of action of the different formulations of insulin and the risk of insulin accumulation or stacking after repeated insulin boluses.

Appendix 2. Literature search strategies for clinical effectiveness evidence

Search strategy for NICE update search
Medline (Ovid)

1. Meta-analysis.pt.
2. diabet*.tw.
3. (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw.
4. lada.tw.
5. (dm1 or iddm or t1d* or dka).tw.
6. (dm2 or t2d* or mody or niddm).tw.
7. (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw.
8. (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw.
9. (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw.
10. (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw.
11. (DM adj4 (earl* or sudden onset or juvenile or child*)).tw.
12. (DM adj4 (keto* or acidi* or gastropare*)).tw.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. Blood Glucose Self-Monitoring/ or Monitoring, Ambulatory/ or Blood Glucose/
15. (continu* or flash or real-time or "real time" or realtime).tw.
16. 14 and 15
17. (continu* adj4 glucose adj4 monitor*).tw.
18. (ambulatory adj4 glucose adj4 monitor*).tw.
19. (CGM or CGMS or CBGM).tw.
20. Extracellular Fluid/ or Extracellular Space/
21. ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw.
22. IPRO2*.tw.
23. (("real time" or real-time or realtime or retrospective*) adj4 (glucose adj4 monitor*)).tw.

24. (RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM").tw.
25. flash.tw.
26. FGM.tw.
27. glucorx.tw.
28. (medtronic* adj4 (enlight* or veo* or guardian* or envision*)).tw.
29. (Senseonic* adj4 eversense*).tw.
30. (Dexcom* adj4 (G4* or G5* or G6* or 7* or seven*)).tw.
31. (medtrum* adj4 (A6* or TouchCare*)).tw.
32. (freestyle* adj4 navigator*).tw.
33. ((freestyle* adj4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*)).tw.
34. "free style libre*".tw.
35. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 13 and 35
37. animals/ not humans/
38. 36 not 37
39. limit 38 to english language
40. randomized controlled trial.pt.
41. randomi?ed.mp.
42. placebo.mp.
43. 40 or 41 or 42
44. (MEDLINE or pubmed).tw.
45. systematic review.tw.
46. systematic review.pt.
47. meta-analysis.pt.
48. intervention$.ti.
49. 44 or 45 or 46 or 47 or 48
50. 43 or 49
51. 39 and 50
52. limit 51 to dt=20210511-20221010

Embase (Ovid)

1. exp diabetes mellitus/
2. diabet*.tw.
3. (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw.
4. lada.tw.
5. (dm1 or iddm or t1d* or dka).tw.
6. (dm2 or t2d* or mody or niddm).tw.
7. (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw.
8. (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw.
9. (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw.
10. (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw.
11. (DM adj4 (earl* or sudden onset or juvenile or child*)).tw.
12. (DM adj4 (keto* or acidi* or gastropare*)).tw.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. blood glucose monitoring/
15. glucose blood level/
16. glucose level/
17. 14 or 15 or 16
18. (continuous or flash or real-time or "real time" or realtime).tw.
19. 17 and 18
20. (continu* adj4 glucose adj4 monitor*).tw.
21. (ambulatory adj4 glucose adj4 monitor*).tw.
22. (CGM or CGMS or CBGM).tw.
23. extracellular fluid/
24. ((extracellular* or interstitial* or intercellular*) adj4 (fluid* or space)).tw.
25. IPRO2*.tw.
26. IPRO2*.dv.
27. (("real time" or real-time or retrospective*) adj4 (glucose adj4 monitor*)).tw.

28. (RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM").tw.
29. flash.tw.
30. FGM.tw.
31. glucorx.tw.
32. (medtronic* adj4 (enlight* or veo* or guardian* or Envision*)).tw.
33. (enlight* or veo* or guardian*).dv.
34. (Senseonic* adj4 eversense*).tw.
35. eversense*.dv.
36. (Dexcom* adj4 (G4* or G5* or G6* or 7* or seven*)).tw.
37. (G4* or G5* or G6* or G7*).dv.
38. (medtrum* adj4 (A6* or TouchCare*)).tw.
39. (A6* or TouchCare*).dv.
40. (freestyle* adj4 navigator*).tw.
41. navigator*.dv.
42. ((freestyle* adj4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*)).tw.
43. (libre* or FSL-Pro* or "FSL Pro*" or FSLPro*).dv.
44. continuous glucose monitoring system/
45. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. 13 and 45
47. nonhuman/ not human/
48. 46 not 47
49. limit 48 to english language
50. random:.tw.
51. placebo:.mp.
52. double-blind:.tw.
53. 50 or 51 or 52
54. (MEDLINE or pubmed).tw.
55. exp systematic review/ or systematic review.tw.
56. meta-analysis/
57. intervention$.ti.

58. 54 or 55 or 56 or 57
59. 53 or 58
60. 49 and 59
61. limit 60 to (conference abstract or conference paper or "conference review")
62. 60 not 61
63. limit 62 to dc=20210511-20221231

PsycINFO (Ebsco)

1. DE "Diabetes Mellitus"
2. TI diabet* OR AB diabet* OR KW diabet*
3. TI ((DM N4 ("type 1" or type1 or "type I" or "type one" or T1 or TI))) OR AB ((DM N4 ("type 1" or type1 or "type I" or "type one" or T1 or TI)))
4. TI lada OR AB lada
5. TI ((dm1 or iddm or t1d* or dka)) OR AB ((dm1 or iddm or t1d* or dka))
6. TI ((dm2 or t2d* or mody or niddm)) OR AB ((dm2 or t2d* or mody or niddm))
7. TI ((DM N4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*))) OR AB ((DM N4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)))
8. TI ((DM N4 onset* N4 (maturit* or adult* or slow*))) OR AB ((DM N4 onset* N4 (maturit* or adult* or slow*)))
9. TI ((DM N4 depend* N4 (non-insulin* or non insulin* or noninsulin*))) OR AB ((DM N4 depend* N4 (non-insulin* or non insulin* or noninsulin*)))
10. TI ((DM N4 (earl* or sudden onset or juvenile or child*))) OR AB ((DM N4 (earl* or sudden onset or juvenile or child*)))
11. TI ((DM N4 (keto* or acidi* or gastropare*))) OR AB ((DM N4 (keto* or acidi* or gastropare*)))
12. TI ((DM N4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II))) OR AB ((DM N4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)))
13. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14. DE "Blood Sugar"

15. TI (continuous or flash or real-time or "real time" or realtime) OR AB (continuous or flash or real-time or "real time" or realtime)
16. #14 AND #15
17. TI continu* N4 glucose N4 monitor* OR AB continu* N4 glucose N4 monitor*
18. TI (ambulatory N4 glucose N4 monitor*) OR AB (ambulatory N4 glucose N4 monitor*)
19. TI ((CGM or CGMS or CBGM)) OR AB ((CGM or CGMS or CBGM))
20. TI (((extracellular* or interstitial* or intercellular*) N4 (fluid* or space))) OR AB (((extracellular* or interstitial* or intercellular*) N4 (fluid* or space)))
21. TI IPRO2* OR AB IPRO2*
22. TI ((("real time" or real-time or retrospective*) N4 (glucose N4 monitor*))) OR AB ((("real time" or real-time or retrospective*) N4 (glucose N4 monitor*)))
23. TI ((RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM")) OR AB ((RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM"))
24. TI flash OR AB flash
25. TI FGM OR AB FGM
26. TI glucorx OR AB glucorx
27. TI ((medtronic* N4 (enlight* or veo* or guardian* or Envision*))) OR AB ((medtronic* N4 (enlight* or veo* or guardian* or Envision*)))
28. TI (Senseonic* N4 eversense*) OR AB (Senseonic* N4 eversense*)
29. TI ((Dexcom* N4 (G4* or G5* or G6* or 7* or seven*))) OR AB ((Dexcom* N4 (G4* or G5* or G6* or 7* or seven*)))
30. TI ((medtrum* N4 (A6* or TouchCare*))) OR AB ((medtrum* N4 (A6* or TouchCare*)))
31. TI (freestyle* N4 navigator*) OR AB (freestyle* N4 navigator*)
32. TI (((freestyle* N4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*))) OR AB (((freestyle* N4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*)))
33. TI "free style libre*" OR AB "free style libre*"
34. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
35. #13 AND #34
36. PT randomized controlled trial.pt.

37. TI randomi?ed OR AB randomi?ed OR KW randomi?ed
38. TI placebo OR AB placebo OR KW placebo
39. TX (MEDLINE or pubmed)
40. TX systematic review
41. PT systematic review
42. PT meta-analysis
43. TI intervention*
44. #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
45. #35 AND #44
46. #35 AND #44

The Cochrane Library

1. MeSH descriptor: [Diabetes Mellitus] explode all trees
2. (diabet*):ti,ab,kw
3. ((DM near/4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I))):ti,ab,kw
4. (lada):ti,ab,kw
5. ((dm1 or iddm or t1d* or dka)):ti,ab,kw
6. ((dm2 or t2d* or mody or niddm)):ti,ab,kw
7. ((DM near/4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II))):ti,ab,kw
8. ((DM near/4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw):ti,ab,kw
9. ((DM near/4 onset* near/4 (maturit* or adult* or slow*))):ti,ab,kw
10. ((DM near/4 depend* near/4 (non-insulin* or non insulin* or noninsulin*))):ti,ab,kw
11. ((DM near/4 depend* near/4 (non-insulin* or non insulin* or noninsulin*))):ti,ab,kw
12. ((DM near/4 (keto* or acidi* or gastropare*))):ti,ab,kw
13. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14. MeSH descriptor: [Blood Glucose Self-Monitoring] this term only

15. MeSH descriptor: [Monitoring, Ambulatory] this term only
16. MeSH descriptor: [Blood Glucose] this term only
17. #14 OR #15 OR #16
18. ((continu* or flash or real-time or "real time" or realtime)):ti,ab,kw
19. #17 AND #18
20. ((continu* near/4 glucose near/4 monitor*)):ti,ab,kw
21. ((ambulatory near/4 glucose near/4 monitor*)):ti,ab,kw
22. ((CGM or CGMS or CBGM)):ti,ab,kw
23. MeSH descriptor: [Extracellular Fluid] this term only
24. MeSH descriptor: [Extracellular Space] this term only
25. (((extracellular* or interstitial* or intercellular*) near/4 (fluid* or space))):ti,ab,kw
26. (IPRO2*):ti,ab,kw
27. ((("real time" or real-time or retrospective*) near/4 (glucose near/4 monitor*))):ti,ab,kw
28. ((RTCGM or RT-CGM or "RT CGM" or R-CGM or RCGM or "R CGM")):ti,ab,kw
29. (flash):ti,ab,kw
30. (FGM):ti,ab,kw
31. (glucorx):ti,ab,kw
32. ((medtronic* near/4 (enlight* or veo* or guardian*))):ti,ab,kw
33. ((Senseonic* near/4 eversense*)):ti,ab,kw
34. ((Dexcom* near/4 (G4* or G5* or G6* or 7* or seven*))):ti,ab,kw
35. ((medtrum* near/4 (A6* or TouchCare*))):ti,ab,kw
36. ((freestyle* near/4 navigator*)):ti,ab,kw
37. (((freestyle* near/4 libre*) or (FSL-Pro* or "FSL Pro*" or FSLPro*))):ti,ab,kw
38. "free style libre*"
39. #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38
40. #13 AND #39
41. (clinicaltrials or trialsearch):so
42. #40 not #41 with Cochrane Library publication date Between May 2021 and

Dec 2022, in Trials

43. #40 not #41 with Cochrane Library publication date Between May 2021 and Dec 2022, in Cochrane Reviews

Trials registries

Clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) were also searched. Search strategies for these registries are available upon request.

Search strategy for HRQoL outcomes

Medline (EBSCO)

1. AB (diabet* OR DM) N2 (Type 1 OR Type I OR "type one" or T1 OR TI)) OR TI (diabet* OR DM) N2 (Type 1 OR Type I OR "type one" or T1 or TI))
2. AB (T1D OR IDDM) OR TI (T1D OR IDDM)
3. AB ((diabet* OR DM) N3 (autoimmun* or auto immun* or brittle or labile or juvenile OR insulin depend* or insulin deficien*)) OR TI ((diabet* OR DM) N3 (autoimmun* or auto immun* or brittle or labile or juvenile OR insulin depend* or insulin deficien*))
4. (MH "Diabetes Mellitus, Type 1+")
5. AB Continu* N3 glucose N3 monitor* OR TI Continu* N3 glucose N3 monitor*
6. AB (("real-time" OR "real time" OR "intermittently scanned" OR "intermittently-scanned") N2 glucose N3 monitor*) OR TI (("real-time" OR "real time" OR "intermittently scanned" OR "intermittently-scanned") N2 glucose N3 monitor*)
7. AB (CGM OR CGMs OR CBGM OR "RT CGM" OR R-CGM OR RCGM OR "R CGM" OR rtCGM OR rt-CGM OR IS-CGM OR isCGM OR "FGM") OR TI (CGM OR CGMs OR CBGM OR "RT CGM" OR R-CGM OR RCGM OR "R CGM" OR rtCGM OR rt-CGM OR IS-CGM OR isCGM OR "FGM")
8. AB (Eversense OR "Guardian Connect" OR "Medtronic Guardian") OR TI (Eversense OR "Guardian Connect" OR "Medtronic Guardian")
9. AB Medtronic N3 enlite OR TI Medtronic N3 enlite
10. AB "glucose sensor*" OR TI "glucose sensor*"
11. AB (freestyle* N4 (navigator* OR libre)) OR TI (freestyle* N4 (navigator* OR libre))
12. AB (Dexcom* N4 (G4* or G5* or G6* or 7* or seven*)) OR TI (Dexcom* N4 (G4* or G5* or G6* or 7* or seven*))
13. #1 OR #2 OR #3 OR #4
14. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
15. (MM "Quality of Life")
16. TX ("Quality of life" OR "Life quality" OR quality-of-life)
17. (MM "Personal Satisfaction")
18. AB "personal satisfaction" OR TI "personal satisfaction"
19. AB "patient satisfaction" OR TI "patient satisfaction"

20. (MM "Patient Satisfaction")
21. (MM "Activities of Daily Living")
22. AB "Activities of Daily Living" OR TI "Activities of Daily Living"
23. (MM "Quality-Adjusted Life Years")
24. AB "Quality-Adjusted Life Years" OR TI "Quality-Adjusted Life Years"
25. (MM "Personal Autonomy")
26. TI "Personal autonomy" OR AB "Personal autonomy"
27. (MM "Happiness")
28. TI Happiness OR AB Happiness
29. TI "Patient preference*" OR AB "Patient preference*"
30. (MM "Patient Preference")
31. TI "fear of death" OR AB "fear of death"
32. TI "Self-Concept" OR AB "Self-Concept"
33. (MM "Self Concept")
34. (MM "Family Relations")
35. TI "Family Relations" OR AB "Family Relations"
36. (MM "Religion")
37. TI Religion OR AB Religion
38. (MM "Social Support")
39. TI "social support" OR AB "social support"
40. TI "financial support" OR AB "financial support"
41. (MM "Financial Support")
42. TI "positive experience" OR AB "positive experience"
43. TI "diabetes distress" OR AB "diabetes distress"
44. AB ((hypoglycaem* OR hypoglycem*) N3 (fear* or worry or worries or anxiety or anxious or confidence)) OR TI ((hypoglycaem* OR hypoglycem*) N3 (fear* or worry or worries or anxiety or anxious or confidence))
45. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44
46. MH "Randomized Controlled Trial" OR PT "Randomized Controlled Trial" OR TI

random* N2 trial OR AB random* N2 trial OR TI placebo* OR TI "single blind*" OR TI "double blind*" OR TI "triple blind*" OR AB placebo* OR AB "single blind*" OR AB "double blind*" OR AB "triple blind*"

47. MH "Cross Sectional Studies" OR TI ("cross sectional" OR transverse OR prevalence) N1 (study OR analys* OR design OR method*) OR (AB ("cross sectional" OR transverse OR prevalence) N1 (study OR analys* OR design OR method*)
48. MH "Cohort Studies" OR MH "Longitudinal Studies" OR MH "Prospective Studies" OR MH "Follow Up Studies" OR MH "Retrospective Studies" OR MH "Case Control Studies" OR TI (cohort OR longitudinal OR prospective OR "follow up" OR retrospective OR "case control" OR "case referent" OR "case comparison") N1 (study OR analys* OR design OR method*) OR AB (cohort OR longitudinal OR prospective OR "follow up" OR retrospective OR "case control" OR "case referent" OR "case comparison") N1 (study OR analys* OR design OR method*)
49. #46 OR #47 OR #48
50. #13 AND #14 AND #45 AND #49

Appendix 3: Clinical effectiveness outcomes data

Table A3.1 HbA1c outcomes by comparison type extracted from UK guidance documents

Outcome	Effect estimate	Participants	GRADE¥	Source
rtCGM vs SMBG				
Change from baseline HbA1c (%) - ≤ 3 months	Could not differentiate	346[114, 121, 123]	Very low	NICE
Change from baseline HbA1c (%), ≤ 6 months	No meaningful difference*	1259[114, 115, 119, 122, 127-129, 209]	Very low	NICE
Change from baseline HbA1c (%), >6 months	MD -0.52 (-0.80, -0.24) Favours rtCGM	123[120]	Very low	NICE
Change in HbA1c (mmol/mol) ≤ 6 months	No meaningful difference	477[115, 127, 129]	Low	NICE
HbA1c (mmol/mol) ≤ 3 months	Could not differentiate	82[123]	Very low	NICE
Achieved target HbA1c <7.5% ≤ 3 months	Could not differentiate	155[114]	Very low	NICE
Achieved target HbA1c < 7.5% ≤ 6 months	RR 2.02 (1.18, 3.46)	155[114]	Low	NICE
Achieved target HbA1c <7.0% ≤ 3 months	Could not differentiate	155[114]	Low	NICE
Achieved target HbA1c < 7.0% ≤ 6 months	RR 1.80 (1.00, 3.22)	155[114]	Low	NICE
isCGM vs SMBG				
Change from baseline HbA1c (%)	No meaningful difference*	238[124]	Moderate	NICE
Change from baseline HbA1c (mmol/mol)	No meaningful difference*	238[124]	Moderate	NICE
HbA1c (%) at 6 months	Difference in adjusted means (SE) 0.00 (0.059) p=0.9556	238[124]	-	SHTG
HbA1c (mmol/mol) at 6 months	Difference in adjusted means (SE) 0.0 (0.65) p=0.9543	238[124]	-	SHTG
rtCGM vs isCGM				
Achieved target HbA1c less than 7.0% ≤ 6 months	RR 1.50 (1.09, 2.06)	254[113]	Moderate	NICE

HbA1c (%)≤ 6 months	No meaningful difference*	254[113]	High	NICE

Key: GRADE - Grading of Recommendations Assessment, Development and Evaluation; HbA1c – glycated haemoglobin; isCGM – intermittently scanned continuous glucose monitoring; MD – mean difference; mmol/mol – millimoles per mole; NICE – National Institute for Health and Care Excellence; RR – relative risk; mmol/mol – millimoles per mole; rtCGM – real-time continuous glucose monitoring; SHTG – Scottish Health Technologies Group; SMBG – self-monitoring of blood glucose.
Source: NICE 2022,[2] SHTG.[112]

¥ GRADE certainty of evidence as reported by the report authors
*The point of clinically meaningful difference was determined to be a 0.5% change in HbA1c (5.5 mmol/ mol)

Table A3.2 HbA1c outcomes by comparison type from update search for RCTs

Outcome	Effect estimate	Participants	Source
rtCGM vs SMBG			
No new trials relevant to this comparison identified.			
isCGM vs SMBG			
Change from baseline HbA1c (%)	No meaningful difference*	81	Secher 2021[109]
Change from baseline HbA1c (%) at 6 months	aMD −0.5 (−0.7 to −0.3), p<0.001	141	Leelarathna 2022[110]
Achieved target HbA1c ≤7.0% at 6 months	OR 2.43 (0.76 to 7.78)	141	Leelarathna 2022[110]
Achieved target HbA1c ≤7.5% at 6 months	OR 2.47 (1.08 to 5.68)	141	Leelarathna 2022[110]
HbA1c (%) at 6 months	aMD −0.5 (−0.7 to −0.3), p<0.001	141	Leelarathna 2022[110]
Reduction in HbA1c from baseline ≥0.5 percentage points at 6 months	OR 4.74 (2.10 to 10.71)	141	Leelarathna 2022[110]
Reduction in HbA1c from baseline ≥1.0 percentage points at 6 months	OR 4.30 (1.67 to 11.09)	141	Leelarathna 2022[110]
rtCGM vs isCGM			
HbA1c at day 120	aMD -0.1 [-0.3; 0.1] p = 0.408	90	Renard 2022[111]

Key: aMD – adjusted mean difference**;** HbA1c – glycated haemoglobin; isCGM – intermittently scanned continuous glucose monitoring; OR – odds ratio; rtCGM – real-time continuous glucose monitoring; SMBG – self-monitoring of blood glucose.
*The point of clinically meaningful difference was determined to be a 0.5% change in HbA1c (5.5 mmol/ mol)

Table A3.3 Glycaemic event outcomes by comparison type extracted from UK guidance documents

Outcome	Effect estimate	Participants	GRADE	Source
rtCGM vs SMBG				
Hypoglycaemia event duration (minutes) ≤ 3 months	MD -31.60 (-50.90, -12.30)	109[121]	Very low	NICE
Hypoglycaemia event duration (minutes) ≤ 6 months	MD -37.80 (-44.60, -31.00)	52[129]	High	NICE
Severe hypoglycaemia ≤ 6 months	RR 0.65 (0.44, 0.97)	1000[114, 119, 121, 128, 209, 210]	Low	NICE
Severe hypoglycaemia ≥ 6 months*	RR 2.46 (1.02, 5.92)	123[120]	Very low	NICE
Hypoglycaemia (events/day) <3.9 mmol/l ≤ 3 months	Could not differentiate	109[121]	Very low	NICE
Hypoglycaemia (events/week) <3 mmol/l ≤ 6 months	No meaningful difference	399[116, 119, 127]	Low	NICE
Hypoglycaemia (events/week) <3.9 mmol/l ≤ 6 months	No meaningful difference	310[116, 119, 129]	High	NICE
Nocturnal Hypoglycaemia (% of time) <3.9 mmol/l ≤ 6 months	MD -3.97 (-6.95, -0.98)	194[116, 129]	Very low	NICE
Nocturnal hypoglycaemia number of events / night <3.9 mmol/l ≤ 6 months	No meaningful difference	335[116, 127, 129]	High	NICE
isCGM vs SMBG				
Nocturnal hypoglycaemia [2300-0600] (time in h) less than< 3.1mmol/l	MD -0.30 (-0.32, -0.28)	238[124]	Moderate	NICE
Hypoglycaemia <3.1 mmol/l	Could not differentiate	241[124]	Very low	NICE
Severe hypoglycaemia	Could not differentiate	241[124]	Very low	NICE
Time (hours) in glucose <3.9mmol/L (70mg/dL) per 24 hours	Difference in adjusted means: -1.24 (0.239) (-38.0%) p<0.0001	238[124]	-	SHTG
Time (hours) in glucose <3.9mmol/L (70mg/dL) per 7 hours (23.00-06.00)	Difference in adjusted means: -0.47 (0.118) (-39.8%) p<0.0001	238[124]	-	SHTG
Number of hypoglycaemic events <3.9mmol/L (70mgldL) per 24 hours	Difference in adjusted means: -0.45 (0.089) (-25.8%) p<0.0001	238[124]	-	SHTG
Number of hypoglycaemic events <3.9mmol/L (70mgldL) per 7 hours (23.00-06.00)	Difference in adjusted means: -0.14 (0.029) (-33.2%) p<0.0001	238[124]	-	SHTG
Time (hours) in glucose >13.3mmol/L (240mg/dL) per 24 hours	Difference in adjusted means: -0.37 (0.163) (-19.1%) p=0.0247	238[124]	-	SHTG

rtCGM vs isCGM				
Nocturnal hypoglycaemia [0000 - 0600] less than 3.9 mmol/l ≤ 3 months	MD -3.96 (-7.30, -0.62)	60[125]	Moderate	NICE
Nocturnal hypoglycaemia [0000-0600] less than 3.0 mmol/l ≤ 3 months	MD -2.79 (-4.90, -0.68)	60[125]	Moderate	NICE
Severe hypoglycaemia (events) ≤ 6 months	RR 0.08 (0.03, 0.25)	254[113]	High	NICE

Key: GRADE - Grading of Recommendations Assessment, Development and Evaluation; HbA1c – glycated haemoglobin; isCGM – intermittently scanned continuous glucose monitoring; MD – mean difference; mg/dl - milligrams per decilitre; mmol/ll – millimoles per litre; NICE – National Institute for Health and Care Excellence; RR – relative risk; rtCGM – real-time continuous glucose monitoring; SHTG – Scottish Health Technologies Group; SMBG – self-monitoring of blood glucose.
Source: NICE 2022,[2] SHTG.[112]
¥ GRADE certainty of evidence as reported by the report authors

Table A3.4 Glycaemic event outcomes by comparison type from update search for RCTs

Outcome	Effect estimate	Participants	Source
rtCGM vs SMBG			
No new trials relevant to this comparison identified.			
isCGM vs SMBG			
Time in hypoglycaemia (<3.9 mmol/l)	No meaningful difference	81	Secher 2021[109]
Time in hyperglycaemia (>10 mmol/l)	No statistically significant difference	81	Secher 2021[109]
Episode of severe hypoglycaemia	isCGM 0%, SMBG 3%	156	Leelarathna 2022[110]
rtCGM vs isCGM			
No new trials relevant to this comparison identified			

Key: isCGM – intermittently scanned continuous glucose monitoring; mmol/l - millimole per litre; rtCGM – real-time continuous glucose monitoring; SMBG – self-monitoring of blood glucose.

Table A3.5 NICE time in range outcomes by comparison type

Outcome	Effect estimate	Participants	GRADE	Source
rtCGM vs SMBG				
Time in range (%) [3.9/4 - 10 mmol/l] ≤ 6 months	MD 7.03 (4.88, 9.19)	1023[114, 119, 126-129]	Very low	NICE
isCGM vs SMBG				
Time in range (%) [3.9/4 - 10 mmol/l] 6 months	MD 4.16 (3.84, 4.48)	238[124]	Moderate	NICE
rtCGM vs isCGM				
Time in range (%) [3.9/4 - 10 mmol/l] ≤ 3 months	MD 5.56 (0.31, 10.81)	100[125, 211]	Low	NICE
Time in range (%) [3.9/4 - 10 mmol/l] ≤ 6 months	MD 6.85 (4.36, 9.34)	254[113]	Moderate	NICE

Key: GRADE - Grading of Recommendations Assessment, Development and Evaluation; isCGM – intermittently scanned continuous glucose monitoring; MD – mean difference; NICE – National Institute for Health and Care Excellence; rtCGM – real-time continuous glucose monitoring; SMBG – self-monitoring of blood glucose.
Sources: NICE 2022.[2]

Table A3.6 Time in range outcomes by comparison type from update search for RCTs

Outcome	Effect estimate	Participants	Source
rtCGM vs SMBG			
No new trials relevant to this comparison identified			
isCGM vs SMBG			

Time in range (%) [3.9 - 10 mmol/l] 6 months	% difference of 3.9 [−12 to 23], p = 0.660.	81	Secher 2021[109]
Time in range, 70–180 mg/dl 6 months	aMD 9.0 (4.7 to 13.3)	137	Leelarathna 2022[110]
rtCGM vs isCGM			
Mean difference in Time in range 70 -180mg/dL Between D90 and D120	aMD 4.7% (95% CI 1.0; 8.4; p = 0.013)	90	Renard 2022[111]

Key: aMD – adjusted mean difference; rtCGM – real-time continuous glucose monitoring; SMBG – self-monitoring of blood glucose; isCGM – intermittently scanned continuous glucose monitoring.

Table A3.7 NICE and trial-based hospitalisation outcomes by comparison

Outcome	Effect estimate	Participants	GRADE	Source
rtCGM vs SMBG				
Diabetic ketoacidosis ≤ 6 months	Could not differentiate	849[114, 119, 128, 209, 210]	Very low	NICE
Diabetic ketoacidosis > 6 months	Could not differentiate	123-[120]	Very low	NICE
Hospitalisations ≤ 6 months	Could not differentiate	203-[128]	Very low	NICE
isCGM vs SMBG				
Hospital admission for diabetic ketoacidosis	isCGM 1%, SMBG 0%	156	N/A	Leelarathna 2022
Clinically significant ketosis event without hospitalisation	isCGM 0%, SMBG 3%	156	N/A	Leelarathna 2022[110]
rtCGM vs isCGM				
No relevant RCT data reported				
isCGM non-comparative				

Hospital admissions to internal medicine	Pre- vs. post-isCGM: reduced hospital admissions from 19.0 per 100 person years to 15.8 per 100 person years	-[147]	-	HTW
Change in visits to diabetes/endocrine specialists	Pre- vs. post-isCGM: reduced from 117.4 to 83.3 per 100 patient years	-[147]	-	HTW
Change in primary care visits	Pre- vs. post-isCGM: 1033.4 to 829.1 per 100 patient years	-[147]	-	HTW

Key: GRADE - Grading of Recommendations Assessment, Development and Evaluation; HTW – Health Technology Wales; isCGM – intermittently scanned continuous glucose monitoring; NICE – National Institute for Health and Care Excellence; rtCGM – real-time continuous glucose monitoring; SMBG – self-monitoring of blood glucose;
Source: Health Technology Wales,[167] Leelarathna 2022,[110] NICE 2022.[2]

Table A3.8 Additional clinical effectiveness outcomes data for type 1 diabetes in adults

Outcome	Treatment effect	Participants	GRADE	Source
rtCGM vs SMBG				
Time below range (%) less than 55mg/dL ≤ 6 months	MD -3.15 (-5.19, -1.11) and effect is less than the MID*	116	Very low quality	NICE
Time below range (%) less than 63mg/dL ≤ 6 months	MD -2.04 (-3.86, -0.22) and effect is less than MID	116	Very low quality	NICE
Time above range greater than 13.9 mmol/l ≤ 6 months	MD -3.08 (-4.45, -1.72) and effect is less than MID	319	Very low quality	
Glycaemic variability: SD ≤ 6 months	MD -8.75 (-11.55, -5.95)	298	Moderate	NICE
Glycaemic variability: coefficient of variation ≤ 6 months	MD -4.35 (-6.72, -1.99),	584	Very low	NICE
Glycaemic variability: MAGE ≤ 6 months	MD -19.64 (-26.41, 12.88)	282	Moderate quality and effect is less than MID	NICE
Severe adverse events (SAE) ≤ 6 months	no meaningful difference or could not be differentiated	158	Very low	NICE
isCGM vs SMBG				
Time below range (%) < 3.9 mmol/l	MD -5.17 (-5.42, -4.91)	238	Moderate	NICE
Time below range (%) < 3.1 mmol/l	MD -3.42 (-4.85, -1.99)	238	Low	NICE
Time below range (%) < 2.5 mmol/l	MD -2.29 (-2.44, -2.14)	238	Moderate	NICE
Time below range (%) < 2.2 mmol/l	MD -1.92 (-2.05, -1.79)	238	Moderate	NICE
Time below range, <70 mg/dl	aMD −3.0 (−4.5 to −1.4)	137		Leelarathna 2022
Time above range > 13.9 mmol/l	MD -1.54 (-1.71, -1.37)	238	Moderate	NICE
Time above range, >180 mg/dl	aMD −6.0 (−11.0 to −0.9)	137		Leelarathna 2022
Time above range, >250 mg/dl	aMD −6.5 (−10.5 to −2.6)	137		Leelarathna 2022
Glucose level — mg/dl	aMD −11 (−20 to 0)	137		Leelarathna 2022
Mean glucose	No statistically significant difference	81		Secher 2021
Glycaemic variability: SD	MD -5.00 (-5.29, -4.71)	238	Moderate	NICE
Glucose SD — mg/dl	aMD −9 (−14 to −5)	137		Leelarathna 2022
Glycaemic variability: coefficient of variation	MD -4.40 (-4.56, -4.24)	238	Moderate	NICE
Coefficient of variation of the glucose level — %	aMD −3.5 (−5.3 to −1.8)	137		Leelarathna 2022
glucose CV	No statistically significant difference	81		Secher 2021

Outcome	Treatment effect	Participants	GRADE	Source
Percent of time spent with glucose level at <63 mg/dl	aMD −2.6 (−3.9 to −1.3)	137		Leelarathna 2022
Percent of time spent with glucose level at <54 mg/dl	aMD −2.0 (−3.0 to −1.0)	137		Leelarathna 2022
Percent of time spent with glucose level at <50 mg/dl	aMD −1.8 (−2.6 to −0.9)	137		Leelarathna 2022
Percent of time spent with glucose level at >300 mg/dl	aMD −4.1 (−6.7 to −1.4)	137		Leelarathna 2022
Glycaemic variability: MAGE	MD -8.00 (-8.76, -7.24)	238	Moderate	NICE
CGM monitor malfunction	RR 21.17 (1.25, 357.32)	241	Moderate	NICE
Discontinuation	Could not differentiate	241	Very low	NICE
Discontinuation	Discontinued isCGM with alarms (n=2/78) Discontinued control (n=8/78) • Private Purchase of isCGM (n=3) • NHS Prescription of isCGM (n=5)	156	-	Leelarathana 2022
Serious adverse events	Could not differentiate	241	Very low	NICE
rtCGM vs isCGM				
Time below range (%) less than 3.9 mmol/l ≤ 3 months	MD -2.56 (-4.25, -0.88) and effect is less than the MID	100	Low quality	NICE
Time below range less than 3.0 mmol/l ≤ 6 months	MD -0.35 (-0.61, -0.09)	254	Moderate quality and effect is less than MID	NICE
Time below range <54mg/dL 120 days	aMD -1.6 [-3.1; -0.1] P = 0.039	90	-	Renard 2022
Mean absolute difference in time spent below range <54 mg/dL between D90 and D120	-1.6% (95% CI -3.1; -0.1 [23 minutes]; P = 0.039)	90		Renard 2022
Time below range <70mg/dL 120 days	aMD -1.8 [-4.1; 0.5] P = 0.129	90	-	Renard 2022
Time above range greater than 13.9 mmol/l ≤ 3 months	MD -4.19 (-8.00, -0.38)	60	Moderate	NICE
Time above range >180mg/dL 120 days	aMD -3.3, [-7.3; 0.7] P = 0.106	90	-	Renard 2022
Time above range >250mg/dL 120 days	aMD -1.0, [-4.0; 2.0] P = .503	90	-	Renard 2022

Outcome	Treatment effect	Participants	GRADE	Source
Glycaemic variability: SD ≤ 6 months	MD -0.33 (-0.45, -0.21)	254	Moderate	NICE
Glycaemic variability: coefficient of variation ≤ 6 months	MD -1.38 (-2.30, -0.46) effect is less than MID	254	Moderate	NICE
Glycaemic variability: coefficient of variation 120 days	aMD -0.5, [-2.6; 1.6] P = 0.641	90	-	Renard 2022
Glycaemic variability: MAGE ≤ 3 months	Showed no meaningful difference or could not be differentiated	60	Moderate	NICE

* Minimally important difference (MID) means that the point estimate is in the zone of equivalence.
Key: aMD – adjusted mean difference; GRADE - Grading of Recommendations Assessment, Development and Evaluation; MAGE – mean amplitude of glucose excursions; MD – mean difference; MID – minimally important difference; SD – standard deviation.
Source: NICE 2022,[2] Leelarathna 2022,[110] Renard 2022,[111] Secher 2021.[109]

Table A3.9 Additional clinical effectiveness outcomes data for diabetes in pregnancy

Outcome	Treatment effect	Participants	GRADE	Source
rtCGM vs SMBG				
Preconception period (women who are planning to become pregnant): Maternal outcomes at ≤ 6 months				
Adverse event- local reaction (skin changes during trial)	RR: 5.04 (2.07, 12.29)	109	High	NICE
It was not possible to differentiate between the two monitoring systems for the additional outcomes				NICE
During pregnancy: Maternal and infant outcomes at ≤ 6 months				
For the additional assessed outcome (pregnancy loss/miscarriage) it was not possible to differentiate between monitoring systems.				NICE
During pregnancy: Maternal and infant outcomes at > 6 months				NICE
Adverse event- local reaction due to CGM monitor (skin changes during trial)	RR 6.18 (3.08, 12.40)	207	High	NICE
It was not possible to differentiate between monitoring systems for the additional assessed outcome serious adverse events				NICE
During pregnancy – women who conceived during 24-week planning pregnancy trial Very small sample size for outcomes (range 24 – 31 participants).				NICE
No additional outcomes				NICE
isCGM vs SMBG				
NICE did not identify any RCTs that compared isCGM to SMBG.				NICE
rtCGM vs isCGM				
NICE did not identify any RCTs that compared rtCGM to isCGM.				NICE

Key: GRADE - Grading of Recommendations Assessment, Development and Evaluation; isCGM – intermittently scanned continuous glucose monitoring; NICE – National Institute for Health and Care Excellence; RR – relative risk; rtCGM – real-time continuous glucose monitoring; SMBG – self-monitoring of blood glucose.
Source: NICE 2020.[1]

Table A3.10 Ongoing trials

Title of study	Authors	Clinical trials reference number	Status	Expected completion date
From clinical trial registries				
In-hospital diabetes management with flash glucose monitoring (isCGM) - the INDIGO Study, Part B	University of, Aarhus; Aarhus University, Hospital	NCT04630925	Recruiting	Dec-23
In-hospital diabetes management with flash glucose monitoring (isCGM) - the INDIGO study, Part A	University of, Aarhus; Aarhus University, Hospital	NCT04650945	Recruiting	Dec-23
Effects of novel flash glucose monitoring system on glycemic control in adult patients with type 1 diabetes mellitus	Sun Yat-sen, University	NCT03522870	Recruiting	Dec-21
The management of glucose control and hypoglycemic prevention using continuous glucose monitoring system in patients with type 1 diabetes	Severance Hospital Diabetes Center, Division of Endocrinology and Metabolism, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea	NCT04684030	Recruiting	Aug-22
RT-CGM in young adults at risk of DKA	Imperial College, London; DexCom, Inc	NCT04039763	Recruiting	Jun-22
Use of CGM in kidney transplant recipients	Dahlia, M. Zuidema;	NCT04783441	Recruiting	Dec-24

Title of study	Authors	Clinical trials reference number	Status	Expected completion date
	DexCom, Inc; University of California, Davis			
GLYPALCARE STUDY - multicenter, randomized study for evaluating continuous glucose monitoring (CGM) by using FreeStyle Libre 2 (FSL2) for preventing hyperglycemia/hypoglycemia crisis in advanced oncological patients	Antea Foundation; Abbott Diabetes Care	NCT04942756	Active, not recruiting	Jun-22
Assessment of the impact of real-time continuous glucose monitoring on people presenting with severe hypoglycaemia	Imperial College, London; London Ambulance Service	NCT03748433	Completed	Sep-21
Published protocols				
Protocol for a randomized, crossover trial to decrease time in hypoglycemia by combined intervention of the usage of intermittent-scanning continuous glucose monitoring device and the structured education regarding its usage: effect of intermittent-scanning continuous glucose monitoring to glycemic control including hypoglycemia and quality of life of patients with type 1 diabetes mellitus study (ISCHIA Study) [212]	Suzuki, Shota; et al.			Protocol published 2021 – expected completion date not reported

Appendix 4. Subgroup of users above treatment targets at baseline

The NICE type 1 diabetes guideline recommends that adults with T1DM aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications.[213] To determine what proportion of trial participants (if any) had achieved this target before the initiation of CGM (rtCGM or isCGM), baseline HbA1c data were considered from all RCTs included in the NICE NG17 evidence review and the three RCTs identified in the update search, with the following observations.

- Eight trials (seven from the NICE evidence review and one from the update search) preselected for participants who were above treatment targets at study enrolment.[110, 114-123]
- Several other RCTs had eligibility criteria related to treatment control targets:
    - While not completely excluding participants outside of the treatment target, two studies focused their criteria on participants with HbA1c levels close to target, specifying levels of HbA1c <7.5%[124] and HbA1c ≤7.5%[126] in their respective trial eligibility criteria.
    - An additional RCT from the update search by Renard et al., included individuals who were required to have spent more than 1.5 hours per day below 70 mg/dL over the preceding 28 days to be eligible for inclusion.[111]
- Across the RCTs, mean HbA1c at baseline ranged from 6.7% in the IMPACT trial (which limited enrolment to those with HbA1C ≤ 7.5% at baseline)[124] to 9.1% in the rtCGM arm of Tanenberg et al. (trial enrolment limited to those with baseline HbA1C >7.9%).[121]
- Analyses associated with four trials aimed to examine the impact of baseline HbA1c on outcomes. The trials involved were the DIAMOND trial[114, 214], the GOLD trial (a post-hoc analysis)[117], a follow-on study of the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring (JDRF-CGM) trial[215] and the 'Wireless Innovation for Seniors with Diabetes Mellitus' (WISDM) trial.[128]
    - The DIAMOND trial compared ongoing monitoring with rtCGM and SMBG. The main publication[114] reported that there was no significant interaction between baseline HbA1c and HbA1c at 24 weeks (p-value for interaction 0.16). A secondary publication for the DIAMOND trial

assessed the impact of baseline time in range (TIR) on TIR at follow-up. Mean increase in TIR was greater with rtCGM relative to SMBG for all three baseline categories (16 minutes per day for baseline TIR <40%, 77 minutes per day for baseline TIR <50%, and 88 minutes per day for baseline TIR <60%).[214]

- The GOLD RCT compared rtCGM with SMBG in adults with T1DM treated with multiple daily insulin injections. A post-hoc analysis of the trial (n=142) with follow-up of up to 26 weeks aimed to identify characteristics of responders to rtCGM in relation to reductions in HbA1c and percentage time spent in hypoglycaemia. Using pairwise Spearman correlation, Ólafsdóttir et al. found a significant relationship between treatment differences in HbA1c, time in hypoglycaemia and TIR.[117] The study found that people with higher HbA1c at baseline experience a statistically significant greater reduction in HbA1c following introduction of rtCGM, with mean reduction in percentage HbA1c ranging from −0.23%, 95%CI, -0.39 to -0.07) to −0.56%, 95%CI, -0.71 to -0.41) for the 25th to 75th percentile, respectively. There was no statistically significant interaction between the percentage of time with low glucose levels below 54 mg/dL (<3.0 mmol/L) at randomization visit, the percentage of time with low glucose levels below 70 mg/dL (<3.9 mmol/L) at randomisation visit, or the percentage of time with high glucose levels above 250 mg/dL (>13.9 mmol/L) at randomisation visit and HbA1c at last observation carried forward.

- A follow-on study by the JDRF study group whereby the control arm also switched to rtCGM included a subgroup analysis of glycemic indices by baseline HbA1c. . This found that, at six months follow-up, while there were increases in the median minutes per day in range (71-180 mg/dL) relative to baseline in both subgroups (HbA1c <7%, HbA1c ≥7%), the change from baseline was only statistically significantly for those with baseline HbA1c ≥7%).[215] For hypoglycemia outcomes, the change from baseline was only statistically significant in the subgroup with HbA1c <7.0% at baseline and for hyperglycemia outcomes, the change from baseline was only statistically significant for those with HbA1c ≥7% at baseline.

- A study by Pratley et al. in older adults with T1DM (≥60 years) compared rtCGM with SMBG and found there was no interaction between baseline HbA1c (HbA1c <7.5% vs. HbA1c ≥7.5%) and the

treatment effect of time with glucose levels less than 70 mg/dL (p-value for interaction 0.09).[128]

Appendix 5. Additional quality of life outcomes data

Table A5.1 NICE quality of life outcomes by comparison type

Outcome	Effect estimate	Participants	GRADE	Source
rtCGM vs SMBG				
Diabetes distress – PAID ≤ 6 months	No meaningful difference	226[216]	Moderate	NICE
Diabetes Treatment Satisfaction Questionnaire (DTSQ)	Could not differentiate	369[115, 210]	Very low	NICE
Short Form Health Survey SF-8 physical – 3 months	No meaningful difference	82[123]	Very low	NICE
SF-8 mental – 3 months	Could not differentiate	82[123]	Very low	NICE
World Health Organization 5-item (WHO-5) general wellbeing index – 6 months	No meaningful difference	279[115]	High	NICE
SF-12 physical – 6 months	No meaningful difference	226[216]	Moderate	NICE
SF-12 mental – 6 months	No meaningful difference	226[216]	Moderate	NICE
Fear of hypoglycaemia (HFS)≤ 6 months	No meaningful difference	226[216]	Moderate	NICE
Fear of hypoglycaemia (HFS-II) ≤ 6 months	No meaningful difference	96[210]	Low	NICE
Fear of Hypoglycaemia (HFS-SWE) ≤ 6 months	No meaningful difference	280[115]	High	NICE
Hypoglycaemia awareness - Clarke score ≤ 6 months	No meaningful difference	303[114, 129, 210]	Moderate	NICE
Hypoglycaemia awareness - GOLD score	No meaningful difference	148[129, 210]	High	NICE
isCGM vs SMBG				
This comparison was not addressed in NG17.				
rtCGM vs isCGM				
DTSQ - status ≤ 6 months	MD 2.34 (1.15, 3.53) Effect is less than MID	254[113]	Moderate	NICE
Hypoglycemia fear scale (worry) ≤ 6 months	MD -2.62 (-4.52, -0.72) Effect is less than MID	254[113]	Moderate	NICE
Quality of life - physical health ≤ 3 months	Could not differentiate	60[125]	Moderate	NICE
Quality of life - psychological health ≤ 3 months	Could not differentiate	60[125]	Moderate	NICE
Quality of life - social relationships ≤ 3 months	Could not differentiate	60[125]	Moderate	NICE
Quality of life - environment ≤ 3 months	Could not differentiate	60[125]	Moderate	NICE

Key: GRADE - Grading of Recommendations Assessment, Development and Evaluation; isCGM – intermittently scanned continuous glucose monitoring; MD – mean difference; MID – minimally important difference; NICE – National Institute for Health and Care Excellence; rtCGM – real-time continuous glucose monitoring; SF – Short Form Health Survey; SMBG – self-monitoring of blood glucose.
Sources: NICE 2022.[2]

Table A5.2 Quality of life outcomes by comparison type from update search for RCTs

Outcome	Effect estimate	Participants	Source
rtCGM vs SMBG			
This comparison was not addressed in the trials.			
isCGM vs SMBG			
Diabetes Treatment Satisfaction Questionnaire (DTSQ) – 24 weeks	aMD 7.0 (5.2 to 8.7)	134	Leelarathna 2022
DTSQs, DTSQc	Improved satisfaction (5.6 units p < 0.001)	90	Secher 2021
Glucose Monitoring Satisfaction Survey (GMSS) Total	aMD 0.7 (0.5 to 0.9)	134	Leelarathna 2022
Type 1 Diabetes Distress Scale (T1DDS)	aMD -0.1 (-0.3 to 0.04)	134	Leelarathna 2022
Patient Health Questionnaire 9-item version (PHQ-9)	aMD -0.4 (-1.9 to 1.1)	134	Leelarathna 2022
Diabetes fear of injecting and self-testing questionnaire – fear of self-injection (D-FISQ FSI)	aMD -0.3 (-1.1 to 0.4)	134	Leelarathna 2022
D-FISQ - Fear of self-testing (FST)	aMD 1.5 (0.1 to 3.0)	134	Leelarathna 2022
The revised Diabetes Eating Problem Survey (DEPSR)	aMD -1.2 (-3.1 to 0.8)	134	Leelarathna 2022
Diabetes quality of life (ADDQoL-19), total score	Worsened in isCGM (−0.5, p =0.018)	90	Secher 2021
rtCGM vs isCGM			
This comparison was not addressed in the trials.			

Key: aMD – adjusted mean difference; isCGM – intermittently scanned continuous glucose monitoring; MD – mean difference; rtCGM – real-time continuous glucose monitoring; SF – Short Form Health Survey; SMBG – self-monitoring of blood glucose.
Sources: Leelarathna,[110] Secher 2021.[109]

Appendix 6. PubMed search strategy for economic evidence

- Database: PubMed
- Provider: National Library of Medicine, National Centre for Biotechnology Information (NLM NCBI)
- Date of search: 20 June, 2022
- Number of search results: 359

	Details	Free text terms	Thesauri terms
Population	Adults with type 1 diabetes	"type 1 diabet*" or "type I diabet*" or "type one diabet*" or "insulin dependent diabet*" or "juvenile onset diabet*" or "diabetic ketoacidosis" OR T1DM or "T1 DM" or T1D or IDDM	*MeSH:* Diabetes Mellitus, Type 1 (don't explode) Diabetic Ketoacidosis (explode)
Intervention	rtCGM and isCGM	"glucose monitor*" or "glucose sensor*" or FreeStyle or Dexcom or "Guardian Connect" or "Medtronic Guardian" or "Eversense XL" OR CGM or CGMs or FGM or FLFGM or rtCGM or isCGM	*MeSH:* None found
Study design	cost-effectiveness studies, cost-utility studies & economic evaluations	Standard HIQA filter for economic evaluations: ((((((((((((((((((models, economic[mesh]) OR "economics, pharmaceutical"[mesh]) OR "economics, medical"[mesh]) OR "health care costs"[mesh]) OR "decision support techniques"[mesh]) OR "cost-benefit analysis"[mesh]) OR "Cost of illness"[mesh]) OR "cost savings"[mesh]) OR "Hospital costs"[mesh]) OR "economic"[ti]) OR ("costs and cost analysis"[mesh])) OR economic evaluation*[ti]) OR economic analy*[ti]) OR cost analy*[ti]) OR cost eff*[ti]) OR cost benefit*[ti]) OR cost utilit*[ti]) OR ("economics"[mesh])) OR cost*[Title/Abstract])±	

±(Note: PubMed flagged that [ti/ab] was an unsupported field so this part of the search was updated to the supported field [Title/Abstract]

Appendix 7. Overview of cost-effectiveness evaluations

This appendix provides a more detailed description of the individual studies included in the review of cost-effectiveness studies (Section 5.1).

Non-industry funded economic evaluations

Health Quality Ontario

In February 2018, Health Quality Ontario published a HTA on rtCGM for T1DM.[168] The HTA was limited to continuous glucose monitoring (CGM) devices authorised for use in Canada at the time the HTA was undertaken, so did not consider isCGM devices. Health Quality Ontario estimated the cost effectiveness and budget impact of CGM compared with SMBG in people with type 1 diabetes, by undertaking a de novo economic evaluation. The cost-effectiveness analysis compared rtCGM with SMBG in adults using multiple daily insulin injections and rtCGM with SMBG in adults using an insulin pump. It was conducted from the payer's perspective, using a discount rate of 1.5% for costs and QALYs and a lifelong time horizon. It was reported that CGM was associated with higher costs and small increases in QALYs. It was concluded that CGM was not cost-effective at commonly used willingness-to-pay (WTP) thresholds (reported to be usually $50,000/QALY gained in Ontario). The adjusted ICERs in (QALY/Irish €) were €706,576 per QALY gained for the comparison of the standalone rtCGM versus SMBG in adults using multiple daily insulin injections, and €496,208 per QALY gained for the standalone rtCGM when compared to SMBG in adults using an insulin pump. The ICERs were associated with substantial uncertainty. Based on an estimated target population of 113,000 people with diagnosed type 1 diabetes and assuming a 20% annual increase in adoption of CGM, the net budget impact of publicly funding CGM in Ontario ranged from $8.5 million in year one to $16.2 million in year five.

National Institute for Health and Care Excellence

Two clinical guideline evidence reviews with health economic analyses were identified, their clinical impact aspects are discussed in section 4.1.

In March 2022, NICE published a series of evidence reviews and recommendations relating to the use of CGM in adults with type 1 diabetes.[2] A de novo economic evaluation was conducted as part of this assessment comparing the cost effectiveness of rtCGM vs SMBG, and isCGM vs SMBG in this population. Two scenarios were considered in which reduced fear of hypoglycaemia was and was not included as an additional utility. In the first scenario (reduced fear of hypoglycaemia

not included) isCGM was a cost-effective alternative to SMBG at a willingness-to-pay threshold of £20,000 per QALY (estimated ICER of £10,157 per QALY gained); rtCGM only appeared cost effective at a WTP threshold of £30,000 threshold (estimated ICER of £24,436 per QALY). In the second scenario (additional utility benefit associated with reduced fear of hypoglycaemia included), rtCGM was cost effective compared with SMBG at a threshold of £20,000 per QALY, with an estimated ICER of £16,351 per QALY. Inclusion of reduced fear of hypoglycaemia as an additional utility, resulted in lower ICERs (that is, more cost effective) for rtCGM. In this scenario, isCGM was not added to the model because it was already reported as clearly cost effective and there is a lack of data on fear of hypoglycaemia with isCGM.[2] The higher ICERs for rtCGM than those for isCGM, were noted to be principally driven by the higher costs used for the devices in the base-case analysis. The NICE committee noted that there was limited evidence directly comparing rtCGM and isCGM, the technologies were rapidly evolving with newer versions being released over time, and although isCGM monitoring was currently cheaper than rtCGM, there was no guarantee this would remain the case in the future.

In March 2020, NICE published an evidence review[1] and recommendations relating to the use of CGM in women with type 1 diabetes who are planning to become pregnant or who are already pregnant. No existing cost–utility studies applicable to glucose monitoring in pregnancy was found in a literature review. An original health economic analysis was undertaken comparing the cost effectiveness of three possible interventions to each other: rtCGM, isCGM (flash) and SMBG. In the base case cost-utility analysis, isCGM was found to dominate both rtCGM and SMBG as it was both less expensive and resulted in the highest QALY gain (although, in the comparison with rtCGM, the difference was very small). Although isCGM (flash) was found to be the cost-effective option in the economic modelling, the NICE committee noted limitations with the model and evidence base which, coupled with their clinical experience and expertise, led them recommending rtCGM over flash for use in women with type 1 diabetes during pregnancy.

Scottish Health Technologies Group

In July 2018, the Scottish Health Technologies Group published an Evidence Note[179] and associated Advice on the clinical and cost effectiveness of FreeStyle Libre the isCGM system for people with diabetes treated with intensive insulin therapy. Of note the economic model from this HTA has been included in several of the more recently published HTAs mentioned by others in this section. An NHS perspective, lifetime horizon and discount rate of 3.5% was used for all costs and benefits. Initial findings from a de novo cost effectiveness analysis reported that FreeStyle Libre was cost effective for people with T1DM. The ICER for FreeStyle Libre compared with SMBG ranged from £2,459 to £12,340 per QALY in T1DM, depending on the

modelling approach considered. The adjusted ICERs in (QALY/Irish €) were €3,049 and €15,303, respectively. One-way sensitivity analyses indicated FreeStyle Libre was still likely to be cost effective under a wide range of scenarios and cost saving against SMBG when a mean number of eight blood glucose tests per day was considered. Assuming an uptake rate of 30% in year 1 rising to 50% by year 5, the budget impact for NHS Scotland of FreeStyle Libre was estimated to be £3.3m in year 1 rising to £6.8m by year 5 in the T1DM population.

Health Technology Wales

In July 2021, Health Technology Wales published an evidence appraisal report[167] and corresponding guidance regarding the use of isCGM for the management of diabetes. A de novo economic model was developed to estimate the cost effectiveness of introducing isCGM, using the FreeStyle Libre device, for people with T1DM (and T2DM who require daily injections of insulin). The model focused on the impact of isCGM on the cost of glucose monitoring, managing hypoglycaemia and the associated impact on quality of life. A UK NHS and personal social services (PSS) perspective, 50 year time horizon (to cover lifetime) and 3.5% discount rate for costs and benefits were applied.

- The findings of this model indicated that the use of isCGM was a cost-effective intervention compared with SMBG with ICERs of £4,706 per QALY gained for T1DM, at a willingness-to-pay threshold of £20,000 per QALY gained. The adjusted ICERs in (QALY/Irish €) were €5,492 per QALY gained. Sensitivity analysis showed that the key areas of uncertainty were the baseline SMBG testing frequency and the quality of life benefits associated with reducing non-severe hypoglycaemic events.[167]

- Evidence from three cost-utility analyses[112, 217, 218] identified in a literature review conducted as part of the HTW assessment showed the potential for isCGM to be cost effective in cost per QALY terms. However, there was uncertainty around key assumptions in the analyses, such as the inclusion of a process-related improvement in quality of life associated with using flash glucose monitoring. This improvement was based on a study, which elicited preferences from the general population rather than people with diabetes.[167]

- Economic evidence (from the de novo model and previously published literature) showed the potential for the higher upfront costs of isCGM systems to be offset, at least partially, by reductions in the frequency of SMBG tests and non-severe hypoglycaemic events. It was noted that further cost savings and benefits with isCGM may be achieved through a reduction in severe hypoglycaemic events or improvements in HbA1c. However, there was uncertainty around these potential effects.[167]

- In September 2019, HTW published an evidence appraisal report[143] and corresponding guidance[196] regarding rtCGM in pregnant women with T1DM. In a literature review, one economic study[219] was identified that analysed the overall costs associated with the use of rtCGM plus SMBG compared with standard management (SMBG alone) in pregnant women with T1DM. This study reported a reduction in complications which led to a net saving in the rtCGM plus SMBG group. De novo modelling, using a cost-minimisation approach, was undertaken by HTW to estimate the overall resource impact of rtCGM, used as an adjunct to SMBG, compared with SMBG alone on the basis of the results of this previously published study and in the context of clinical practice in NHS Wales. The results showed that rtCGM was likely to lead to overall costs savings of approximately £1,029 per pregnancy, with the cost savings largely driven by a reduction in the incidence and duration of neonatal intensive care unit (NICU) admission. However, there was uncertainty regarding NICU estimates. It was noted that there was insufficient evidence to develop a detailed evaluation of CGM plus SMBG in comparison with flash glucose monitoring.

- A budget impact analysis was conducted as part of this assessment,[143] and depending on the population estimates and adoption uptake levels, implementation of CGM in pregnant women with type 1 diabetes was estimated to result in annual cost savings for NHS Wales of between £52,994 and £334,425.

García-Lorenzo et al. 2018

A systematic review with a cost-effective analysis published in 2018 from Spain by García-Lorenzo *et al.*,[177] was based on an electronic search up until February 2017. They compared rtCGM to SMBG in adults with T1DM and T2DM using a Markov model. A Spanish Health Service perspective, lifetime horizon and discount rate of 3% were applied. In the T1DM sub-group the mean incremental cost per person was €118,135, the mean incremental QALY was 0.05 per patient and the ICER was €2,554,723 per QALY gained. The adjusted ICER in (Irish €) was €3,292,186 per QALY gained. The authors concluded that rtCGM was not cost effective when compared with SMBG.

This study has received criticism from Moreno Fernandez 2019[220] for the methods used to calculate cost effectiveness. Specifically, the criticism focused on the studies used to calculate the reduction in costs, the exclusion of short-term costs associated with hypoglycaemia, focusing exclusively on an rtCGM system by Medtronic. It was claimed that calculation using the Dexcom G5 (also available in Spain at the time of the study) would have resulted in an ICER within the WTP threshold of €25,000 used at that time in Spain.

McQueen et al. 2011

A Markov cohort analysis[172] was conducted by McQueen et al. in the U.S. comparing three rtCGM systems (Guardian Real - Time, Dexcom seven, and MiniMed Paradigm Real - Time) and SMBG to SMBG alone in adults with T1DM on intensive insulin therapy. A societal perspective, time horizon of 33 years, (assuming a life expectancy of 73 years) and discount of 3% for costs and QALYs were applied. In the base case analysis, rtCGM plus SMBG was associated with a gain in quality adjusted life expectancy of 0.523 QALYs and an increase of USD $ in mean total lifetime costs when compared with SMBG alone. The authors reported that use of rtCGM plus SMBG led to an ICER of USD $45,033 per QALY and concluded that rtCGM systems with SMBG is a cost-effective solution when compared with SMBG alone for adults with an A1c level greater than 8%. The adjusted ICER in (QALY/Irish €) was €53,030 per QALY gained. The authors highlighted the fact that they did not model hypoglycaemic events, as a limitation in the analysis.

Norwegian Institute of Public Health

In August 2018, the Norwegian Institute of Public Health (NIPH) published a single technology assessment on isCGM.[221] This report examined the cost effectiveness of isCGM compared with SMBG for individuals with type 1 (and 2) Diabetes Mellitus, based on an economic model that was submitted by a third party. The submitter's base case suggested that the technology is dominant for individuals with T1DM, that is, that FreeStyle Libre is a cheaper and more effective technology. Of note, the WTP threshold in Norway was not stated. However, the NIPH was critical of the submitted model as it was assessed to lack transparency and flexibility. Given these issues, the NIPH concluded that the ICER estimates were unreliable and thus the cost effectiveness of isCGM could not be determined. For this reason, this HTA is mentioned for informational purposes, and its analysis is not reported in this rapid HTA.

Industry-funded economic evaluations

Bilir et al. 2018

A cost-effectiveness analysis published in 2018 by Bilir et al.[178] compared isCGM with SMBG for people with T1DM receiving intensive insulin treatment in Sweden. A Swedish payer/societal perspective, 50-year time horizon (assumed equal to lifetime) and 3% discount of costs and effects were applied. The base case results reported that the direct medical costs (unit cost year = 2016) were Swedish Krona SEK 1,222,333 for isCGM versus SEK 989,051 for SMBG. isCGM was associated with 0.80 QALYs for an ICER of SEK 291,130/QALY. The adjusted ICER in (Irish €) was €26,710/QALY. Ten different scenarios were explored and ICERs for all scenarios

remained under SEK 400,000/QALY. The authors concluded that isCGM led to a modest reduction in costs and when compared to SMBG is cost effective. Sweden does not have a national WTP threshold however this figure was chosen because it was the average ICER at which other interventions have been approved. The authors acknowledge that SEK 500,000/QALY is considered the informal threshold and much greater WTP thresholds have been used in the past.[178] This study was funded by Abbott Diabetes Care.

Chaugule et al. 2017

In 2017, Chaugule et al. published a cost-effectiveness analysis from the Canadian societal perspective comparing rtCGM (Dexcom G5 Mobile) versus SMBG alone people with T1DM using multiple daily injections (MDI).[169] They applied a 50-year time horizon and a discount rate of 1.5% to costs and outcomes. In the base case analysis, rtCGM led to an additional 3.35 QALYs and an ICER of $33,789 CAD/QALY versus SMBG alone. Based on this, the authors found the rtCGM system cost effective at a WTP threshold of CAD$50,000/QALY. The adjusted ICER in (Irish €) was €21,765 per QALY gained. In the sensitivity analysis, changing the discount rate, baseline starting utility or baseline starting %HbA1c level made no difference, however changing the severe hypoglycaemic event reduction rate had a moderate impact. Increasing the severe hypoglycemic event reduction rate from 50% to 75% resulted in an ICER of Canadian dollars $29,140/QALY gained and decreasing the rate from 50% to 25% resulted in an ICER of $39,662/QALY. Increasing and decreasing hypoglycemia-related disutilities by 50% produced ICERs of $65,363/QALY gained and $22,783/QALY gained, respectively. Dexcom, Inc. provided funding support for this study.

Huang et al. 2010

Huang et al. conducted a cost effectiveness analysis in the US comparing three rt-CGM devices (DexCom Seven, Medtronic Guardian, and Abbott FreeStyle Navigator) to SMBG for six months.[171] There were two study groups: a cohort with A1C ≥ 7.0% stratified into three pre-specified age-groups (8–14, 15–24, and ≥25 years), and a cohort with A1C <7.0% of all ages. The societal perspective and a lifetime time horizon (for the lifetime analyses) were applied. A discount rate was not provided. The base case analysis for the adult (aged 25 years or older) A1C ≥7.0% resulted in an ICER of US dollars $98,679/QALY with 95% confidence intervals (CIs) ranging from $60,007 (fourth quadrant dominant) to $86,582 (second quadrant dominated). This range increased the uncertainty about the ICER point estimate. The authors noted that rtCGM was not cost effective at the $50,000 WTP threshold, but highlighted that recent studies had argued that the threshold should be between $109,000 and $297,000/QALY. The adjusted ICER in (QALY/Irish €) was €112,049. Results for the A1C < 7.0% cohort were not broken down by age, so it was not

possible to extract the data for adults meeting the inclusion criteria for this rapid HTA. The CGM systems were provided at a reduced cost by each manufacturer. Lifescan and Abbott Diabetes Care supplied SMBG elements. Multiple authors received consulting, speaker, research or travel reimbursement fees from industry (Abbott Diabetes Care, Medtronic MiniMed, Roche, Lifescan, Animas Corp).

Isitt et al. 2022

A cost-effectiveness analysis published in 2022[174] compared rtCGM (Dexcom G6) with SMBG and rtCGM (Dexcom G6) with isCGM (FreeStyle Libre 1) in adults with T1DM. The Australian healthcare payer perspective, a lifetime horizon and a discount rate of 5% for costs and clinical outcomes were applied. Compared with SMBG, rtCGM was associated with an increase of 1.199 QALYs, an AUD $21,596 increase in mean total lifetime costs and an ICER of AUD $18,020 per QALY gained. The adjusted ICER in (Irish €) was €10,250/ QALY. The likelihood of rtCGM being cost effective was 99.7% when a WTP threshold of AUD $50,000 per QALY gained, was applied. Compared with isCGM, rtCGM was associated with an increase of 0.569 QALYs, an AUD $11,064 decrease in mean total lifetime costs and an ICER of AUD $19,455 per QALY gained. The adjusted ICER in (Irish €) was €11,066/ QALY. The likelihood of rtCGM being cost effective was 89.4% when a WTP threshold of AUD $50,000 per QALY gained, was applied. The authors concluded that in adults with T1DM and inadequate glycaemic control (HbA1c ≥ 59 mmol/mol [7.5%]), rtCGM is a cost-effective management option in maintaining optimal glycaemic control. This study was funded by Dexcom.

Roze et al. 2020

Published in 2020, Roze et al. conducted a health economic analysis from a UK perspective using data sourced from the DIAMOND trial.[166] The analysis compared rtCGM (Dexcom G6) and SMBG alone in adults with T1DM. They applied the UK healthcare payer perspective (National Health Service and personal social services) perspective, a lifetime time horizon and a discount rate of 3.5% to future costs and clinical outcomes. In the base case analysis, rtCGM was associated with an incremental gain of 1.49 QALYs, an increase of GBP 14,234 in mean total lifetime costs and an ICER of GBP 9,558 per QALY gained. The adjusted ICER in (Irish €) was €11,396/QALY. The likelihood of rtCGM being cost effective compared with SMBG was 99%. Dexcom provided funding for this study and multiple authors were either Dexcom employees or had received consulting fees from Dexcom.

Roze et al. 2021

Roze et al. also conducted a health economic analysis from the Canadian perspective comparing rtCGM (Dexcom G6) and SMBG in adults with T1DM, published in

2021.[170] They applied a public payer perspective, a lifetime time horizon and a discount rate of 1.5% for costs and clinical outcomes. They reported that rtCGM was associated with a mean gain of 2.09 QALYs, an increase of CAD $ 35,353 in mean direct lifetime costs and an ICER of CAD $16,931 per QALY gained when a WTP threshold of CAD $50,000 per QALY gained, was applied. The adjusted ICER in (Irish €) was €10,745/QALY. The likelihood of rtCGM being cost effective compared with SMBG was 99.7%. The authors noted that the higher cost of the rtCGM system CAD $57,737 was in part offset by lower costs associated with reduced long-term complications and delayed mean time to onset of some long-term complications. Dexcom funded this study and multiple authors were Dexcom employees or had received consulting fees from Dexcom.

Roze et al. 2021

In a third study published in 2021, Roze et al.[176] used (Dexcom G4) data from the DIAMOND trial and projections to compare rtCGM (Dexcom G6) with SMBG in adults with T1DM living in France. A payer perspective, lifetime time horizon and discount rate 4% for future costs and clinical outcomes (as recommended by Haute Autorité de Santé) were applied. They found that rtCGM was associated with a mean gain in of 1.38 QALYs, a €21,087 increase in mean lifetime costs and an ICER of €15,285 per QALY gained. The adjusted ICER in (QALY/Irish €) was €16,391/QALY. Even though France does not have a WTP threshold, when a threshold of €50,000 was applied the likelihood of rtCGM being considered cost effective compared to SMBG was 100%. This analysis was funded by Dexcom who also paid the publishing journal's rapid service fee.

Wan et al. 2018

Published in 2018, Wan et al. conducted two cost-effectiveness analyses (CEAs) from the societal perspective in the US, the first within the DIAMOND RCT[173] using observed trial data and the second was a lifetime CEA using a modified Sheffield T1D policy model. They compared rtCGM (Dexcom G4 although two of the sensitivity analyses not reported here considered Dexcom G5) versus SMBG in people with T1DM and elevated HbA1c levels (≥7.5%) using multiple daily injections of insulin. A societal perspective and discount rate of 3% for costs and health utilities were applied. This study was partly funded by Dexcom.

- During the six month duration of the within-trial CEA, there was no clinically or statistically significant difference in QALYs between the two groups. For the rtCGM group there was an average increased total cost of USD $3,796, $2,554 of which was the cost of the rtCGM device. Due to the lack of difference between QALYs, an ICER was not calculated. The authors reported that rtCGM was dominated by SMBG.

- In the long-term CEA the base case analysis reported that the increase in quality-adjusted life expectancy was 0.54 QALYs. The ICER in the base-case was estimated at $98,108 per QALY. The adjusted ICER in (Irish €) was €90,782 per QALY. The lifetime analysis accounted for the potential for reductions in the risk of major T1DM complications such as blindness, end-stage renal disease, amputation as well as myocardial infarction, stroke and heart failure. In approximately 90% of the 200 probabilistic sensitivity analyses (PSA), rtCGM was cost effective at a WTP threshold of USD $100,000 per QALY.

Zhao et al. 2021

In a cost effectiveness study[175] from China, Zhao et al. conducted an RCT analysis and a real-world evidence scenario where they modelled the HbA1c treatment effect in a hypothetical cohort using parameters closest to the Chinese population with T1DM. They compared isCGM (FreeStyle Libre - the individual version and FreeStyle Libre H – the hospital version) with self-monitoring of blood glucose/point of care testing (SMBG/POCT) in adults with T1DM and T2DM receiving insulin therapy. The authors applied the Chinese societal perspective, a lifetime horizon and a 5% discount rate to costs and health outcomes.

- In the RCT scenario isCGM was associated with an incremental benefit of 1.22 QALYs and an increased cost of Chinese yuan (CNY) 元58,021 when compared with SMBG/POCT for adults with T1DM. When a WTP threshold of 元217,341 was applied, isCGM was cost effective and led to an ICER of 元 47,363 per QALY gained, for adults with T1DM.
- In the RWE scenario, isCGM was associated with an incremental benefit of 1.32 QALYs and a decreased cost of 元1718. isCGM dominated SMBG/POCT in adults with T1DM.

The authors reported that although isCGM was more expensive than SMBG/POCT, costs associated with acute events such as diabetic ketoacidosis and hypoglycaemia (and indirect costs such as productivity loss) may offset costs. This study was funded by Abbott Diabetes Care who also paid the publishing journal's rapid service fee, and the employer of four of the authors received funds from Abbott.