Clinical Guideline

A Practical Approach to the Management of Continuous Glucose Monitoring (CGM) / Real-Time Flash Glucose Scanning (FGS) in Type 1 Diabetes Mellitus in Children and Young People Under 18 years

FOR STAFF Healthcare professionals involved in care of children and young people with Type 1 Diabetes Mellitus

PATIENTS Children and young people with diabetes mellitus

This guideline is intended for use in managing continuous glucose monitoring (CGM) or real-time flash glucose scanning (FGS) for all children and young people under 18 years with Type 1 diabetes mellitus.

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Introduction

Real-time continuous glucose monitoring (CGM) and flash glucose scanning (FGS) are new and evolving technologies in the management of type I diabetes. They offer the potential to improve glycaemic control and reduce hypoglycaemia. In addition CGM can be linked to insulin pump therapy providing sensor augmented pump technology (SAPT). Many families and children are keen to have the opportunity to benefit from these technologies. However they are relatively expensive and there may be tensions between families, support groups and clinicians who feel that the technology is likely to be beneficial and should be made available and commissioners/funders who are understandably concerned about costs within constrained budgets. In order to ensure that healthcare professionals, families and children are appropriately informed and educated on these technologies, the Association of Children’s Diabetes Clinicians (ACDC) has developed a comprehensive guideline to help identify which patients may be most likely to benefit and how these technologies may be practically implemented and utilised in order to maximise the clinical benefits.

The National Institute of Clinical Excellence (NICE) has produced two guidelines relevant to the use of CGM. The ACDC guideline has been developed within the framework of the existing NICE guidance. In its clinical guideline regarding the management of children and young people with type I and type II diabetes NG18 published in August 2015 NICE made a number of recommendations regarding the clinical scenarios in which the use of CGM may be appropriate [1]. A further diagnostics guidance DG21 published in February 2016 also made recommendations regarding the use of sensor augmented pump therapy and in particular which sensors and pumps should be considered [2]. A further publication Medtech Innovation Briefing (MIB) 51 regarding the Medtronic Minimed™ 640G has also been produced [3].

This guideline has 2 key sections:

Section 1  A review of the evidence to support the use of CGM and FGS and recommendations regarding patient selection, criteria for regular use, criteria for diagnostic use and circumstances where technology should be withdrawn. It covers sport and driving.


This section is intended as an introduction for paediatric diabetes teams to support implementing CGM, FGS and SAPT. As part of the guideline, ACDC has also produced a series of patient information leaflets that will support structured education for families and children for each system and an education resource toolkit for diabetes healthcare professionals to facilitate the structured education program. All these material will be available free on the ACDC website www.a-c-d-c.org
Overview of Pertinent NICE guidance

The NICE recommendations in its guideline NG 18 for the management of children and young people with diabetes regarding the use of CGM are as follows [1]:

1.2.62 Offer ongoing real-time continuous glucose monitoring with alarms to children and young people with type 1 diabetes who have:

- frequent severe hypoglycaemia or
- impaired awareness of hypoglycaemia associated with adverse consequences (for example, seizures or anxiety) or
- inability to recognise, or communicate about, symptoms of hypoglycaemia (for example, because of cognitive or neurological disabilities).

1.2.63 Consider ongoing real-time continuous glucose monitoring for:

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

1.2.64 Consider intermittent (real-time or retrospective) continuous glucose monitoring to help improve blood glucose control in children and young people who continue to have hyperglycaemia despite insulin adjustment and additional support.
The NICE guidance is the framework within which this detailed guideline has been developed. Technology is rapidly evolving and formal guidelines inevitably lag behind the latest technology available. NICE has also issued a diagnostics guidance DG21 relating to sensor augmented pump therapy (SAPT) and when it should be considered [2]. DG21 suggested that:

"NICE recommends the use of sensor augmented pump therapy systems (specifically the integrated Minimed Paradigm Veo insulin pump and CGM system) for children and young people with type 1 diabetes providing:

- they have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion
- the system is used under the supervision of a multidisciplinary team who are experienced and appropriately trained in integrated sensor augmented insulin pump therapy"

There must be agreement that the CYP with diabetes and/or their parents(s)/carer(s):

- agrees to use the sensors for at least 70% of the time
- understands how to use it and is physically able to use the system
- agrees to use the system while having a structured education programme on diet and lifestyle, and counselling.

Once commenced, the sustained use of the MiniMed Paradigm Veo system should only continue providing there is evidence that:

- they have a decrease in the number of hypoglycaemic episodes that is sustained. Appropriate targets for such improvements should be set.

Individuals with type 1 diabetes already using the Minimed Paradigm Veo or G4 Platinum CGM systems who do not meet the recommendations within the NICE guidance should continue with its use until it deemed appropriate by the child or young person and their diabetes team to discontinue.

"MiniMed Paradigm Veo system is recommended as an option for managing blood glucose levels in people with type 1 diabetes only if they have disabling hypoglycaemia"

"The Vibe and G4 PLATINUM CGM system shows promise but there is currently insufficient evidence to support its routine adoption in the NHS for managing blood glucose levels in people with type 1 diabetes"

"MiniMed™ 640G system has not been assessed in the guidance, and the recommendations, therefore, do not relate to its routine use in the NHS"
NICE has produced a Medtech Innovation Briefing (MIB) regarding the Medtronic Minimed™ 640G (which was not included in the DG21 review as it was not at that stage available) [3]. MIBs are not NICE guidance. They differ in format, contain no judgement on the value of the technology and do not constitute a guidance recommendation. MIBs are commissioned by NHS England and produced in support of the NHS 5 Year Forward View, specifically as one of a number of steps which will accelerate innovation in new treatments and diagnostics. MIB51 suggests that:

“There is no evidence that the Medtronic Minimed™ 640G system has any further benefit in reducing the risk of hyperglycaemia compared with any other pump systems” (MIB51)

Recommended use of the Medtronic Minimed™ 640G (3) include:

- Children and young people with type 1 diabetes who experience problematic blood glucose levels undertaking capillary self-monitoring and multiple daily injections
- those who have difficulty identifying hypoglycaemia
- those with a history of severe hypoglycaemia
- those susceptible to nocturnal hypoglycaemia
- those with a fear of either daytime or night time hypoglycaemia

The NICE guidance does not currently cover the use of the FreeStyle Libre system, by Abbott which is a flash glucose scanning (FGS) or sensor glucose monitoring device (without alarms). It is not a true real-time continuous glucose monitoring system. However many parents are self funding this (as it is less expensive than full CGM). Reimbursement is not yet available on the NHS.

The NICE Quality Standard for Children and Young People (QS125, published July 2016) also include a quality statement regarding CGM in Type 1 Diabetes:

Quality statement 4: Continuous glucose monitoring in type 1 diabetes
Children and young people with type 1 diabetes who have frequent severe hypoglycaemia are offered ongoing real-time continuous glucose monitoring with alarms

Rationale
Continuous glucose monitoring helps children and young people with type 1 diabetes and their family members or carers (as appropriate) to respond more quickly to changes in blood glucose levels throughout the day. For children and young people with frequent severe hypoglycaemia (particularly those who have difficulty recognising or reporting it), continuous glucose monitoring can help to improve their control of blood glucose and HbA1c levels.
**Devices Available for CGM and FGS**

<table>
<thead>
<tr>
<th>Stand alone systems</th>
<th>Sensor augmented pumps</th>
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<tbody>
<tr>
<td><strong>Medtronic Minimed™ 640G with Smart Guard and VEO with Low Glucose Suspend</strong></td>
<td><strong>Medtronic 640g &amp; Enlite Sensor</strong></td>
</tr>
<tr>
<td><strong>Dexcom CGM G4</strong></td>
<td><strong>Animas Vibe with Dexcom G4</strong></td>
</tr>
<tr>
<td><strong>Dexcom CGM G5</strong></td>
<td></td>
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<tr>
<td><strong>The FreeStyle Libre System (Flash Glucose Sensing)</strong></td>
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- **Stand alone systems**
  - Medtronic Minimed™ 640G with Smart Guard and VEO with Low Glucose Suspend
  - Dexcom CGM G4
  - Dexcom CGM G5
  - The FreeStyle Libre System (Flash Glucose Sensing)

- **Sensor augmented pumps**
  - Medtronic 640g & Enlite Sensor
  - Animas Vibe with Dexcom G4

- It can be used as a stand alone system (Medtronic Guardian with Enlite sensor. It is more commonly used as an integrated system where insulin pump acts as a receiver of CGM data. The auto suspend feature helps in suspending the pump if glucose level hits a continuous glucose monitoring system which can be used as a stand-alone or integrated with Animas pump where CGM data can be viewed on the pump.

- Continuous Glucose monitoring system which can be used alone. It can send data wirelessly to a compatible smart phone. It is FDA approved and CE mark approved in Europe to make treatment decisions upon its results and is a newer version compared to G4. G5 is the first remote glucose sensor.

- The Sensor continuously measures glucose every minute and it stores this glucose data every 15 minutes. The Sensor stores up to 8 hours of glucose data, so you only needs to scan the Sensor 3 times in a 24-hour period to capture the complete glycaemic picture.

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threshold (VEO) or is predicted to hit a threshold in the next 30 minutes (640G). The 640g has superseded the Veo monitoring system that is licenced to make dosing decisions from without checking with a finger prick.

approximately 90-days of glucose history and notes you enter about activities, such as taking insulin, eating food, or exercising.

| MARD | 13.6% | 15% - Paediatrics | 10% - Paediatrics |
| Sensor Glucose Measurement | Every 5 mins | Every 5 mins | Every 5 mins |
| Licence | Age 2 and above | Age 2 and above | Age 2 and above |
| Sensor | | | |
| Duration | 6 days | 7 days | 7 days | 14 days |
| Calibration | Yes | Yes - Twice per day | Yes – Twice per day | No |
| Alarms | Yes | Yes | Yes | No |
| Trend Arrows | Yes | Yes | Yes | Yes |
| Predictive low glucose suspend | Yes | No | No | No |
| Charging | Transmitter should be charged after 6 days of usage. Needs charging for 20 mins. | Receiver needs charging every 3 days. Transmitter has battery that lasts 6 months. Needs replacement after that | Transmitter has battery that lasts 3 months. Needs replacement after that | A fully charged Reader battery should last up to 7 days. Battery life may vary depending on usage. |
| Transmission | Sensor and transmitter to be worn together with pump. Sensor should be inserted at | Receiver has to be within 6 metres of the transmitter to receive transmission | Receiver and/or smart phone device has to be within 6 metres of the transmitter to receive | Every time the Reader is flashed near the sensor |
| **BG testing compatibility** | Bayer meter is compatible with the pump and sensor. For calibration if test done on the compatible meter, it will automatically enter the BG levels for calibration | Blood glucose reading has to be entered manually into the Dexcom receiver or Animas vibe pump | Blood glucose reading has to be entered manually into the Dexcom receiver/Smart phone Device | The Reader can also be used as a manual blood glucose or blood ketone testing device. It is compatible with FreeStyle Optium test strips |
| **Waterproofing** | Pump and transmitter is waterproof up to 3.6 metres for up to 24 hours | Receiver is not waterproof. Pump, Sensor and transmitter is waterproof for up to 2.44 metres for a maximum of 24 hours | Receiver is not waterproof. Sensor and transmitter is waterproof for up to 2.44 metres for a maximum of 24 hours | Reader is not water resistant. Sensor is water-resistant for 30 min in up to 1 metre deep water |
| **Compatible with Diasend** | No | Yes | Yes | Yes |
| **Ability to have followers** | No | No | Yes | Yes |
| **Costs*** | £585 for starter pack Sensor cost: £3195 per year if worn 365 days/year | Initial Starter Kit = £661.25 ex VAT for G4 receiver + 1 Transmitter + 1 sensor Total annual cost up to £3,255 including sensors and 2 transmitters. 1 G4 transmitter = £260 With Animas Vibe – Pump starter kit £500 excl VAT- £600 incl VAT (1 transmitter & 4 sensors). Four Sensors £186 excl VAT (£223 incl VAT). Annual cost £3088 excl VAT (£3,705 incl VAT) | Initial Starter Kit = £251.25 for 1 transmitter + 1 sensor (Optional receiver = £275) Total annual cost up to £3,260 including sensors and 4 transmitters 1 G5 transmitter = £200 | Initial cost: £133 Starter Pack (a Reader and two 14-day sensors) £48.29 per 14-day sensor. You can order up to 10 sensors per order. |

*Note prices of hardware are constantly changing and may vary*
MARD scores

MARD scores (Mean Absolute Relative Difference) relate to the accuracy of the sensor. A combination of the MARD score and Clarke Error Grid plots define the accuracy of CGM systems. MARD scores for meters to measure capillary blood glucose are typically 5-10%. Bear in mind the score does vary and accuracy does vary according to the level of the blood glucose. Accuracy may fluctuate depending on whether the blood sugar is high or the blood sugar is low. Accuracy may also fluctuate during the lifetime of the sensor. Typically it is thought to decline as the sensor ages. A MARD score <10% is generally considered reliable enough to make treatment decision. Only the Dexcom G5 is licenced for treatment decisions. In other cases a confirmatory blood glucose sample should obtained. The other factor that needs to be taken into account is the time delay in the recording of CGM sensors.

CGM Systems measure glucose levels in the interstitial fluid not directly in the blood. Therefore time is needed these two levels to achieve equilibrium. If the blood sugar is rising rapidly or the blood sugar is falling rapidly there can be a noticeable difference. The average physiological time delays assumed to be in the range of 5 to 10 minutes for CGM.

The lag time for the FreeStyle Libre which is a flash glucose monitor is 4.5 – 4.8 minutes.
Section 1: Evidence to Support the Use of CGM and Recommendations Regarding Patient Selection, Criteria for Regular Use and Use in Diagnostics

Evidence Review

Several systematic reviews and meta-analyses have been undertaken examining the impact of CGM on HbA1c and hypoglycaemia in particular. These included a review by NICE and a Cochrane systematic review amongst others [1, 4]. In addition to reviewing these studies, as part of the development of the guideline a series of additional separate but overlapping literature searches were undertaken to address specific questions not covered within the scope of previous systematic reviews. The search strategies for the guideline are outlined in Appendix A. Details and discussion of the evidence underpinning the use of CGM and results of the individual studies that underpin the guideline are detailed in Appendix B. The evidence and subsequent recommendations were graded according to the quality and strength of the evidence (See Appendix C).

On reviewing the literature the guideline development group noted the following key limitations:

- The studies are only of a short duration. Some studies suggest that the beneficial effect of CGM declines over time [4].
- Study numbers are small and often only a small proportion of those are children. Younger children are especially poorly studied. Few studies considered children less than 8 years. Given the small numbers many studies were not adequately powered to detect statistical differences.
- Studies concentrate on older children. It may be more useful in those too young to be aware of hypoglycaemia or to manage their diabetes independently? This question is not addressed in the published literature
- The assumption is that improving HbA1c and reducing glucose variability with CGM will reduce complications but no studies have been of a sufficient duration to test this hypothesis.
- Some devices studied are no longer commercially available. Is new technology better than that available for older studies? More recent studies tend to show improved results. It is unclear whether this is related to technological advances or whether the technology is being used more effectively?
- A significant number of patients declined to be involved in studies [5]. This suggests that CGM use is not desirable for all patients. In addition, those who agreed to be included in studies may be more motivated with regards to their treatment, than the general clinic population.
- Use of CGM may decline over time. In studies less than 50% of individuals used CGM >70% of the time and at 1 year 41% had discontinued use altogether [6, 7]. The reasons eg physical issues (eg skin, pain), effort of use or effect on QOL (eg alarms) is not clear.
- The patient selection process is poorly reported in many studies.
- All of the major trials excluded patients with the highest incidence of hypoglycaemia and those with severe hypoglycaemia. The primary end-points in most trials were reduction in HbA1c and not hypoglycaemia reduction.

The guideline group reached the following conclusions:

- The evidence base for CGM is weak with many studies underpowered and not definitively conclusive. Evidence was most prevalent for impact on HbA1c and on incidence of hypoglycaemia (Level 1-). Few if any studies addressed the impact on quality of life, economic impact or on aspects of CGM use such as exercise.

- CGM has been shown to lead to modest reduction in HbA1c both with insulin pump therapy (CSII) and in those on multiple daily injections (MDI). However this was not demonstrated universally in all studies. Improvement was approximately 0.3-0.5% HbA1c in the majority of studies (Level 1-). Individual RCT’s demonstrated stronger evidence of benefit that systematic reviews and meta-analyses.

- CGM reduces the incidence of hypoglycaemia, particularly nocturnal hypoglycaemia, both with CSII and MDI (Level 1+). But again this effect was not demonstrated in all studies. CGM seems to have the most positive effect on reducing (but not eliminating) hypoglycaemia in motivated patients with good metabolic control who are compliant with sensor wear.

- The efficacy of CGM improves with greater frequency of use. The highest efficacy is seen with usage >60% of the time (Level 1++)

- Fear of hypoglycaemia is reduced with sensor augmented pump therapy (SAPT). Some studies suggested improvement in QOL but there has been no rigorous assessment of QOL.

- Sensor augmented low glucose suspend pump therapy reduced the incidence of hypoglycaemic events particularly nocturnal hypoglycaemia [8, 9] (Level 1+)

- Successful use of CGM and SAPT is likely to require intensive support and education. The degree to which support and the more advanced functions of CGM may optimise therapy is not well documented in the published studies

Patient Selection

As previously discussed the NICE guidance states CGM can be considered for use for the following indications:

- Hypoglycaemic seizures
- Frequent severe hypoglycaemia
- Impaired awareness of hypoglycaemia
- Anxiety regarding hypoglycaemia
- Inability to recognise hypoglycaemia due to cognitive or neurological disabilities
- Young children who may not be able to recognise and respond
- Exercise – where high levels of physical activity are undertaken and risk of hypoglycaemia is high
- Hyperglycaemia - To reduce HbA1c, improve glycaemic control or reduce Glycaemic Variation
There are no studies which specifically look at comparative selection of patients for any of the indications above. In view of this the methodologies and results of CGM studies in children and young people (CYP) were reviewed to identify characteristics of the selection criteria utilised, and determine whether there were factors identified in the selection of patients that potentially influenced the outcome of CGM therapy. The findings informed the following recommendations as to whom and when CGM may be appropriate:

The evidence confirms CGM can be an effective and safe intervention for children and young people of any age, socioeconomic status, ethnic or educational background [10]. Psychological variables including fear of hypoglycaemia and perceived burden of diabetes were not predictive of ongoing sustained use of CGM. Similarly race/ethnicity, duration of diabetes, or educational attainment were not predictive of successful CGM use – Grade B [11-14]

**Recommendation 1:** Continuous CGM can be considered for any patient irrespective of age, sex socioeconomic status, ethnic or educational background who meet the NICE criteria. (Grade B)

CGM has proven beneficial in improving HbA1c and reducing time spent in hypoglycaemia in well controlled children on both MDI and on CSII, and can be considered for both therapeutic modalities - Grade A [15]. In children with higher HbA1c (>64 mmol/mol or >8.0%) on MDI evidence suggests CGM and pump therapy may lead to greater improvements in control (-0.81% HbA1c) than those on pump alone (-0.57% HbA1c), though improvement was seen in HbA1c in both groups [16].

**Recommendation 2:** Continuous CGM can be considered in children on CSII or MDI therapy (Grade A)

Hypoglycaemia is the key limiter to good glycaemic control and a history of seizure is likely to adversely affect glycaemic control, predispose to further seizures and induce parental anxiety. In older or adolescent children fear of further hypoglycaemic seizures and embarrassment regarding such incidents significantly adversely affects control [17].

**Recommendation 3:** Continuous CGM with alarms should be considered in any child of any age who has had a hypoglycaemic seizure (Grade B)

Younger children are unable to recognise and respond to hypoglycaemia. They are at increased risk of neurocognitive sequelae as a consequence of hypoglycaemia and the risk of hypoglycaemic seizures is greatest in younger children [18]. CGM studies in the pre-school children confirmed that the majority of hypoglycaemia events were asymptomatic and only 32% were being detected despite plasma glucose levels being checked 10 times per day. Children under the age of six years with hypoglycaemia unawareness has had six times the risk of a severe hypoglycaemic episode when compared to those without hypoglycaemia unawareness [19].

**Recommendation 4:** Continuous CGM with alarms should be considered in all young children (neonates, infants and preschool children) (Grade A)
Individuals with diagnosed neurodisabilities such as autism or ADHD would also be eligible for consideration for continuous CGM as they may have similar problems in recognising and responding to hypoglycaemia.

**Recommendation 5:** Continuous CGM with alarms should be considered in all children of any age with cognitive or neurodevelopmental problems that impair their ability either to recognise or to respond to hypoglycaemia (Grade D)

The Juvenile Diabetes Research Foundation (JDRF) CGM Study Group assessed the incidence of hypoglycaemia in the non-diabetic childhood population [20]. The comparative incidence of nocturnal hypoglycaemia in healthy non-diabetic individuals was documented and blood glucose rarely fell below 3.3mmol in non-diabetic children

**Incidence of nocturnal hypoglycaemia in non–diabetic Children**

<table>
<thead>
<tr>
<th>Nocturnal BG levels (midnight – 6am)</th>
<th>Age 8 &lt; 15yrs</th>
<th>Age 15 &lt; 25 years</th>
</tr>
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<tbody>
<tr>
<td>≤ 3.9 mmol/l</td>
<td>1.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>≤ 3.3 mmol/l</td>
<td>0.2%</td>
<td>0</td>
</tr>
</tbody>
</table>

In contrast nocturnal hypoglycaemia is common in type I diabetes. Historical studies have reported a prevalence of up to 40% on any given night in children and adolescents with type I diabetes [21-23]. Almost half of these episodes go undetected by carers or individuals with diabetes. The JDRF study recorded hypoglycaemic events in children during 8.5% of nights [20]. On almost a quarter of those nights where hypoglycaemia was documented the hypoglycaemia persisted for 2 hours [20]. Such frequent hypoglycaemia is likely to contribute to counter-regulatory deficit and increased risk of further hypoglycaemia.

Control data from further studies noted that children aged 4 to 10 years spent 6.2% of the time overnight with low blood sugars and children aged 11 to 14 years were hypoglycaemic 10.1% of the time [24]. Hypoglycaemic events are frequently asymptomatic and often unrecognised. In a study in Swedish children only 32% of episodes of hypoglycaemia were detected despite plasma blood glucose levels being checked 10 times daily [19].

Hypoglycaemia unawareness is common. In a study of 656 children aged 6 months to 19 years 29% were determined to have impaired awareness of hypoglycaemia – based on a Clarke score of four or more [18]. These children had twice the risk of having a severe hypoglycaemic episode. Children under the age of 6 years had a sixfold increase in the risk of severe hypoglycaemia if they also had hypoglycaemia unawareness [18].

Not all studies of CGM have demonstrated improvements in hypoglycaemia. The JDRF study and the STAR3 study both failed to show a reduction in hypoglycaemia [6, 10]. However in the STAR3 study there was an improvement in HbA1c without any increase in the incidence of hypoglycaemia. In the JDRF study the primary endpoint was HbA1c and it was not powered to assess the effect on hypoglycaemia. However many of the major trials excluded patients with the highest incidence of hypoglycaemia and those with severe hypoglycaemia. In most studies the primary point was reduction in
HbA1c not reduction in hypoglycaemia [25]. In those studies where hypoglycaemia reduction was defined as the primary point there was significant improvement in rates of hypoglycaemia [15, 26]. Several studies with predictive low glucose suspend in adults have reported a reduction in the rate and severity of hypoglycaemia [8, 27]. In the paediatric population similar reductions in nocturnal hypoglycaemia have been noted [9, 28] Numerous systematic reviews and several meta-analyses have been undertaken [1, 4, 29-31]. The Floyd [29] review included 14 studies and demonstrated CGM showed a greater reduction in HbA1c than capillary blood glucose monitoring and periods of time spent in hypoglycaemia were shorter. There are no randomised control studies of FGS (Libre) in children and little published evidence at present. Only one study in adults examined the incidence of hypoglycaemia. Time spent in hypoglycaemia was reduced from 3.4 hours daily to 2.0 hours daily with individuals flashing the glucose reading a mean 15 times daily [32]. FGS does not have alarms to alert individual regarding hypoglycaemia.

**Recommendation 6:** CGM with alarms should be considered in frequent hypoglycaemia and in nocturnal hypoglycaemia (Grade B)

**Recommendation 7:** CGM with alarms should be considered in situations where individuals have unawareness of hypoglycaemia (Grade B)

Evidence of this may come from any of the following sources

- Evidence from diagnostic CGM to suggest that individuals have period of significant hypoglycaemia of which they are unaware. Periods with glucose <2.6 mmol for >20 minutes during waking day (Grade C)
- A score >4 on the Clarke hypoglycaemia unawareness questionnaire (Grade C)
- A score ≥4 on the Gold hypoglycaemia unawareness Likert scale (Grade C)

Hypoglycaemia unawareness should be assessed using one of the following tools [33] (See Appendix D) (Evidence Level 2+):

- Clarke Score [34] – An 8 item questionnaire of impaired hypoglycaemia awareness. A score of 4 or more suggests hypoglycaemia unawareness. Ly et al., adapted it for use in children and used the Clarke score in two studies [9, 18]: For children up to the age of 10 years or those who were unable to fill out the questionnaire, parents or care providers were asked to complete it. For children aged between 10 and 12 years, both care providers and children completed the questionnaire. Children aged 12 years completed the questionnaires independently. The test-retest reliability of this questionnaire was verified by retesting the first 100 patients and/or care providers.

- Gold Likert Scale [35] - A single question "“do you know when your hypos are commencing?” on a Likert scale of 1 (always) - 7 (never). A score of > or equal to 4 suggests impaired hypoglycaemia awareness

Anxiety and fear of hypoglycaemia can impact on overall diabetes control [36] (Evidence level 2+). Fear of hypoglycaemia impacts negatively on diabetes control [37]. CGM has the potential to reduce parental anxiety [38]. However, published CGM trials do not measure fear of hypoglycaemia as a consistent
outcome making its use problematic. Use of CGM to address parental fear of hypoglycaemia was supported by the guideline group provided that a recognised assessment tool was employed and improvement documented (Evidence Level 4). The fear of hypoglycaemia – parent version is a valid measure of “fear of hypoglycaemia” and the worry and behaviour sub-scales have recently validated on Norwegian mothers and fathers [39]. Children's Hypoglycaemia Fear Survey (CHFS) and the parental measure: Hypoglycemia Fear Survey - Parent (HFS-P) which has also been adapted for parents of very young children Parents of Young Children (HFS-PYC) are recommended [40]. Both have been validated within UK populations.

There are 2 main subscales; behaviour and worry. Scoring involves taking the mean result from all questions answered on each subscale (See Appendix E). There is no defined clinical cut-off [36]. However a mean score of 2 or over on the worry subscale of the CHSF and HSF-P, and mean score of 3 or over on the HSF-PYC, would indicate the need for consideration of CGM. Additionally, if there was one very highly rated element (rated 'often' or above; 3 or over on CHSF and HSF-P, 4 or over on HSF-PYC) despite a mean score lower than 2 on CHSF and HSF-P or 3 on HSF-PYC, this may prompt consideration of CGM (Evidence Level 4).

**Recommendation 8:** CGM with alarms should be considered in individuals where anxiety or fear of hypoglycaemia is high (Grade D)

A score on CHFS and HSF-P worry subscale of >3 (or mean score greater than 2) or a score of >4 on the HFS-PYC worry subscale (or mean score greater than 3) would support trial of CGM (Grade D)

There is evidence of improvement in outcomes in individuals with both pre-existing well-controlled diabetes (HbA1c <7.5%) and also in those with poorer metabolic control and baseline HbA1c >8%. The study by Battelino et al demonstrated that in those with good control at the outset there was a 48% reduction in the time spent in the hypoglycaemic range and an increase in the proportion of time with the blood glucose within the normal range with a mean of 17.6 hours versus 16 hours per day [26] (Evidence level 1+). There was also a relative reduction in mean HbA1c of 0.23%. In line with many other studies there was a strong correlation with the consistency and frequency of sensor usage. Those who used sensors most frequently had the best incremental outcomes [10, 16, 26, 41]. Similarly in the ASPIRE study (adults only) there was evidence of improvement in both HbA1c and hypoglycaemia [15].

In patients with poor control, the study by Raccah et al examined a group of individuals with a baseline HbA1c greater than 8.0% demonstrated a significant reduction in HbA1c [16]. The JDRF study in 2009 demonstrated an improvement in HbA1c in individuals with a baseline HbA1c of 7% or more across all age ranges [10]. This study recruited groups aged 8-14 years in whom sensor use was 50% at six months, aged 15-24 years in whom 30% were using sensors at six months and age 25+ where sensor use was 83% at six months. In a study of young people (>8 years) and adults with an HbA1c >8.0% there was evidence of a reduction in HbA1c of approximately 0.5% - though little evidence of impact on hypoglycaemia [42].

Most studies did not include many children with very high HbA1c at baseline. As a result there is very little evidence in the literature of the effect on HbA1c in individuals with HbA1c above 11-12%. It has been suggested that there is little benefit in those with HbA1c >10.0% [43]. In a one month trial of 40 adolescents with poor control using CGM no significant improvement in HbA1c at 3 months was seen in those with starting HbA1c above 10% [44] (Level 2-). In a single RCT of 200 children and young people (using the glucoWatch) where individuals with HbA1c up to 11% were included no overall improvement in HbA1c was seen, though those with greater pre CGM adherence had better outcomes [38]. There is no literature on outcomes with FGS (the FreeStyle Libre system).
Recommendation 9: CGM can be considered for improving diabetes control in children & young people by reducing HbA1c and/or reducing the time spent in hypoglycaemia, with any HbA1c < 10% (Grade B)

Recommendation 10: There is little evidence to support CGM use to reduce HbA1c or hypoglycaemia in those children with a very high HbA1c >10%, it is therefore not recommended (Grade D)

Exercise Management

The impact of exercise on glucose metabolism is affected by the type, duration (short, prolonged or intermittent) and intensity of exercise. Differences in insulin regimens and the necessity to maintain near normal blood glucose levels before, during and after exercise poses a significant challenge. In individuals with type 1 diabetes, sustained aerobic exercise generally leads to a decline in blood sugar. Up to 86% of adolescents with blood glucose levels <6.7mmol and 13% of those with glucose levels 6.7–8.3 mmol/L prior to sustained aerobic exercise (for 75 min) experienced hypoglycaemia [45]. Conversely in high-intensity anaerobic exercise increased catecholamines and lactate frequently result in post exercise hyperglycaemia [46, 2009].

There is a paucity of research in children and young people into intermittent high-intensity exercise such as football, hockey and spontaneous play in children where a mixture of both aerobic and anaerobic exercise is undertaken. Late hypoglycaemia can occur in all forms of exercise – aerobic, anaerobic or mixed. There is an increased glucose requirement in order to maintain euglycaemia in adolescents with type I diabetes. This persists for between 90 minutes post exercise and up to 7 to 11 hours post exercise and can exhibit a biphasic response with late hypoglycaemia [47].

Experience of CGM use in diabetes sports camps data suggest that sensors are accurate and well tolerated during exercise although some replacement of sensors was required [48]. CGM detected significantly more hypoglycaemia and hyperglycaemia than capillary glucose monitoring. In well-controlled young adults the handling of glucose excursions during exercise appears to be improved [49]. In a cohort of 25 children and adolescents aged 8 to 17 years attending a two-week sports camp, commitment use of CGM significantly reduced the quantities of carbohydrate required to manage hypoglycaemia avoiding overcompensation with carbohydrate [50]. (Evidence - Level 3).

The number of studies specifically addressing exercise is small – a literature search only identified five pertinent studies. The limited number of studies suggests that CGM can be worn reliably and with reasonable accuracy during and after exercise (Evidence Level 3). It is more effective in detecting hypoglycaemia particularly late-onset hypoglycaemia than capillary blood glucose monitoring (Evidence Level 3). Hypoglycemic risk may be increased both at the time of exercise and also in the 24 hours following activity [47]. CGM has also been used successfully during physical exercise in adolescents, again noting unrecognised hypoglycaemia [48]. CGM has also been used to delineate post-exercise nocturnal hypoglycaemia [51].

Maintaining blood sugars within the normal range will improve sporting performance in young people and potentially reduce parental anxiety particularly regarding late-onset hypoglycaemia. The guideline development group felt continuous CGM should be considered in the following situations:
Recommendation 11: Continuous CGM should be considered for exercise in children and young people in the following circumstances: (Evidence - Grade D)

- For those competing or exercising regularly. It can be used to optimise glycaemic control (including carbohydrate and insulin adjustment) before, during and after exercise to maximise the effect of exercise on improving diabetes control and ensure that potential sporting performance is optimised.
- For adolescents trying to lose weight but fearful of the hypoglycaemic effects of exercise
- For those who have had a severe episode of hypoglycaemia following sporting activity and cannot resume activity
- For those in whom there is concern regarding overcompensation with additional carbohydrate for activity
- Those involved in high endurance sporting activities where it is difficult to test blood sugar
- For those where exercise results in unpredictable hypoglycaemia

Diagnostic Use of Systems

Diagnostic use (whether retrospective and/or real-time) usually involves intermittent use of sensors to help identify patterns of glucose excursion and to guide therapeutic change in the following:

- Suspected nocturnal hypoglycaemia and/or early morning hyperglycaemia
- Suspected unrecognised hypoglycaemia eg exceptionally low HbA1c without reported hypoglycaemia
- HbA1c above individualised target despite intensified insulin therapy apparently optimised with self-monitoring
- Persistent disabling hypoglycaemia

CGM has also been used intermittently as a management tool and diagnostic instrument for people with diabetes and their healthcare providers to understand blood glucose trends during various forms of exercise, unusual stress, illnesses, steroid medications or menstrual cycles [52]. There is evidence to support the benefit of intermittent use of continuous glucose monitoring as an educational motivational tool in poorly controlled adolescents. In a study of 40 patients with a mean age of 14 years and an initial mean HbA1c of 9.3% individuals were offered a month of CGM support [44]. Across the cohort HbA1c improved from 9.3% to 8.8% (Evidence level 2-). However individuals with HbA1c >10% did not appear to achieve a significant improvement. In those with a mean HbA1c < 10% at the start of the study HbA1c fell from mean 8.5% to 7.9% (0.6% improvement) whereas those with a mean HbA1c >10% did not show any significant improvement (HbA1c 11.2% at the start of the study and 10.9% of the end) [44].

A single retrospective cohort study suggests that for poor diabetes control (any HbA1c) patients should additionally meet the following criteria [53]:

- willingness to complete 4 capillary blood glucose measurements per day and complete a diary on insulin doses, food intake and exercise and activity for minimum of 4 days duration
- willingness to have a review session to learn from the findings
Recommendation 12: Intermittent or diagnostic CGM should be considered for:

- Suspected nocturnal hypoglycaemia
- Suspected unrecognised hypoglycaemia
- HbA1c above individualised target despite apparently optimised with self-monitoring
- Evidence of benefit is limited in those with HbA1c >10% and should only be undertaken in exceptional circumstances in this group (Evidence - Grade C)

Recommendation 13: Families and young people should be willing to undertaking 4 blood tests each day and to complete diaries. (Evidence - Grade D)

There is no data to identify the optimal number of CGM systems that should be available per diabetes clinic. However based on the 2014/15 National Paediatric Diabetes Audit only 4.9% had HbA1c <48 mmol/mol (6.5%), 11.6% <53 mmol/mol (7.0%) and 22% <58 mmol/mol (7.5%) and conversely 42.8% have an HbA1c >69 mmol/mol (8.5%) and 29.1% >75 mmol/mol (9.0%). The incidence of nocturnal hypoglycaemia is reported at up to 40% [22] with approximately 10% have prolonged hypoglycaemia each night [20]. Hypoglycaemia unawareness occurs in approximately 29% of individuals [18]. Given that a diagnostic study is likely to require two weeks of data (to generate a meaningful ambulatory glucose profile) a single system would likely be available for 15 to 18 patient runs per year allowing for patients delaying returning systems and staff constraints in getting patients up to take them on and off. The members of the guideline group drew on their personal experience which suggests that systems were only available two thirds of the time. A proportion of patients will require continuous CGM and will require a prolonged trial prior to commencing their own personal system. Approximately 50% are likely to require diagnostic CGM. (Level 4 Evidence).

Recommendation 14: Diabetes clinics should have diagnostic CGM systems available to them (Grade A)

Criteria to Withdraw Systems

CGM systems are a cost to the NHS. Whilst they can be very valuable, if they are used infrequently, with insufficient engagement in the structured education process required to maximise benefit and the intended benefits are not realised then they should be withdrawn

Literature evidence shows that increased sensor wear of more than 60% of the time is associated with improvement HbA1c [11, 41, 54]. Baseline factors found to be associated with greater CGM use in month 6 were age>25 years and more frequent self-reported pre-study capillary blood glucose measurements [10]. In addition, CGM use during the 1st month of the trial was predictive of longer term use of CGM 6 months later [11, 54, 55]. Common barriers to use included insertion pain, system alarms and body image issues; while common benefits included glucose trend data, opportunities to self-correct out-of-range glucose levels and to detect hypoglycaemia [10].

Recommendation 15: Withdraw continuous CGM after 1 month if:

- CGM has not been used 60-70% of the time – 5 days a week minimum (Grade A)
• Family have not attended all 4 Education step 1,2,3,4 sessions unless extenuating circumstances (Grade D)

Recommendation 16: Withdraw CGM at 3 months if:
• CYP does not wear it for at least 5 days a week. (Grade A)
• No improvement in glycaemic control – eg HbA1c did not improve by >0.5% if it was >7.5% at start of CGM therapy [13, 14, 42]
• No improvement in scores on fear of hypoglycaemia scales where CGM was introduced for anxiety
• No improvement in hypoglycaemia unawareness if introduced for hypoglycaemia unawareness (Clarke or Gold score)
• No reduction in frequency of hypoglycaemia – particularly nocturnal hypoglycaemia (assessed from CGM download)
• Its use for sport/exercise is not being optimised

If HbA1c was >7.5% at initiation of sensor use for poor glycaemic control it would be reasonable to expect an improvement of 0.5%. In those < 7.5% then maintenance of HbA1c would be expected and reduction in hypoglycaemia, hypoglycaemia unawareness etc.

 Recommendation 17: Benefit from CGM should be clearly evidenced and documented in the notes (Best Practice Point)

CGM does not need to be reviewed for withdrawal if it was introduced following hypoglycaemic seizures and provided it is being used > 5 days per week or in younger children providing it is in regular use

CGM / FGS Systems and Schools

Children of all ages need a robust plan for managing their diabetes at school [56]. Teachers and school nurses will need additional guidance and education on how CGM/FGS data should be factored into care decisions. Written individualized diabetes related health-care plans should be agreed upon between parents, school nurses, professional caregivers and teachers, and the diabetes healthcare team. A structured educational program should be provided for preschools and schools that includes information about and practical training for the use of these new diabetes-related technologies [57].

Overall studies have shown that CGM is well tolerated in schools (Evidence - Level 3). Most studies report children are more self-confidence and independent and with improved satisfaction with diabetes management for staff, parents and children and little disruption due to alarms [58, 59]. Others, however, noted it might disrupt school life and frequent alarms may give the school the impression that the child's diabetes is problematic. Consideration could be given to adjusting the threshold for the alarm settings for school such as increasing the high blood sugar threshold to reduce the frequency of alarms (Evidence – Level 4).

Parents of children with diabetes need support when using CGM. Many feel guilty about their child's diabetes and become stressed or anxious when they see their child’s glucose level going high or low. This may result in a desire to react to all blood glucose excursions in order to return to the target range as quickly as possible. Some parents may have unrealistic expectations of the intensity of care that their child should receive at school. This is particularly relevant for younger children who will be totally
dependent on their caregivers for their diabetes management. It is important that both parents expectat
ions of CGM technology and expectations for the level of support that the school can provide are realistic. It is vital that discussions are had with all parties prior to commencing CGM to prevent any potential conflict (Evidence – Level 4).

Remote monitoring tools can give parents insight into what is happening during their child’s school day and during overnight school trips, which may reduce anxiety about diabetes management. However there is little published evidence regarding the utility of such technology.

Studies of longer-term CGM use (6 months) have found that, despite benefiting from reduction in HbA1c, children and adolescents may not be willing to wear a device as often, or for as prolonged a period of time as is required to result in consistently improved glucose metabolism.

Recommendation 18: An individualised care plan should be put in place for every child on CGM (Grade – Best Practice)
Recommendation 19: Structured education should provided for nursery and teaching staff supervising the child (Grade – Best Practice)
Recommendation 20: Consideration should be given to adjusting alarm thresholds if disruptive at school (Grade – Best Practice)
Recommendation 21: Expectations between parents and staff at preschool/school need to be clearly agreed to avoid conflict (Grade – Best Practice)

CGM / FGS and Driving

Current DVLA (Driver and Vehicle Licensing Agency) rules state that patients with diabetes treated with insulin must comply with blood glucose testing no more than 2 hours before the start of the first journey and every 2 hours while driving. Drivers must also undertake regular blood glucose testing, at least twice daily, including on days when not driving. Blood glucose testing must be done on a meter with a memory function and three months of blood glucose readings whilst on insulin must be available. Continuous glucose monitoring (CGM) and flash glucose scanning (FGS) systems measure interstitial glucose and are not approved by the DVLA, therefore drivers must also monitor capillary blood glucose levels as outlined above.

https://www.gov.uk/diabetes-driving
https://www.gov.uk/guidance/diabetes-mellitus-assessing-fitness-to-drive

Recommendation 22: Patients using CGM and/or flash glucose scanning (FGS) monitoring should be made aware of the requirement to also test their blood glucose in accordance with DVLA rules.

Studies with the best clinical outcomes were those in whom there was a “run-in” period. It is therefore suggested that all patients have a trial for 4 weeks with a loan CGM system before they are provided with their own personal system. This provides an opportunity to predict who is likely to benefit from continuing CGM [11] and also to address physical issues with sensors. In those studies with no run in subsequent drop out and discontinuation of CGM was high – up to 50% [14, 15]. In younger children (< 4 years) approximately 20% discontinued during the trial phase due to sensor problems. Of those who completed the trial phase and continued with CGM therapy only 40% were using it on a regular daily basis after six months [12]. Studies in slightly older children (aged 4 - 9 years) showed similar results with only approximately 40% of patients wearing it for six or more days a week after six months of usage [13]. The frequency with which CGM was used in the first month of therapy was a strong predictor of the likelihood that individuals will continue to use it after six months [11].

Recommendation 23: All children should have a month’s trial with a loan system before being provided with their own personal CGM system

In younger children sensor augmented pump therapy with low glucose suspend may have advantages but children on MDI and other CSII systems still benefit from CGM (Level 4)

Recommendation 24: It is important to consider the CGM system type for age and whether aiming to link to CSII and potential benefit from predictive low glucose suspend technology (Grade D)

If CGM is being considered in addition to the initiation of insulin pump therapy (in patients on MDI), then CGM should be commenced in the weeks before CSII rather than after CSII in order to achieve optimal adherence [16]. This is not possible with all systems as some CGM systems are linked to pumps. However there is some evidence that it may improve outcome (Evidence level 4).

Recommendation 25: If CGM is to be commenced in addition to CSII as a therapeutic tool to improve control the CGM should be commenced prior to CSII (Grade D).

An initial training of a minimum of 4 separate sessions is likely to ensure maximum benefit is derived. Patients and carers need to commit to training in CGM, including the practical aspects and the assessment and interpretation of results, as well as the day to day management based on CGM trends together with regular skills assessment questionnaire in order to maintain CGM skills. One study has shown that skill test scores for CGM correlates with the degree of improvement of diabetes control with CGM and another demonstrated improved adherence to CGM with higher treatment adherence pre-CGM (Level 4) [38, 42]

Recommendation 26: Patients/ carers commencing CGM must commit to formal CGM training and regular skills assessment (Grade D)

Recommendation 27: Patients/ carers commencing CGM must commit to CGM download with diabetes team contact (minimum monthly in the first 6 months) and subsequent regular download (Grade D)
Getting Started with the CGM or FGS System

The ACDC Guideline Group has produced a 4 step educational training package with patient education materials (patient leaflets) and education resource toolkit for the paediatric diabetes team to facilitate education. These are intended to be delivered over 4 separate sessions as patients commence CGM or FGS. These are freely available in the ACDC website at www.a-c-d-c.org

STEP 1:
Getting started with CGM system
Understanding the basic knowledge of your CGM system
Learn to identify trends and patterns

STEP 2:
Further understanding of trend arrows
Learn to actively use target glucose range

STEP 3:
Recap the target glucose range
Optimise the effect of CGM using trend arrows
How to use the total dose percentage adjustment tool
How to use the insulin sensitivity factor tool (ISF))

STEP 4:
How to use the Ambulatory Glucose Profile (AGP)
Diasend/Software downloads

Appendix A: Literature Search – Evidence for CGM or Sensor Augmented Pump Therapy

Medline search using the MeSH headings
- Type 1 Diabetes Mellitus
- AND childs OR adoles OR juvenile OR paediatric
- Continuous Glucose Monitoring OR Sensor Augmented Pump

Inclusion Criteria
- RCTs or Meta-analyses and reviews containing RCTs
- At least some patients under 18
- Type 1 Diabetes

Exclusion criteria
- Not written in English
- Assess Glucowatch system as this has been withdrawn
- Analyse technology not commercially available (eg experimental closed loop systems)

Reference lists from review articles (Raj 2016, Acerini 2016) were also checked to ensure no studies were missed.
Literature search strategy – “What level of exercise justifies CGM”

Medline search using the MeSH headings

- Type 1 Diabetes Mellitus
- AND child OR adoless OR juvenil OR paediatric
- AND hypo OR juvenile OR paediatric
- Continuous Glucose Monitoring OR Sensor Augmented Pump

Inclusion Criteria

- RCTs or Meta-analyses and reviews containing RCTs
- At least some patients under 18
- Type 1 Diabetes
- Review papaers

Exclusion criteria

- Not written in English

Literature search strategy – “What level of exercise justifies CGM”

Medline search using the following headings:

- Exercise OR sport OR athlete
- AND CGM OR self monitoring
- Limit – last 15 years

292 papers but only 5 considered CGM and exercise

Literature Search strategy – “Criteria to withdraw CGM”

- Continuous glucose sensors OR sensor augumented Pump Therapy
- AND Child or adolescent or Paediatrics
- AND ADHERENCE


3 papers identified but none deemed Relevant

Hand search of references and review articles yielded 5 relevant articles
Appendix B: Review of Evidence and Limitations of Evidence Underpinning NICE Recommendations

NICE had very specific criteria as to which studies should be considered within its evidence review comparing CGM to spot capillary blood glucose monitoring (SMBG) in NG18. It relied very heavily on the published Cochrane systematic review from Langendam 2012. This Cochrane review included 22 studies although the majority of these were not considered appropriate within the tight remit of the NICE guidance review. Of the 868 papers identified as part of the NICE review only four were included in its evidence synthesis. (See Figure 1).

In paediatric patients diagnosed with established diabetes for over a year NICE identified and included only three studies relevant to HbA1C and only two studies were considered relevant to the incidence of hypoglycaemia. One study examined parental satisfaction. There were no studies available that included an assessment of the impact on quality of life. Figure 2 illustrates the studies included in the NICE guidance review.
Figure 3 illustrates the forest plots developed to assess the impact of continuous glucose monitoring on overall glycaemic control (assessed by HbA1c). The top panel relates to the use of continuous real-time CGM and the lower panel to intermittent or “diagnostic” use of CGM. There were small but non-significant improvements in HbA1c. In studies looking at intermittent or diagnostic use HbA1c improved by 0.3%. Figure 4 illustrates the Forest plot from the NICE guidance looking at the incidence of hypoglycaemia in established patients with diabetes. The limited number of studies included in the meta-analysis demonstrated a non-significant improvement in HbA1c. There was a similar non-significant improvement in hypoglycaemia.
Although the nice guidance evidence review did not identify evidence demonstrating a benefit of CGM over capillary blood glucose monitoring on either HbA1c or hypoglycaemia the members of the guideline development group based on their collective experience felt that CGM was effective in specific circumstances hence the guidelines recommendations supporting and recommending it’s use in NG18 (see Figure 5).
The evidence review for the technology appraisal conducted by NICE DG 21 included a broader range of studies. It did consider children as a separate group and examined 6 studies:

One study Ly 2013 reported CGM data with low glucose suspend vs CSII. Two studies reported data for CGM without low glucose suspend vs CSII alone (Hirsch 2008 & Bergenstal 2010). The remaining 3 studies reported data for CGM & CSII vs MDI and capillary blood sugars. (See Figure 6)
The analyses looked at the following areas:

- CGM & CSII compared to CSII alone (with SMBG) (Figure 7)
- Low glucose suspend (Veo) vs CGM & CSII without low glucose suspend (Figure 8)
- CGM & CSII compared to MDI and spot capillary blood glucose monitoring (Figure 9)

Once again whilst not reaching significance the difference in HbA1c between sensor augmented pump therapy and pump therapy alone was almost 0.5%. There was no evidence that the low glucose suspend pump (Veo) reduced HbA1c compared to CGM & CSII without low glucose suspend but there was a nonsignificant reduction on severe hypoglycaemia. When pump therapy supported by CGM was compared to MDI and SMBG there was a significant reduction in HbA1c of 0.5%.

![Figure 6: List of studies included in NICE Diagnostics Guidance DG21](image.png)

<table>
<thead>
<tr>
<th>Study</th>
<th>Veo</th>
<th>Integrated CSII + CGM</th>
<th>CSII+ SMBG</th>
<th>MDI+ SMBG</th>
<th>Mean baseline age, years (SD); age range, years</th>
<th>Mean baseline HbA1c % (SD)</th>
<th>Previous pump use, months</th>
<th>Follow-up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ly et al., 2013</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>19 (12); 4-50</td>
<td>7.5 (0.8)</td>
<td>&gt; 6</td>
<td>6</td>
</tr>
<tr>
<td>Hirsch et al., 2008</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>33 (16); 12-17</td>
<td>8.7 (0.9)</td>
<td>&gt; 6</td>
<td>6</td>
</tr>
<tr>
<td>Bergenstal et al., 2010</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>12 (3); 7-18</td>
<td>8.3 (0.5)</td>
<td>Naive</td>
<td>12</td>
</tr>
<tr>
<td>Wentrob et al., 2003</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>12 (1.5); 8-14</td>
<td>8 (1)</td>
<td>NR</td>
<td>3.5</td>
</tr>
<tr>
<td>Thraikill et al., 2011</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>12 (3); 8-18</td>
<td>11.5 (2.4)</td>
<td>Naive</td>
<td>6, 12</td>
</tr>
<tr>
<td>Doyle et al., 2004</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>13 (3); 8-21</td>
<td>8.1 (1.2)</td>
<td>Naive</td>
<td>3.7</td>
</tr>
</tbody>
</table>

NR, not reported.
**Figure 8:** Low glucose suspend (Veo) vs CGM & CSII without low glucose suspend - HbA1c and incidence of severe hypoglycaemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MiniMed Veo system (n=46)</th>
<th>CSII + SMBG (n=49)</th>
<th>Difference at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HbA1c levels, % (95% CI)</td>
<td>Baseline 7.6 (7.4 to 7.9)</td>
<td>Follow-up 7.5 (7.3 to 7.7)</td>
<td>Baseline 7.4 (7.2 to 7.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow-up 7.4 (7.2 to 7.7)</td>
<td>Baseline 0.07 (0.2 to 0.3), p = 0.55</td>
</tr>
<tr>
<td>Number of people with hypoglycaemic events</td>
<td>0/41</td>
<td>6/45</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Figure 9:** Insulin pump therapy & CGM was compared with MDI & capillary testing

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Integrated CSII + CGM (n=78)</th>
<th>MDI + SMBG (n=81)</th>
<th>Difference at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HbA1c levels, % (SD)</td>
<td>Baseline 8.3 (0.6)</td>
<td>Follow-up 7.9 (NR)</td>
<td>Baseline 8.3 (0.5)</td>
</tr>
<tr>
<td>Number of people with severe hypoglycaemic events (patients with severe hypoglycaemic events/total number of patients)</td>
<td>4/78</td>
<td>4/81</td>
<td>-0.5 (95% CI -0.8 to -0.2), p &lt; 0.001 NS</td>
</tr>
</tbody>
</table>

Authors: ACDC Guideline Development Group N Wright, SM Ng, JC Agwu, P Adolfsson, J Drew, J Pemberton, M Kershaw, S Bissell, C Moudiotis, F Regan, C Gardner, A Astle, A Adams, G Adams, P Manning, A Timmis, A Soni, E Williams
b) Cochrane Review and Yeh Systematic Review

NICE relied very heavily on the Langendam 2012 Cochrane review. Data was extracted from the Cochrane review rather than from the original papers. The Cochrane review included 3 studies for children:

- Bergenstal 2010
- Juvenile 2008
- Kordonouri 2010

And included 2 studies in adolescents:

- Juvenile 2008
- Hirsch 2008

Several of the other studies included both adults and children but didn't report the data for young people separately. (Battelino 2011; Deiss 2006; Juvenile 2009; O'Connell 2009; Raccah 2009)

The key analyses are illustrated:

![Figure 10: Cochrane data synthesis examining CGM & change in HbA1c - Children](image)

It demonstrated a small improvement in HbA1c that was not significant (Figure 10 & 11). However there was a significant difference in the proportion of children with an improvement of >0.5% HbA1c in those who had used CGM suggesting that those who benefited demonstrated clinically important gains in HbA1c.
If one looked at all the studies included (both adult and paediatric) there was a consistent trend across studies for improvement in HbA1c. (see Figure 12).

The Cochrane review demonstrated that there was limited evidence to support the use of CGM but in line with other studies of CGM noted that the impact on HbA1c was greatest where the proportion of time an individual uses CGM was greatest. Unfortunately few studies included children < 8 years and the results of meta-analyses in children and young people may be influenced by the fact that in the Juvenile 2008 study, the largest and the most heavily weighted in meta-analyses, the 15-25 group only used the sensors 30% of the time (the least frequent users).
The Cochrane review reached the following conclusions:

“There is limited evidence for the effectiveness of real-time continuous glucose monitoring (CGM) use in children, adults and patients with poorly controlled diabetes. The largest improvements in glycaemic control were seen for sensor-augmented insulin pump therapy in patients with poorly controlled diabetes who had not used an insulin pump before. There are indications that higher compliance of wearing the CGM device improves glycosylated haemoglobin A1c level (HbA1c) to a larger extent.”

A further much larger systematic review by Yeh in 2012 included larger numbers of studies than either the NICE or the Cochrane reviews. It demonstrated a statistically significant improvement in HbA1c of CGM compared to capillary glucose monitoring without any increase in the incidence of hypoglycaemia. It included the following meta-analysis (although this included both adults and children) – Figure 13:

It concluded:

“For glycaemic control, real-time-CGM is superior to SMBG and sensor-augmented insulin pumps are superior to MDI and SMBG without increasing the risk for hypoglycemia.”
Figure 13: Meta analysis from Yeh 2012 demonstrating an improvement in HbA1c with CGM.

Figure 14. Comparison of rt-CGM with SMBG and SAP use with MDI plus SMBG among patients with T1DM.
As part of the ACDC review of the literature a further literature search was undertaken. The search strategy and detailed comments on each individual study considered is in Appendix A and Appendix B

Details of studies included in this guideline:

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Results</th>
<th>Recruited patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASPIRE Study-In home (Automation to Simulate Pancreatic Insulin Response)</strong> Bergenstal et al (2013) [8]</td>
<td>RCT of 247 adults and teens were studied, comparing the MiniMed Veo™ sensor augmented pump (SAP) therapy with low glucose suspend (LGS) feature ON, with SAP therapy alone</td>
<td>• Hypoglycaemic events were significantly reduced by 31.4% • Nocturnal hypo events were significantly reduced by 31.8% • The duration &amp; severity of nocturnal hypos was reduced by 37.5% (as measured by area under curve (AUC)) These results were achieved without compromising on HbA1c or significant rebound hypoglycaemia No improvement in QOL seen</td>
<td>Recruited patients with a high level of hypoglycaemia especially nocturnal Only older teenagers included</td>
</tr>
<tr>
<td><strong>Ly et al (2013) [9]</strong></td>
<td>A RCT of 95 children and adults that compared the rates of severe hypoglycaemia in patients with impaired hypo awareness when randomised to CSII versus Sensor Augmented Pump (SAP) with the Low Glucose Suspend (LGS) feature ON over a 6 month period. Severe hypoglycaemia was defined as coma or seizure associated with hypoglycaemia.</td>
<td>• Significant reduction in the number of severe hypoglycaemic events • Events were reduced from 21.9 to 0.0 events per 100 patient years in the LGS group versus 24.8 to 26.7 events per 100 patient years in the control group (p=0.017) • Significant reduction exposure to hypoglycaemia. • Exposure to glucose values below 70mg/dl and 60mg/dl were significantly reduced in the LGS group compared to control (p=0.006 and p=0.009 respectively) • Reduced fear of hypoglycaemia was shown in the LGS group.</td>
<td>Only older children Education and increased clinical contact given</td>
</tr>
<tr>
<td><strong>INTERPRET Norgaard et al (2013) [60]</strong></td>
<td>6 month pan European observational study assessing the effectiveness of Sensor Augmented Insulin Pumps showed that patients with a HbA1c of &gt;8% showed a reductions in HbA1c of 0.43%</td>
<td>Subjects strongly agreed (mean 8.2 ± 2.4 on a 10-point Likert-scale) that SAP alarms were helpful and help them improve control. Data from 263 patients (38% male; mean age, 28.0 ± 15.7 years [range, 1-69 years]; body mass index, 23.3 ± 4.9 kg/m(2); diabetes duration, 13.9 ± 10.7 years; CSII duration, 2.6 ± 3 years) were collected. HbA1c was 8.1 ± 1.4%; 82% had suboptimal HbA1c (≥ 7%). The average sensor use for 12 months was 30% (range, 0-</td>
<td>Observational study Real life use of SAP More adult patients than paediatric</td>
</tr>
</tbody>
</table>
94%), and sensor use decreased with time (first 3 months, 37%; last 3 months, 27%). Factors associated with improvement in HbA1c after 12 months in patients with baseline HbA1c ≥ 7% were high baseline HbA1c (P<0.001), older age group (P<0.001), and more frequent sensor use (P = 0.047). Significantly less hospitalisation, increased treatment satisfaction, and reduced fear of hypoglycaemia were reported after 12 months of SAP.

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Findings</th>
<th>Methodology of original studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeh et al (2012) meta-analysis [30]</td>
<td>33 randomised, controlled trials in children or adults that compared CSII with MDI (n=19), rt-CGM with SMBG (n=10), or sensor-augmented insulin pump use with MDI and SMBG (n=4).</td>
<td>Compared with SMBG, rt-CGM achieved a lower HbA1c level (between-group difference of change, 0.26% [95% CI, 0.33% to 0.19%]) without any difference in severe hypoglycaemia. SAP use decreased HbA1c levels more than MDI and SMBG did in persons with type 1 diabetes mellitus (between-group difference of change, 0.68% [CI, 0.81% to 0.54%]). These effects were dependent on CGM adherence rates and was highest in those studies where ‘sensor’ adherence was sustained at levels of 60% or above. CGM does not appear to have any significant impact on patient QoL when compared to standard methods of blood glucose monitoring.</td>
<td>Often poor</td>
</tr>
<tr>
<td>Garg (2012) In-clinic ASPIRE [61]</td>
<td>Randomised crossover trial of SAP with low glucose suspend (Medtronic)</td>
<td>Automatic suspension of insulin delivery significantly reduced the duration and severity of induced hypoglycaemia without causing rebound hyperglycaemia.</td>
<td>Small number of teenagers, no younger children. Short term SAP use with exercise</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Results</td>
<td>Limitations</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>SWITCH Battelino et al (2012) [62]</td>
<td>Randomised, controlled, cross-over multicentre study designed to investigate the efficacy of adding sensing to existing insulin pump treated patients, for a 6 month period in type 1 patients aged between 6 years – 70 years, with inadequate metabolic control (7.5%&lt;HbA1c&lt;9.5%) despite 1+ year on CSII.</td>
<td>The Sensor On arm showed an overall 0.51% reduction in HbA1c in patients that wore the sensor more than 70% of the time. Significantly less time was spent within the hypoglycaemic range (&lt;3.8 mmol/l) during the Sensor On vs. Sensor Off (19 vs. 31 minutes/day; P = 0.009). 15.3 fewer SMBG tests per month were performed in the Sensor ON arm (P&lt;0.001)</td>
<td>Small number of children, mainly &gt;10yrs Run in period of intensive support prior to study Doesn’t include those with very poor control</td>
</tr>
<tr>
<td>Battelino et al (2011) [26]</td>
<td>Randomised, controlled, multicentre study, 120 children and adults on intensive therapy for type 1 diabetes and a screening level of HbA1c &lt;7.5% were randomly assigned to a control group performing conventional home monitoring with a blood glucose meter and wearing a masked CGM every second week for five days or to a group with real-time continuous glucose monitoring. The primary outcome was the time spent in hypoglycaemia over a period of 26 weeks.</td>
<td>CGM was associated with reduced time spent in hypoglycaemia and a concomitant decrease in HbA1c in children and adults with type 1 diabetes. The time per day spent in hypoglycaemia was significantly shorter in the CGM group than in the control group (mean ± SD 0.48 ± 0.57 and 0.97 ± 1.55 h/day, respectively; ratio of means 0.49; 95% CI 0.26-0.76; P = 0.03). HbA1c at 26 weeks was lower in the CGM group than in the control group (difference -0.27%; 95% CI -0.47 to -0.07; P = 0.008). Time spent in 70 to 180 mg/dL normoglycaemia was significantly longer in CGM group compared with the control group (mean hours per day, 17.6 vs. 16.0, P = 0.009).</td>
<td>Masked CGM used intermittently with clinician dose adjustment Included only patients with good control</td>
</tr>
<tr>
<td>Pickup meta-analysis (2011) [63]</td>
<td>Meta-analysis was carried out on 6 Randomised Controlled Trials: The aim of the study was to analyse the benefit of CGM vs. SMBG. There were a total of 449 patients within the CGM arm vs. 443 in the SMBG arm</td>
<td>If sensors used the majority of the time: If the starting HbA1c was 7% this resulted in a 0.5% reduction where as if the starting HbA1c was 10% a 0.9% reduction was seen The use of CGM with insulin pump therapy has been shown to significantly lower glycaemic variability by MAGE vs. pump therapy alone</td>
<td>Issues with quality of methodology of original studies</td>
</tr>
<tr>
<td>STAR 3;Bergenstal et al (2010) [6]</td>
<td>Multicentre RCT over 12 months was designed to evaluate the impact of Sensor Augmented Pump therapy on HbA1c compared to those who are using Multiple Daily Injection (MDI)</td>
<td>Study found that patients randomised to Sensor Augmented Insulin Pump (SAP) therapy had a mean HbA1c reduction of 0.8% (7.5% from an 8.3% baseline) compared with a reduction of 0.2% (8.1% from a baseline of 8.3%) in the</td>
<td>Excluded those with good control Intensive education and support given</td>
</tr>
<tr>
<td>Study</td>
<td>Details</td>
<td>Results</td>
<td>Comments</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>ONSET study: Kordonouri et al (2010) [64]</td>
<td>160 children (aged 1-16 years, mean ± SD: 8.7 ± 4.4 years; 47.5% girls) were randomised to receive insulin pump treatment with continuous glucose monitoring or conventional self-monitoring blood glucose measurements. The primary outcome was the level of HbA(1c) after 12 months.</td>
<td>HbA(1c) was not significantly different between the two groups, but patients with regular sensor use had lower values (mean 7.1%, 95% CI 6.8-7.4%) compared with the combined group with no or low sensor usage (mean 7.6%, 95% CI 7.3-7.9%; p=0.032). At 12 months, glycaemic variability was lower in the sensor group (mean amplitude of glycaemic excursions 80.2 ± 26.2 vs 92.0 ± 33.7; p=0.037). Higher C-peptide concentrations were seen in sensor-treated 12- to 16-year-old patients (0.25 ± 0.12 nmol/l) compared with those treated with insulin pump alone (0.19 ± 0.07 nmol/l; p=0.033). Severe hypoglycaemia was reported only in the group without sensors (four episodes). Regular sensor use is associated with improved glycaemic control.</td>
<td>Studies SAP use in young children (but none &lt;4yrs) No subgroup analysis for this group but no adverse effects. Intensive education and support given.</td>
</tr>
<tr>
<td>ASAP Study O’Connell et al (2009) [65]</td>
<td>Open label, multicentre RCT 62 patients (13–40 years) with HbA1C ≤8.5% were randomised 1:1 to determine the impact on glycaemic control of patient-led use of sensor-guided pump management vs. standard insulin pump therapy.</td>
<td>A 0.43% reduction in mean HbA1c was shown in the intervention group compared with the control group. Post-hoc analysis showed there was a 0.6% HbA1C reduction (p=0.025) observed in the younger subjects (13.0 -19.0 years) Participants with 70% sensor use had 0.51% lower HbA1C (p=0.04) These improvements in glycaemic control occurred despite no additional patient-clinician contact over the study period or specific advice as to how to interpret the glucose trend information.</td>
<td>Only older children Large drop out rate for CGM (nearly 20%) Those with poor control excluded.</td>
</tr>
<tr>
<td>Weinheimer et al (2009) [7]</td>
<td>Following a 13-wk trial of daily Navigator use, 45 children with T1D [10.7 +/- 3.7 yr, range 4.6-17.6, 24 using CSII and 21 using MDI used the Navigator for an additional 13 wk.</td>
<td>Navigator use was initially slightly higher in the CSII users than in the MDI users but declined similarly in both groups by 22-26 wk. After 26 wk, 11 (46%) of 24 CSII users and 7 (33%) of 21 MDI users were using the Navigator.</td>
<td>Device used prior to trial.</td>
</tr>
<tr>
<td>Juvenile Diabetes Research Foundation study (2008) [10]</td>
<td>2 x 26 week RCT designed to evaluate the effect of CGM on HbA1c for patients with type 1 patients who had a HbA1c of between 7% -10%. 83% of patients were on insulin pumps. The study included 114 children and 110 adolescents. The primary outcome measure reported in the change in HbA1c from baseline at 26 weeks. Secondary outcomes were the time spent in target glucose range, glucose variability and hypoglycaemic episodes</td>
<td>No statistically significant differences in glycaemic control overall. The study found that for patients who wore CGM for 6 days or more reduced HbA1c by: • Greater than 0.7% in the Paediatric group (Age 8-14) • Greater than 0.5% in the age 15-24 and &gt; 25 age group. These outcomes were achieved without increasing the risk of hypoglycaemia. It was also shown that patients within the CGM arm spent 17% longer in target glucose range (3.9-10 mmol/l), 24% less time within the hyperglycaemic range (&gt;10mmol/l) and does not increase the time spent in the hypoglycaemic range.</td>
<td>Short Small numbers of children and no sub group analysis only come from a sub group analysis not planned at the start of the study.</td>
</tr>
<tr>
<td>Hirsch et al (2008) [66]</td>
<td>6-month, randomised, multicentre, treat-to-target study enrolled 146 subjects treated with continuous subcutaneous insulin infusion between the ages of 12 and 72 years with type 1 diabetes and initial A1C levels of &gt;or=7.5%. Subjects were randomised to pump therapy with real-time CGM (sensor group [SG]) or to pump therapy and self-monitoring of blood glucose only (control group [CG]). Clinical effectiveness and safety were evaluated.</td>
<td>A1C levels decreased (P&lt;0.001) from baseline (8.44+/-.70%) in both groups (SG, -0.71+/-0.71%; CG, -0.56+/-0.072%); however, between-group differences did not achieve significance. SG subjects showed no change in mean hypoglycemia area under the curve (AUC), whereas CG subjects showed an increase (P=0.001) in hypoglycemia AUC during the blinded periods of the study. The between-group difference in hypoglycemia AUC was significant (P&lt;0.0002). Greater than 60% sensor utilisation was associated with A1C reduction (P=0.0456). 14 severe hypoglycemic events occurred (11 in the SG group and three in the CG group, P=0.04).</td>
<td>Only small number of children and no sub group analysis Blinded CGM analysed by clinicians and insulin doses adjusted by study team Increased education and support given</td>
</tr>
</tbody>
</table>

Golicki et al (2008) Included five trials involving 131 Included five trials involving 131 Small number of...
### Meta-analysis [67]

- **Participants:** 27 children (12 male) with type 1 diabetes participated in this single-blind, randomised, controlled trial. Participants (age: 11.4 ± 3.7 yr, range: 7-17 yr) were randomised to an intervention group (n = 18) or a control group (n = 9). Both groups wore the CGM for 72-h periods at 0, 2, and 4 months. Adjustments in therapy for the intervention group were based on both CGM and self-monitoring of blood glucose (SMBG) data, while only SMBG data were used for the control group. HbA1c was determined at 0, 2, 4, and 6 months.

- **Results:** Greater reduction in HbA1c with CGM -0.61% vs 0.28% with no increase in hypoglycaemia. Very small blinded CGM analysed by clinicians and insulin doses adjusted short term use of CGM Intensive education and support given as well as SAP

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### Lagarde et al (2008) [68]

- **Participants:** 27 children (12 male) with T1DM participated in this single-blind, randomised, controlled trial. Participants (age: 11.4 ± 3.7 yr, range: 7-17 yr) were randomised to an intervention group (n = 18) or a control group (n = 9). Both groups wore the CGM for 72-h periods at 0, 2, and 4 months. Adjustments in therapy for the intervention group were based on both CGM and self-monitoring of blood glucose (SMBG) data, while only SMBG data were used for the control group. HbA1c was determined at 0, 2, 4, and 6 months.

- **Results:** Greater reduction in HbA1c with CGM -0.61% vs 0.28% with no increase in hypoglycaemia. Very small blinded CGM analysed by clinicians and insulin doses adjusted short term use of CGM Intensive education and support given as well as SAP

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- **Participants:** 3 month Randomised Controlled Trial (RCT) comparing CGM to Self-Monitoring Blood Glucose (SMBG). 162 patients were randomised equally to Continuous use of CGM, 3 days use every other week or a control group using SMBG.

- **Results:** 50% of patients using full time CGM after 3 months had an HbA1c of reduction of ≥1% and 26% had an HbA1c reduction of ≥ 2%

- **Other:** Older children Only recruited those with poor control Short duration, but at the time longest CGM study
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Study Design</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yates et al (2006) [5]</td>
<td>36 subjects aged 12-15 were recruited if they had an HbA1c (A1C) &lt;10% and had been on CSII or glargine for at least 3 months. Thirty-six subjects were randomised to insulin adjustment on the basis of 72 h of CGM every 3 weeks or intermittent self-monitoring of blood glucose (SMBG) for 3 months. Mean baseline A1C was 8.2% (n = 19) in the CGM group and 7.9% (n = 17) in the control group.</td>
<td>There was a significant improvement in A1C from baseline values in both groups, but there was no difference in the degree of improvement in A1C at 12 weeks between the CGM (-0.4% [95% CI -0.7 to -0.1]) and the control group (-0.4% [-0.8 to 0.2]). In the CGM group, improved A1C was at the cost of increased duration of hypoglycemia.</td>
<td>Intermittent use of masked CGM with frequent clinician reviews</td>
<td>Funded by manufacturer of device</td>
</tr>
<tr>
<td>Heptulla et al (2004) [70]</td>
<td>Eight patients with T1DM (age 7.5-17 yr) wore CGM (Medtronic) for 3 d before and 3 months after initiation of insulin pump therapy. The CGM, which measures interstitial glucose concentrations every 5 min for a 72-h period, was used to evaluate glucose profiles.</td>
<td>HbA1C was reduced (p &lt; 0.007) following 3 mo of CSII. Post-CSII continuous glucose profiles demonstrated an overall improvement in hourly mean glucose over a 24-h period (p &lt; 0.001) as well as a reduction in the area under the curve for glucose (27 +/- 4 prepump vs. 8.6 +/- 1.4 mg/dL/d postpump, p &lt; 0.004). This improvement was a result of an attenuation of the maximal postprandial glycemic excursions. Postbreakfast 349 +/- 24 vs. 267 +/- 16 mg/dL, p &lt; 0.003; lunch 340 +/- 16 vs. 217 +/- 20 mg/dL, p &lt; 0.003. Post dinner average similarly decreased after 3 months of CSII by 22%, p &lt; 0.04.</td>
<td>Very small Blinded CGM analysed by clinicians and insulin doses adjusted</td>
<td>Short term use of CGM Intensive education and support given as well as SAP</td>
</tr>
<tr>
<td>Ludvigsson and Hanas (2004) [71]</td>
<td>Controlled crossover study including 27 diabetic patients aged 12.5 +/- 3.3 (mean; standard deviation; range: 5-19) years. All patients were treated with intensive insulin therapy, 14 with multiple injections, and 13 with pumps. The patients were randomised into an open or blind study arm. Both arms wore the CGM sensor for 3 days every 2 weeks. CGM profiles were used in the open study arm to adjust insulin therapy at follow-up visits every 6 weeks. Both the patients and the diabetes team were masked to the CGM profiles in the blinded arm, and insulin therapy adjustments were based solely on 7-point BG profiles.</td>
<td>HbA1c decreased significantly in the open arm (from 7.70%-7.31%) but not in the blind arm (7.75%-7.65%). A total of 26/27 patients experienced daytime low subcutaneous glucose (&lt;3.0 mmol/L; 8 episodes/day; duration 58 +/- 29 minutes; 5.5% of total time), and 27/27 patients had at least 1 nocturnal episode of low subcutaneous glucose (.4 episodes/night; duration 132 +/- 81 minutes; 10.1% of total time).</td>
<td>Intermittent use of masked CGM with regular clinician review and dose adjustment</td>
<td></td>
</tr>
</tbody>
</table>
Chase et al (2001) [72]

Eleven children with type 1 diabetes and HbA1c values consistently >8.0% were randomized either to the Continuous Glucose Monitoring System group or to the control group. The CGM group used 6 3-day sensors within a 30-day period. Both groups self-monitored their blood glucose levels a minimum of 4 times daily. HbA1c levels were measured at the start, at 1-month, and after 3 months of study.

The 5 children using the CGM had 17 asymptomatic episodes (85%) of glucose levels below 60 mg/dL (3.25 mmol/L) and 3 symptomatic episodes (15%) during the night in the study month. The 6 control children had 4 symptomatic nocturnal low episodes during the month. After the 30-day period of wearing the CGM, the 5 children had a significantly lower mean HbA1c value compared with their initial value (mean +/- standard error of the mean [SEM] decrease =.36% +/- .07%). The mean decrease for the controls was 2% +/- 2%. After 3 months, 4 of the 5 children who used the CGM continued to have lower HbA1c values in comparison to their initial values (mean +/- SEM decrease = 1.04% +/- .43%). Three of the 6 control participants also had lower HbA1c values at 3 months (mean +/- SEM decrease for the group =.62% +/- .44%). No severe hypoglycemic events occurred in either the CGM or the control groups.

Pilot study therefore never designed to be statistically significant. Studies a masked CGM system analysed regularly by clinicians and insulin doses adjusted by study clinicians. Only included patients with poor control. Very short duration.
Appendix C: Criteria Used to Assess Levels of Evidence and Strength of Recommendations

**LEVELS OF EVIDENCE**

1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++ High quality systematic reviews of case control or cohort or studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3 Non-analytic studies, e.g. case reports, case series
4 Expert opinion

**GRADES OF RECOMMENDATIONS**

A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, or
A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

Good practice points

Recommended best practice based on the clinical experience of the guideline development group
Appendix D: Scores to Assess Hypoglycaemia

CLARKE HYPOGLYCEMIC INDEX SCORE – Score ≥4 = hypoglycaemia unawareness

1) Check the category that best describes you: (check only one)
   - I always have symptoms when my blood sugar is low 0
   - I sometimes have symptoms when my blood sugar is low 1
   - I no longer have symptoms when my blood sugar is low 1

2) Have you lost some of the symptoms that used to occur when your blood sugar was low?
   - yes 1
   - no 0

3) In the past 6 months how often have you had moderate hypoglycemia episodes? (Episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself)
   - never 0
   - once or twice 1
   - every other month 1
   - once a month 1
   - more than once a month 1

4) In the past year how often have you had severe hypoglycemia episodes? (Episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose)
   - never 0
   - once or twice 1
   - every other month 1
   - once a month 1
   - more than once a month 1

5) How often in the last month have you had readings <70mg/dL (or <3.5mmol/L) with symptoms?
   - never 0
   - 1 time/week 1
   - 2 to 3 times/week 1
   - 4 to 5 times/week 1
   - almost daily 1

6) How often in the last month have you had readings <70mg/dL without symptoms?
   - never 0
   - 1 to 3 times 1
   - 1 time/week 1
   - 2 to 3 times/week 1
   - 4 to 5 times/week 1
   - almost daily 1

7) How low does your blood sugar need to go before you feel symptoms?
   - 3.4-3.9mmol/L 0
   - 2.8-3.3mmol/L 1
   - 2.2-2.7mmol/L 1
   - <2.2mmol/L 1

8) To what extent can you tell by your symptoms that your blood sugar is low?
   - Never 1
   - rarely 1
   - sometimes 1
   - often 1
   - always 0

GOLD SCORE

"Do you know when your hyps are commencing?"

<table>
<thead>
<tr>
<th>Awareness</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>


April 2017 Review 2020
Appendix E: Scales That Can Be Used to Assess Hypoglycaemia

**Hypoglycaemia Fear Questionnaire – Parent**

This survey is intended to find out more about how low blood sugar makes your child feel and behave. Please answer the following questions as frankly as possible.

**Behaviour** – Below is a list of things that people whose children have diabetes do in order to avoid low blood sugar. Circle one of the numbers to the right that best describes what you do during your daily routine to avoid your child having low blood sugar.

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Very often</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feed my child large snacks at bedtime</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. Avoid allowing my child to be away from me when his/her sugar is likely to be low</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Try to run a little high to be on the safe side</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. Keep my child’s sugar higher when he/she will be away from me</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. Feed my child as soon as I feel or see the first signs of low blood sugar</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. Reduce my child’s insulin when I think his/her blood sugar is low</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. Keep my child’s blood sugar higher when I know he/she is planning to be at a long event (e.g. school, party)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. Always carry fast-acting sugar</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. Don’t allow my child to play excessively when I think his/her blood sugar is low</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. Check my child’s blood sugar often when he/she is planning to be at a long event (e.g., school, party)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Worry – below is a list of concerns people whose children have diabetes sometimes have. Please read each item carefully (do not skip any). Circle one of the numbers to the right that best describes how often you worry about each item because of low blood sugar.

<table>
<thead>
<tr>
<th>11. Not recognizing that my child is having a hypoglycaemic event</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Very often</th>
</tr>
</thead>
</table>

| 12. Not having food or fruit juice with me for my child            | 1     | 2      | 3         | 4     | 5         |
| 13. Having my child dizzy or pass out in public                  | 1     | 2      | 3         | 4     | 5         |
| 14. Feeling that my child will have a low blood sugar while he/she is asleep | 1     | 2      | 3         | 4     | 5         |
| 15. My child embarrassing him/herself in front of friends/family in a social situation | 1     | 2      | 3         | 4     | 5         |
| 16. My child having a low blood sugar when he/she is away from me | 1     | 2      | 3         | 4     | 5         |
| 17. My child being disoriented                                   | 1     | 2      | 3         | 4     | 5         |
| 18. My child losing control                                      | 1     | 2      | 3         | 4     | 5         |
| 19. No one being around to help my child during a hypoglycemic event | 1     | 2      | 3         | 4     | 5         |
| 20. My child making a mistake or having an accident at day care/school | 1     | 2      | 3         | 4     | 5         |
| 21. My child getting a bad evaluation at day care/school because of something that happens when his/her sugar is low | 1     | 2      | 3         | 4     | 5         |
| 22. My child having seizures                                     | 1     | 2      | 3         | 4     | 5         |
| 23. My child developing long-term complications from frequent low blood sugars | 1     | 2      | 3         | 4     | 5         |
| 24. My child feeling light headed or faint                        | 1     | 2      | 3         | 4     | 5         |
| 25. My child having an insulin reaction                           | 1     | 2      | 3         | 4     | 5         |
| 26. My child having a hypoglycemic event while I’m driving        | 1     | 2      | 3         | 4     | 5         |
**Hypoglycaemia Fear Questionnaire – Patient**

This survey is intended to find out more about how low blood sugar makes you feel and behave. Please answer the following questions as frankly as possible.

**Behaviour** – Below is a list of things that people who have diabetes do in order to avoid low blood sugar. Circle one of the numbers to the right that best describes what you do during your daily routine to avoid having low blood sugar

<table>
<thead>
<tr>
<th>1. Eat large snacks at bedtime</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Very often</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Avoid being alone when my sugar is likely to be low</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Try to run a little high to be on the safe side</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. Keep my sugar higher when I will be alone for a while</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. Eat something as soon as I feel the first signs of low blood sugar</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. Reduce my insulin when I think my blood sugar is low</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. Keep my blood sugar higher when I know I am planning to be at a long event (e.g. school, party)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. Always carry fast-acting sugar</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. Avoid a lot of exercise when I think my blood sugar is low</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. Check my blood sugar often when I am planning to be at a long event (e.g., school, party)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
## Worry

Below is a list of concerns people who have diabetes sometimes have. Please read each item carefully (do not skip any). Circle one of the numbers to the right that best describes how often you worry about each item because of low blood sugar.

<table>
<thead>
<tr>
<th>Concern</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Very often</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Not recognizing/realising that I am having a hypoglycemic event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Not having food or fruit juice with me</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13. Feeling dizzy or passing out in public</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14. Having a low blood sugar while I am asleep</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>15. Embarrassing myself in front of friends/family in a social situation</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>16. Having a hypoglycaemia while I am alone</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>17. Appearing stupid or drunk</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18. Losing control</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. No one being around to help me during a hypoglycemic event</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>20. Making a mistake or having an accident at school</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>21. Getting a bad evaluation at school because of something that happens when my sugar is low</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>22. Having seizures</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>23. Developing long-term complications from frequent low blood sugars</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>24. Feeling light headed or faint</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>25. Having an insulin reaction</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
References


56. JDRF, *JDRF School toolkit*.


