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Produced by:	Vicky Head, Stuart Keeble, Shamsher Diu	**Date ratified:**	2014 07 10
Public Health Programme: Children and Young People Working Age Older People Health Protection Screening Healthcare commissioning Public Health Development	Healthcare Commissioning	**Copyholders:**	Dr. Shamsher Diu Consultant in Public Health
		Next review due:	Feb 2016
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1. Policy Summary

This policy covers the management Continuous Glucose Monitoring (CGM) systems with criteria for referrals and treatment.

2. Acknowledgement

The authors are grateful for the invaluable support of the North East London Commissioning Support Unit in ensuring liaison with individual service and business managers at the James Paget University Hospital, the Norfolk and Norwich University Hospital, Norwich and the Queen Elizabeth Hospital and their efforts to consult with clinicians in the appropriate specialities at every stage of the development of this policy. Individuals who contributed to this process are acknowledged in Appendix 1.

3. Definition

Continuous glucose monitoring (CGM) systems are used in Type 1 Diabetes, as a diagnostic tool to temporally help patients better manage their blood glucose levels (short term CGM) or as a continuous aid in the glycaemic control (long term CGM). The CGM system measures glucose levels displays glucose levels and any rate of change every few minutes.

4. Background

Continuous glucose monitoring (CGM) systems use a small needle-like sensor, implanted just below the skin, to measure glucose levels in interstitial fluid. Readings are transmitted to a display unit, worn like a pager, which displays glucose levels and rate of change every few minutes. Alarm functions can be used to alert the user to high or low readings, or to rapidly rising or falling levels. CGM is more expensive than conventional self-monitoring of blood glucose (SMBG) through finger-prick tests. Costs per year are around £3-4,000, compared to under £1,000 for SMBG. Although CGM reduces the frequency of SMBG, it does not replace it entirely as the system needs to be calibrated with blood glucose measures twice a day.

Due to a significant number of individual funding requests having been received by local commissioners in the context of a lack of national guidance on this system, a comprehensive review of evidence examining the clinical and cost effectiveness of CGM in the management of diabetes was produced by Norfolk Public Health in December 2013 (Appendix 2).

5. Policy for Continuous Glucose Monitoring (CGM)

Long term*[1] real-time CGM for diabetic patients will NOT be routinely funded.

5.1. For adults or children funding will be approved if ALL of the following criteria are met/agreed to:

a. The patient suffers from insulin-treated diabetes

b. The problems have been present for at least 12 months, AND the patient (or parent/carer) is taking all reasonable measures to mitigate the adverse consequences of problematic hypo- or hyperglycaemia:

- The patient is on optimised insulin therapy either with multiple daily injections in a basal-bolus regime or continuous subcutaneous insulin infusion (insulin pump therapy).
- The patient is appropriately engaged with diabetes care, including attending regular specialist diabetes follow-up as recommended by the specialist diabetes team.
- The patient is performing adequate self-monitored blood glucose measurements (SMBG). For patients with problematic glycaemic control a minimum of seven blood tests daily is recommended.
- The patient is adherent to dietary advice, including, where available attending an approved, intensive educational programme

c. The patient is unable to achieve a good level of glycaemic control, with An average of four or more recordings of blood sugar recordings of under 3.0 mmol*[4] per week or has an HbA1c of 10% (86 mmol/mol) or more.

d. The patient suffers from recurrent disabling symptomatic hypoglycaemic episodes that are significantly affecting day to day life*[3] defined as:

- Two or more episodes of severe hypoglycaemia in the previous 12 months defined as follows:
- Children: altered mental status and cannot assist in their care, [or] is semiconscious or unconscious, or in coma ± convulsions *[2]
- Adults - there is documented evidence of requiring assistance of another person to aid recovery or there is documented problematic hypoglycaemic unawareness with significant adverse impact on quality of life

e. Approval will be granted for an initial period of six months. If adequate compliance is not achieved CGM must be withdrawn. Approval after six months use is dependent on appropriate compliance with CGM device:

- The patient should use the device for at least six days per week and for a minimum of 60% of the time (i.e. the patient is using the device for 60% for each of the days). Ideally the compliance needs to be between 80-100%). If adequate compliance is not achieved CGM must be withdrawn.
- The anticipated objectives of CGM (improvement in problematic hypoglycaemia) being met at 6 months and sustained

f. The Provider agrees to report the outcomes of CGM use after 6 months and annually thereafter for the lifetime of the supplied device. The Provider agrees to participate constructively and in a timely manner in an annual audit of all patients approved under this policy

5.2. For Pregnant women, long-term real-time CGM will not be funded routinely for diabetes during pregnancy.

*[1] Long term is defined as seven day or longer for CGM

*[2] There is an accepted international definition of severe hypoglycaemia in a child. The child [has]:

- altered mental status and cannot assist in their care, [or]
- is semiconscious or unconscious, or in coma ± convulsions"

[http://www.ispad.org/sites/default/files/resources/files/ispad_guidelines_2009_-_hypoglycemia_-_corrected_2013.pdf]

*[3] The accepted adult definition is very similar to the wording in the policy:

"Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions"

[http://www.ndei.org/ADA-Endocrine-Society-diabetes-guidelines-hypoglycemia.aspx]

*[4] Hypoglycaemia is defined as blood glucose <3.0 mmol/L, (from Marks V in Oxford Textbook of Medicine, 4th Edition. Eds; Warrell DA et al. OUP 2003).

Clinical effectiveness

It is recommended that the implementation of this policy is monitored through a professionally-led clinical audit cycle. Please discuss this with your directorate/ healthcare governance lead. If you would require any advice in conducting an audit then contact joanne.creaser@norfolk.gov.uk in Public Health, Norfolk County Council, who can advise you in preparing the audit, measuring performance, making or sustaining improvements in the care of patients referred for Continuous Glucose Monitoring in line with this policy.

APPENDIX 1

This draft policy has been developed through consultation with the following:

Name	Designation	CCG/Acute provider
CCG clinicians		
Michael Dennis	Prescribing Advisor	NHS Great Yarmouth and Waveney CCG
Dr Renee Kathuria	GP Partner	NHS Great Yarmouth and Waveney CCG
Dr Hitesh Kumar	GP representative	NHS Great Yarmouth and Waveney CCG
Prof David Scott	Clinical Advisor	NHS Great Yarmouth and Waveney CCG
Dr Alasdair Lennox	GP representative	NHS North Norfolk CCG
Dr Brian Cole	GP representative	NHS Norwich CCG
Dr Chris Dent	GP representative	NHS Norwich CCG
Dr Les Cooper	GP representative	NHS South Norfolk CCG
Louise Stevens	CCG representative	NHS West Norfolk CCG
Dr Paul Williams	GP	NHS West Norfolk CCG

CCG Colleagues		
Kathryn Griffiths	Project Management Specialist	(representing) NHS Great Yarmouth and Waveney CCG
Ellis Layward	Commissioning Manager	NHS North Norfolk CCG
Lindsay Springall	Commissioning Manager	NHS Norwich CCG
Louise Browning	Independent Consultant	(representing) NHS South Norfolk CCG
Ann Donkin	Chief Officer	NHS South Norfolk CCG
Jan Sanders	Commissioning Manager	NHS West Norfolk CCG

Acute provider colleagues		
Dr Nigel Huston	Clinical Director – Diabetes	James Paget University Hospital NHSFT
Dr Frank Grinnell	Clinical Lead	James Paget University Hospital NHSFT
Dr Srinivasan		James Paget University Hospital NHSFT

Ramalingam		
Dr Maya Venu		James Paget University Hospital NHSFT
Tim Shayes	Business Manager	Norfolk and Norwich University Hospital NHSFT
Stephen Day	Head of Commissioning Information	Norfolk and Norwich University Hospital NHSFT
Dr Vipan Datta	Consultant Paediatrician,	Norfolk and Norwich University Hospital NHSFT
Dr Rosemary Temple	Consultant in Diabetes & Endocrinology).	Norfolk and Norwich University Hospital NHSFT
Dr Nandu Thalange	Consultant Paediatric Endocrinologist	Norfolk and Norwich University Hospital NHSFT
Dr Vipan Datta	Consultant Paediatrician, Diabetes and Endocrinology	Norfolk and Norwich University Hospital NHSFT
Dr Adrian Jennings	Clinical Lead - Endocrinology	Queen Elizabeth Hospital NHS Trust, King's Lynn
Mr Raj Shekhar	Clinical Director	Queen Elizabeth Hospital NHS Trust, King's Lynn

Public Health Team		
Vicky Head	Specialist Registrar in Public Health Registrar	Norfolk County Council
Stuart Keeble	Specialist Registrar in Public Health	Norfolk County Council
Dr Shamsher Diu	Consultant in Public Health	Norfolk County Council

APPENDIX 2

Draft updated evidence and guideline review examining the effectiveness of long term real time Continuous Glucose Monitoring.

Produced by:

Stuart Keeble

Specialty Registrar in Public Health

Supervised by:

Shamsher Diu

Consultant in Public Health

23 December 2013

1. Background

Continuous glucose monitoring (CGM) systems use a small needle-like sensor, implanted just below the skin, to measure glucose levels in interstitial fluid. Readings are transmitted to a display unit, worn like a pager, which displays glucose levels and rate of change every few minutes. Alarm functions can be used to alert the user to high or low readings, or to rapidly rising or falling levels. CGM is more expensive than conventional self-monitoring of blood glucose (SMBG) through finger-prick tests. Costs per year are around £3-4,000, compared to under £1,000 for SMBG. Although CGM reduces the frequency of SMBG, it does not replace it entirely as the system needs to be calibrated with blood glucose measures twice a day. Norfolk and Waveney PCTs and subsequent CCGs have received 5 individual funding requests for CMG since 2009. All have been requested on the basis of exceptional problems with hypoglycaemia and hypoglycaemia-unawareness (Head 2012).

In June 2012 a review of guidelines and evidence examining the clinical and cost effectiveness of long term (LT) real time (RT) continuous glucose monitoring (CGM) compared to self-monitoring blood glucose (SMBG) in the management of diabetes was prompted due to more than 3 applications via the Individual Funding Request panel. The review aimed to:

1. Summarise current national guidelines and systematic reviews on the use and effectiveness of CGM in the management of diabetes;
2. Review in detail the evidence for the effectiveness of CGM compared to SMBG in
    a. maintaining good glycaemic control among type 1 diabetic
    b. reducing frequency and duration of hypoglycaemic episodes among patients that are prone to severe hypoglycaemia or have hypoglycaemia unawareness;
    c. maintaining glycaemic control during pregnancy;
3. Review cost-effectiveness analyses of the use of CGM compared to SMBG;
4. Propose a funding policy for NHS Norfolk and Waveney.

Due to the reconfiguration of the health service (e.g. PCT becoming CCGs and Public Health moving to local government) the policy was never taken forward.

Aim and objective of update

The aim of this review was to update the evidence base and incorporate findings (published since June 2012) into an updated draft CGM funding policy for Norfolk and Waveney CCGs.

The objectives were to:

1. Search the literature to identify new guidelines, systematic reviews, primary studies and cost effectiveness studies relating to CGM published since June 2012.
2. Review the quality of new studies.
3. Update the proposed funding policy to take into account new evidence.

Method

This evidence update adopted the same literature search strategy as before and for each topic (e.g. maintaining good glycaemic control, reducing frequency and duration of hypoglycaemic episodes etc.) provided a:

a) Summary of findings from the previous review,
b) Description of new evidence
c) Summary of all findings and recommendations (taking into account the quality and strength of the evidence).

This document should be read alongside the original evidence review.

Definition of long term CGM

CGM can be used as a diagnostic tool to temporally help patients better manage their blood glucose levels (short term CGM) or as a continuous aid in the glycaemic control (long term CGM). Short term CGM is typically characterised by a 'one off' use for 72 hours or intermittently e.g. a 72 hours period every month for 2 or 3 months. Whilst long term CGM is characterised by the continuous use of a monitoring device 7 days a week for the long term future e.g. years.

The current document relates to long term CGM. Any other use falls outside the remit of the proposed policy.

Quality of evidence and strength of recommendations

The quality of studies within the literature can be extremely variable, therefore limitations need to be taken into account when drawing conclusion and making recommendations. Within this document we have where possible provided an indication of the quality of the evidence and strength of recommendation.

Evidence and recommendations have been rated according to NICE hierarchy of evidence and grading of recommendations (see figure 1 below).

Figure 1: Nice Hierarchy of evidence

Hierarchy of evidence	
Grade	Type of evidence
Ia	Evidence from a meta-analysis of randomized controlled trials
Ib	Evidence from at least one randomized controlled trial
IIa	Evidence from at least one controlled study without randomization
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from observational studies
IV	Evidence from expert committee reports or experts
Grading of recommendation	
Grade	Evidence
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated from category I evidence
C	Directly based on category III evidence or extrapolated from category I or II evidence
D	Directly based on category IV evidence or extrapolated from category I, II or III evidence

Findings from the updated review of guidelines and evidence

UK guidelines

This section described the evidence from UK guidelines on Type I Diabetes in relation to CGM

Findings from original evidence review
Current NICE (2004, 2008) and SIGN (2010) guidelines were published before a number of recent systematic reviews and meta-analyses and are based on older and more clinician-focused application of the technology. As they stand, the guidelines suggest that the permanent use of real-time CGM systems:
- Should be offered to children and young people experiencing problems with hypoglycaemia unawareness or repeated hypo- or hyperglycaemia;
- Should not be offered routinely to adults;
- Should not be offered routinely for use during pregnancy.

Findings from evidence update

A search of the NICE website, Cochrane library, Trip and SIGN databases did not identify any additional guidance since the original search in June 2012.

Summary

As noted above the current guidelines were produced before the recent publication of systematic reviews examining LT RT CGM. The recommendations provided by the guidelines should therefore be seen as a starting point for developing a local policy and be augmented using the more recent evidence.

Summary of systematic reviews on the effectiveness of RT CGM compared to SMBG in control glycaemic levels

This section describes the findings of systematic reviews comparing the effectiveness of LT RT CGM vs. SMBG in controlling glycaemic levels in type 1 diabetic patients.

Findings from original evidence review

There was strong evidence from meta-analyses of RCTs (including a Cochrane Review) that use of real-time CGM in the general population with Type 1 diabetes was associated with a reduction in HbA1c of 0.2 to 0.3% compared to SMBG alone. This difference is statistically significant but is of marginal clinical significance.

The Cochrane Review[1] noted that the greatest reductions in HbA1c were achieved among new users of a sensor-augmented insulin pump therapy, who had poorly controlled diabetes and had not used an insulin pump before. Pickup *et al*'s meta-analysis[2], based on individual-level data from six RCTs, suggests greater reductions are associated with higher frequency of use and higher baseline HbA1c. Overall, they suggest that a patient with baseline HbA1c of 10%, who used a CGM sensor continuously, would experience a reduction in HbA1c of about 0.9%. Pickup *et al* argue, therefore, that the most appropriate use of CGM is likely to be when targeted at those people with Type 1 diabetes who continue to have a high HbA1c despite best endeavours, and who are willing to use CGM frequently.

Findings from evidence update

Since June 2012, 4 systematic reviews[3-6] of RCTs examining the effectiveness of RT CGM compared to SMBG in treating Type 1 diabetes were published (see appendix A for a description of the papers). The review findings accord with those of the previous evidence review with a reduction in HbA1c ranging from 0.18% to 0.3% (see table 1). The reviews did not examine the effectiveness of CGM for different baseline values of HbA1c.

Golden & Sapir (2012)[4] and Yeh et al (2012)[6] found that a higher level of LT RT CGM adherence (e.g. length of time which the device was used) was associated with larger decreases in HbA1c compared to SMBG. In both reviews 60% adherence was found to be a critical value to ensure optimal benefit from LT RT CGM.

Summary

LT RT CGM was shown to offer a statistically significant decrease in HbA1c compared to SMBG (-0.18 to -0.3%) but the difference were of marginal clinical significance (Level Ia evidence).

LT RT CGM provides a greater clinical benefit for those patients with higher baseline HbA1c (Level Ia evidence). Therefore those patients, who continue to have a high HbA1c despite concerted efforts to reduce HbA1c, may disproportionately benefit from LT RT CGM.

Patients need to be motivated to gain greatest benefit from LT RT CGM, with HbA1c reducing linearly with each day of use. Adherence of 60% (sensor used 60% of time) or higher is needed to decrease HbA1c by the optimal amount (Level Ia evidence).

Recommendation

Based on these findings we recommend that:

1. LT RT CGM should not be routinely funded for adults and children (Grade A).
2. LT RT CGM should only be considered for motivated patients (defined as those patients adhering to physician treatment guidance for the previous year - Grade B) unable to achieve a good level of glycaemic control.
3. Funding should be reviewed regularly with continuation contingent on CGM adherence of 6 days a week and at least 60% of the time (Grade B).

Table 1: Results of the systematic reviews examining difference in HbA1c between LT RT CGM and SMBG

Author, year and patient group	**End point of intervention**	**Mean Difference in HbA1c change between baseline and end point**	**Number of patients in meta-analysis**
Review update			
Poolsup et al,2013 T1D[7]	3-6 months	-0.18% (0.35 to -0.02)	633 (5 studies)
Floyd et al, 2012 T1D[3]	4-26 weeks	-0.3% (CI -0.5 to -0.2)	6 studies
Golden and Sapir, 2012 T1D[4]	12-52 weeks	-0.30% (CI -0.37 to -0.22)	9 studies
Yeh et al, 2012 T1D[6]	Not stated	-0.26% (CI -0.33 to -0.19)	1066 (10 studies)
Original review			
Langendam *et al,* 2012 T1D[1]	6 months	-0.2% (CI -0.4 to -0.1%)	963 (6 studies)
Szypowska *et al,* 2012 T1D[8]	3-12 months	-0.25% (CI -0.34 to -0.17%)	948 (7 studies)
Wojciechowski *et al,* 2011 T1D[9]	3-6 months	-0.27% (CI -0.34 to -0.19%)	1,045 (8 studies)
Pickup *et al*, 2011 T1D[2]	13-26 weeks	-0.3% (CI -0.43 to -0.17%)	892 (6 studies)
Hoecks *et al,* 2011 T1D & T2D[10]	3-18 months	Range -0.3 to -0.7% (no meta-analysis)	NA
Gandhi *et al,* 2011 T1D & T2D[11]	unknown follow up	-0.27% (CI -0.44 to -0.1%)	Not stated in abstract

Summary of evidence on the effectiveness of RT CGM compared to SMBG in controlling hypoglycaemic events and managing hypoglycaemia among hypoglycaemia-prone or unaware populations

This section describes

Hypoglycaemic events

Findings from original evidence review
The systematic review found that CGM has no significant positive or negative effect on the occurrence of severe hypoglycaemia. The individual-level meta-analysis by Pickup *et al* is the only study to show a significant finding in relation to CGM use, in terms of a lower time spent in hypoglycaemic glucose ranges.

The lack of significant findings is potentially misleading, however, given that episodes of severe hypoglycaemia were very rare in the studies and the studies were therefore not adequately powered. Furthermore, the studies were not conducted in hypoglycaemia-prone or hypoglycaemia unaware populations (indeed, some RCTs specifically excluded these patients), so the findings do not necessarily apply to these groups. Therefore, while the routine use of CGM does not appear to affect the occurrence of severe hypoglycaemia among the general diabetic population, its use in the management of repeated severe hypoglycaemia, including in patients with hypoglycaemia unawareness, has not been established through randomised controlled trials.

Findings from evidence update

Among the 4 systematic reviews only 2 papers examined differences in severe hypoglycaemic events and time spent in hypoglycaemia for long term rt CGM. Again there was little or no difference between rt CGM and SMBG for both severe hypoglycaemic events and time spent in hypoglycaemia (see table 2 for results).

Summary
Of the 8 systematic reviews examined only the individual level patient data meta-analysis by Pickup et al (2011)[(2)] identified a favourable effect of CGM on time spent in hypoglycaemic glucose ranges. No other studies found a significant difference between SMBG and CGM.

Table 2: Results of systematic reviews comparing risk of hypoglycaemic events and time spent in hypoglycaemia between LT RT CGM and SMBG

Author, year and patient group	Severe hypo events	Time spent in hypoglycaemia
Golden and Sapir, 2012[4] T1D	No difference: RR 0.95 among CGM (CI 0.53 to 1.69) [10 Studies]	No difference in time spent in hypoglycaemia range (<70 mg/dL) [4 studies]
Yeh et al, 2012[6] T1D	No difference: RR 0.88 among CGM (CI 0.53 to 1.46) [9 studies]	No difference in time spent in hypoglycaemia range (<3.9 mmol/L) [4 studies]
Langendam *et al,* 2012[1] T1D	No difference: RR 1.05 among CGM users (CI 0.63-1.77) [6 studies, n=689]	Not studied.
Szypowska *et al,* 2012[8] T1D	No difference in incidence (RR 0.69, CI 0.41-1.14) [6 studies, n=864]	"No difference."
Wojciechowski *et al,* 2011[9] T1D	No difference: RR 0.83 (CI 0.47-1.45) [4 studies, n=not stated]	No difference (WMD -0.01 CI -1.49-1.46) [2 studies, n=143]
Pickup *et al*, 2011[2] T1D	No difference in incidence (1.4 CI 0.87-2.25) [n=775]	Reduced median exposure to hypoglycaemia (Area under curve -0.28 CI -0.46 to -0.09) [6 studies, n=892]
Hoecks *et al,* 2011[10] T1D & T2D	Concluded no difference (but no meta-analysis)	Concluded no difference (but no meta-analysis)
Gandhi *et al,* 2011[11] T1D & T2D	"Data for the incidence of severe or nocturnal hypoglycaemia were sparse and imprecise."	Not stated in abstract.

Use of CGM in hypoglycaemia-prone or unaware populations

Findings from original evidence review

There is some evidence to suggest that CGM can reduce hypoglycaemia in patients who are prone to, or unaware of, hypoglycaemia, and that CGM can be used to restore hypoglycaemia awareness to an extent.

All three studies are small; two in particular have significant methodological flaws. Therefore, while all provide some evidence of a positive impact of CGM on hypoglycaemia, the evidence-base cannot yet be considered robust.

The studies would, however, suggest that use of CGM may help patients with significant problems with hypoglycaemia. Given the difficulties of managing severe hypoglycaemia when associated with hypoglycaemia unawareness, and the implications of repeated severe glycaemic episodes on individuals and emergency services, it would seem appropriate to fund CGM in this patient group.

Findings from evidence update

One additional study was identified by the review update. Choudhary et al (2013)[12] used a retrospective audit to evaluate the effect of CGM (> 1 year) on the frequency of severe hypoglycaemia (SH) in 35 type 1 diabetic patients with established hypoglycaemia unawareness despite optimized medical therapy. They found that over a 1-year follow-up period (following the introduction of CGM), the median rates of SH were reduced from 4.0 (interquartile range [IQR] 0.75-7.25) episodes/patient-year to 0.0 (0.0-1.25) episodes/patient-year ($P < 0.001$), and the mean (±SD) rates were reduced from 8.1 ± 13 to 0.6 ± 1.2 episodes/year ($P = 0.005$). HbA1c was reduced from 8.1 ± 1.2% to 7.6 ± 1.0% over the year ($P = 0.005$). The mean Gold score (a score of ≥4 implies impaired

awareness of hypoglycaemia), measured in 19 patients, did not change: 5.1 ± 1.5 vs. 5.2 ± 1.9 (P = 0.67). The study used no controls and was retrospective. The sample was also small and selective in nature (with patients receiving considerable education before the intervention). Overall the study provides weak evidence (Level 3)

Summary

Within the literature there was some, albeit weak evidence (level III evidence), that RT LT CGM may be of benefit in reducing severe hypoglycaemia among those patients with hypoglycaemia unawareness compared to SMBG. Further RCTs are needed to provide more robust evidence.

Recommendations

1. LT RT CGM should only be considered for those patients with severe hypoglycaemia unawareness (Level D)

Use of CGM in pregnancy

Findings from original evidence review

The literature search identified no studies on the effectiveness of real-time CGM compared to SMBG during pregnancy. There was one RCT showing a positive effect of intermittent retrospective CGM during pregnancy, in terms of glycaemic control and pregnancy outcomes, but no studies have used real-time CGM in this population.

Findings from evidence update

Secher et al (2013)[7] undertook a randomised control trial of pregestational diabetic pregnant women (123 type T1D and 31 T2D) to assess the effect of CGM (compared to SMBG only) on prevalence of large for gestational age infants (primary outcome), prevalence of preterm delivery and or severe neonatal hypoglycaemia (secondary outcome). The study also considered differences in HbA1c and number of severe or mild hypoglycaemic events. The intervention was based on intermittent real-time CGM for 6 days at 8, 12, 21, 27 and 33 weeks on top of routine pregnancy care for pregestational diabetes, with the researchers supporting participants to use CGM continuously (only 5 patients adopted this approach). Analysis of type I diabetic patients found no difference in large for gestational age infants prevalence of preterm delivery and/or severe neonatal hypoglycaemia and no difference in HbA1c or severe hypoglycaemic events. Although this evidence is of good quality (Level 1b) with a reasonable Jadad quality score (3/5) its application for our current purpose is limited as only 5 of the 123 patients agreed to undertake RT CGM continuously (the rest were monitored intermittently) (see appendix y for appraisal of evidence).

Summary

There is a clear gap in the evidence examining the effect of LT RT CGM in pregnancy, the limited studies that do exist focus on intermittent use of CGM. Given the lack of evidence it is not possible to draw a judgement on the effectiveness of LT RT CGM in pregnancy and further research is needed to help with our understanding.

Recommendation

1. LT RT CGM should not be routinely funded for pregnant women.

Cost effectiveness

Findings from original evidence review

Two cost-effectiveness analyses compare CGM use with SMBG only. Both are based on US costs. Huang *et al*'s study[13] is part of the Juvenile Diabetes Research Foundation CGM trials and is based on the population in the clinical trial. Their analysis takes account of the modest quality of life gain their studies showed while using CGM. McQueen *et al*'s study[14] is based on a hypothetical general population and is more focused on the cost of longer-term progression to complication-states. Both studies assume a 0.5% improvement in HbA1c associated with CGM use, which is higher than indicated by the Cochrane Review.

Cost-effectiveness analyses based on US costs indicate that routine CGM is unlikely to be cost-effective in UK patients with Type 1 diabetes, given a willingness-to-pay threshold of £30,000 per QALY, although studies based on UK-specific costs would be needed to confirm this.

These studies provide early evidence that CGM is unlikely to be cost-effective in the general diabetic population. To be more confident, UK-based studies are needed, taking account of nationally-specific costs and rates of progression to long-term complications.

Findings from evidence update

No further studies on the cost effectiveness of the CGM were identified in the literature

Summary

The current evidence on cost effectiveness suggests CGM is either borderline cost effective (ICER of £28k per QALY) or considerably above the £30,000 willingness to pay threshold (ICER £50,000 to £62,000). Although the studies adopted methodologically robust approaches the underlying assumptions of a 0.5% reduction in HbA1c and relatively high HbA1c level at baseline limit any conclusions. Further economic analysis is needed which examines the effect of different baseline HbA1c levels reduction levels on cost effectiveness. LT RT CGM should therefore be reserved for those patients who may derive a disproportionately large benefit from such treatment.

Recommendation

1. LT RT CGM should not be routinely funded

Proposed funding policy

Based on the available evidence and recommendations we propose that:

1) Long-term real-time CGM should NOT be funded routinely for diabetic adults or children unless patients meet all of the following criteria:

   a. The patient suffers from insulin-treated diabetes
   b. There is evidence of adherence to a physician-recommended diabetic treatment plan e.g. at least one year,
   c. Patients are unable to achieve a good level of glycaemic control.

d. Patients experiences severe hypoglycaemia unawareness
e. Patients experience 2 or more severe hypoglycaemia events in last year defined as:
    - *Children* - altered mental status and cannot assist in their care, [or] is semiconscious or unconscious, or in coma ± convulsions
    - *Adults* - requiring assistance of another person for recovery

and

Documented, recurrent disabling symptomatic hypoglycaemic episodes significantly affecting day to day life.

2) Long-term real-time CGM should NOT be funded routinely for diabetes during pregnancy.

3) Funding for all patients should be reviewed after 6 months and then yearly thereafter with patients requiring minimum sensor adherence of 6 days a week and at least 60% (e.g. the patient is actively using the device 60% of the time) to justify the continuation of funding.

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Appendix A: Summary of evidence from review update

Systematic reviews and meta-analysis of studies comparing CGM with SMBG

Study and inclusion criteria	Studies included	Outcome measures	Results	Notes
Poolsup et al [5] **Year:** 2013 **Journal:** Diabetology & Metabolic Syndrome **Study type:** Systematic review and meta-analysis **Inclusion criteria**: 1)RCT trials comparing currently available CGM device with SMBG in patients with type 1 diabetes paediatrics (<=18yrs) or type 2 diabetes adults (>=18yrs) 2) Reporting HbA1c as an outcome measure 3) Duration of intervention at least 8 weeks Search to May 2013	10 studies included Chase et al, 2001 Deiss et al, 2006 Lagarde et al, 2006 Yates et al, 2006 JDRF, 2008 Bergenstal et al, 2010 Kondonouri et al, 2010 Battelino et al, 2012 Bukara-Radujkovic et al, 2011 Mauras et al, 2012	1^0 Outcome: Mean difference in HbA1c between CGM and SMBG	Meta-analysis across paediatrics using RT showed a small decline in HbA1c [Mean change in HbA1c of -0.18% (95% CI -0.35% to -0.02%) 5 RCTs, 633 patients, I^2 48%]	Reports on retrospective and real time CGM Study level data only High levels of Heterogeneity Potential publication bias highlighted by author. Robust study selection method and quality assessment of studies
Floyd et al[3] **Year:** 2012 **Journal:** Diabetes Science and Technology **Study type:** Systematic review and meta-analysis **Inclusion criteria**: RCT, English Language, Subjects with T1D Use of subcutaneous CGM in outpatients setting Reporting changes in HbA1c and/ or hyperglycaemia or hypoglycaemia. Search to November 2009	Deiss et al, 2006 Hirsch et al, 2008 JDRF, 2008 Cosson et al, 2009 O'Connell et al, 2009 Peyrot et al, 2009 Raccah et al, 2009	1^0 Outcome: Absolute HbA1c change from baseline to study end. 2^0 Outcome: HbA1c change during intervention, hypo frequency, durations (min/day) of hypo, profound hypo, normoglycemia and hyper	6 RCTs HbA1c – For continuous CGM patients small decline -0.4 (95% CI -0.5, -0.2) P<0.0001	Combined analysis for RT and R – which reduced reporting on secondary outcomes. Didn't report detailed measures of heterogeneity Study level data Large gap in time between search and reporting. Robust study selection method and quality assessment of studies

Study and inclusion criteria	Studies included	Outcome measures	Results	Notes
Yeh et al[6] **Year: 2012** **Journal:** Annals of Internal Medicine **Study type:** Systematic review and meta-analysis **Inclusion criteria**: Studies comparing rt-CGM with SMBG (at least 3 fingersticks per day) RCTs that evaluated process measures, intermediate outcomes, QOL, or severe hypoglycaemia and RCTs and observational studies with a concurrent comparative group that evaluated microvascular or macrovascular outcomes or morbidity Type 1 diabetes Search to February 2012	Deiss et al, 2006 Tamborlane et al, 2008 O'Connell et al, 2009 Beck et al, 2009 Battelino et al, 2012 Raccah et al, 2009 Hirsch et al, 2008 Mauras et al, 2012	1^0 Outcome: Process measures Intermediate outcomes QOL Severe hypoglycaemia	Of the 33 RCTs included in the review 10 addressed comparative effect of rt-CGM Versus SMBG. 2 studies were excluded due to heterogeneity in design. **HbA1c**: Meta-analysis across all age groups showed a small mean difference in difference, although there was evidence of statistical heterogeneity [Mean change in HbA1c of -0.26% (95% CI -0.33% to -0.19%) 10 RCTs, 1066 patients, I^2 69.9%] **Severe Hypoglycaemia:** incidence of severe hypoglycaemia did not differ between rt-CGM and SMBG [pooled relative risk, 0.88 (95% CI 0.53, 1.46) 9 RCTs] **Other Hypoglycaemia outcomes**: no difference in time spent in hypoglycaemia range (<3.9 mmol/L) [4 studies] **Hyperglycaemia** – There was evidence of significant reduction in time spent in hyperglycaemia range (>10.0 mmol/L). [Mean between group difference of -68.56 mins/day (95% CI -101.17 to -35.96) 3 RCTs] **QOL:** In 4 studies there was no difference **Adherence** – when only studies with adherence >60% were included the reduction in HbA1c increased and the level of heterogeneity reduced. [Mean change in HbA1c of -0.36% (95% CI -0.44% to -0.27%) 7 RCTs, 705 patients, I^2 40.8%]	Robust study selection method and assessment of quality of studies. Mixture of delivery e.g. CSII and MDI

Study and inclusion criteria	Studies included	Outcome measures	Results	Notes
Golden and Sapir[4] **Year: 2012** **Journal:** Journal of managed care pharmacy **Study type:** Systematic review and meta-analysis **Inclusion criteria**: Adults, adolescents, and children with a formal diagnosis of diabetes mellitus and pregnant women with pre-existing diabetes T1DM and T2DM Studies that compared rt-CGM with SMBG (at least 3 fingersticks per day) Search to July 2011	Deiss et al, 2006 Hirsch et al, 2008 Tamborlane et al, 2008 O'Connell et al, 2009 JDRF, 2008 Battelino et al, 2012 Raccah et al, 2009	1^0 Outcome: HbA1c Hyperglycaemia Severe and non-severe hypoglycaemia Ratio of basal to bolus insulin and quality of life	9 RCTs addressed the comparative effect of rt-CGM Versus SMBG. 2 studies were excluded due to heterogeneity in design. **HbA1c**: Meta-analysis across all age groups showed a small mean difference in difference, although there was evidence of statistical heterogeneity [Mean change in HbA1c of -0.30% (95% CI -0.37% to -0.22%) 9 trials, I^2 64.6%] (**Strength of evidence: High)** **Severe Hypoglycaemia:** incidence of severe hypoglycaemia did not differ between rt-CGM and SMBG [pooled relative risk, 0.95 (95% CI 0.53, 1.69) 10 RCTs] (**Strength of evidence**: low) **Non severe Hypoglycaemia**: no difference in time spent in hypoglycaemia range (<7) [4 studies] (**Strength of evidence: Moderate)** **Hyperglycaemia** – There was evidence of significant reduction in time spent in hyperglycaemia range (<180 mg/dl). [Mean between group difference of -68.56 mins/day (95% CI -101.17 to -35.96) 4 RCTs] (**Strength of evidence: Moderate)** **QOL:** 3 studies examined quality of life, for well-being of parents there was no difference, for physical component of general QOL there was improvement in physical component (favouring CGM) and no difference for mental component. There was no difference in Diabetes QOL survey and Hypo fear survey found children and adults feared hypoglycaemia less with CGM. (**Strength of evidence: Low)** **Adherence** – when only studies with adherence >60% were included the reduction in HbA1c increased and the level of heterogeneity reduced. [Mean change in HbA1c of -0.36% (95% CI -0.44% to -0.27%) 7 RCTs, I^2 40.8%]	Higher quality Systematic review and meta-analysis Large number of sub analysis

Randomised control trial comparing LT RT CGM with SMBG for pregnant women

Study	Study characteristics	Intervention	Outcome	Results	Comments
Secher et al, 2013[7] **Title:** The Effect of Real-time Continuous Glucose Monitoring in Pregnant Women with Diabetes **Journal:** Diabetes Care	**Study design**: Unblinded prospective randomised control trial **Participants:** Pregnant women with pregestational diabetes (123 T1D and 31 T2D). 27 seven women with T1D were on insulin pump. Baseline Hba1c 6.6 - CGM and 6.8 controls Setting: Patients referred to the Center for Pregnant women with Diabetes in Denmark	Participants randomised to routine care (n=75) or routine care and Intermittent real-time CGM (Medtronic Minimed Guardian Real-Time Continuous Glucose Monitoring System with Sof-Sensor) for 6 days at 8, 12, 21, 27 and 33 weeks (n=79)	1^0 Outcome: Prevalence of large for gestational age infants. 2^0 Outcome: Prevalence of preterm delivery and or severe neonatal hypoglycaemia.	49 out of 79 women with T1D or T2D used real time CGM per protocol. Near continuous real time CGM (at least 60% of time) was used by 5 women. 3 patients in intervention arm and 2 patients in control arm were loss to follow up due to miscarriage. For type 1 diabetes • there was no difference in HbA1c for the sub population of women with T1D • No of mild and severe hypoglycaemic events were similar between CGM and Control Overall there was no difference in the prevalence of large gestational age infants (45% CGM vs 34%, p=0.19) and pre term delivery and/or severe neonatal hypoglycaemia (29% CGM vs 22%, P=0.36)	RCT assessed mainly intermittent RT CGM HbA1c was not primary or secondary outcome. Controls were not blinded. Although intermittent CGM in protocol, patients were encouraged to use CGM continuously. **Quality of Evidence:** Level Ib

Retrospective observational study

Study	Study characteristics	Study	Outcome	Results	Comments
Choudhary et al, 2013[12] **Title:** Real time Continuous Glucose Monitoring Significantly Reduces Severe Hypoglycaemia in Hypoglycaemia-Unaware Patients with Type 1 Diabetes **Journal:** Diabetes Care	**Study design**: Retrospective audit **Participants:** 35 Adult type 1 diabetic patients with ongoing problematic hypoglycaemia leading to limitations in daily living despite structured education with or without CSII who then used CSII or MDI for at least 12 months. Setting: Patients being treated at a specialist centre experienced in diabetes insulin pump.	Retrospective case not audit where information before and after a year of CGM were extracted from patient notes	1^0 Outcome: Severe Hypoglycaemia HbA1c Hypoglycaemia unawareness (Gold score)	Median (IQR) rate of Severe Hypoglycaemia events was reduced from 4.0 to 0.0 (P<0.001) HbA1c for all patients reduced from 8.1 to 7.8 (P<0.007) at 1 year There was no difference in gold scores (p=0.67)	No controls Retrospective study Highly specific population **Quality of Evidence:** Level III

Appendix B

Critical appraisal of Secher et al 2013 RCT of CGM for pregnant women.

1. Did the trial address a clearly focused issue?	**Y/N**
The focus of the trial can be assessed using PICO **P**opulation studied - Pregnant women with pregestational diabetes (123 T1D and 31 T2D). 27 seven women with T1D were on insulin pump. **I**ntervention - routine care and Intermittent real-time CGM (Medtronic Minimed Guardian Real-Time Continuous Glucose Monitoring System with Soft-Sensor) for 6 days at 8, 12, 21, 27 and 33 weeks **C**omparator - routine care **O**utcomes considered - Prevalence of large for gestational age infants, prevalence of preterm delivery and or severe neonatal hypoglycaemia. The trial generally addressed a clearly focused question. However there was some inconsistencies in the planned method of monitoring (intermittent CGM) and the type offered by the researchers (all patients were encouraged to adopt continuous long term CGM).	**?**
2. Was the assignment of patients to treatments randomised?	**Y/N**
Computer generated randomisation was used and treatment allocation was concealed using automated telephone allocation service via and independent organisation.	**Y**
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	**Y/N**
5 women were excluded/ didn't finish the trial due to miscarriages. Patients were analysed using "Intention to treat".	**Y**
4. Were patients, health workers and study personnel 'blind' to treatment?	**Y/N**
Neither the participants or researchers were blinded to the conditions. Blinding is not possible as RT CGM is designed to provide real time feedback on glycaemic level to users. It would not be possible or ethical to provide patients with a sham/fake CGM device.	**N**
5. Were the groups similar at the start of the trial?	**Y/N**
At baseline patients in the intervention and control arms had similar diabetes (duration, HbA1c, Insulin dose, severe hypoglycaemia, elevated urine albumin excretion, SMPG measurements per day, diabetic retinopathy), lifestyle (smoking, pregestational BMI) and pregnancy characteristics (gestational age, nulliparous).	**Y**
6. Aside from the experimental intervention, were the groups treated equally?	**Y/N**
Apart from the CGM device itself the patients in the intervention arm received more contact with health care professionals. For instance participants in the intervention arm received a scheduled phone call the day following the insertion of the sensor. It would have been more valid to provide the control arm with similar contact time.	**N**
7. How large was the treatment effect?	
The study measured over 40 different outcomes with the primary outcome defined as prevalence of large for gestational age infants, 45% Vs 34% (P=0.19) and secondary prevalence of preterm delivery and or severe neonatal hypoglycaemia. 29% Vs 22% (p=0.36). There was no difference in the outcome between intervention and control arms. There was also no difference in any of the secondary outcomes between intervention and control arms.	**N/A**
8. How precise was the estimate of the treatment effect?	**N/A**
The authors did not calculate confidence intervals for proportions, only P-values were calculated, so it is not possible to judge the precision of the estimate	

9. Can the results be applied in your context?	**Y/N**
This was a Danish based study which means the participants were of Northern European origin, similar to the UK population. The Denmark health system is based on health insurance which makes it more difficult to generalise to the English NHS system. However the participants were given the CGM equipment and disposables for free. The current study included 31 type II diabetic which are not included in the current policy development however the authors did provide sub analysis for type I diabetics. The study included only 5 patients who utilised long term RT CGM whilst the rest used intermittent RT CGM. This means the current findings are not completely applicable to our context and provide little information for our specific requirements	**?**
10. Were all clinically important outcomes considered?	**Y/N**
The study did include the outcomes we were interested in however they were not the primary outcomes. The study did not provide any information on the number of hypoglycaemic events and time spent in hypoglycaemic range.	**N**
11. Are the benefits worth the harms and costs?	**Y/N**
The study did not identify any benefits as there was no difference between intervention and control arms. The study also did not discuss harms for instance the length of time patients spent in hyperglycaemia due to the CGM device. Considering only five patients agreed to wear the device long term information on harm caused by equipment e.g. discomfort could also have been provided.	**N**

Jadad quality score for Secher et al 2013 RCT of CGM for pregnant women.

Jadad Score Calculation		
Item	**Score**	**Score**
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1	1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1	1
Was the study described as double blind?	0/1	0
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1	0
Was there a description of withdrawals and dropouts?	0/1	1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/-1	0
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/-1	0

JADAD score 3/5