Evidence Review for  
Treatment: Continuous Blood Glucose Monitoring in combination with an Insulin Pump for those patient’s with type 1 diabetes.

Prepared by: Clare Johns (Senior Technician – Pharmaceutical Commissioning, NHS Surrey)  
January 2010

1. Purpose of the Review
NHS Surrey routinely funds insulin pumps in line with NICE guidance (TA151 (July 2008)) ‘Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus’.

One insulin pump that is available (Minimed Paradigm® Veo™ System) from a company called Medtronic has the capability of providing Continuous Glucose Monitoring (CGM) to the user (REAL-time). Currently this service is not commissioned by NHS Surrey and the following review will consider the evidence available to support the use of CGM in combination with an insulin pump. It is not within the scope of this document to provide guidance on diagnosis of diabetes or the use of other devices used to continually monitor glucose (either personal or professional CGM)

2. Appropriateness

2.1 The patient:
Patients with type 1 diabetes who meet criteria for funding of an insulin pump (NICE TA151) but fail to achieve optimal glycaemic control from continuous subcutaneous insulin infusions

The primary treatment goal in insulin dependent diabetes is tight glucose control to minimise complications associated with diabetes.

2.2 The problem:
Definition:
Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or alternatively, when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

Effects and prognosis:
Patients with type 1 diabetes are treated with insulin injections and a healthy diet, regular exercise is recommended. Commonly two to four injections are given per day, the aim of this is to mimic the body’s natural release of insulin.

If optimal glycaemic control is not achieved appropriate patients will be considered for insulin pump therapy as follows:

Continuous subcutaneous insulin infusions (insulin pump therapy) would be considered in line with NICE Technology Appraisal (TA151) for those adult patients where:

- Attempts to achieve target haemoglobin A1c (HbA1c) levels with multiple daily injections (MDIs) resulting in the person experiencing disabling hypoglycaemia (repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life) or the patients HbA1c levels have
remained high (that is, at 8.5% or above) on MDI therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.

AND
- as a treatment option for children younger than 12 years with type 1 diabetes mellitus provided that: MDI therapy is considered to be impractical or inappropriate

Monitoring of glycaemia.
- Self monitoring of glycaemic control by patients on a daily basis
- HbA1c testing should be performed routinely in all patients with diabetes, first to document the degree of glycaemic control at initial assessment, then as part of continuing care.

Etiology:
The World Health Organization (WHO) estimates that more than 180 million people worldwide have diabetes. This number is likely to more than double by 2030. In 2005, an estimated 1.1 million people died from diabetes. Almost 80% of diabetes deaths occur in low and middle-income countries. Almost half of diabetes deaths occur in people under the age of 70 years; 55% of diabetes deaths are in women. WHO projects that diabetes death will increase by more than 50% in the next 10 years without urgent action. Most notably, diabetes deaths are projected to increase by over 80% in upper-middle income countries between 2006 and 2015.

- Type 1 diabetes (previously known as insulin-dependent or childhood-onset) is characterized by a lack of insulin production. Without daily administration of insulin, Type 1 diabetes is rapidly fatal.
  - Symptoms include excessive excretion of urine (polyuria), thirst (polydipsia), constant hunger, weight loss, vision changes and fatigue. These symptoms may occur suddenly.

World Health Organisation:
The current WHO diagnostic criteria for diabetes are as follows
- fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl).

Despite the limitations with the data from which the diagnostic criteria for diabetes are derived, the current criteria distinguish a group with significantly increased premature mortality and increased risk of microvascular and cardiovascular complications.

NICE clinical Guideline (CG15) ‘Type 1 Diabetes in children, young people and adults’
This guideline states ‘The diagnosis of type 1 diabetes in children and young people should be based on the criteria specified in the 1999 World Health Organization report on the diagnosis and classification of diabetes mellitus.’

2.3The Intervention:
The Minimed Paradigm VEO System is a pump which provides a continuous subcutaneous infusion of insulin to an individual (REAL-time). It has the additional capability of continuous glucose monitoring. The pump can be used alone to deliver insulin or with the CGM function.
How does it work:
The Minimed Paradigm VEO System measures interstitial fluid every 5 minutes 24 hours a day via a glucose sensor. The results can have up to a 10 minute lag time in which it takes to display the recording during periods of rapidly changing blood glucose. The readings are transmitted wirelessly via a transmitter (the MiniLink). The information is then displayed on the insulin pump*. 

NB: See information from clinician at Imperial (below) regarding lag time. Calibration is required with finger-stick tests up to 4 times a day. CGM supplements, but does not replace, conventional blood glucose testing. The glucose sensor reads the glucose content in the interstitial fluid. Calibration is a process to assist in determining the correct interstitial glucose values.

Question: Why Calibration? (information from the Medtronic website)
‘Calibration is like buying a watch and setting the time for the first time. Glucose sensors are similar in nature. To initialise a glucose sensor, you need to enter a meter reading to give the system a starting point. And, just as a watch needs to be adjusted occasionally, so does a glucose sensor. You need to enter at least 2 meter readings a day - once every 12 hours. This aligns the glucose sensor with the meter so that continuous glucose monitoring (CGM) readings are representative of your blood glucose level. Calibration should be done during stable blood glucose period and try to enter values during stable high and low levels’

Medtronic provide a glucose meter with wireless transmission which transmits blood glucose readings wirelessly to the insulin pump.

Care setting:
The technology would be currently provided by the home care company Medtronic.

Frequency:
Information provided by clinicians locally suggests that the intervention would be lifelong but intermittent.

2.4 Alternative treatments:
Insulin Pump therapy (without CGM) funded line with NICE TA151.

3. Effectiveness

3.1 Expected benefits
Continuous Glucose Monitoring provides insights into low & high glucose levels.

3.2 Side-effects/complications
Bleeding, bruising and skin irritation from the glucose sensor under the skin, plus the possible side effects of the insulin pump which include:
- A skin reaction at the site of the needle or cannula
- Infections at the site of the needle or cannula
- Low blood sugar levels (hypoglycemia)
- High blood sugar levels (usually due to pump malfunction or problems with the cannula, needle, or tubing).

3.3 Review of Evidence (See Appendix 1. for search strategy & summary of results)
(Please see appendix 2 for hierarchy of evidence quality)

Appendix 1 contains the supporting evidence for CGM in combination with an insulin pump.
Summary:
In April 2009 Oxford Health Plans which is a United Healthcare company in America developed a clinical policy for CGM, evidence from uncontrolled studies showed limited evidence of efficacy for insulin pump therapy & CGM.

The Real Trend study (December 2009) was a 6-month, randomized, parallel-group, two-arm, open-label study (132 adults and children with uncontrolled type 1 diabetes (A1C >/=8%)). The conclusion from the trial was that CGM-enabled insulin pump therapy improves glycemia more than conventional pump therapy during the first 6 months of pump use in patients who wear CGM sensors at least 70% of the time.

The juvenile diabetes research foundation CGM study group (Oct 2008) published results from a multicentre clinical trial of 322 patients (over 8 years of age). Patients were randomly assigned to receive either CGM or a control group performing home monitoring with a blood glucose meter. The benefits from this study appeared to be closely related to age in this study.

Hirsch et al (2008) published results from a 6-month randomized, multicenter, treat-to-target study. Subjects treated with continuous subcutaneous insulin infusion between the ages of 12 and 72 years with type 1 diabetes and initial A1C levels of ≥7.5%. Subjects were randomized to pump therapy with real-time CGM (sensor group [SG]) or to pump therapy and self-monitoring of blood glucose only (control group [CG]).

Conclusions from the trial were A1C reduction was no different between the two groups. Subjects in the CG group had increased hypoglycemia area under the curve (AUC) and number of events during blinded CGM use; however, there was no increase in hypoglycemia AUC or number of events in the SG group. Subjects with greater sensor utilization showed a greater improvement in A1C levels.

O’Connell MA et al (July 2009) published results from an open multicentre parallel randomised controlled trial conducted at 5 tertiary diabetes centres with 62 patients aged between 13 & 40 years. Conclusions from the trial were that individuals established on insulin pump therapy can employ sensor-guided pump management to improve glycaemic control. An apparent dose-dependent effect of sensor usage was noted; however, frequent use of this technology (> or =70%) was not universally acceptable.

Peterson K et al (March 2009) published results of a small trial involving 42 patients with diabetes (n= 39 Type 1 diabetes) (n=3 type 2 diabetes) over a 3 month study period. The conclusions from the trial were that Insulin pump therapy & CGM resulted in significant improvement in HbA1c which appeared within one month and remained throughout the 3 month study period. No significant improvement in HbA1c was seen in the control group.

4. Summary of Key Points for Consideration

4.1 National guidance:
NICE Clinical Guidelines (CG015) ‘Type 1 Diabetes in children, young people and adults’ acknowledges that CGMS has a role in the assessment of, 
Adults with type 1 diabetes with consistent glucose control problems on insulin therapy notably:
- Repeated hyper or hypoglycaemia at the same time of day
- Hypoglycaemia unawareness
- Unresponsiveness to insulin dose adjustments

The clinical guideline also states that continuous glucose monitoring systems should be offered to:

**Children and young adults** with type 1 diabetes that suffer from:
- Repeated hypo/hyperglycaemia and/or hypo-unawareness

### 4.2 Potential benefits over existing treatments

Insulin pump therapy with CGM provides a full picture of a patient’s glucose patterns.

It allows the patient to set personal alerts so that an alarm sounds if a patient’s glucose level reaches or goes beyond the target that has been set by the patient.

There is also a low glucose suspend alarm that will alert and suspend delivery of insulin to prevent hypoglycaemia. The patient can interrupt this feature at any time.

### 4.3 Potential drawbacks

The patient is required to alter their insulin delivery dependent on the glucose readings taken by the glucose sensor. It is not a closed loop system (i.e. the pump does not alter the insulin delivery automatically).

Patients are required to calibrate the device up to 4 times a day. A blood glucose monitor is provided by the company.

### 4.4 Budgetary Impact

**Cost: Insulin Pump alone:**

<table>
<thead>
<tr>
<th></th>
<th>Year 1 (based on current Medtronic price list)</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Pump</td>
<td>£2850.00</td>
<td>N/A</td>
</tr>
<tr>
<td>Insertion Device</td>
<td>£21.50</td>
<td>N/A</td>
</tr>
<tr>
<td>Infusion Sets (based on 2 or 3 day* change) Average Cost</td>
<td>£1325.57 - £1718.33</td>
<td>£1325.57 - £1718.33</td>
</tr>
<tr>
<td>Reservoirs (based on 2 or 3 day change) Average Cost</td>
<td>£321.36 - £428.48</td>
<td>£321.36 - £428.48</td>
</tr>
<tr>
<td>Batteries (12 batteries)</td>
<td>£12.75</td>
<td>£12.75</td>
</tr>
<tr>
<td><strong>Total Cost</strong></td>
<td><strong>£4531.18 - £5031.06</strong></td>
<td><strong>£1659.68 - £2159.56</strong></td>
</tr>
</tbody>
</table>

Medtronic pumps have a warranty of 4 years, so expect the 1st year cost every 4 years.

*The following information is from the Medtronic

- *The 2 or 3 day change relates to which cannula the patient is using normally for Teflon cannulas (this includes Quick Sets, Silhouette Sets) then the change is every 3 days. For steel needle cannulas (this includes Easy Sets) then the change is every 2 days. It is suggested that patients in pregnancy
should change every 2 days regardless of type of infusion set. The best suitable infusion set for a patient would be guided by body type of patient, injection site history, suitability of infusion sites (on body), and allergy’.

<table>
<thead>
<tr>
<th>Insulin Pump &amp; Continuous Glucose monitoring</th>
<th>Year 1 (based on current Medtronic price list)</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the above plus:</td>
<td></td>
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<tr>
<td>CGMs system</td>
<td>£450.00*</td>
<td>N/A</td>
</tr>
<tr>
<td>Sensors (box of 10)**</td>
<td>Based on continuous use: £2250.00*** (5 sensors/month)</td>
<td>£2250.00</td>
</tr>
<tr>
<td>£375.00</td>
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</tbody>
</table>

- *If the CGMs is purchased separately to the pump the cost is £750.00
- **Sensors are normally changed every 6 days
- ***This is an approximate cost. Not all sensors will last for 6 days so cost may be slightly more for continuous use. The cost would be considerably less for intermittent use. But the expiry of the sensors would need to be taken into consideration.

NB: See comments from clinician at Imperial (below) regarding number of sensors/month

Sensor Expiry
Glucose sensors have a 6 month expiry from the date of manufacture. If the glucose sensors are being used intermittently there may be an increased cost as the sensors expire before they are used.

Precedent setting:
Insulin Pumps are already funded in line with NICE Technology Appraisal 151 ‘Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus’. There will not be an increase in the number of new patients if this treatment is funded; however there will be an increase in the total cost for patients where CGM is considered appropriate.

The clinicians envisage this therapy being available from there centres for on average 5-8 patients per year. So if we extrapolate that to each Surrey trust (ASPH, ESTH, FPH, RSCH, SASH, Kingston). 50 patients per year approximately from the information from clinicians
The clinicians also envisage the therapy only be available intermittently rather than continuously.

Is there any evidence of NHS provision of this treatment in other PCTs, especially within the South East Coast SHA?

A South West London PCT funds this treatment in line with the NICE clinical Guideline for assessment only of all paediatric patients and specific adults in line with the NICE clinical guidelines.

5. Conclusion & Recommendations
NICE Clinical Guideline (CG 015) acknowledges that CGMS has a role in the assessment of patients with type 1 diabetes with consistent glucose control

Consensus statements
British society for Paediatric Endocrinology & Diabetes (2009)  
‘Potential clinical indications:

**Therapeutic use (real-time)** – this requires continuous use of sensors and users need time to develop their strategy of use
- Further optimisation of pump therapy regimens when HbA1c cannot be consistently lowered below 7.5% (or 6.1% in pregnancy)
- Protection against recurrent disabling hypoglycaemia, and for those with hypoglycaemia unawareness or debilitating fear of hypoglycaemia
- Need to ensure avoidance of even modest hyperglycaemia e.g. pregnancy

When continuous use does not result in any clinical improvement, either in terms of glycaemic control or patient-related benefit, CGM should be discontinued'.

**Diabetes UK**
For clarification the CGM in combination with an insulin pump is a REAL-time monitor. Insulin Pump with CGM is one of a number of Real-time monitors but the only one incorporating an insulin pump.

**Position Statement: (September 2008)**

**Where is it useful?**
REAL – Time glucose monitoring can be used intermittently and also for longer periods of time (2-3 months) in those that want intensive therapy and education. It has the added value of adding an extra dimension to intensive therapy for diabetes as the interstitial glucose values are immediately available to patients in the absence of the person’s health care professional. It must be explained to the person that there is up to a 10 minute lap period between the reading and when it is displayed and that all readings must be calibrated before taking action due to the percentage of error that the monitors can have against blood glucose readings.

People with diabetes and their health care professional can learn how blood glucose levels react to insulin, physical activity, food and different medication types and doses aiding in better self management.

Studies have shown that across all HbA1c levels through the use of REAL – Time monitors there may be improvements in time spent within the blood glucose target range. REAL-Time monitors have the ability to reveal hyperglycaemia show reductions in hyperglycaemia without associated increased hypoglycaemia and improvements in HbA1c may also occur.

**Recommendations:**
Based on the information detailed in this document the options are:
1. NHS Surrey will not routinely fund continuous glucose monitoring
2. Fund continuous glucose monitoring in addition to insulin pumps for patients that meet NICE (TA151) & the following criteria:
   - Patients with hypo-unawareness or frequent/unpredictable hypoglycaemia
3. Fund the above but for a limited number of sensors per year/patient
4. One clinician has suggested the PCT purchase a number of mini link transmitter kits which includes transmitter, charger, tester, battery, sen-serter and box of 10 sensors)
   ‘however it may be more cost effective for the PCT to purchase a bulk number of maybe 4-6 monitors for use with different patients rather than each patient be funded for one. I have to be honest and say I

don’t know if patients would need them lifelong again if the PCT/Trust owned some they could be used intermittently and again would be much more cost effective’.

Appendix 1: Evidence search

Search terms used: Continuous Glucose monitoring and Insulin Pumps

<table>
<thead>
<tr>
<th>Resource</th>
<th>Used in this review?</th>
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<tbody>
<tr>
<td>A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog,</td>
<td>✓</td>
</tr>
<tr>
<td>National Institute of Health and Clinical Excellence (NICE) <a href="http://www.nice.org.uk/">http://www.nice.org.uk/</a></td>
<td>✓ (through NHL)</td>
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<tr>
<td>NICE produces national guidance in three areas of health:</td>
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<tr>
<td>1. Public health - guidance on the promotion of good health and the prevention of ill health</td>
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<tr>
<td>2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS</td>
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<tr>
<td>3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.</td>
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<tr>
<td>Bandolier <a href="http://www.medicine.ox.ac.uk/bandolier/index.html">http://www.medicine.ox.ac.uk/bandolier/index.html</a></td>
<td>✓ (through NHL)</td>
</tr>
<tr>
<td>Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.</td>
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<tr>
<td>Centre for Reviews and Dissemination <a href="http://www.york.ac.uk/inst/crd/">http://www.york.ac.uk/inst/crd/</a></td>
<td>✓ (through NHL)</td>
</tr>
<tr>
<td>CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database</td>
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<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN) <a href="http://www.sign.ac.uk/">http://www.sign.ac.uk/</a></td>
<td>✓</td>
</tr>
<tr>
<td>Scottish equivalent of NICE</td>
<td>✓</td>
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<tr>
<td>Medical Services Advisory Committee (Australia) <a href="http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home">http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home</a></td>
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</table>
The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.

Canadian Agency for Drugs and Technologies in Health (CADTH)  
http://www.cadth.ca/index.php/en/home  
The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.

Evidence retrieved

Guidelines  
NICE Guidance:  
NICE Clinical Guidelines (CG015) (September 2004) ‘Type 1 Diabetes in children, young people and adults’ acknowledges that CGMS has a role in the assessment of,  
Adults with type 1 diabetes with consistent glucose control problems on insulin therapy notably:  
- Repeated hyper or hypoglycaemia at the same time of day  
- Hypoglycaemia unawareness  
- Unresponsiveness to insulin dose adjustments

The clinical guideline also states that continuous glucose monitoring systems should be offered to:  
Children and young adults with type 1 diabetes that suffer from:  
- Repeated hypo/hyperglycaemia and/or hypo-unawareness

In making their recommendations the NICE committee considered the following trials using a professional CGM system that collected glucose data over a period of time and this information was downloaded for analysis.  
- Chase 2001: Continuous subcutaneous glucose monitoring in children with type 1 diabetes)  
- (Ludvigsson J, Hanas R: Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes Pediatrics 2003)

NICE also considered 24 other studies that evaluated the use of invasive Continuous glucose monitoring compared with blood glucose monitoring but these studies were not in patient’s using Insulin Pump therapy in combination with CGM.

Other Evidence:

Information received from www.oxfordhealth.com

Clinical policy for the Oxford Health Plans which is a United Healthcare company in America. This is information from a clinical policy they have developed. (April 2009)

Insulin Pump and Continuous Glucose Monitoring System: Two uncontrolled studies and a technology assessment report were found that assessed the MiniMed Paradigm REAL Time System when used as open-loop system (current FDA approved indication). Another technology assessment report assessed the device when used as closed-loop system.
In a small preliminary study of the Paradigm REAL Time System, Mastrototaro et al. (2006) evaluated the glucose monitoring functions of this device to guide patients in self-administration of insulin. This study enrolled 20 patients with type 1 diabetes who were employees of the device manufacturer. After a mean follow-up of 10 months, mean A1C levels had decreased from 7.4% to 6.3%.

Halvorson et al. (2007) enrolled 10 pediatric patients with type 1 diabetes into an uncontrolled study of the Paradigm REAL-Time System. Over the course of the study, mean A1C levels decreased from 8.1% to 7.8%; the time spent in hypoglycemia decreased and the time spent in hyperglycemia decreased.

The Canadian Agency of Drugs and Technologies in Health (CADTH) published a report on the Paradigm Real-Time System. (Pohar, 2007). The report concluded that based on the limited amount of published research to date, the impact of the Paradigm Real-Time System on long-term glycemic control, prevention of diabetic complications, or quality of life is unclear. The report included four studies, three of which were abstracts presented at the 2007 ADA Scientific Sessions. (Lee et al, 2007; Peyrot and Rubin, 2007; Buckingham et al, 2007; Hirsch et al, 2007) Limitations of the studies noted by CADTH included: small patient populations, inexperienced pump users, selection of patients with poor baseline glycemic control, and a possible overlap of patient populations. They also stated that the studies did not evaluate improvement or increased likelihood of reaching glycemic targets. Three uncontrolled studies demonstrated improvement in glycemic control or a reduction in symptomatic hypoglycemic episodes, or favorable acceptance and ease of use of the system (Pohar, 2007).

Hayes, Inc. (2007) reviewed clinical evidence supporting the use of the closed-loop use of the Paradigm REAL-Time System and reported conclusions that the results of the two reviewed studies (Steil et al., 2006; Chee et al., 2006) failed to provide conclusive evidence that the closed-loop use of the system is a safe and effective method for blood glucose management.

Reviews:
- Cochrane collaboration has prepared a review protocol but no review has taken place at this time.
- Consensus statements from the British society for Paediatric Endocrinology & Diabetes (2009) & Diabetes UK (Statements above)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Number of participants</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td><strong>Title:</strong> Incremental Value of Continuous Glucose Monitoring When Starting Pump Therapy in Patients With Poorly Controlled Type 1 Diabetes <strong>The Real Trend study.</strong>  &lt;br&gt;<strong>Citation:</strong> Diabetes Care, 01 December 2009, vol./is. 32/12(2245-2250), 01495992  &lt;br&gt;<strong>Author(s):</strong> Raccah D et al.</td>
<td>The Real Trend study was a 6-month, randomized, parallel-group, two-arm, open-label study.  &lt;br&gt;132 adults and children with uncontrolled type 1 diabetes (A1C &gt;/=8%)</td>
<td>• A total of 115 patients completed the study. Between baseline and trial end, A1C improved significantly in both groups (PRT group -0.81 +/- 1.09%, P &lt; 0.001; CSII group -0.57 +/- 0.94%, P &lt; 0.001), with no significant difference between groups. When the 91 patients who were fully protocol-compliant (including CGM sensor wear &gt;/=70% of the time) were considered, A1C improvement was significantly greater in the PRT group (P = 0.004) (PRT group -0.96 +/- 0.93%, P &lt; 0.001; CSII group -0.55 +/- 0.93%, P &lt; 0.001). Hyperglycemia parameters decreased in line with improvements in A1C with no impact on hypoglycemia.  &lt;br&gt;<strong>CONCLUSIONS</strong> CGM-enabled insulin pump therapy improves glycemia more than conventional pump therapy during the first 6 months of pump use in patients who wear CGM sensors at least 70% of the time.</td>
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<tr>
<td><strong>Title:</strong> Continuous Glucose Monitoring and Intensive Treatment of Type 1 Diabetes <strong>Multicentre clinical trial.</strong>  &lt;br&gt;Patients were already receiving intensive therapy for type 1 diabetes. Randomly assigned to receive:  &lt;br&gt;322 patients (over the age of 8 years)</td>
<td>The changes in glycated haemoglobin levels in the two study groups varied markedly according to age group (P=0.003), with a significant difference among patients</td>
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</table>
Group 1: Continuous glucose monitoring
Group 2: Control group performing home monitoring with a blood glucose meter.
All the patients were stratified into three groups according to age and had a glycated haemoglobin level of 7.0 to 10.0%. The primary outcome was the change in the glycated haemoglobin level at 26 weeks.

25 years of age or older that favored the continuous-monitoring group (mean difference in change, −0.53%; 95% confidence interval [CI], −0.71 to −0.35; P<0.001). The between-group difference was not significant among those who were 15 to 24 years of age (mean difference, 0.08; 95% CI, −0.17 to 0.33; P=0.52) or among those who were 8 to 14 years of age (mean difference, −0.13; 95% CI, −0.38 to 0.11; P=0.29). Secondary glycated haemoglobin outcomes were better in the continuous-monitoring group than in the control group among the oldest and youngest patients but not among those who were 15 to 24 years of age. The use of continuous glucose monitoring averaged 6.0 or more days per week for 83% of patients 25 years of age or older, 30% of those 15 to 24 years of age, and 50% of those 8 to 14 years of age. The rate of severe hypoglycemia was low and did not differ between the two study groups; however, the trial was not powered to detect such a difference.

Conclusion:
The results indicate that continuous glucose monitoring improves glycated haemoglobin levels and may enhance the management of type 1 diabetes in adults who have the motivation to use this technology and the
| **Title:**  
Sensor-Augmented Insulin Pump Therapy: Results of the First Randomized Treat-to-Target Study  
Citation: Diabetes Technology & Therapeutics Volume 10, Number 5, 2008 (Page 377-383)  
**Author(s):** Irl B. Hirsch et al. | This 6-month randomized, multicenter, treat-to-target study. Subjects treated with continuous subcutaneous insulin infusion between the ages of 12 and 72 years with type 1 diabetes and initial A1C levels of ≥7.5%. Subjects were randomized 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. | 146 patients | capability to incorporate it into their own daily diabetes management. Further work is needed to identify and address the lack of effectiveness of continuous glucose monitoring in children and adolescents.  
**Results:** A1C levels decreased \((P< 0.001)\) from baseline \((8.44 \pm 0.70\%)\) in both groups (SG, \(-0.71 \pm 0.71\%\); CG, \(-0.56 \pm 0.072\%\)); 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 hypoglycaemia AUC was significant \((P < 0.0002)\). Greater than 60% sensor utilization was associated with A1C reduction \((P=0.0456)\). Fourteen severe hypoglycemic events occurred (11 in the SG group and three in the CG group, \(P = 0.04)\).  
**Conclusions:** A1C reduction was no different between the two groups. Subjects in the CG group had increased hypoglycemia AUC and number of events during blinded CGM use; however, there was no increase in hypoglycemia AUC or number of events in the SG group. Subjects with greater sensor utilization showed a greater improvement in A1C levels.
<table>
<thead>
<tr>
<th>Title</th>
<th>An open multicentre parallel randomised controlled trial was conducted at five tertiary diabetes centres.</th>
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<tr>
<td>Citation</td>
<td>Diabetologia. 2009 Jul;52(7):1250-7. Epub 2009 Apr 25.</td>
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<td>Author/s:</td>
<td>O’Connell MA et al.</td>
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<td>AIMS:</td>
<td>To assess the impact of patient-led sensor-guided pump management on glycaemic control, and compare the effect with that of standard insulin pump therapy.</td>
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<td>Results:</td>
<td>Sixty-two participants were recruited and randomised; 5/31 and 2/31 withdrew from intervention and control groups, respectively, leaving 26/31 and 29/31 for the intention-to-treat analyses. When adjusted for baseline values, the mean end-of-study HbA1c was 0.43% lower in the intervention group compared with the control group (95% CI 0.19 to 0.75%; p = 0.009). No difference was observed in CGM-derived time in target (measured difference 1.72; 95% CI -5.37 to 8.81), hypoglycaemic (0.54; 95% CI -3.48 to 4.55) or hyperglycaemic (-2.18; 95% CI -10.0 to 5.69) range or in glycaemic variability (-0.29; 95% CI -0.34 to 0.28). Within the intervention group, HbA1c was 0.51% lower in participants with sensor use &gt; or =70% compared with participants with sensor use &lt;70% (95% CI -0.98 to -0.04, p = 0.04). Five episodes of device malfunction occurred.</td>
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<td>Conclusions/Interpretation:</td>
<td>Individuals established on insulin pump therapy can employ sensor-guided pump management to improve glycaemic control. An apparent dose-dependent effect of sensor usage was noted; however, frequent use of this technology (&gt; or =70%) was not universally acceptable.</td>
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| Title: | Benefits of three-month |
| AIMS: | To assess the evolution of HbA1c over the course of a 3- |
| Type 1 diabetics (n=39) | METHODS: Compliant PWDs using insulin pump with insulin aspart for several |
continuous glucose monitoring for persons with diabetes using insulin pumps and sensors.

**Citation:**
Biomedical papers of the Medical Faculty of the University Palacký, Olomouc, Czechoslovakia, March 2009, vol./is. 153/1(47-51), 1213-8118

**Author(s):**

- month period in two cohorts of persons with type 1 (n=39) or type 2 (n=3) diabetes (PWD): 1) PWD on Paradigm 722 using sensors for continuous glucose monitoring (CGM group), 2) PWD on other types of insulin pumps performing intensive self-monitoring as before (3 to 6 times/d) on glucometer Linus, Wellion, Agamatrix (control group).

- Type 2 diabetics (n=3) previous months were included in the study. Seventeen were put on Paradigm 722 with CGM and 25 were included in the control group. Paired t-test and the statistical program SPSS v.15.0 were used to analyze the data.

**RESULTS:** There was no significant difference in age between the two groups (P=0.996), in diabetes duration (P=0.482) or in daily insulin dose (P=0.469). In the CGM group (but not in the control group) HbA1c/IFCC dropped from 6.98+/-0.43 % to 5.98+/-0.36 % (P=0.006) within 1 month and remained reduced.

**CONCLUSION:** The use of the Paradigm 722 insulin pump with CGM resulted in significant improvement in HbA1c which appeared within one month and remained throughout the whole 3-month study period. No significant improvement in HbA1c was seen in the control group.
Appendix 2: Grading of evidence

- Ia: systematic review or meta-analysis of randomised controlled trials
- Ib: at least one randomised controlled trial
- IIa: at least one well-designed controlled study without randomisation
- IIb: at least one well-designed quasi-experimental study, such as a cohort study
- III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case–control studies and case series
- IV: expert committee reports, opinions and/or clinical experience of respected authorities

Appendix 3 References:

2. The Real Time Study Diabetes Care, 01 December 2009, vol./is. 32/12(2245-2250), 01495992 Raccah D et al.
5. Benefits of three-month continuous glucose monitoring for persons with diabetes using insulin pumps and sensors. Biomedical papers of the Medical Faculty of the University Palacký, Olomouc, Czechoslovakia, March 2009, vol./is. 153/1(47-51), 1213-8118 Peterson K., Zapletalova et al.

Appendix 4 Correspondence