

Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system)

Diagnostics guidance

Published: 12 February 2016

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1 Recommendations

- 1.1 The MiniMed Paradigm Veo system is recommended as an option for managing blood glucose levels in people with type 1 diabetes only if:
- they have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion and
 - the company arranges to collect, analyse and publish data on the use of the MiniMed Paradigm Veo system (see section 7.1).
- 1.2 The MiniMed Paradigm Veo system should be used under the supervision of a trained multidisciplinary team who are experienced in continuous subcutaneous insulin infusion and continuous glucose monitoring for managing type 1 diabetes only if the person or their carer:
- 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 and
 - agrees to use the system while having a structured education programme on diet and lifestyle, and counselling.
- 1.3 People who start to use the MiniMed Paradigm Veo system should only continue to use it if they have a decrease in the number of hypoglycaemic episodes that is sustained. Appropriate targets for such improvements should be set.
- 1.4 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. Robust evidence is needed to show the clinical effectiveness of using the technology in practice.
- 1.5 People with type 1 diabetes who are currently provided with the MiniMed Paradigm Veo system or the Vibe and G4 PLATINUM CGM system by the NHS for clinical indications that are not recommended in this NICE guidance should be able to continue using them until they and their NHS clinician consider it appropriate to stop.

During the development of this guidance, NICE became aware that a new integrated sensor-augmented pump therapy system, the MiniMed 640G system (Medtronic), has become available. The evidence for the MiniMed 640G system has not been assessed in the guidance, and the recommendations, therefore, do not relate to its routine use in the NHS. For further information on the MiniMed 640G system please see the related NICE [Medtech innovation briefing](#).

2 The technologies

- 2.1 Two integrated sensor-augmented pump therapy systems were identified during scoping as relevant to the assessment (see [section 4](#) for additional details).
- 2.2 The integrated sensor-augmented pump therapy systems, which combine continuous glucose monitoring with continuous subcutaneous insulin infusion, are intended to help people with type 1 diabetes manage their blood glucose levels. The systems are designed to continuously measure interstitial glucose levels (every few minutes) and allow immediate real-time adjustment of insulin therapy. The systems produce alerts if the glucose levels become too high or too low. The MiniMed Paradigm Veo system can also automatically suspend insulin delivery if there is no response to a low-glucose warning.

3 Clinical need and practice

The problem addressed

- 3.1 The purpose of this assessment is to evaluate the clinical and cost effectiveness of the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system for managing blood glucose levels in people with type 1 diabetes.
- 3.2 Using these integrated sensor-augmented pump therapy systems may improve glucose control and consequently may reduce the number of diabetes-related complications and improve the quality of life for people with type 1 diabetes. They may also make it easier for people to adhere to treatment. The ability of the MiniMed Paradigm Veo system to automatically suspend insulin delivery may help to reduce the incidence of severe and nocturnal hypoglycaemia, and its associated anxiety. Both systems may also offer benefits to the NHS through cost and resource savings by reducing the number of hospital admissions and consultations for diabetes-related complications, and by achieving optimum blood glucose control more quickly.

The condition

- 3.3 Type 1 diabetes is a chronic metabolic disorder caused by the destruction of insulin-producing cells in the pancreas that leads to an absolute lack of the hormone and subsequent loss of blood glucose control. As a result, blood glucose levels become too high and lifelong treatment with insulin is needed. Type 1 diabetes typically develops in children and young adults. It is estimated that about 370,000 adults and 24,000 children and young people in the UK have type 1 diabetes.
- 3.4 Achieving good control of blood glucose levels with insulin can reduce the risk of developing both short- and long-term diabetes-related complications. Short-term complications of diabetes include diabetic ketoacidosis, a life-threatening acute metabolic emergency caused by high blood glucose levels (hyperglycaemia), and hypoglycaemia, which happens when blood sugar levels become too low as a result of insulin therapy.
- 3.5 Hypoglycaemia can be mild, which is corrected by eating or drinking sugar, or severe, which is defined by the need for help from another person for recovery.

The main symptoms of hypoglycaemia are blurred vision, dizziness, fatigue, hunger and sweating. More severe symptoms include confusion, convulsions, coma and death. Severe symptoms may be associated with disabling hypoglycaemia, which can happen often and without warning for some people with type 1 diabetes. In children, especially those younger than 5 years, severe hypoglycaemia can cause long-term cognitive impairment. Hypoglycaemia can also occur during sleep (nocturnal hypoglycaemia) and is particularly serious because the person cannot detect its symptoms while sleeping and may not awake during an episode. Although death from nocturnal hypoglycaemia is rare, it can occur in extreme cases. Repeated hypoglycaemia can also lead to an impaired awareness of hypoglycaemia, in which people with type 1 diabetes are often less able to notice when they have hypoglycaemia. Fear of recurrent hypoglycaemia not only decreases quality of life in the short-term but can also hinder treatment adherence and good glycaemic control.

- 3.6 Long-term complications of chronically elevated blood glucose levels include retinopathy and blindness, peripheral and autonomic nephropathy, renal failure, ischaemic heart disease, stroke, neuropathy, and foot ulceration.
- 3.7 Diabetes that complicates pregnancy is also becoming more common, and it is estimated that up to 5% of about 700,000 women who give birth in England and Wales each year have pre-existing or gestational diabetes. Maternal risks of pre-existing diabetes include recurrent hypoglycaemia, progression of retinopathy, nephropathy, and increased incidence of pre-eclampsia (especially in women with microvascular disease) and operative delivery. Fetal risks of pre-existing maternal diabetes include structural congenital abnormality and intrauterine death. Neonatal complications include excessive birth weight (macrosomia), premature delivery and associated complications, birth trauma resulting from conditions such as shoulder dystocia, hypoglycaemia, and neonatal death.

The diagnostic and care pathways

- 3.8 Treatment of type 1 diabetes is by insulin therapy to achieve blood glucose control. Blood glucose levels are monitored to determine the type and amount of insulin needed to regulate blood glucose levels. These interventions are described in more detail in sections 3.9, 3.10 and 3.11.

Insulin therapy

- 3.9 There are various types of insulin, distinguished by their rate of onset and duration of action, that can be combined into different regimens depending on a person's individual needs. Insulin therapy can be delivered by multiple daily insulin injections or by continuous subcutaneous insulin infusion using an insulin pump. The care pathways for insulin therapy for adults and children are outlined in NICE's guidelines on [type 1 diabetes in adults](#), [diabetes in children and young people](#), and [diabetes in pregnancy](#) and in NICE's technology appraisal guidance on [continuous subcutaneous insulin infusion](#).

Monitoring blood glucose

- 3.10 Blood glucose concentrations vary widely during a 24-hour period and from day to day in diabetes. Blood glucose measurements are taken after several hours of fasting, usually in the morning before breakfast (fasting blood glucose level), and before and after each meal to measure the change in glucose concentration (postprandial blood glucose level). Levels of blood glucose can be measured by testing a drop of blood using a glucose meter (capillary blood testing), or by a continuous glucose monitor that does frequent automated testing of interstitial tissue glucose and is calibrated to reflect blood glucose. The care pathways for measuring blood glucose for children and adults are outlined in NICE's guideline on [type 1 diabetes in adults](#), [diabetes in children and young people](#), and [diabetes in pregnancy](#).
- 3.11 Long-term monitoring of blood glucose control is achieved by measuring glycated haemoglobin (HbA1c levels), which reflect average blood glucose levels over the preceding 3 months. People with type 1 diabetes should aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, as recommended in NICE guidelines on [type 1 diabetes in adults](#) and [diabetes \(type 1 and type 2\) in children and young people](#). The assessment for this guidance was based on a target HbA1c value of 58.5 mmol/mol (7.5%) or less. This was informed by the NICE guideline on [diagnosis and management of type 1 diabetes in children, young people and adults](#), which was current at the time of the assessment. For people with diabetes, the higher the HbA1c value, the greater the risk of developing diabetes-related complications. The care pathways for monitoring HbA1c levels for adults and children are outlined in NICE's guidelines on [type 1 diabetes in adults](#), [diabetes in children and young people](#), and [diabetes in pregnancy](#).

4 The diagnostic tests

The interventions

MiniMed Paradigm Veo system

- 4.1 The MiniMed Paradigm Veo system (Medtronic) is an integrated sensor-augmented pump therapy system that has 3 components:
- An Enlite glucose sensor that is placed under the skin to continuously measure the glucose levels in interstitial fluid (the thin layer of fluid between blood capillaries and the body's cells).
 - An insulin pump that delivers insulin continuously to the subcutaneous tissue through an infusion set.
 - A MiniLink non-implanted transmitter that sends glucose-level readings wirelessly from the sensor to the pump.
- 4.2 The system produces an alarm sound if glucose levels become too high or low, if levels are rapidly changing, or if the system predicts that levels will be too high or too low in the near future. It has an automated low-glucose suspend function that works independently of user action and stops insulin delivery for 2 hours if there is no response to the alert.
- 4.3 The system is intended to be used with standard capillary blood glucose tests because the sensor measures interstitial glucose levels rather than capillary blood glucose levels. Because glucose moves from the capillaries to tissues, there is a lag between blood and interstitial glucose levels of at least 15 minutes and so a minimum of 2 capillary blood glucose tests per day are needed for calibration. The lag increases when blood glucose levels are changing rapidly, so although trends in interstitial glucose are representative of blood glucose changes, absolute interstitial glucose values do not always match blood glucose levels. Further capillary blood glucose tests may be needed to confirm the value displayed on the pump by the continuous glucose monitor, before making any adjustments to diabetes therapy.
- 4.4 The insulin pump in the system continuously delivers insulin from a storage reservoir through an infusion set, consisting of thin plastic tubing and a cannula

that is placed under the skin. The pump can be programmed to deliver a basal rate of insulin throughout the day, with higher infusion rates triggered by pushing a button on the pump at meal times. The higher infusion rate may be a bolus dose (that is a dose taken specifically at meal times to keep glucose levels under control after a meal) or periodic doses over a period of time. It can also deliver different basal rates of insulin at different times of the day and night. The company's instructions for use state that the infusion set and reservoir should be replaced every 2 to 3 days.

- 4.5 The MiniMed Paradigm Veo system is compatible with the CareLink software platform (Medtronic), which is designed to allow users to upload their data from the MiniMed Paradigm Veo system so that clinicians can evaluate the person's glycaemic control, notice any trends and adjust their therapy as appropriate.

Vibe and G4 PLATINUM CGM system

- 4.6 The Vibe and G4 PLATINUM CGM system is an integrated sensor-augmented pump system that has 3 components:
- The Vibe CGM-enabled insulin pump (Animas) that delivers insulin continuously.
 - The G4 PLATINUM sensor (Dexcom) that continuously monitors interstitial glucose levels.
 - A non-implanted transmitter (Dexcom) that sends glucose-level readings wirelessly from the sensor to the pump.
- 4.7 The sensor is placed under the skin and measures interstitial glucose levels. It is approved for up to 7 days of use. The system produces glucose-level readings in real-time and glucose trend information. There is an alarm that alerts the user if the glucose levels become too high or too low, or if the levels are rapidly changing. The system also has a default low-glucose alarm that cannot be altered by the user. It does not have an automated low-glucose suspend function. There is a lag between blood and interstitial glucose levels of at least 15 minutes and so at least 2 capillary blood glucose tests per day are needed to calibrate the system, before making any adjustments to diabetes therapy.
- 4.8 The insulin pump in the Vibe and G4 PLATINUM CGM system delivers insulin continuously from a storage reservoir through a cannula placed under the skin.

The pump can be programmed to deliver a basal rate of insulin throughout the day, with the option of triggering higher infusion rates at meal times, either as a bolus dose or over a period of time. The pump can also be programmed for different basal rates of insulin at different times of the day and night.

- 4.9 The Vibe and G4 PLATINUM CGM system is compatible with Diasend, a software platform that allows users to upload data from their pump for interpretation, to adjust settings and to keep a food database. Users can share their data with healthcare professionals, who can then use it to assess glucose trends and inform changes in therapy.

The comparators

- 4.10 To reflect the combinations of technologies that may be used by people with type 1 diabetes to monitor blood glucose levels and administer insulin therapy in current practice, 4 comparators are included:
- capillary blood testing with continuous subcutaneous insulin infusion
 - capillary blood testing with multiple daily insulin injections
 - continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated devices)
 - continuous glucose monitoring with multiple daily insulin injections.

5 Outcomes

The Diagnostics Advisory Committee ([section 10](#)) considered evidence from a number of sources ([section 11](#)). Full details of all the evidence are in the [committee papers](#).

How outcomes were assessed

- 5.1 The assessment consisted of a systematic review of the clinical-effectiveness data for the MiniMed Paradigm Veo system, the Vibe and G4 PLATINUM CGM system and comparator technologies.
- 5.2 In total, 54 publications reporting the results of 19 studies met the inclusion criteria. These studies included either the intervention or comparator technologies in a treatment arm. Two studies included data for the MiniMed Paradigm Veo system, 1 of which compared the system with an integrated sensor-augmented pump therapy system without a low-glucose suspend function (included as a clinical proxy for the Vibe and G4 PLATINUM CGM system in the absence of any data for this technology), and a further 7 studies included data for the integrated sensor-augmented pump therapy system without a low-glucose suspend function. The remainder of the studies reported data for capillary blood testing with continuous subcutaneous insulin and capillary blood testing with multiple daily insulin injections. No studies reported data for either continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated devices) or continuous glucose monitoring with multiple daily insulin injections. Of the 19 included studies:
- 10 included adults only
 - 3 included children only
 - 3 included a mixed population (adults and children) but did not report data for each group separately
 - 2 included a mixed population and reported data for adults and children separately
 - 1 included pregnant women only.
- 5.3 The 1 study that included pregnant women only reported data for capillary blood testing with continuous subcutaneous insulin infusion and capillary blood testing with multiple daily insulin injections. Because no comparative data were

found to assess the clinical effectiveness of the integrated sensor-augmented pump therapy systems in pregnant women, this study was not included in the analyses.

- 5.4 All the studies were randomised controlled trials. The methodological quality of each study was appraised using the Cochrane risk of bias tool. Eleven of the 19 studies were rated as a high risk of bias, primarily because the patients, clinicians and assessors were not blinded to the allocation of interventions and glycated haemoglobin (HbA1c) results were interpreted with knowledge of the treatment allocation. Of the remaining 8 studies, 4 were rated as unclear risk of bias and 4 were rated as low risk of bias.
- 5.5 There was substantial heterogeneity in the populations included in the studies. Nine studies included people who had not used an insulin pump before, and only 4 studies reported including people who had experienced hypoglycaemia before the trial.
- 5.6 The results of the studies were presented as a narrative synthesis and combined into network meta-analyses where possible. Direct head-to-head meta-analyses were done using a fixed-effect model unless significant heterogeneity was observed. Indirect meta-analyses were done according to the method devised by Bucher et al. (1997).

Clinical effectiveness in adults

- 5.7 Twelve studies reported data for adults: 10 studies done solely in adults and 2 studies reported subgroup data for adults.

MiniMed Paradigm Veo system

- 5.8 One study (ASPIRE in-home) compared the MiniMed Paradigm Veo system with an integrated sensor-augmented pump therapy system (no low-glucose suspend) at 3-month follow-up in adults with type 1 diabetes. This study included people who had experienced 2 or more nocturnal hypoglycaemic events during the study run-in phase, but excluded people who had experienced more than 1 episode of severe hypoglycaemia in the 6 months before study recruitment. The study reported that hypoglycaemic events occurred less often in the MiniMed Paradigm Veo system group (3.3 ± 2.0 weekly events per patient

compared with 4.7 ± 2.7 weekly events per patient; $p < 0.001$), and this effect was consistent when the results were restricted to nocturnal hypoglycaemic events (1.5 ± 1.0 weekly events per patient compared with 2.2 ± 1.3 weekly events per patient; $p < 0.001$). The study also reported that, for the MiniMed Paradigm Veo system, the mean hypoglycaemic area under the curve (AUC; derived from the magnitude and severity of the sensor-measured glucose level) was significantly lower (less severe) for all hypoglycaemic events combined ($p < 0.001$) and for nocturnal hypoglycaemia ($p < 0.001$). There were no statistically significant differences in change in HbA1c, capillary blood glucose values, insulin use, diabetic ketoacidosis, quality of life, device-related serious adverse events, or death.

5.9 Data from the ASPIRE in-home study were used in a network analysis to compare the MiniMed Paradigm Veo system with:

- the integrated sensor-augmented pump therapy system with no low-glucose suspend
- capillary blood testing with continuous subcutaneous insulin infusion
- capillary blood testing with multiple daily insulin injections.

None of the 3 additional studies incorporated into the network analysis reported whether they included people who had experienced hypoglycaemia. The network analysis included change in HbA1c and diabetic ketoacidosis at 3-month follow-up as outcomes. No statistically significant differences were seen in any of the comparisons.

Integrated sensor-augmented pump therapy system (no low-glucose suspend)

5.10 Five further studies included integrated sensor-augmented pump therapy in a treatment arm. One study (Hirsch et al. 2008) compared an integrated sensor-augmented pump therapy system (no low-glucose suspend) with capillary blood testing and continuous subcutaneous insulin infusion. This study did not exclude people with hypoglycaemia unawareness. The study reported no statistically significant difference in change in HbA1c (%) between the groups at 6-month follow-up (-0.0364% ; standard error 0.1412; $p = 0.80$).

5.11 The remaining 4 studies (Hermanides et al. 2011; Lee et al. 2007; Peyrot et al. 2009; Bergenstal et al. 2010) compared the integrated sensor-augmented pump therapy system (no low-glucose suspend) with capillary blood testing combined

with multiple daily insulin injections. Inclusion or exclusion criteria for hypoglycaemia were not stated in 3 of these studies. Bergenstal et al. (2010) excluded people with hypoglycaemia unawareness. The studies reported multiple outcomes at various follow-up points.

- 5.12 Three-month follow-up (2 studies): 1 study (Lee et al. 2007) reported a statistically significant difference in the change in HbA1c (%) in favour of the integrated sensor-augmented pump therapy system (no low-glucose suspend; -0.97 ; $p=0.02$). This difference was not statistically significant in Peyrot et al. (2009; -0.69 ; $p=0.071$). No statistically significant differences were found for hypoglycaemic events, diabetic ketoacidosis or serious adverse events in either study.
- 5.13 Six-month follow-up (1 study): Hermanides et al. (2011) reported no statistically significant difference for hypo- or hyperglycaemic events. Statistically significant differences in favour of the integrated sensor-augmented pump therapy system were found for the following outcomes:
- change in HbA1c % (-1.1 ; 95% confidence interval [CI] -1.47 to -0.73)
 - number of people with HbA1c $\leq 7\%$ (53 mmol/mol; $14/41$ compared with $0/36$; $p<0.001$)
 - daily insulin use (difference of -11.0 units per day; 95% CI -16.1 to -5.9 ; $p<0.001$)
 - quality of life measured by the SF-36 (difference of 7.9 ; 95% CI 0.5 to 15.3 ; $p=0.04$).
- 5.14 Twelve-month follow-up (1 study, excluded people with hypoglycaemia unawareness): Bergenstal et al. (2010) reported no statistically significant differences for hypoglycaemic AUC, severe hypoglycaemia or diabetic ketoacidosis. Statistically significant differences in favour of the integrated sensor-augmented pump therapy system (no low-glucose suspend) were seen for the following outcomes:
- change in HbA1c % (-0.6 ; 95% CI -0.8 to -0.4 ; $p<0.001$)
 - number of people with HbA1c $< 7\%$ (53 mmol/mol; $57/166$ compared with $19/163$; $p<0.001$)
 - hyperglycaemic AUC (3.74 compared with 7.38 ; $p<0.001$)

- improved quality of life measured by the SF-36 (difference of 3; 95% CI 1.36 to 4.64)
- fear of hypoglycaemia measured by the Hypoglycaemia Fear Survey (difference of -6.5; 95% CI -9.76 to -3.27).

5.15 All 5 studies were incorporated into several network analyses that were done to calculate effect estimates for the integrated sensor-augmented pump therapy system (no low-glucose suspend). The results of the analyses suggested that there was a statistically significant reduction in HbA1c % (weighted mean difference -1.10; 95% CI -1.46 to -0.74), and a statistically significant difference in the proportion of people with HbA1c <7% (53 mmol/mol; relative risk 25.55; 95% CI 1.58 to 413.59) in favour of the integrated sensor-augmented pump therapy system (no low-glucose suspend) when compared with capillary blood testing with multiple daily insulin injections. Quality of life (measured by the Diabetes Treatment Satisfaction Questionnaire) associated with integrated sensor-augmented pump therapy was also significantly improved when compared with both capillary blood testing with continuous subcutaneous insulin infusion (weighted mean difference 5.90; 95% CI 2.22 to 9.58) and capillary blood testing with multiple daily insulin injections (weighted mean difference 8.60; 95% CI 6.28 to 10.92).

Supplementary data

- 5.16 In addition to the studies incorporated into the network analyses, 2 observational studies and 1 randomised cross-over study were included in a supplementary narrative analysis carried out by the External Assessment Group. The SWITCH study reported a randomised cross-over study to assess the clinical effectiveness of an integrated sensor-augmented pump therapy system. The study included 81 adults and 72 children, from 8 European sites, who used continuous subcutaneous insulin infusion. All patients had an integrated sensor-augmented pump therapy system with an activated sensor, and were randomised to alternate sequences of sensor use over a 12-month period. The study concluded that using the sensor was associated with a reduction in HbA1c (-0.43%; 95% CI -0.32 to -0.55) and a decrease in the time spent in hypoglycaemia.
- 5.17 Choudhary et al. (2011) reported a study designed to assess the low-glucose suspend function of the MiniMed Paradigm Veo system over a 3-week period in 28 adults from 6 UK centres. The study had a 2-week run-in period with the

low-glucose suspend function deactivated, after which patients were divided into 4 groups according to their duration of hypoglycaemic events. The study concluded that using low-glucose suspend was associated with a significant reduction in duration of nocturnal hypoglycaemia in the group with the highest duration of hypoglycaemia during the run-in period (mean 75.1 ± 54 compared with 10.2 ± 18 minutes per day; $p=0.02$).

- 5.18 Choudhary et al. (2013) reported a retrospective audit of 35 adults attending a specialist clinic, with established problematic hypoglycaemia or impaired awareness of hypoglycaemia while on optimal medical therapy. The patients were given a continuous glucose monitor in addition to either continuous subcutaneous insulin infusion or multiple daily injections. Outcomes were audited after 12 months. Of the 35 patients, 23 used the MiniMed Paradigm Veo system and 3 used the Vibe and G4 PLATINUM CGM system. The audit reported that the median rate of severe hypoglycaemia was reduced from 4.0 (interquartile range 0.75 to 7.25) episodes per patient-year at baseline to 0.0 (interquartile range 0.0 to 1.25) episodes per patient-year at 12 months ($p<0.001$). HbA1c levels were also reduced from $8.1 \pm 1.2\%$ to $7.8 \pm 1.0\%$ at 12 months ($p=0.007$). The final mean HbA1c level and median severe hypoglycaemia rate did not differ between patients who used the system with low-glucose suspend and those who did not.

Clinical effectiveness in children

- 5.19 Six studies reported data for children, including 1 study (Ly et al. 2013) that reported data for the MiniMed Paradigm Veo system. Of the remaining 5 studies, 2 reported data for an integrated sensor-augmented pump therapy system without low-glucose suspend (used as a proxy for the Vibe and G4 PLATINUM CGM system), and 3 reported data for comparator technologies only (capillary blood testing with continuous subcutaneous insulin infusion and capillary blood testing with multiple daily insulin injections).
- 5.20 One study (Ly et al. 2013) reported results for the MiniMed Paradigm Veo system compared with capillary blood testing and continuous subcutaneous insulin infusion at 6-month follow-up in a mixed population aged 4–50 years. Seventy per cent of the patients were aged under 18 years, and people with an impaired awareness of hypoglycaemia were included. The study reported a statistically significant difference in the rate of hypoglycaemic events, with a

lower rate of events in the MiniMed Paradigm Veo system group (incidence rate ratio 3.6; 95% CI 1.7 to 7.5; $p < 0.001$). No statistically significant differences were reported for change in HbA1c, the number of people experiencing hypoglycaemic events or the hypoglycaemia unawareness score.

5.21 One study (Hirsch et al. 2008) compared an integrated sensor-augmented pump therapy system (no low-glucose suspend) with capillary blood testing and continuous subcutaneous insulin infusion. The study included data for the change in HbA1c (%) at 6 months and found no statistically significant difference between the technologies.

5.22 One study (Bergenstal et al. 2010) compared an integrated sensor-augmented pump therapy system (no low-glucose suspend) with capillary blood testing and multiple daily insulin injections, and reported multiple outcomes at 12-month follow-up. There was a statistically significant change in HbA1c % (-0.5 ; 95% CI -0.8 to -0.2 ; $p < 0.001$) and a statistically significant lower hyperglycaemic AUC (>250 mg/dl; 9.2 compared with 17.64; $p < 0.001$) in favour of the integrated sensor-augmented insulin pump therapy. No statistically significant differences were seen for the following outcomes:

- proportion with HbA1c $\leq 7\%$ (53 mmol/mol)
- the number of people having severe hypoglycaemic events
- the rate of severe hypoglycaemic events
- hypoglycaemia AUC (defined as <70 mg/dl)
- number of patients with diabetic ketoacidosis
- quality of life (measured by the Paediatric Quality of Life Inventory and Hypoglycaemia Fear Survey).

5.23 In a network analysis, the MiniMed Paradigm Veo system was compared with an integrated sensor-augmented pump therapy system (no low-glucose suspend) and with capillary blood testing with continuous subcutaneous insulin infusion. Data from Ly et al. (2013) and Hirsch et al. (2008) were included in the analysis. The network analysis included 1 outcome, change in HbA1c at 6 months, and showed no statistically significant difference between the technologies.

Additional clinical-effectiveness analyses for the economic model

- 5.24 A full network analysis of 14 studies was done to calculate estimates of change in HbA1c and severe hypoglycaemic event rates in adults for each of the interventions and for 2 of the comparators (capillary blood testing with continuous subcutaneous insulin infusion and capillary blood testing with multiple daily injections). This analysis included 10 studies that reported data for adults only, 2 studies that reported subgroup data for adults and 2 studies that reported data for a mixed population (adults and children).
- 5.25 The results of the network analysis suggested that there were statistically significant changes in HbA1c in favour of both the MiniMed Paradigm Veo system (weighted mean difference -0.66 ; 95% CI -1.05 to -0.27) and the integrated sensor-augmented pump therapy system without the low-glucose suspend (weighted mean difference -0.70 ; 95% CI -1.05 to -0.30) when compared with capillary blood testing with multiple daily insulin injections. The results also suggested that there was a statistically significant difference in the severe hypoglycaemic event rate in favour of capillary blood testing with continuous subcutaneous insulin infusion when compared with the integrated sensor-augmented pump therapy system without the low-glucose suspend (weighted mean difference 3.23 ; 95% CI 1.10 to 9.49). This network analysis was subject to bias because data from different populations and studies with different lengths of follow-up were pooled, which resulted in substantial heterogeneity across the studies.

Costs and cost effectiveness

Systematic review of cost-effectiveness evidence

- 5.26 The External Assessment Group did a search to identify studies investigating the cost effectiveness of the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system. Two studies were included and were appraised using the Drummond et al. (1996) checklist.
- 5.27 Kamble et al. (2012) reported the results of a cost-effectiveness analysis that compared an integrated sensor-augmented pump therapy system (no low-glucose suspend) with capillary blood testing and multiple daily insulin injections from the perspective of the US healthcare system. The study used the

IMS CORE Diabetes Model with a time horizon of 60 years and included a population with an average age of 41.3 years and with inadequately controlled type 1 diabetes. The study reported that, when all health effects included in the IMS CORE Diabetes Model were taken into account, the Vibe and G4 PLATINUM CGM system was not cost effective, with incremental cost-effectiveness ratios (ICERs) of \$229,675 and \$168,104 per quality-adjusted life year (QALY) gained assuming a sensor life of 3 or 6 days respectively.

- 5.28 Ly et al. (2014) reported the results of a cost-effectiveness analysis that compared the MiniMed Paradigm Veo system with capillary blood testing and continuous subcutaneous insulin from the perspective of an Australian healthcare system. The study used a de novo decision analytic model that included a population with type 1 diabetes and an impaired awareness of hypoglycaemia. The model had a time horizon of 6 months and incorporated severe hypoglycaemic events only. The study reported that the MiniMed Paradigm Veo system was cost effective, with an ICER of AU\$40,803 for people aged 12 years or over.
- 5.29 A manuscript by Roze et al. (2015), which was unpublished and non-peer reviewed at the time of guidance development, reported the results of a cost-effectiveness analysis that compared the MiniMed Paradigm Veo system with capillary blood testing and continuous subcutaneous insulin infusion. The study used the IMS CORE Diabetes Model to model an adult population with inadequately controlled type 1 diabetes over a lifetime time horizon. The analysis took the perspective of the NHS and had a discount rate of 3.5% for costs and 1.5% for effects. The study reported that the MiniMed Paradigm Veo system was cost effective, with an ICER of £12,233 per QALY gained.

Economic analysis

- 5.30 The External Assessment Group used the IMS CORE Diabetes Model to assess the cost effectiveness of the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system in adults with type 1 diabetes who are eligible to receive an insulin pump, in accordance with NICE's technology appraisal guidance on [continuous subcutaneous insulin infusion for the treatment of diabetes mellitus](#).

Model structure

- 5.31 The structure of the IMS CORE Diabetes Model is a simulation model designed to predict the long-term health outcomes and costs associated with the management of both type 1 and type 2 diabetes. The model structure comprises 17 interdependent Markov sub-models that represent the most common diabetes-related complications. This includes stroke, peripheral vascular disease, diabetic retinopathy, hypoglycaemia and ketoacidosis.
- 5.32 The model was adapted to reflect the NHS and personal social services perspective, the population and interventions included in the assessment, and parameters were inflated to 2015 values where necessary. The model was run as a cohort simulation with a time horizon of 80 years.

Model inputs

- 5.33 The model was populated with data from the clinical-effectiveness review, published literature and routine sources of cost and prevalence data. Where appropriate, parameter estimates were taken from the [draft NICE guideline on type 1 diabetes](#). If published data were unavailable, the External Assessment Group used expert opinion to derive estimates to populate the model. A discount rate of 3.5% was applied to both costs and effects.
- 5.34 One of the comparators listed in the final scope, continuous glucose monitoring with multiple daily insulin injections, was excluded from the analysis because no data were found for this comparator in the clinical-effectiveness review. In addition, the clinical effectiveness of the comparator, non-integrated continuous glucose monitoring and continuous subcutaneous insulin therapy, was assumed to be equivalent to that of the Vibe and G4 PLATINUM CGM system (as derived from data for an integrated sensor-augmented pump therapy system with no low-glucose suspend function) because no data were found for this comparator.
- 5.35 The clinical-effectiveness outcomes included in the model were reduction in HbA1c from baseline and number of severe hypoglycaemic events. A baseline HbA1c value of 7.26% was applied and estimates of mean HbA1c change from baseline were derived from the clinical-effectiveness review. The values showed that HbA1c increased from baseline for capillary blood testing with continuous subcutaneous insulin infusion (0.05) and capillary blood testing with multiple

daily insulin injections (0.64), but decreased for the MiniMed Paradigm Veo system (-0.02), Vibe and G4 PLATINUM CGM system (-0.06) and non-integrated continuous glucose monitoring with continuous subcutaneous insulin infusion (-0.06).

- 5.36 In the IMS CORE Diabetes Model, the change in HbA1c level was assumed to happen within the first 12 months, thereafter annual progression occurred (that is, a 0.045% increase in HbA1c each year). The value for annual progression was chosen to correspond with the assumptions made in the economic model for the [draft NICE guideline on type 1 diabetes](#), and was taken from the Diabetes Control and Complications Trial.
- 5.37 Severe hypoglycaemic event rates for the interventions and the comparators were estimated from the clinical-effectiveness review. The rate of severe hypoglycaemic events was lowest for the MiniMed Paradigm Veo system (1.9584 per 100 patient-years) and highest for capillary blood testing with multiple daily insulin injections (19.584 per 100 patient-years). No baseline event rates were needed for this parameter because the model assumed that these values were treatment specific.

Costs

- 5.38 Costs included in the model were associated with the primary prevention of diabetes-related complications, managing diabetes-related complications, treating diabetes (including the costs of the interventions), and related hospital costs. NHS costs were taken from routinely available data and from related NICE clinical guidelines. The costs of the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system were £2961.62 and £3195.48 respectively. A total cost per year for the technologies was calculated assuming a 4-year lifespan for the insulin pumps, which takes into account the need to replace consumables such as insulin cannulas and reservoirs, glucose monitoring sensors and transmitters, and batteries. The total cost per year for the MiniMed Paradigm Veo system was £4862.10 and for the Vibe and G4 PLATINUM CGM system was £5298.65. The costs of comparator technologies were taken from the [draft NICE guideline on type 1 diabetes](#) and from the published literature. In the base-case analysis, comparator technology costs were weighted by UK market share.

Health-related quality of life

5.39 The utility values applied to each health state were derived from the published literature. A disutility of -0.012 was applied to a severe hypoglycaemic event, which also incorporated the disutility associated with fear of hypoglycaemia.

Base-case analysis

5.40 For the purposes of decision-making, the ICERs per QALY gained or lost were considered. The following key assumptions were applied in the base-case analysis:

- The population has a mean age of 41.6 years, has had diabetes for a mean duration of 27.1 years, and has a mean HbA1c of 7.26%.
- The insulin pumps used in the integrated systems and as stand-alone devices have a lifetime of 4 years.
- Four capillary blood tests are needed each day for monitoring blood glucose with either continuous glucose monitoring or capillary blood testing.
- Forty-eight units of short-acting insulin are used each day for continuous subcutaneous insulin infusion.
- Forty-eight units of insulin are used each day for multiple daily insulin injections, with twice-daily insulin detemir (long-acting; 24 units in total) and 3 boluses of short-acting insulin at meal times (24 units in total).
- Three HbA1c tests are needed each year.
- Treatment effects (HbA1c) are estimated as the mean reduction from the baseline value derived from the clinical-effectiveness review. This reduction occurs over the first year, then annual progression (0.045%) occurs.
- The clinical effectiveness of the Vibe and G4 PLATINUM CGM system and the continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated) system are equivalent. The clinical-effectiveness data for these technologies were derived from the integrated sensor-augmented pump therapy system with no low-glucose suspend function.
- The probability of death from a severe hypoglycaemic event is 0%.

- 5.41 The results of the probabilistic base-case analysis suggested that the MiniMed Paradigm Veo system was not cost effective when compared with capillary blood testing with multiple daily insulin injections (£123,375 per QALY gained) and capillary blood testing with continuous subcutaneous insulin infusion (£730,501 per QALY gained). The Vibe and G4 PLATINUM CGM system was not cost effective when compared with capillary blood testing with multiple daily insulin injections (£133,323 per QALY gained) and capillary blood testing with continuous subcutaneous insulin infusion (£668,789 per QALY gained).
- 5.42 When the MiniMed Paradigm Veo system was compared with continuous glucose monitoring with subcutaneous insulin infusion (non-integrated), it was associated with an incremental QALY loss (-0.0192) and had an ICER of £422,849 saved per QALY lost. This was driven by the non-integrated system having the highest decrease in HbA1c from baseline in the clinical-effectiveness review. This decrease in HbA1c led to a decrease in the number of lifetime diabetes-related complications, which compensated for the higher number of hypoglycaemic events observed with the non-integrated system, despite the MiniMed Paradigm Veo system having the lowest number of lifetime hypoglycaemic events (0.622 severe hypoglycaemic events per person). Compared with the non-integrated continuous glucose monitoring and continuous subcutaneous insulin infusion, the cost effectiveness of the Vibe and G4 PLATINUM CGM system was driven by the cost of the comparator, which resulted in the Vibe and G4 PLATINUM CGM system having an incremental cost of £674.
- 5.43 The cost-effectiveness plane for the base-case probabilistic sensitivity analysis showed a positive correlation between costs and QALYs, with the treatments that included continuous glucose monitoring associated with both increased cost and increased QALYs. The results of the probabilistic sensitivity analysis were also plotted on a cost-effectiveness acceptability curve, which showed that the probability of technologies that contain continuous glucose monitoring being cost effective was 0% for all maximum acceptable ICERs included in the analysis. This was because the cost of the technologies was too large to be offset by the additional QALYs gained when compared with capillary blood testing.
- 5.44 Two alternative base-case scenarios were also run. The first scenario excluded multiple daily insulin injections and assumed all insulin therapy was delivered by continuous subcutaneous insulin infusion. This was intended to reflect the

recommendation made in NICE's technology appraisal guidance on [continuous subcutaneous insulin infusion for the treatment of diabetes mellitus](#), which supports using continuous subcutaneous insulin infusion as an option when multiple daily insulin injections are not considered appropriate. The results of this full incremental analysis showed that when capillary blood testing with multiple daily insulin injections was excluded from the analysis, the MiniMed Paradigm Veo system and Vibe and G4 Platinum CGM system were extendedly dominated (that is, dominated by a combination of 2 alternatives) and dominated (has higher costs and worst outcomes) respectively, by the non-integrated system. The cost-effectiveness acceptability curve for this analysis showed that capillary blood testing with continuous subcutaneous insulin infusion was the strategy with the greatest probability of being cost effective.

- 5.45 The second scenario excluded comparators that included capillary blood testing and assumed all glucose monitoring was done using continuous glucose monitoring. This was intended to show the impact of the low-glucose suspend function of the MiniMed Paradigm Veo system. The results of this full incremental analysis showed that the MiniMed Paradigm Veo system was the least expensive strategy. The Vibe and G4 PLATINUM CGM system remained dominated by the non-integrated system, largely because the technologies were assumed to be equally effective but the Vibe and G4 PLATINUM CGM system was more expensive. The cost-effectiveness acceptability curve for this analysis showed that the MiniMed Paradigm Veo system was the strategy with the highest probability of being cost effective at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained.

Analysis of alternative scenarios

- 5.46 Several scenario analyses were done to assess the impact of the assumptions made in the base-case analysis. The following assumptions were assessed:
- applying the baseline population characteristics from the [draft NICE guideline on type 1 diabetes](#)
 - frequency of daily capillary blood tests
 - amount of insulin used a day

- no progression of HbA1c after 1 year
- no HbA1c change in year 1
- rates of severe hypoglycaemic events
- mortality of 4.9% for severe hypoglycaemia
- method of estimating QALYs
- 4-year time horizon
- addition of a utility increment for fear of hypoglycaemia
- average annual cost for non-integrated systems without market share weighting.

5.47 The ICERs changed substantially under the following assumptions:

- no change in HbA1c in year 1
- mortality rate of 4.9% for severe hypoglycaemia
- utility increment of 0.0329 for fear of hypoglycaemia.

5.48 The ICERs did not change substantially in the remaining scenarios modelled, including when a relative risk for severe hypoglycaemic events of 0.125 was applied to the MiniMed Paradigm Veo system.

5.49 The ICERs changed substantially when it was assumed that there was no change in HbA1c in the first year. In this scenario, the Vibe and G4 PLATINUM CGM system was dominated when compared with all 3 comparators included in the analysis, the MiniMed Paradigm Veo system dominated in the comparison with the non-integrated system and had ICERs of £3,344,672 and £4,871,356 per QALY gained when compared with capillary blood testing with multiple daily insulin injections and capillary blood testing with continuous subcutaneous insulin infusion respectively.

5.50 The ICERs changed substantially when it was assumed that severe hypoglycaemia had a mortality rate of 4.9%. In this scenario, the Vibe and G4 PLATINUM CGM system was dominated when compared with capillary blood testing with continuous subcutaneous insulin infusion, had an ICER of £126,689 per QALY gained when compared with capillary blood testing with multiple daily

insulin injection and an incremental cost of £657 when compared with the non-integrated system. The MiniMed Paradigm Veo system dominated in comparison with the non-integrated system and had ICERs of £87,818 and £374,626 per QALY gained when compared with capillary blood testing and multiple daily insulin injections and capillary blood testing with continuous subcutaneous insulin infusion respectively.

- 5.51 The ICERs also changed substantially when a utility increment of 0.0329 was applied to represent a reduction in fear of hypoglycaemia. This utility increment was applied only to the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system. In this scenario, the MiniMed Paradigm Veo system dominated in comparison with the non-integrated system and had ICERs of £64,012 and £74,088 per QALY gained when compared with capillary blood testing with multiple daily insulin injections and capillary blood testing with continuous subcutaneous insulin infusion respectively. The Vibe and G4 PLATINUM CGM system had ICERs of £70,103 and £74,089 per QALY gained when compared with capillary blood testing with multiple daily insulin injections and capillary blood testing with continuous subcutaneous insulin infusion respectively. When compared with the non-integrated system, the addition of the utility increments resulted in the Vibe and G4 PLATINUM CGM system having 0.5824 incremental QALYs and an ICER of £1157 per QALY gained.

Analysis of population subgroups

- 5.52 The External Assessment Group also produced supplementary analyses for 2 population subgroups, adults who have difficulty maintaining target HbA1c and adults who often have hypoglycaemic events. Supplementary literature searches were done to inform the analyses and additional evidence networks were constructed to calculate treatment effects. These analyses included a utility decrement of -0.064 and a mortality rate of 0.01596 for severe hypoglycaemic events.
- 5.53 For the first population subgroup, adults who had difficulty maintaining target HbA1c, the clinical evidence was restricted to studies that included patients with a baseline HbA1c of 8.5% or more and supplementary evidence was included to complete the network. HbA1c treatment effects were taken from Pickup et al. (2011) and the Eurythmics study. Treatment effects were assumed to be equivalent for the MiniMed Paradigm Veo system, the Vibe and G4

PLATINUM CGM system and non-integrated continuous glucose monitoring with continuous subcutaneous insulin infusion (mean reduction of -0.23 from baseline). In the base-case analysis for this population, it was assumed that the baseline HbA1c was 8.6% and the rate of hypoglycaemia was 0.

- 5.54 The results of the base-case analysis for adults who had difficulty maintaining target HbA1c suggested that the MiniMed Paradigm Veo system was not cost effective compared with capillary blood testing with multiple daily injections and capillary blood testing with subcutaneous insulin infusion, which had ICERs of £86,334 and £79,281 per QALY gained respectively. Similarly, the Vibe and G4 PLATINUM CGM system was not cost effective compared with capillary blood testing with multiple daily injections and capillary blood testing with continuous subcutaneous insulin infusion, which had ICERs of £95,017 and £92,674 per QALY gained respectively. In the comparison with the non-integrated continuous glucose monitoring and continuous subcutaneous insulin infusion system, the MiniMed Paradigm Veo system dominated and the Vibe and G4 PLATINUM CGM system was dominated, although these comparisons were driven solely by cost.
- 5.55 The assumptions around treatment effects, incidence of severe hypoglycaemia and the impact of reduced duration of sensor use were investigated in 4 scenario analyses, which largely resulted in less favourable ICERs than those reported for the base case. Lower ICERs were obtained for the MiniMed Paradigm Veo system when it was assumed that the low-glucose suspend function resulted in a lower incidence of hypoglycaemia when compared with capillary blood testing with multiple daily injections (£81,255 per QALY gained) and capillary blood testing with continuous subcutaneous insulin infusion (£62,025 per QALY gained).
- 5.56 For the second population subgroup, adults who experienced frequent hypoglycaemic events, the clinical evidence was restricted to studies that included patients with a baseline HbA1c of 8.5% or less and supplementary evidence was included to complete the network. It was assumed that the population had HbA1c (7.26%) that remained stable, but they had frequent hypoglycaemic events. Rates of severe hypoglycaemia were calculated using incidence rate ratios reported in the ASPIRE and STAR-3 studies, and pooled estimates from Hirsch et al. (2008), the SWITCH study and Battelino et al. (2011). Incidence rates for severe hypoglycaemia ranged from 4.33 per

100 patient-years for the MiniMed Paradigm Veo system to 38.36 per 100 patient-years for capillary blood testing with multiple daily insulin injections. An incidence rate of 33.33 per 100 patient-years was applied to both the Vibe and G4 PLATINUM CGM system and non-integrated continuous glucose monitoring with continuous subcutaneous insulin infusion.

- 5.57 The results of the base-case analysis for adults who had frequent hypoglycaemic events suggested that the MiniMed Paradigm Veo system was not cost effective compared with capillary blood testing with multiple daily injections and capillary blood testing with continuous subcutaneous insulin infusion, which had ICERs of £188,124 and £189,326 per QALY gained respectively. When compared with non-integrated continuous glucose monitoring and continuous subcutaneous insulin infusion, the MiniMed Paradigm Veo system dominated. The Vibe and G4 PLATINUM CGM system was dominated when compared with both capillary blood testing with continuous subcutaneous insulin infusion and non-integrated continuous glucose monitoring with continuous subcutaneous insulin infusion. When compared with capillary blood testing with multiple daily injections, the Vibe and G4 PLATINUM CGM system had an ICER of £1,538,493 per QALY gained.
- 5.58 The assumptions around HbA1c treatment effects and impact of fear of hypoglycaemia were investigated in 3 scenario analyses, which resulted in more favourable ICERs than those reported for the base case. The lowest ICERs were produced when a utility increment of 0.0329 associated with a reduced fear of hypoglycaemia was applied to both the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system. This resulted in the MiniMed Paradigm Veo system dominating non-integrated continuous glucose monitoring with continuous subcutaneous insulin infusion and having ICERs of £80,692 and £57,857 per QALY gained when compared with capillary blood testing with multiple daily injections and capillary blood testing with continuous subcutaneous insulin infusion respectively. The Vibe and G4 PLATINUM CGM system had an ICER of £1161 per QALY gained compared with non-integrated continuous glucose monitoring with continuous subcutaneous insulin infusion, but ICERs of £141,953 and £124,144 per QALY gained when compared with capillary blood testing with multiple daily injections and capillary blood testing with continuous subcutaneous insulin infusion respectively.

6 Considerations

Current practice

- 6.1 The Committee discussed the current care pathway for people with type 1 diabetes in the NHS. It heard from clinical specialists that care for people with type 1 diabetes is usually offered in stages, depending on whether target HbA1c is maintained or if they have had disabling hypoglycaemia. The Committee heard that standard practice is for people to self-monitor their blood glucose levels with a glucose meter (capillary blood glucose testing) and to have insulin therapy with multiple insulin injections throughout the day (multiple daily insulin injections). It was aware that people who have difficulty maintaining target HbA1c or who have disabling hypoglycaemia with multiple daily insulin injections are eligible for continuous subcutaneous insulin infusion (insulin pump therapy) in accordance with NICE's technology appraisal guidance on [continuous subcutaneous insulin infusion for the treatment of diabetes mellitus](#). The Committee noted that people who continue to have difficulty despite using continuous subcutaneous insulin infusion may sometimes be offered continuous glucose monitoring through individual funding requests, but if they have extreme difficulty they may be considered for an allogeneic pancreatic islet cell transplantation. The Committee concluded that based on current clinical practice, the integrated sensor-augmented pump therapy systems were most likely to have benefit in people who are being considered for continuous glucose monitoring.
- 6.2 The Committee discussed the impact of type 1 diabetes and the perceived benefits of the integrated sensor-augmented pump therapy systems with patient and carer experts. The Committee heard that one of the greatest fears for people with type 1 diabetes and their carers is severe hypoglycaemia. The Committee heard from clinical specialists that around 30% of people with type 1 diabetes have problematic hypoglycaemia, which can affect many aspects of daily life and result in substantial anxiety. The Committee heard that using the integrated sensor-augmented pump therapy systems could provide greater independence for children and young adults with type 1 diabetes by enabling participation in sports and giving reassurance when they stay away from home. It also acknowledged that the technologies could offer similar advantages to adults. The Committee noted that using the MiniMed Paradigm Veo system with the low-glucose suspend function could reduce anxiety substantially,

particularly in carers of children and young adults who may experience disrupted sleep for many years because of fear of the risk of nocturnal hypoglycaemia. The Committee recognised that the integrated sensor-augmented pump therapy systems have the potential to offer substantial benefits to people with type 1 diabetes and their carers, particularly for those who have had disabling hypoglycaemia.

Clinical evidence

- 6.3 The Committee reviewed the evidence available on the clinical effectiveness of the MiniMed Paradigm Veo system, and the Vibe and G4 PLATINUM CGM system. It noted that there was substantial heterogeneity in the characteristics of the included populations, particularly for baseline HbA1c levels, exclusions relating to severe hypoglycaemia, age of patients and previous use of continuous subcutaneous insulin infusion. It also noted that there was heterogeneity in the primary clinical endpoints and length of follow-up. The Committee concluded that the substantial heterogeneity in the studies limited the number of comparisons that could be drawn from the available data.
- 6.4 The Committee considered the validity of HbA1c as a primary endpoint in the studies included in the meta-analyses. The Committee heard from clinical specialists that HbA1c was an established and accepted surrogate outcome measure that has been shown to be associated with clinical outcomes. The Committee concluded that using HbA1c in the analyses was reasonable and provided a link to long-term outcomes.
- 6.5 The Committee noted that no published studies reported comparative data for the Vibe and G4 PLATINUM CGM system and so the External Assessment Group had included data from an integrated sensor-augmented pump therapy system without low-glucose suspend as a clinical proxy. The Committee acknowledged that there were no data to suggest that the effectiveness of the Vibe and G4 PLATINUM CGM system was equivalent to the proxy system and concluded that in the absence of comparative data, the clinical effectiveness of the Vibe and G4 PLATINUM CGM system was unknown.
- 6.6 The Committee considered the validity of the network meta-analyses. It noted that 3 sets of network meta-analyses were available: 1 for adults, 1 for children and 1 for the economic modelling, which included estimates derived from mixed

populations over multiple follow-up time points. The Committee considered that most of the effect estimates were based on indirect comparisons that were drawn from studies with less than 12 months follow-up. It also noted that no clinical data were available for 2 of the comparators included in the final scope: continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated) and continuous glucose monitoring with multiple daily insulin injections. The Committee concluded that the effect estimates derived from the network meta-analyses, particularly those constructed for the economic model, were limited because they were most likely confounded by indirect comparisons, small sample sizes and heterogeneity in both the included populations and duration of follow-up.

- 6.7 The Committee considered the results of the network meta-analyses for adults. It noted that direct evidence from the ASPIRE in-home study showed that at 3 months follow-up, the MiniMed Paradigm Veo system significantly reduced both daytime and nocturnal hypoglycaemic event rates compared with an integrated subcutaneous insulin infusion and continuous glucose monitoring system. It also noted that no impact on HbA1c was seen in the ASPIRE in-home study, although the study was not powered to detect changes in HbA1c. Also, no impact on HbA1c was seen in indirect comparisons with capillary blood testing and continuous subcutaneous insulin infusion and capillary blood testing with multiple daily injections. The Committee concluded that it was plausible that the MiniMed Paradigm Veo system may have clinical benefit for adults with type 1 diabetes who experience frequent episodes of severe hypoglycaemia.
- 6.8 In addition to the meta-analyses for adults, the Committee also considered data from 1 randomised cross-over study (the SWITCH study) and 2 observational studies (Choudhary et al. 2011; Choudhary et al. 2013) that were included in a narrative analysis of supplementary evidence. The Committee noted that although the SWITCH study included a mixed population, it supported using continuous glucose monitoring sensors to decrease the amount of time spent in hypoglycaemia. In addition, the Committee considered that although the 2 observational studies contained small numbers of patients, they provided evidence that in highly selected populations it was plausible that using integrated sensor-augmented pump therapy systems could have benefit for people with frequent episodes of hypoglycaemia. Further, the Committee noted that Choudhary et al. (2011) provided proof-of-concept data for the low-glucose suspend function of the MiniMed Paradigm Veo system, which

appeared to reduce the duration of nocturnal hypoglycaemia in a high-risk group, and heard from clinical specialists that the study population appeared to be representative of the population in which the MiniMed Paradigm Veo system would be used in practice. The Committee concluded that the supplementary data from these 3 studies supported the conclusions drawn from the network meta-analyses.

- 6.9 The Committee considered the results of the network meta-analyses for children. It noted that direct evidence from Ly et al. (2013) showed that the MiniMed Paradigm Veo system significantly reduced the rate of moderate and severe hypoglycaemic events when compared with capillary blood testing and continuous subcutaneous insulin infusion at 6-month follow-up. It also noted that the MiniMed Paradigm Veo system did not have a significant impact on HbA1c at 6 months. The Committee considered that although Ly et al. (2013) included a mixed population, most of the patients ($\approx 70\%$) were aged less than 18 years and it was the only evidence available to provide an indication of the likely clinical impact of the system in children. The Committee concluded that it was plausible that the MiniMed Paradigm Veo system may have clinical benefit for children with type 1 diabetes who experience frequent episodes of severe hypoglycaemia.
- 6.10 The Committee discussed the overall strength of the evidence base for the integrated sensor-augmented pump therapy systems. It considered that, despite limited evidence to suggest that the MiniMed Paradigm Veo system may have benefit in reducing rates of severe hypoglycaemia, the overall evidence base to support using the integrated sensor-augmented pump therapy systems was weak. The Committee heard from clinical specialists and patient experts that companies often provide online software for people to upload data from their sensor-augmented pump therapy system to a company-maintained database. It was also suggested that these data are rarely analysed and published. The Committee concluded that these technologies and their successive versions could offer substantial benefits to patients and that robust data need to be generated to support the claimed benefits of these technologies and their reimbursement value.

Cost effectiveness

- 6.11 The Committee considered the cost-effectiveness analyses for the MiniMed Paradigm Veo system. It noted that 3 base cases were available, but that none included a comparison with continuous glucose monitoring and multiple daily injections because of a lack of clinical-effectiveness data. The Committee noted that the cost-effectiveness analyses were done using the IMS CORE Diabetes Model. It discussed the advantages and disadvantages of the model, and heard from experts that although the model was well validated its structure and underlying clinical data were likely to favour interventions that are aimed at reducing HbA1c and associated long-term complications. The Committee heard from the External Assessment Group that the impacts of short-term outcomes associated with hypoglycaemic events are more difficult to capture in the model because, unlike change in HbA1c, the rate of hypoglycaemia cannot be changed over time. The Committee also heard from clinical specialists that the risk equations included in the model were dated and may underestimate the risk of long-term complications for people with type 1 diabetes. The Committee concluded that despite its extensive validation, the IMS CORE Diabetes Model may not be suitable for investigating the impact of interventions on short-term clinical outcomes, and that it was likely that this impact could have been undervalued in the analyses.
- 6.12 The Committee considered the treatment-effect estimates that had been used in the economic modelling. It noted that these treatment effects were limited by the heterogeneity in the meta-analyses constructed for the economic model. It heard from clinical specialists that in the mixed population base case, it was implausible that HbA1c increases from baseline with continuous subcutaneous insulin infusion because this is an intervention that is intended to reduce HbA1c. Further, it also heard that for the population who experience hypoglycaemia, the assumption that the hypoglycaemic event rate is equivalent for capillary blood testing with continuous subcutaneous insulin infusion and continuous glucose monitoring with continuous subcutaneous insulin infusion was likely to be implausible because the addition of continuous glucose monitoring is intended to reduce the occurrence of hypoglycaemia. The Committee concluded that, in general, the cost-effectiveness analyses could not be considered robust because the insufficient evidence base for clinical effectiveness leads to a large amount of uncertainty in the incremental clinical-effect estimates.

- 6.13 The Committee heard from clinical specialists that the analysis most relevant to using the MiniMed Paradigm Veo system in clinical practice is the base case that includes people who are assumed to have frequent hypoglycaemic events. However, the Committee heard that there may also be a small but clinically significant group of people who have both frequent hypoglycaemia and uncontrolled HbA1c, which may be as a result of brittle diabetes. The Committee also acknowledged that people who have frequent hypoglycaemic events may have increased HbA1c because they try to avoid hypoglycaemia and considered that in practice it was likely that there would be an overlap in the populations modelled for this assessment. However, the Committee concluded that despite the limitations of the clinical-evidence base, the analysis for people who have frequent hypoglycaemic events should be considered further because of the plausible clinical benefit in this subgroup.
- 6.14 The Committee considered the cost-effectiveness analyses for the MiniMed Paradigm Veo system in the severe hypoglycaemia population. The Committee noted that the technology was not cost effective when compared with capillary blood testing with multiple daily injections (£188,100 per quality-adjusted life year [QALY] gained) and capillary blood testing with continuous subcutaneous insulin infusion (£189,300 per QALY gained), but considered that the incremental cost-effectiveness ratios (ICERs) for these comparisons were likely to reduce to between £57,900 to £85,300 per QALY gained when treatment effects for HbA1c and an additional utility increment for fear of hypoglycaemia were included. The Committee also noted that the MiniMed Paradigm Veo system dominated when compared with continuous glucose monitoring and continuous subcutaneous insulin infusion (non-integrated), but acknowledged that this comparison was mainly driven by cost. The Committee concluded that at face value, the analyses suggested that the MiniMed Paradigm Veo system could not be considered cost effective when compared with capillary blood testing with multiple daily injections and capillary blood testing with continuous subcutaneous insulin infusion because of the high incremental cost of the technology.
- 6.15 The Committee considered the impact of hypoglycaemia and heard from patient and carer experts that fear of severe hypoglycaemic events was associated with a substantial impact on quality of life. Fear of hypoglycaemia may lead to people restricting their daily activities and can cause significant anxiety for carers, particularly parents who may have to wake several times a night to check on

their child. The Committee also heard that severe hypoglycaemic events could have a substantial impact on quality of life that extends beyond the perspective of the NHS and personal social services. For example, children may miss school because of a hypoglycaemic event, and adults may need to be absent from work to recover. The Committee concluded that severe hypoglycaemia has a sustained impact on quality of life and can limit usual daily activities for people with type 1 diabetes and their carers.

6.16 The Committee questioned the extent to which the ICERs produced for the severe hypoglycaemia population reflected the benefits associated with a reduction in hypoglycaemic events. The Committee heard from the External Assessment Group that although additional utility increments for fear of hypoglycaemia had been included in scenario analyses, it is possible that the studies from which the utility values were derived had not captured the persistent fear of catastrophic events. Additionally, the Committee heard from clinical specialists that severe hypoglycaemic events may have a substantial impact on ambulance services. The Committee agreed that it was likely that the full impact of hypoglycaemia had not been captured in the model. Further, it considered that persistent fear of hypoglycaemia could be fully captured in the model if published evidence was available. The Committee concluded that although the analysis for people with frequent hypoglycaemia was highly uncertain, it was likely that the benefits of the technologies were not fully captured in the ICER and that it was plausible that the MiniMed Paradigm Veo system with low-glucose suspend would have benefit in a highly selected population.

6.17 The Committee questioned the extent to which the cost-effectiveness analyses are applicable to children and young people. The Committee heard from the External Assessment Group that the CORE Diabetes Model could not be adapted for use in children because of the underlying risk equations that were incorporated in the model. The Committee considered that, in general, the ICERs would most likely be lower for children than those available for adults because of the increased risk of adverse outcomes over a longer duration of disease. The Committee also heard from clinical specialists and patient and carer experts that the low-glucose suspend function of the MiniMed Paradigm Veo system could be of greater benefit in younger children who may have an unpredictable response to insulin and rapid onset of hypoglycaemia. The Committee concluded that it was plausible that the ICERs for the MiniMed

Paradigm Veo system would be lower if they were extrapolated to children, particularly those who experience frequent hypoglycaemic events.

- 6.18 The Committee discussed Roze et al. (2015), which was submitted to the Committee as a pre-publication manuscript. The Committee noted that the ICERs included in the manuscript were substantially different to those produced by the External Assessment Group's analyses. The Committee heard from the External Assessment Group that the treatment effects used in the different analyses were the primary driver of the differences in the ICERs. The Committee concluded that the more conservative combination of HbA1c changes and hypoglycaemic event rates applied in the analyses by the External Assessment Group provided a fairer assessment of the incremental benefits associated with using integrated sensor-augmented pump therapy.

Additional considerations

- 6.19 The Committee heard from a clinical specialist that young children are often considered to have greater sensitivity to insulin than adults, which can make the management of type 1 diabetes more unpredictable in this population. The Committee noted that the use of the MiniMed Paradigm Veo system should be considered for younger children, particularly those of pre-school age who may be at risk of rapid onset of severe hypoglycaemia.
- 6.20 The Committee noted that no clinical-effectiveness data were available for using integrated sensor-augmented pump therapy systems in pregnant women. The Committee agreed that this was an important subgroup and wished to encourage further research in this area.
- 6.21 The Committee considered the rapid pace of development of new technologies designed to help with monitoring blood glucose levels in people with type 1 diabetes, and noted the importance of the progress in developing closed-loop systems and the artificial pancreas. The Committee acknowledged that new versions of the integrated sensor-augmented pump therapy systems were becoming available to the NHS and wished to encourage evidence generation on the clinical effectiveness of these new technologies.

7 Recommendations for further research

- 7.1 The Committee recommended that the company collect data on people using the MiniMed Paradigm Veo system and successor technologies with low-glucose suspend function, which should be analysed and published to show the system's impact on improving control of disabling hypoglycaemia. Key outcomes that could be presented include frequency and duration of hypoglycaemic events, time spent in hypoglycaemia, and number and duration of low-glucose suspend events.
- 7.2 The Committee recommended further research to quantify the impact of hypoglycaemia on quality of life for people with type 1 diabetes and their carers. Future research should include adults and children and should capture the impact of persistent anxiety associated with the fear of catastrophic events related to severe hypoglycaemic events.
- 7.3 The Committee recommended further data collection to assess the impact of episodes of hypoglycaemia on healthcare resource use. The Committee noted that sources of routinely collected data, such as hospital episode statistics, the national diabetes audit and ambulance service call-out data, could be combined to meet this objective.
- 7.4 The Committee recommended further research to investigate the clinical effectiveness of the integrated sensor-augmented insulin pump therapy systems in younger children and pregnant women. No data are currently available for these subgroups and their inclusion in future studies is encouraged.
- 7.5 The Committee recommended that health economic models are developed to capture the impact of interventions on short-term outcomes such as hypoglycaemia. In addition, the feasibility of incorporating more recently developed risk prediction models for cardiovascular disease such as QRisk2 and observational data from registries such as the Swedish National Diabetes Register into health economic models for type 1 diabetes should be explored.

8 Implementation

NICE has developed tools, in association with relevant stakeholders, to help organisations put this guidance into practice. In addition NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in [section 7](#) into its guidance research recommendations database (available on the [NICE website](#)) and highlight these recommendations to public research bodies.

9 Review

NICE reviews the evidence at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about new information relating to the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Andrew Dillon
Chief Executive
February 2016

10 Diagnostics Advisory Committee members and NICE project team

Diagnostics Advisory Committee

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

Standing Committee members

Professor Adrian Newland

Chair, Diagnostics Advisory Committee

Dr Mark Kroese

Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Dr Phil Chambers

Research Fellow, Leeds Institute of Cancer and Pathology, University of Leeds

Dr Sue Crawford

GP Principal, Chillington Health Centre

Professor Erika Denton

National Clinical Director for Diagnostics, NHS England, Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

Dr Steve Edwards

Head of Health Technology Assessment, BMJ Evidence Centre

Mr David Evans

Lay member

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Mr John Hitchman

Lay member

Professor Chris Hyde

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Mr Matthew Lowry

Director of Finance and Infrastructure, Doncaster and Bassetlaw Hospitals NHS Foundation Trust

Dr Michael Messenger

Deputy Director and Scientific Manager, NIHR Diagnostic Evidence Co-operative, Leeds

Dr Peter Naylor

GP, Chair Wirral Clinical Commissioning Group

Dr Dermot Neely

Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

Ms Gail Norbury

Consultant Clinical Scientist, Guy's Hospital

Dr Simon Richards

Vice President Regulatory Affairs, EME, Alere Inc

Dr Deirdre Ryan

Consultant Cellular Pathologist, Royal London Hospital

Dr Steve Thomas

Consultant Vascular and Cardiac Radiologist, Sheffield Teaching Hospitals Foundation Trust

Mr Paul Weinberger

Chief Executive Officer, DiaSolve Ltd, London

Professor Anthony Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, St Thomas' Hospital

Specialist Committee members

Dr Karen Anthony

Consultant in Diabetes and Endocrinology, The Whittington Hospital NHS Trust

Dr Andrew Day

Consultant Medical Biochemist, University Hospitals Bristol NHS Foundation Trust

Dr Bobby Huda

Consultant Physician in Diabetes/Metabolic Medicine and General Internal Medicine, Barts Health NHS Trust

Ms Alexandria Moseley

Lay member

Mr David Sowerby

Lay member

Ms Jane Walsh

Lay member

NICE project team

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

Rebecca Albrow

Topic Lead

Sarah Byron

Technical Adviser

Robert Fernley

Project Manager

11 Sources of evidence considered by the Committee

The diagnostics assessment report was prepared by Kleijnen Systematic Reviews Ltd:

- Riemsma R, Corro Ramos I, Birnie R et al. Type 1 diabetes: Integrated sensor-augmented pump therapy systems for managing blood glucose levels (The MiniMed Paradigm Veo system and Vibe and G4 PLATINUM CGM system), a systematic review and economic evaluation. February 2015.

Registered stakeholders

The following organisations accepted the invitation to participate in this assessment as registered stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report and the diagnostics consultation document.

Manufacturers of technologies included in the final scope:

- Medtronic Limited
- Dexcom
- Johnson & Johnson/Animas

Other commercial organisations:

- Cellnovo Ltd
- OmniPod
- Roche Diagnostics

Professional groups and patient/carers groups:

- Royal College of Physicians
- Royal College of Pathologists
- Dose Adjustment for Normal Eating (DAFNE)
- Diabetes Inpatient Specialist Nurse UK Group
- Juvenile Diabetes Research Foundation (JDRF)

- INPUT Patient Advocacy

- Diabetes UK

Research groups:

- University of Southampton
- Institute of Metabolic Science, University of Cambridge

Associated guideline groups:

None

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government
- BIVDA
- Advanced Therapeutics UK Limited

Glossary

Disabling hypoglycaemia

People with type 1 diabetes may experience 'disabling hypoglycaemia', which is when hypoglycaemic episodes occur frequently or without warning so that the person is constantly anxious about having more episodes. This can have a negative effect on quality of life.

About this guidance

NICE diagnostics technologies guidance is designed to help the NHS adopt efficient and cost-effective medical diagnostic technologies more rapidly and consistently.

The programme concentrates on pathological tests, imaging, endoscopy and physiological measurement, since these represent most of the investigations performed on patients. The types of products that might be included are medical diagnostic technologies that give greater independence to patients, and diagnostic devices or tests used to detect or monitor medical conditions. Diagnostic technologies may be used for various purposes: diagnosis, clinical monitoring, screening, treatment triage, assessing stages of disease progression, and risk stratification.

This guidance was developed using the NICE [diagnostic technologies guidance](#) process.

We have produced a [summary for patients and carers](#). [Tools](#) to help you put the guidance into practice and information about the [evidence](#) it is based on are also available.

Your responsibility

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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ISBN: 978-1-4731-1650-4

Accreditation

