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Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic review and economic evaluation

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National Institute for Health Research

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Abstract

Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic review and economic evaluation

Rob Riemsma,[1]* Isaac Corro Ramos,[2] Richard Birnie,[1] Nasuh Büyükkaramikli,[2] Nigel Armstrong,[1] Steve Ryder,[1] Steven Duffy,[1] Gill Worthy,[1] Maiwenn Al,[2] Johan Severens[2] and Jos Kleijnen[1,3]

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Background: In recent years, meters for continuous monitoring of interstitial fluid glucose have been introduced to help people with type 1 diabetes mellitus (T1DM) to achieve better control of their disease.

Objective: The objective of this project was to summarise the evidence on the clinical effectiveness and cost-effectiveness of the MiniMed® Paradigm™ Veo system (Medtronic Inc., Northridge, CA, USA) and the Vibe™ (Animas® Corporation, West Chester, PA, USA) and G4® PLATINUM CGM (continuous glucose monitoring) system (Dexcom Inc., San Diego, CA, USA) in comparison with multiple daily insulin injections (MDIs) or continuous subcutaneous insulin infusion (CSII), both with either self-monitoring of blood glucose (SMBG) or CGM, for the management of T1DM in adults and children.

Data sources: A systematic review was conducted in accordance with the principles of the Centre for Reviews and Dissemination guidance and the National Institute for Health and Care Excellence Diagnostic Assessment Programme manual. We searched 14 databases, three trial registries and two conference proceedings from study inception up to September 2014. In addition, reference lists of relevant systematic reviews were checked. In the absence of randomised controlled trials directly comparing Veo or an integrated CSII + CGM system, such as Vibe, with comparator interventions, indirect treatment comparisons were performed if possible.

Methods: A commercially available cost-effectiveness model, the IMS Centre for Outcomes Research and Effectiveness diabetes model version 8.5 (IMS Health, Danbury, CT, USA), was used for this assessment. This model is an internet-based, interactive simulation model that predicts the long-term health outcomes and costs associated with the management of T1DM and type 2 diabetes. The model consists of 15 submodels designed to simulate diabetes-related complications, non-specific mortality and costs over time. As the model simulates individual patients over time, it updates risk factors and complications to account for disease progression.

Results: Fifty-four publications resulting from 19 studies were included in the review. Overall, the evidence suggests that the Veo system reduces hypoglycaemic events more than other treatments, without any differences in other outcomes, including glycated haemoglobin (HbA_{1c}) levels. We also found significant results in favour of the integrated CSII + CGM system over MDIs with SMBG with regard to HbA_{1c} levels and quality of life. However, the evidence base was poor. The quality of the included studies was generally low, often with only one study comparing treatments in a specific population at a specific follow-up time. In particular, there was only one study comparing Veo with an integrated CSII + CGM system and only one study comparing Veo with a CSII + SMBG system in a mixed population. Cost-effectiveness analyses indicated that MDI + SMBG is the option most likely to be cost-effective, given the current threshold of £30,000 per quality-adjusted life-year gained, whereas integrated CSII + CGM systems and Veo are dominated and extendedly dominated, respectively, by stand-alone, non-integrated CSII with CGM. Scenario analyses did not alter these conclusions. No cost-effectiveness modelling was conducted for children or pregnant women.

Conclusions: The Veo system does appear to be better than the other systems considered at reducing hypoglycaemic events. However, in adults, it is unlikely to be cost-effective. Integrated systems are also generally unlikely to be cost-effective given that stand-alone systems are cheaper and, possibly, no less effective. However, evidence in this regard is generally lacking, in particular for children. Future trials in specific child, adolescent and adult populations should include longer term follow-up and ratings on the European Quality of Life-5 Dimensions scale at various time points with a view to informing improved cost-effectiveness modelling.

Study registration: PROSPERO Registration Number CRD42014013764.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Cost-effectiveness analysis An economic analysis that converts effects into health benefits and describes the costs for additional health gains.

Decision modelling A mathematical construct that allows the comparison of the relationship between costs and outcomes for alternative health-care interventions.

Diabetic ketoacidosis Occurs when the body is unable to use blood glucose because of inadequate insulin. Instead, fat is broken down as an alternative source of fuel; this process leads to the build-up of by-products called ketones.

False negative Incorrect negative test result (e.g. the number of diseased persons with a negative test result).

False positive Incorrect positive test result (e.g. the number of non-diseased persons with a positive test result).

Glycated haemoglobin test The glycated haemoglobin test measures diabetes management over 2–3 months.

Hyperglycaemic and hypoglycaemic area under the curve The area under the curve is the product of the magnitude and duration of the sensor-measured glucose level above or below a specified cut-off level. Higher values for this calculation indicate more numerous, severe or protracted glycaemic events.

Hypocalcaemia Low blood calcium level.

Hypomagnesaemia Low levels of magnesium in the blood.

Impaired awareness of hypoglycaemia When people with diabetes, usually type 1 diabetes, are frequently unable to notice when they have low blood sugar.

Incremental cost-effectiveness ratio The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.

Index test The test whose performance is being evaluated.

Integrated CSII + CGM An integrated continuous glucose monitoring and insulin pump system intended to aid the effective management of diabetes, without a low glucose suspend function.

Ketonaemia The presence of an abnormally high concentration of ketone bodies in the blood.

Ketonuria The presence of abnormally high amounts of ketones and ketone bodies (by-products of the breakdown of cells) in the urine. Ketonuria is a sign seen in badly controlled diabetes.

Low glucose suspend function Stops insulin delivery for 2 hours if there is no response to a low glucose warning.

Markov model An analytical method particularly suited to modelling repeated events or the progression of a chronic disease over time.

Meta-analysis Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.

Meta-regression Statistical technique used to explore the relationship between study characteristics and study results.

MiniMed® Paradigm™ Veo System (Medtronic Inc., Northridge, CA, USA) An integrated continuous glucose monitoring and insulin pump system intended to aid the effective management of diabetes, with added insulin suspend function intended to prevent hypoglycaemia, including nocturnal hypoglycaemia.

Opportunity costs The costs of forgone outcomes that could have been achieved through alternative investments.

Polycythaemia An abnormally increased concentration of haemoglobin in the blood, as a result of either a reduction in plasma volume or an increase in red blood cell numbers.

Publication bias Bias arising from the preferential publication of studies with statistically significant results.

Quality-adjusted life-year A measure of health gain, used in economic evaluations, in which survival duration is weighted or adjusted by a patient's quality of life during the survival period.

Quality of life An individual's emotional, social and physical well-being, and their ability to perform the ordinary tasks of living.

Receiver operating characteristic curve A graph which illustrates the trade-offs between sensitivity and specificity which result from varying the diagnostic threshold.

Reference standard The best currently available diagnostic test, against which the index test is compared.

Retinopathy Diabetic retinopathy is a common complication of diabetes. It occurs when high blood sugar levels damage the cells at the back of the eye (known as the retina). If it is not treated, it can cause blindness.

Sensitivity Proportion of people with the target disorder who have a positive test result.

Specificity Proportion of people without the target disorder who have a negative test result.

True negative Correct negative test result (i.e. the number of non-diseased persons with a negative test result).

True positive Correct positive test result (i.e. the number of diseased persons with a positive test result).

Type 1 diabetes mellitus A condition in which the body does not produce insulin.

Vibe™ (Animas® Corporation, West Chester, PA, USA) and Dexcom G4® PLATINUM (Dexcom Inc., San Diego, CA, USA) system An integrated continuous glucose monitoring and insulin pump system intended to aid the effective management of diabetes, without a low glucose suspend function.

List of abbreviations

AUC	area under the curve
BG	blood glucose
BMI	body mass index
CEAC	cost-effectiveness acceptability curve
CGM	continuous glucose monitoring
CHF	congestive heart failure
CI	confidence interval
CSII	continuous subcutaneous insulin infusion
CSII + CGM	non-integrated, stand-alone continuous subcutaneous insulin infusion and continuous glucose monitoring
CSII + SMBG	continuous subcutaneous insulin infusion with self-monitoring of blood glucose by capillary blood testing
CVD	cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis
EQ-5D	European Quality of Life-5 Dimensions
HbA_{1c}	glycated haemoglobin
HCHS	Hospital and Community Health Services
HFS	Hypoglycaemia Fear Survey
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IMS CDM	IMS Centre for Outcomes Research and Effectiveness diabetes model (IMS Health, Danbury, CT, USA)
LGS	low glucose suspend
MD	mean difference
MDI	multiple daily insulin injection
MDI + CGM	multiple daily insulin injections with continuous monitoring of blood glucose
MDI + SMBG	multiple daily insulin injections with self-monitoring of blood glucose by capillary blood testing
MI	myocardial infarction
NICE	National Institute for Health and Care Excellence
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PVD	peripheral vascular disease
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SAP	sensor-augmented insulin pump
SAPT	sensor-augmented pump therapy
SBP	systolic blood pressure
SD	standard deviation
SMBG	self-monitoring of blood glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
WMD	weighted mean difference

Plain English summary

People who have type 1 diabetes need treatment with insulin every day. They usually inject themselves multiple times each day using a needle and syringe. Some people use a device called an insulin pump which can give them a continuous dose of insulin through a needle in the skin. Getting the dose of insulin treatment right is essential in order to avoid people having too much sugar (hyperglycaemia) or too little sugar (hypoglycaemia) in their blood. In this project, we studied the clinical effectiveness and cost-effectiveness of two insulin delivery systems for the management of type 1 diabetes in adults and children.

The MiniMed® Paradigm™ Veo system (Medtronic Inc., Northridge, CA, USA) is an insulin pump with an in-built glucose monitor and an insulin suspend function that stops (suspends) insulin entering the pump for up to 2 hours. The Vibe™ (Animas® Corporation, West Chester, PA, USA) and G4® PLATINUM CGM (continuous glucose monitoring) (Dexcom Inc., San Diego, CA, USA) system is similar to the MiniMed Veo system, but without the suspend function.

These two insulin delivery systems were compared in patients who inject themselves with insulin multiple times per day and in patients who use insulin pumps, along with either a separate continuous glucose monitor or with self-monitoring of blood glucose (SMBG) by finger prick tests.

We found that the MiniMed Paradigm Veo system reduces hypoglycaemic events in comparison with other treatments, without any differences in other health outcomes; however, the evidence we looked at was limited. We also found that self-injection of insulin multiple times a day along with SMBG by finger prick tests was the combination most likely to be cost-effective.

In summary, our review shows that the Veo system reduces hypoglycaemic events in comparison with other treatments, without any differences in other outcomes. However, the evidence base was poor. Cost-effectiveness analyses indicated that multiple daily insulin injections along with SMBG is the option most likely to be cost-effective, whereas integrated pump + CGM systems and the Veo system are more expensive and less clinically effective than the use of pumps along with separate CGM. No cost-effectiveness modelling was possible for children or pregnant women because of a lack of data.

Scientific summary

Background

Diabetes affects an estimated 3.75 million people in the UK. Approximately 250,000 of these 3.75 million people have type 1 diabetes mellitus (T1DM).

This assessment will focus on the use of integrated sensor-augmented pump therapy systems for people with T1DM.

The characteristic feature of diabetes is high blood glucose (BG) levels, also known as hyperglycaemia. T1DM is caused by the destruction of the pancreatic beta cells that produce insulin, and the mainstay of treatment is injection of insulin, which is necessary to sustain life. Intensive insulin treatment, aimed at tightly controlling BG levels, reduces the risk of the long-term complications of diabetes, such as retinopathy and renal disease. Intensive insulin treatment is a package of care consisting of either multiple daily insulin injections (MDIs) or continuous subcutaneous insulin infusion (CSII) with an insulin pump, frequent testing of BG, self-adjustment of insulin dosages in response to BG levels and lifestyle interventions, such as a restricted diet and undertaking required levels of physical activity.

In recent years, meters for the continuous monitoring of interstitial fluid glucose have been introduced to help people with T1DM to achieve better control of their disease. Increasingly sophisticated integrated methods of glucose monitoring and insulin delivery are designed to provide a closer approximation to the body's natural system and achieve acceptable glycaemic control while minimising the risk of hypoglycaemic episodes. Current continuous glucose monitoring (CGM) systems rely on the user taking action, and this may not occur, particularly at night. Hypoglycaemia that occurs at night is known as nocturnal hypoglycaemia. Alarms may wake people up, but those with nocturnal hypoglycaemic events often sleep through them and recurrent hypoglycaemic events can lead to hypoglycaemia unawareness.

A recent development in CGM/pump technology, available in the UK since 2009, is the MiniMed® Paradigm™ Veo system (Medtronic Inc., Northridge, CA, USA), wherein the CGM device can stop (suspend) the insulin infusion from the pump for up to 2 hours. After that, insulin infusion is restored at a basal rate.

The population considered for the current assessment comprised adults and children with T1DM. The interventions assessed (integrated CGM and insulin pump systems with or without a suspend function) aim to provide better monitoring and dose adjustment and hence achieve acceptable glycaemic control while minimising hypoglycaemic episodes.

Objective

The overall objective of this project was to summarise the evidence on the clinical effectiveness and cost-effectiveness of the MiniMed Paradigm Veo system and the Vibe™ (Animas® Corporation, West Chester, PA, USA) and G4® PLATINUM CGM system (Dexcom Inc., San Diego, CA, USA) for the management of T1DM in adults and children.

To address this objective, we assessed the clinical effectiveness and cost-effectiveness of integrated insulin pump systems compared with:

- CSII with self-monitoring of blood glucose (SMBG) by capillary blood testing (CSII + SMBG)
- MDIs with SMBG by capillary blood testing (MDI + SMBG)
- non-integrated, stand-alone CSII and CGM (CSII + CGM)
- MDIs with CGM (MDI + CGM).

Methods

Assessment of clinical effectiveness

The study populations eligible for inclusion were adults, including pregnant women, and children with T1DM, and the relevant setting was self-use supervised by primary or secondary care. The interventions are described above (see *Background*) and the main outcomes were glycated haemoglobin (HbA_{1c}) levels, the frequency of hyperglycaemic events and the frequency of hypoglycaemic events.

We searched 14 databases, three trial registries and two conference proceedings from inception up to September 2014. Data relating to study details, participants, intervention and comparator tests, and outcome measures were extracted, using a piloted, standard data extraction form. The assessment of the methodological quality of each included study was based on the Cochrane Collaboration quality assessment checklist.

In the absence of randomised controlled trials directly comparing the MiniMed Paradigm Veo System or an integrated CSII + CGM system, such as the Vibe and G4 PLATINUM CGM system, with comparator interventions, indirect treatment comparisons were performed, if possible. Where meta-analysis was considered unsuitable for some or all of the data identified, we employed a narrative synthesis.

Assessment of cost-effectiveness

The IMS Centre for Outcomes Research and Effectiveness diabetes model (IMS CDM) version 8.5 (IMS Health, Danbury, CT, USA) was used for this assessment. This is an internet-based, interactive simulation model that predicts the long-term health outcomes and costs associated with the management of T1DM and type 2 diabetes mellitus. The model consists of 15 submodels designed to simulate diabetes-related complications, non-specific mortality and costs over time. As the model simulates individual patients over time, it updates risk factors and complications to account for disease progression.

Given the degree of validation of the model, and in order to be in line with the updated T1DM National Institute for Health and Care Excellence (NICE) guideline NG17 [National Institute for Health and Care Excellence. *Type 1 Diabetes in Adults: Diagnosis and Management. NICE Guideline (NG17)*. London: NICE; 2015. URL: www.nice.org.uk/guidance/indevelopment/gid-cgwaver122/documents (accessed 15 January 2015)] it was considered important not to use an alternative model or develop a de novo cost-effectiveness model for this evaluation. When possible, we estimated input parameters based on the studies identified in the systematic review. This was done to properly reflect our base-case population (i.e. those with T1DM eligible for an insulin pump). We used the results of indirect comparisons of change in HbA_{1c} levels and the rate ratios of severe hypoglycaemic events to model the treatment effects.

As the IMS CDM is not suitable for modelling long-term outcomes for children and pregnant women (because the background risk adjustment/risk factor progression equations are all based on adults), we had to limit the population for assessment to adults only.

The impact of the uncertainty about a number of input parameters and model assumptions on the model outcomes was explored through probabilistic sensitivity analyses and scenario analyses.

Results

Fifty-four publications resulting from 19 studies were included in the review. Two studies compared the MiniMed Paradigm Veo system with an integrated CSII + CGM system or with CSII + SMBG, respectively. Seven other studies compared an integrated CSII + CGM system with CSII + SMBG (three studies) or with MDI + SMBG (four studies). The remaining studies compared CSII + SMBG with MDI + SMBG (10 studies). None of the studies included a treatment arm with CSII + CGM or MDI + CGM as comparators. Although several studies included the integrated CSII + CGM system as a treatment arm, it is important to note that

none of these studies looked at the Vibe and G4 PLATINUM CGM system; in the included studies, the integrated CSII + CGM system was always a MiniMed Paradigm pump with an integrated CGM system.

Twelve studies reported data for adults, five studies reported data for children and five studies reported data for mixed populations (adults and children). Two of these studies reported data for all three groups. One study included pregnant women.

Most studies (11 out of 19) were rated as having a high risk of bias, four studies were rated with an unclear risk of bias and another four studies were rated as having a low risk of bias.

Twelve studies were included in the analyses for adults. The main conclusion from these trials is that the MiniMed Paradigm Veo system reduces hypoglycaemic events in adults more than the integrated CSII + CGM system does, without any differences in other outcomes, including changes in HbA_{1c} levels. Nocturnal hypoglycaemic events occurred 31.8% less frequently in the MiniMed Veo group than in the integrated CSII + CGM group {1.5 events per patient per week [standard deviation (SD) 1.0 event per patient per week] vs. 2.2 events per patient per week (SD 1.3 events per patient per week); $p < 0.001$}. Similarly, the MiniMed Veo group had significantly lower rates of combined daytime and night-time events than the integrated CSII + CGM group [3.3 events per patient per week (SD 2.0 events per patient per week) vs. 4.7 events per patient per week (SD 2.7 events per patient per week); $p < 0.001$]. Indirect evidence suggests that that there are no significant differences between the MiniMed Paradigm Veo system, CSII + SMBG and MDI + SMBG with regard to change in HbA_{1c} levels at 3-month follow-up. However, if all studies are combined (i.e. combining different follow-up times and including mixed populations), the MiniMed Paradigm Veo system is significantly better than MDI + SMBG, with regard to HbA_{1c} levels [weighted mean difference (WMD) –0.66%; 95% confidence interval (CI) –1.05% to –0.27%].

For the integrated CSII + CGM system versus other treatments, head-to-head results showed significant effects, with regard to HbA_{1c} levels, in favour of the integrated CSII + CGM system compared with MDI + SMBG (WMD –1.1%; 95% CI –1.46% to –0.74%), but not if compared with CSII + SMBG (WMD –0.05%; 95% CI –0.31% to 0.21%); and significant results, with regard to quality of life, in favour of the integrated CSII + CGM system compared with MDI + SMBG (WMD 8.60; 95% CI 6.28 to 10.92) or with CSII + SMBG (WMD 5.90; 95% CI 2.22 to 9.58) were also found.

When comparing CSII versus MDI, only one of six trials showed a significant difference between CSII + SMBG and MDI + SMBG in terms of a change in HbA_{1c} levels: after 16 weeks of the trial, mean HbA_{1c} levels were 0.84% lower (mean = –0.84%, 95% CI –1.31% to –0.36%) lower in the CSII + SMBG group than in the MDI + SMBG group. No differences in the number of severe hypoglycaemic events were found in any trial.

Six studies were included in the analyses for children. None of the studies directly compared the MiniMed Paradigm Veo system with the integrated CSII + CGM system. An indirect comparison was possible using data obtained from 6-month follow-up from two of these studies, but only for HbA_{1c} levels, which showed no significant difference between groups.

One study compared the MiniMed Paradigm Veo system with CSII + SMBG. The only significant difference between treatment groups was the rate of moderate and severe hypoglycaemic events, which favoured the MiniMed Paradigm Veo system.

One study compared the integrated CSII + CGM system with CSII + SMBG. This trial found no significant difference in HbA_{1c} levels between groups [mean difference (MD) after 6 months of 0.4894% (standard error 0.2899%); $p = 0.10$]. One study compared the integrated CSII + CGM system with MDI + SMBG. This trial showed a significant difference in HbA_{1c} levels in favour of the integrated CSII + CGM system (MD after 12 months –0.5%; 95% CI –0.8% to –0.2%), but no significant difference in the number of children achieving HbA1c levels of ≤ 7% (10 out of 78 vs. 4 out of 78; $p = 0.15$). Hyperglycaemia (as determined by BG levels of > 250 mg/dl) was significantly less common in the integrated CSII + CGM

group than in the MDI + SMBG group [area under the curve (AUC) 9.2 (SD 8.08) vs. 17.64 (SD 14.62); $p < 0.001$], but there was no significant difference in the occurrence of hypoglycaemia (as determined by BG levels of < 70 mg/dl) in these groups [AUC 0.23 (SD 0.41) vs. 0.25 (SD 0.41); $p = 0.79$]. There were no significant differences between groups for other outcomes.

For pregnant women, we found only one trial comparing CSII + SMBG with MDI + SMBG, which is not relevant to the decision problem.

The comparator MDI + CGM was not included in the cost-effectiveness analyses, since no evidence was found. In the absence of data comparing the clinical effectiveness of integrated CSII + CGM systems with stand-alone CSII + CGM systems, we assumed, in our cost-effectiveness analyses, that both technologies would be equally effective. The immediate consequence of this assumption is that stand-alone CSII + CGM systems always dominate the integrated CSII + CGM systems since stand-alone systems are cheaper, according to our estimated cost, but equally effective.

Overall, the cost-effectiveness results suggest that technologies which use SMBG (either with CSII or MDIs) are more likely to be cost-effective than the technologies which use CGM, since the higher quality of life and/or life expectancy provided by the latter do not compensate for the difference in costs. The MiniMed Paradigm Veo is extendedly dominated by stand-alone CSII + CGM. This means that CSII + CGM is more effective than MiniMed Paradigm Veo, but also better value, that is that the increase in cost compared with the next most effective choice, which is CSII + SMBG, is less for CSII + CGM than for the MiniMed Paradigm Veo system. We estimated that the incremental cost-effectiveness ratio (ICER) of stand-alone CSII + CGM compared with the next most effective choice, CSII + SMBG, is £660,376 and the ICER of CSII + SMBG compared with the least effective choice, MDI + SMBG, is £52,381. Thus, assuming a common threshold of £30,000 per quality-adjusted life-year (QALY) gained, MDI + SMBG, while being the least clinically effective option, would be considered the optimal choice; when uncertainty is taken into account, at that threshold, MDI + SMBG would have a 98% probability of being the optimal choice.

The finding that CSII + CGM is more effective than the MiniMed Paradigm Veo system might appear to contradict the clinical effectiveness conclusions, but this is explained by the fact that effectiveness is affected by both the difference in hypoglycaemic event rate and HbA_{1c} levels. Although the evidence shows that MiniMed Paradigm Veo is probably better in terms of reducing the hypoglycaemic event rate, it does show a small, albeit not statistically significant, disadvantage in terms of HbA_{1c} levels. Even this small difference seems to be sufficient, as a result of the consequences of hyperglycaemia, to outweigh the difference in hypoglycaemia, which is relatively rare and generally has less severe consequences. However, all of these results should be interpreted with caution as some studies on which effect estimates were based included all T1DM patients, whereas others included patients who had been on a pump for at least 6 months already and others included patients without experience of using a pump but with poor glycaemic control at baseline.

These results remained largely unchanged in scenario analyses, used to assess the potential impact of various input parameters on the model outcomes. Even when a large array of scenarios is considered, MDI + SMBG would be considered the optimal choice in all instances, assuming a threshold of £30,000 per QALY gained.

Conclusions

Overall, the evidence seems to suggest that the MiniMed Paradigm Veo system reduces hypoglycaemic events more than other treatments, without any differences in other outcomes, including changes in HbA_{1c} levels. In addition, we found significant results in favour of the integrated CSII + CGM system over MDI + SMBG with regard to HbA_{1c} levels and quality of life. However, the evidence base was poor. The quality of the included studies was generally low, often with only one study comparing treatments in a

specific population at a specific follow-up time. In particular, the evidence for the two interventions of interest was limited, with only one study comparing the MiniMed Paradigm Veo system with an integrated CSII + CGM system and only one study comparing the MiniMed Paradigm Veo system with CSII + SMBG in a mixed population.

Cost-effectiveness analyses indicated that MDI + SMBG is the option most likely to be cost-effective, given the current threshold of £30,000 per QALY gained, whereas integrated CSII + CGM systems and MiniMed Paradigm Veo are dominated and extendedly dominated, respectively, by stand-alone CSII + CGM. Scenario analyses, used to assess the potential impact of changing various input parameters, did not alter these conclusions. No cost-effectiveness modelling was conducted for children or pregnant women.

Suggested research priorities

In adults, a trial comparing the MiniMed Paradigm Veo system with CSII + SMBG is warranted. Similarly, a trial comparing the Vibe and G4 PLATINUM CGM system, or any integrated CSII + CGM system, with CSII + SMBG is warranted. In children, a trial comparing the MiniMed Paradigm Veo system with the Vibe and G4 PLATINUM CGM system, or any integrated CSII + CGM system, is warranted, as is a trial comparing an integrated CSII + CGM system with CSII + SMBG. For pregnant women, trials comparing the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system, or any integrated CSII + CGM system, with other interventions are warranted.

Future trials should include longer-term follow-ups and ratings on the European Quality of Life-5 Dimensions scale at various time points with a view to informing improved cost-effectiveness modelling.

Study registration

This study is registered as PROSPERO CRD42014013764.

Funding

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Chapter 1 Background and definition of the decision problem(s)

Population

Diabetes affects an estimated 3.75 million people in the UK;[1,2] approximately 250,000 of these affected people have type 1 diabetes mellitus (T1DM).[3]

Type 1 diabetes arises when the body does not produce insulin and is most commonly first diagnosed in the teenage years. T1DM accounts for around 5–15% of all diabetes cases. Type 2 diabetes mellitus (T2DM), which arises when the body develops a resistance to insulin, usually affects people over the age of 40 years. However, T2DM is becoming increasingly more prevalent in younger people, and may be more common in people of South Asian, African Caribbean or Middle Eastern descent. People who are overweight, have inactive lifestyles or a family history of diabetes are at greater risk of developing diabetes.[2,4,5]

The characteristic feature of diabetes is high blood glucose (BG) levels, also known as hyperglycaemia; low BG levels is called hypoglycaemia. Optimal BG levels for most people are 4–7 mmol/l before meals, 6–10 mmol/l at bedtime and 5–15 mmol/l before exercise.[6]

Type 1 diabetes is caused by the destruction of the pancreatic beta cells which produce insulin, and the mainstay of treatment are insulin injections, which are necessary to sustain life. The Diabetes Control and Complications Trial (DCCT)[7] and other studies[8] have shown that intensive insulin treatment, aimed at tightly controlling BG, reduces the risk of the long-term complications of diabetes, such as retinopathy and renal disease. Diabetes is one of the most common causes of blindness and end-stage renal failure.[9–11]

Intensive insulin treatment is a package of care consisting of either multiple daily insulin injections (MDIs) or continuous subcutaneous insulin infusion (CSII) with an insulin pump, frequent testing of BG, self-adjustment of insulin dosages in response to BG levels, as well as lifestyle interventions such as a restricted diet and undertaking required levels of physical activity.

However, insulin injections cannot provide the sort of fine tuning that can be achieved by a healthy pancreas controlled by the body's normal feedback mechanisms, and many people with T1DM do not succeed in achieving good control of their diabetes. This is particularly true in children. The best measure of BG control is glycated haemoglobin (HbA_{1c}). An audit of diabetic control in Scottish children showed that only about 10% achieved the National Institute for Health and Care Excellence (NICE) target of a HbA_{1c} level of $\leq 7.5\%$.[12] In England and Wales, approximately 17% of children and young people with diabetes achieved this NICE target.[13] In 2008, NICE recommended CSII ('insulin pump') therapy as a treatment option for adults and children, aged ≥ 12 years, with T1DM.[14] NICE concluded that CSII therapy had a valuable effect on BG control by reducing HbA_{1c} levels and also reducing associated complications.

The provision of an insulin pump alone is not enough; for a pump to be used effectively, it should be accompanied by intensive management. Hyperglycaemia can be controlled by increasing the amount of insulin injected. However, this can lower BG too far. Low BG is called hypoglycaemia, and this is often the limiting factor in attempts to control hyperglycaemia. NICE was also persuaded that CSII therapy could reduce the rate of hypoglycaemic episodes, and it heard from patient experts that when hypoglycaemia occurs in people using CSII therapy, it does so gradually and there is sufficient time for the pump user to take remedial action.[14]

The symptoms of hypoglycaemia range from feelings of hunger, faintness, sweating, anxiety and sleepiness at the mild end of the spectrum, to confusion, difficulty in speaking and disturbances of behaviour; and at the severe end of the spectrum, loss of consciousness, convulsions and, rarely, death can occur. Hypoglycaemia is assumed to be the main cause of the 'found dead in bed' cases,[15] which, fortunately, are rare.

Hypoglycaemic events can be very frightening, especially in children and for their parents, and fear of hypoglycaemia is very common, not just among those with diabetes but also among relatives and friends. There is particular anxiety among parents of young children, some of whom may allow BG levels to run high in order to avoid hypoglycaemia ('hypo avoidance behaviour').[16]

Parents of young children express considerable anxiety, and may feel a need to get up during the night to check BG levels in their children. BG control may be easier if children are on an insulin pump, but even then parents are likely to set alarms to get up during the night to check that their child is not experiencing hypoglycaemia. Many severe hypoglycaemic events in children occur at night.

As soon as people with diabetes recognise the symptoms, they can consume fast-acting carbohydrates in the form of a sugar-containing food, or just sugar itself, and thereby raise BG levels again. However, there is a particular problem, known as hypoglycaemia unawareness, whereby some people do not develop any warning symptoms. Being unaware of impending hypoglycaemia, such people may not consume sugar-rich foods or sugar in time to prevent a serious hypoglycaemic event. Hypoglycaemia unawareness usually occurs after frequent hypoglycaemic events, and a vicious circle can develop where frequent hypoglycaemic events cause hypoglycaemia unawareness, which leads to more, and more severe, hypoglycaemia, associated with the failure of the body to release the counter-regulatory hormones, such as adrenaline, that cause warning symptoms.

Until recently, self-monitoring of blood glucose (SMBG) meant pricking a part of the body, such as the fingertip, with a needle to make it bleed (sometimes up to 15 times a day), putting a drop of blood on a test strip and measuring BG levels with the aid of a meter. Depending on the result, the patient could then adjust their insulin dose or diet in order to try and keep BG levels within the optimum range.

In recent years, meters for continuous monitoring of interstitial fluid glucose have been introduced to help people with T1DM to achieve better control of their disease. Increasingly sophisticated integrated methods of glucose monitoring and insulin delivery are designed to provide a closer approximation to the body's natural system and achieve acceptable glycaemic control, while minimising the risk of hypoglycaemic episodes. Interventions designed to help people with T1DM to achieve better control include structured education (the dose adjustment for normal eating course[17] or similar courses) and CSII with an insulin pump.

The aim of CSII is to provide a flexible method for administering insulin, which tries to mimic the body's natural pattern of a small amount of insulin being present all the time (basal infusion) and peaks of insulin release after meals (boluses), aided by SMBG by capillary blood testing.

However, there are limits to what can be done with capillary blood testing (and it is painful – even more so than insulin injections). In recent years, devices which continually measure BG (strictly speaking, they actually measure the level of glucose in the subcutaneous tissue) have been introduced. These use a cannula inserted under the skin, which is connected to a glucose meter. The first of these continuous glucose monitoring (CGM) systems merely recorded BG levels for later downloading. However, there are now CGM devices that display interstitial glucose levels – so-called 'real-time CGM' – so that users can see their most recent glucose level (CGM is not actually continuous, as the name suggests, but measures glucose levels every 5–10 minutes). The psychosocial impact of CGM is mixed however, with both positive results with regard to the greater control over diabetes, but also negative impacts resulting from intrusive false alarms and the additional burden and visibility of the disease.[18,19] In addition, CGM does not make capillary blood testing redundant; a minimum of two tests per day is still required to calibrate CGM devices.

The next step in the development of CGM systems was to have integrated alarm facilities, whereby the CGM meter could alert the user to BG levels that are too high or too low. In theory, the user can then adjust insulin dosage, by, for example, reducing the insulin infusion rate if BG levels are too low or showing a decreasing trend. These integrated systems are called 'sensor-augmented pump therapy' (SAPT).

Current CGM systems rely on the user taking action, and this may not occur, particularly at night. Hypoglycaemic events at night are known as nocturnal hypoglycaemia. Alarms may wake people up, but those having nocturnal hypoglycaemic events often sleep through these alarms and recurrent hypoglycaemic events can lead to hypoglycaemia unawareness.

CGM may initially raise anxiety, because it provides much more data on BG levels, and this can lead to more anxiety among patients and parents. False alarms are a particular problem, leading to distrust of the device and a lack of willingness to take appropriate action.

A recent development in CGM/pump technology, which has been available in the UK since 2009, is the Medtronic Veo suspend combination (Medtronic Inc., Northridge, CA, USA); this CGM device can stop (suspend) the insulin infusion from the pump for up to 2 hours. After that, insulin infusion is restored at a basal rate. In practice, few suspensions are for as long as 2 hours because, in most cases, the pump user takes corrective action.[20] A small study (31 patients used this device for 3 weeks), performed in UK centres, reported that 66% of suspend durations were for $\leq$ 10 minutes, that most long episodes of suspension occurred at night and that there was a reduction in nocturnal hypoglycaemia.

After insulin infusion stops, it takes 30 minutes for BG levels to increase,[21] so hypoglycaemic events may be shortened or made less severe, rather than always avoided.

Suspension can be controlled manually by the user, in response to an alarm or after checking real-time results, or automatically by the device. Patients can over-ride the pump and cancel suspension, using food to increase BG levels instead. One problem reported is that sleeping position may cause inaccurately low readings because of tissue compression.[22]

This assessment will focus on the use of integrated SAPT systems in T1DM.[14]

The populations for the current assessment were adults and children with T1DM. The interventions assessed (integrated CGM and insulin pump systems with or without a suspend function) aim to provide better monitoring and dose adjustment and hence achieve acceptable glycaemic control while minimising hypoglycaemic episodes.

Description of the technologies under assessment

The MiniMed® Paradigm™ Veo system (Medtronic Inc., Northridge, CA, USA) and the Vibe™ (Animas® Corporation, West Chester, PA, USA) and G4® PLATINUM CGM system (Dexcom Inc., San Diego, CA, USA) are integrated CGM and insulin pump systems intended to aid the effective management of diabetes. The MiniMed Paradigm Veo System has an added insulin suspend function intended to prevent hypoglycaemia, including nocturnal hypoglycaemia.

The MiniMed Paradigm Veo system

The MiniMed Paradigm Veo system has three components:

1. a small glucose sensor, placed under the skin, which measures glucose levels every 5 minutes, 24 hours per day (this sensor must be replaced every 6 days)
2. the MiniLink™ transmitter (Medtronic Inc., Northridge, CA, USA), which sends the information to the Paradigm Veo insulin pump
3. the Paradigm Veo insulin pump.

The system is complete and stand alone and not directly interchangeable with other manufacturers' pumps or sensors. Many insulin formulations can be used in the insulin pump. In this report, we will focus on only fast-acting insulin formulations, because this type of formulation in the preferred clinical option for use with insulin pumps in the UK.[23]

Continuous glucose monitors measure the level of tissue glucose electronically on a continuous basis (every few minutes). They use a subcutaneous, disposable glucose sensor placed just under the skin to measure interstitial glucose levels. The glucose sensor of the Veo system is replaced every 6 days. The sensor is connected to a non-implanted transmitter (MiniLink) which communicates glucose levels wirelessly to the Paradigm Veo pump. The pump displays BG levels with nearly continuous updates, as well as monitoring rising and falling trends. The pump can prompt a person with diabetes, or a carer, to take action to maintain glucose levels. The insulin pump delivers continuous subcutaneous insulin according to a pre-programmed pattern, which can be adapted by the user or a carer in response to real-time glucose trends.

The MiniMed Paradigm Veo system appears to be unique in that it will actively suspend insulin delivery if it predicts a hypoglycaemic episode. This 'low glucose suspend' (LGS) function stops insulin delivery for 2 hours if there is no response to a low glucose warning.

Users of this system must perform regular (a minimum of two per day) capillary BG tests (such as a finger prick tests), as CGM measures interstitial fluid glucose levels, not capillary BG levels. Further finger prick tests are required to confirm a CGM value before making any adjustments to diabetes therapy.

The pump can be worn on a belt or in a pouch underneath clothes. Insulin is delivered through a small tube (or 'infusion set') placed under the skin. The transmitter is directly connected to the glucose sensor, which is inserted through the skin, usually in the stomach area. The manufacturer's information for use document states that the infusion set should be replaced every 3 days.

The Vibe and G4 PLATINUM CGM system

The Vibe and G4 PLATINUM CGM system is a CGM-enabled insulin pump, integrated with the G4 PLATINUM sensor. It is similar to the MiniMed Paradigm Veo system in that the glucose sensor is placed under the skin and measures interstitial glucose levels rather than capillary BG levels. Confirmatory capillary BG tests are also required to confirm the value displayed by the continuous glucose monitor before making any adjustments to diabetes therapy. The sensor is approved for up to 7 days of wear.

The insulin pump in the Vibe and G4 PLATINUM CGM system also delivers insulin continuously from a refillable storage reservoir by means of a subcutaneously placed cannula and the pump can be programmed to deliver insulin at a basal rate throughout the day, with the option of triggering higher infusion rates at mealtimes, either as a bolus dose or over time. The pump can be programmed to deliver insulin at different basal rates at different times of the day and night.

The system produces glucose level readings in real time, alerts users of high or low readings, and glucose trend information. It does not have an automated LGS function.

Comparators

The scope, as defined by NICE, specifies the following comparator technologies:

- CSII with SMBG by capillary blood testing (CSII + SMBG)
- MDIs with SMBG by capillary blood testing (MDI + SMBG)
- non-integrated, stand-alone CSII and CGM (CSII + CGM)
- MDIs with CGM (MDI + CGM).

Non-integrated, stand-alone CSII and CGM require the simultaneous use, by patients, of both a continuous glucose monitor and a pump to deliver the insulin. The two interventions (Veo and Vibe) also both use a continuous glucose monitor and an insulin pump. However, for the non-integrated, stand-alone CSII and CGM, the two devices are supplied separately and for the Veo and Vibe interventions, these devices are supplied as a 'system', hence the term 'integrated'. Although they may or may not differ in terms of monitoring and insulin delivery, this review will seek to find any differences with regard to their effectiveness and cost-effectiveness (see *Chapter 2*).

Within groups of comparator studies, there may be differences between studies (e.g. populations, interventions and outcomes). The possibility of pooling results from different trials will depend on the extent of these differences. In addition, the comparability of populations in studies evaluating insulin pumps and MDIs is a potential problem. Based on 2008 guidance,[14] NICE recommends CSII as a potential treatment for children ≥ 12 years and adults, who have disabling hypoglycaemia (including anxiety about hypoglycaemia) when trying to attain $HbA_{1c} < 7.5\%$, or HbA_{1c} is constantly $> 8.5\%$, while undergoing multiple daily injection therapy (MDIT). Furthermore, CSII is recommended for children < 12 years when MDIT would not be practical.[14]

In other words, insulin pumps are recommended for people with T1DM for whom MDIs are not suitable. Therefore, it might be problematic to find studies comparing insulin pumps (especially modern pumps such as the integrated systems) with MDIs in comparable populations.

Chapter 2 Objective

The overall objective of this project was to summarise the evidence on the clinical effectiveness and cost-effectiveness of the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system for the management of T1DM in adults and children.

The following research questions have been defined to address the review objective:

- What is the clinical effectiveness of integrated insulin pump systems compared with:
  - CSII + SMBG
  - MDI + SMBG
  - CSII + CGM
  - MDI + CGM.
- What is the cost-effectiveness of integrated insulin pump systems compared with:
  - CSII + SMBG
  - MDI + SMBG
  - CSII + CGM
  - MDI + CGM.

There are two interventions and four comparators. In this report, we will use the following descriptors for these interventions and comparators:

- *MiniMed Veo system* An integrated CGM and insulin pump system with LGS function.
- *Integrated CSII + CGM* Integrated CGM and insulin pump systems without LGS function (such as the Vibe and G4 PLATINUM CGM system). Although the only integrated system available in the UK is the Vibe and G4 PLATINUM CGM system, all integrated systems without a LGS function will be included in this category. This also includes integrated Medtronic systems (such as the Paradigm Revel™ and Paradigm REAL-Time systems).
- *CSII + CGM* An insulin pump with stand-alone continuous glucose monitor.
- *CSII + SMBG* An insulin pump with SMBG.
- *MDI + CGM* MDIs with a continuous glucose monitor.
- *MDI + SMBG* MDIs with SMBG.

Chapter 3 Assessment of clinical effectiveness

Systematic review methods for the assessment of clinical effectiveness

A systematic review was conducted to summarise the evidence on the clinical effectiveness of the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system for the management of T1DM in adults and children. Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination guidance for undertaking reviews in health care,[24] and the NICE Diagnostic Assessment Programme manual.[25]

Inclusion and exclusion criteria

Participants
The study populations eligible for inclusion were adults, including pregnant women, and children with T1DM.

Setting
The relevant setting was self-use supervised by primary or secondary care.

Interventions
The main intervention technology for this appraisal was the MiniMed Paradigm Veo with CGM system and suspend function. In addition, we included fully integrated insulin pump systems as an alternative technology, including the only existing fully integrated system currently available in the UK: the Vibe and G4 PLATINUM CGM system.

Comparators
The scope, as defined by NICE, specified the following comparator technologies:

- capillary blood testing with CSII
- capillary blood testing with MDIs
- CGM with CSII (non-integrated)
- CGM with MDIs.

Studies comparing CSII with MDIs often use different types of monitoring (SMBG or CGM). Unless results were reported separately for the different types of monitoring, such studies were excluded from our review, because they do not allow a comparison of a relevant intervention with the comparators. The same applies to studies comparing CGM with SMBG, without specifying the way in which insulin was delivered (CSII or MDIs).

Outcomes
The main outcomes were:

- HbA_{1c} levels (i.e. change from baseline and the number of participants achieving a specified level of control)
- the frequency of hyperglycaemic events and the number of hyperglycaemic episodes, stratified by severity into ‘mild’ or ‘severe’ if data were available.
- the frequency of (nocturnal) hypoglycaemic events and the number of hypoglycaemic episodes, stratified by severity into ‘mild’ or ‘severe’ if data were available.

Possible secondary outcomes were:

- mean BG levels, including fasting glucose levels
- postprandial glucose levels
- the amount of insulin being administered
- episodes of diabetic ketoacidosis and the number of ketone tests
- health-related quality of life (HRQoL)
- long-term complications of diabetes and treatment, including retinopathy, neuropathy, cognitive impairment and end-stage renal disease
- morbidity and mortality
- adverse events from testing, false results, treatment and sequelae
- the acceptability of the testing method and the method of insulin administration
- anxiety about experiencing hypoglycaemia
- costs, including the costs related to the support received from health professionals.

In pregnant women, additional T1DM-related clinical outcomes included:

- premature birth
- macrosomia (excessive birth weight)
- respiratory distress syndrome in newborns.

Study design

Studies with the following types of study design were eligible for inclusion:

- randomised controlled trials (RCTs) or, if no RCTs were available for comparisons of interventions and comparators, controlled clinical trials
- observational studies for additional information with regard to interventions, if no RCTs were found.

Studies of < 6 weeks' duration and cross-over studies were excluded.

Subgroup analyses

If the evidence and the structure of the cost-effectiveness model were to permit, the following subgroups would be explored:

- pregnant women, and women planning pregnancy (but not including those with gestational diabetes)
- people who need to self monitor their BG level > 10 times a day
- people with T1DM who are having difficulty managing their condition; such difficulties include:
    - not being able to maintain the recommended HbA_{1c} level of 8.5% (69.4 mmol/mol) or less
    - experiencing nocturnal hypoglycaemia
    - an impaired awareness of hypoglycaemia
    - experiencing severe hypoglycaemia, defined as having low BG levels that require assistance from another person to treat.

Search strategy

Systematic literature searches were conducted to identify studies of SAPT for T1DM (specifically the MiniMed Paradigm Veo system and the Vibe and G4 Platinum system), as well as RCTs and economic evaluations of insulin pump/infusion therapy and MDIs for T1DM. Search strategies were developed using the recommendations of the Centre for Reviews and Dissemination guidance for undertaking reviews in health care,[24] and the Cochrane Handbook.[26] The search strategies used relevant search terms, comprising a combination of indexed keywords (e.g. from medical subject headings and the EMBASE thesaurus EMTREE) and free-text terms appearing in the titles and/or abstracts of database records. Search terms were identified through discussion among the review team, by scanning background literature and 'key articles' already

known to the review team, and by browsing database thesauri. The search strategies were structured using search terms for 'type 1 diabetes' in combination with search terms for 'sensor-augmented pump therapy'. Two further search term facets were included to capture 'insulin infusion' and 'multiple daily injections'. In addition, the search strategy for clinical effectiveness studies included a sensitive methodological search filter designed to identify RCTs. The EMBASE search strategy was translated so that it could be run effectively in each of the databases searched. No date or language limits were applied. The main EMBASE search strategies were independently peer reviewed by a second information specialist using the Canadian Agency for Drugs and Technologies in Health peer review checklist.[27]

Details of the full search strategies are presented in *Appendix 1*.

The following databases and resources were searched for relevant RCTs, systematic reviews and health technology assessments:

- MEDLINE (via OvidSP): 1946–2014/Aug week 4
- MEDLINE In-Process Citations and Daily Update (via OvidSP): up to 4 September 2014
- PubMed (National Library of Medicine): up to 5 September 2014
- EMBASE (via OvidSP): 1974–2014/week 34
- Cochrane Database of Systematic Reviews (Wiley Online Library): issue 9/September 2014
- Cochrane Central Register of Controlled Trials (Wiley Online Library): issue 8/August 2014
- Database of Abstracts of Reviews of Effects (Wiley Online Library): issue 3/July 2014
- Health Technology Assessment (HTA) Database (Wiley Online Library): issue 3/July 2014
- Science Citation Index (Web of Science): 1988–29 August 2014
- Latin American and Caribbean Health Sciences Literature (http://lilacs.bvsalud.org/en/): 1982–5 September 2014
- National Institute for Health Research HTA Programme (www.hta.ac.uk/): up to 5 September 2014
- PROSPERO (www.crd.york.ac.uk/prospero/): up to 5 September 2014
- US Food and Drug Administration (www.fda.gov): up to 5 September 2014
- Medicines and Healthcare products Regulatory Agency (www.mhra.gov.uk/): up to 5 September 2014

Completed and ongoing trials were identified by searches of the following trials registries:

- US National Institutes of Health ClinicalTrials.gov (www.clinicaltrials.gov/): up to 2 September 2014
- Current Controlled Trials (www.controlled-trials.com/): up to 5 September 2014
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/): up to 5 September 2014

Conference proceedings were also searched from the organisations: Diabetes UK, the European Association for the Study of Diabetes and the American Diabetes Association (see *Appendix 1*).

The bibliographies of identified research and review articles were checked for relevant studies. As a number of databases were searched, there was some degree of duplication. In order to manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into EndNote X7 (Thomson Reuters, CA, USA) reference management software and duplicate records removed. Rigorous records were maintained as part of the searching process. Individual records within the Endnote reference libraries were tagged with searching information, such as searcher, date searched, database host, database searched, search strategy name and iteration, theme and search question. This enabled the information specialist to track the origin of each individual database record and its progress through the screening and review process.

Inclusion screening and data extraction

Two reviewers independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full-text copies of all studies deemed potentially relevant, after discussion, were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of the studies excluded at the full-paper screening stage are presented in *Appendix 2*.

Data relating to study details, participants, intervention and comparator tests, and outcome measures were extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer checked data extraction and any disagreements were resolved by consensus.

Quality assessment

The methodological quality of included studies was assessed using standard tools.[24] The assessment of the methodological quality of each included study was based on the Cochrane Collaboration quality assessment checklist,[26] as detailed in *Table 1*.

Each study was awarded a 'yes', 'no' or 'unclear/unknown' rating for each individual item in the checklist. Any additional clarifications or comments were also recorded.

Quality assessment was carried out independently by two reviewers. Any disagreements were resolved by consensus. The results of the quality assessment were used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for the design of any future studies. Based on the findings of the quality assessment, recommendations were made for the conduct of future studies.

TABLE 1 The assessment of risk of bias in included RCTs

Domain	Item	Description
Sequence generation	Was the allocation sequence adequately generated?	The method used to generate the allocation sequence should be described in sufficient detail to allow an assessment of whether or not it should produce comparable groups
Allocation concealment	Was allocation adequately concealed?	The method used to conceal the allocation sequence should be described in sufficient detail to determine whether or not intervention allocations could have been foreseen in advance of, or during, enrolment
Blinding of participants, personnel and outcome assessors *Assessments will be made for each main outcome (or class of outcomes)*	Was knowledge of the allocated intervention adequately prevented during the study?	All measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received, should be described. Any information relating to whether or not the intended blinding was effective should also be reported
Incomplete outcome data *Assessments will be made for each main outcome (or class of outcomes)*	Were incomplete outcome data adequately addressed?	The completeness of outcome data for each main outcome should be described, including attrition and exclusions from the analysis. The authors should report any attrition and exclusions, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions and any re-inclusions in analyses
Other sources of bias	Was the study apparently free of other problems that could put it at a high risk of bias?	Overall, the study should be free from any important concerns about bias (i.e. bias from other sources not previously addressed by the other items)

Methods of analysis/synthesis

If meta-analysis was considered unsuitable for some or all of the data identified (e.g. because of the heterogeneity and/or small numbers of studies), we employed a narrative synthesis. Typically, this involves the use of text and tables to summarise data. These allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies were organised according to which therapies were being compared.

The methods used to synthesise the data were dependent on the types of outcome data included, and the clinical effectiveness and statistical similarity of the studies. Possible methods of data synthesis include the types of analysis discussed in the following sections.

Dichotomous outcomes

Dichotomous data were analysed by calculating the relative risk (RR) for each trial using the fixed-effect method or the DerSimonian and Laird[28] random-effects method and the corresponding 95% confidence intervals (CIs).

Continuous outcomes

Continuous data were analysed by calculating the weighted mean difference (WMD) between groups and the corresponding 95% CI. If the standard deviations (SDs) and means were not determinable, they were estimated from the data provided or using a representative value from other studies.

Systematic differences between studies (heterogeneity) were likely; therefore, the random-effects model was used for the calculation of RRs or WMDs if heterogeneity was moderate or high ($I^2 > 50\%$). Heterogeneity was initially assessed by measuring the degree of inconsistency in the studies' results (I^2). The I^2 value describes the percentage of total variation across studies that was due to heterogeneity rather than chance. The value of I^2 can lie between 0% and 100%. Low, moderate and high I^2 values correspond to 25%, 50% and 75%, respectively.

If significant heterogeneity was identified, we planned to formally investigate this using metaregression. In particular, a model was planned to explore the possible modifying effects of the following pre-specified factors: methodological quality of the primary studies, underlying illness and different age groups. The coefficient describing the predictive value of each factor and the overall effect on the main outcome would be modelled, using a fixed-effects model. However, because of the limited number of studies for each comparison, this was not possible.

A funnel plot (plot of the logarithm value of the RR for efficacy against the precision of the logarithm value of the RR) would have been used to estimate potential asymmetry, and this would have been indicative of small study effects. HbA_{1c} levels were chosen as an outcome since these are likely to be reported by the majority of included studies. In addition, the Egger regression asymmetry test[29] would have been used to facilitate the prediction of potential publication biases. This test detects funnel plot asymmetry by determining whether or not the intercept deviates significantly from zero in a regression of the standardised effect estimates against their precision. However, because of the limited number of studies for each comparison, this was not possible.

Network meta-analysis methods

In the absence of RCTs directly comparing the MiniMed Veo system or an integrated CSII + CGM system (such as the Animas Vibe pump with Dexcom's G4 continuous glucose monitor) with the comparators (i.e. CSII + CGM, CSII + SMBG, MDI + CGM or MDI + SMBG), indirect treatment comparisons were performed, if possible. As only limited networks could be formed, a mixed-treatment comparison was not possible. However, if possible, indirect comparisons were made. Although 'head-to-head' comparisons are preferred to indirect methods in health technology assessments, indirect methods are generally considered acceptable; for all methods, consideration of basic assumptions of homogeneity, similarity and consistency, as reported by Song *et al.*,[30] should be applied. For this assessment, where 'head-to-head' trials (i.e. 'A' vs. 'B') of the MiniMed Paradigm Veo with CGM System versus the comparators (CSII + CGM, CSII + SMBG, MDI + CGM or MDI + SMBG) were missing, the effect sizes (RR or mean difference) for

'A' versus 'B' were estimated using 'indirect' methods; for example, effect sizes for 'A' versus 'B' were estimated from 'A' versus 'C' and 'B' versus 'C', where 'C' was a common control group [e.g. CSII + CGM (i.e. CSII with a stand-alone CGM system)]. All indirect comparisons were consistent with International Society for Pharmacoeconomics and Outcomes Research taskforce recommendations for the conduct of direct and indirect meta-analysis and used the method described by Bucher *et al.*[31] A practical issue for indirect comparisons concerns the limitations in the availability of the same outcomes in the studies of interventions that are candidates for an indirect comparison. Only studies that provide the same outcome measures at the same follow-up time can be compared with each other, which may limit the availability of suitable trial networks. Depending on the data available, separate network analyses were performed for each of the subgroups specified in the protocol. Indirect meta-analyses were performed using Microsoft Excel® 2007 (Microsoft Corporation, Redmond, WA, USA), according to the method developed by Bucher *et al.*[31] Effect sizes with 95% CIs were calculated using results from the direct head-to-head meta-analyses. Direct head-to-head meta-analyses were performed using fixed-effect models in Stata™ for Windows, version 13 (StataCorp LP, College Station, TX, USA), unless significant heterogeneity was present, in which case we used random-effects models.

Results of the assessment of clinical effectiveness

Results of literature searches

The literature searches of bibliographic databases identified 9870 references. After initial screening of titles and abstracts, 555 were considered potentially relevant and were ordered for full-paper screening. Of the total of 555 publications considered potentially relevant, 29 could not be obtained within the time scale of this assessment. Most of these 29 unobtainable studies were published before 2000 or were conference abstracts; only four were possibly relevant trials published after 2000, but, based on their abstracts, it was unclear whether or not they fulfilled the inclusion criteria. *Figure 1* shows the flow of studies through the

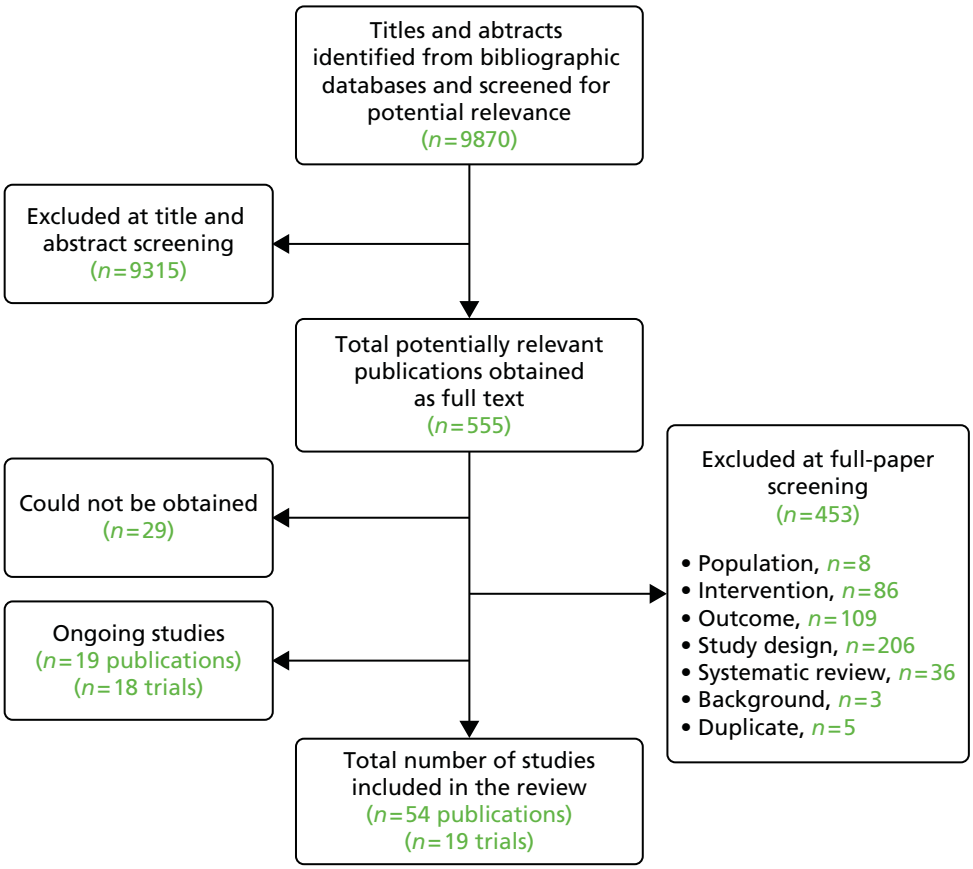

FIGURE 1 Flow of studies through the review process.

review process and *Appendix 2* provides details, with reasons for exclusions, of all the publications excluded at the full-paper screening stage.

Based on the searches and inclusion screening described above, 54 publications resulting from 19 studies were included in the review. In addition, 19 publications of 18 ongoing studies were found (see *Ongoing studies*).

One study[32] compared the MiniMed Veo system (with suspend function) with an integrated CSII + CGM system (MiniMed Veo with suspend function turned off) and another[33] compared it with CSII + SMBG. Seven other studies compared an integrated CSII + CGM system with CSII + SMBG (three studies)[34–36] or with MDI + SMBG (four studies).[37–40] The remaining 10 studies[41–50] compared CSII + SMBG with MDI + SMBG. None of the studies included a treatment arm with CSII + CGM or MDI + CGM as a comparator (*Table 2*). Although several studies included an integrated CSII + CGM system as a treatment arm, it is important to note that none of these studies looked at the Vibe and G4 PLATINUM CGM system; in the included studies, the integrated CSII + CGM system was always a MiniMed Paradigm pump with an integrated CGM system.

Out of the 19 studies, eight were performed in North America[32,34,38–40,46,48,49] and eight in Europe.[36,37,41–45,50] The remaining three studies were performed in Australia (two studies[33,35]) and Israel (one study[47]). Three out of the eight European studies included patients from the UK.[37,41,45]

TABLE 2 Included studies and comparisons

Study	Veo	Integrated CSII + CGM	CSII + CGM	CSII + SMBG	MDI + CGM	MDI + SMBG
Bergenstal *et al.*, 2013 (ASPIRE in-home)[32]	✓	✓				
Ly *et al.*, 2013[33]	✓			✓		
Hirsch *et al.*, 2008[34]		✓		✓		
O'Connell *et al.*, 2009[35]		✓		✓		
Raccah *et al.*, 2009 (RealTrend)[36]		✓		✓		
Hermanides *et al.*, 2011 (Eurythmics)[37]		✓				✓
Lee *et al.*, 2007[38]		✓				✓
Peyrot and Rubin, 2009[39]		✓				✓
Bergenstal *et al.*, 2010 (STAR-3)[40]		✓				✓
Bolli *et al.*, 2009[41]				✓		✓
DeVries *et al.*, 2002[42]				✓		✓
[a]Nosadini *et al.*, 1988[43]				✓		✓
Brinchmann-Hansen *et al.*, 1985 (OSLO)[44]				✓		✓
Thomas *et al.*, 2007[45]				✓		✓
Tsui *et al.*, 2001[46]				✓		✓
Weintrob *et al.*, 2003[47]				✓		✓
Thrailkill *et al.*, 2011[48]				✓		✓
Doyle *et al.*, 2004[49]				✓		✓
Nosari *et al.*, 1993[50]				✓		✓

a The study by Nosadini *et al.* (1988)[43] was a three-arm study that compared two different versions of CSII + SMBG with MDI + SMBG.

Twelve studies reported data for adults, five studies reported data for children and five studies reported data for mixed populations (adults and children). Two of these studies reported data for all three groups. One study included pregnant women (*Table 3*).

Table 4 shows the inclusion criteria, regarding the HbA_{1c} levels and hypoglycaemic events, used in the included studies. Further details of the characteristics of study participants and the interventions, comparators and results are reported in the data extraction tables presented in *Appendix 3*. It is clear from *Table 3* that most studies included patients who had never used a pump before. However, both of the studies looking at the MiniMed Veo system (ASPIRE in-home[32] and Ly *et al.*[33]) included patients who had at least 6 months' experience of using an insulin pump. In addition, baseline HbA_{1c} levels differ considerably among studies. DeVries *et al.*[42] included patients with poor control at baseline who were pump-naive.

TABLE 3 Characteristics of included studies

Study	Population (age range, years)	*n*	Mean baseline age, years (SD)	Mean baseline HbA_{1c} levels, % (SD)	Previous pump use, months	Follow-up, months
Bergenstal *et al.*, 2013 (ASPIRE in-home)[32]	A (16–70)	247	43 (13)	7.2 (0.7)	> 6	3
Ly *et al.*, 2013[33]	M (4–50)	95	19 (12)	7.5 (0.8)	> 6	6
Hirsch *et al.*, 2008[34]	M (12–72)	146	33 (16)	8.4 (0.7)	> 6	6
	A (18–72)			8.3 (0.6)	> 6	6
	C (12–17)			8.7 (0.9)	> 6	6
O'Connell *et al.*, 2009[35]	M (13–40)	62	23 (8.4)	7.4 (0.7)	> 3	3
Raccah *et al.*, 2009 (RealTrend)[36]	M (2–65)	132	28 (16)	9.2 (1)	NR	6
Hermanides *et al.*, 2011 (Eurythmics)[37]	A (18–65)	83	38 (11)	8.6 (0.9)	Naive	6
Lee *et al.*, 2007[38]	A (NR)	16	NR	9 (0.9)	Naive	3.5
Peyrot and Rubin, 2009[39]	A (NR)	29	47 (13)	8.6 (1)	NR	3.7
Bergenstal *et al.*, 2010 (STAR-3)[40]	M (7–70)	495	32 (17)	8.3 (0.5)	Naive	12
	A (19–70)		41 (12)		Naive	12
	C (7–18)		12 (3)		Naive	12
Bolli *et al.*, 2009[41]	A (18–70)	58	40 (11)	7.7 (0.7)	Naive	6
DeVries *et al.*, 2002[42]	A (18–70)	79	37 (10)	9.4 (1.4)	Naive	3.7
Nosadini *et al.*, 1988[43]	A (NR)	96	34 (6)	NR	NR	12
Brinchmann-Hansen *et al.*, 1985 (OSLO)[44]	A (18–45)	45	26 (21)	8.5 (NR)	NR	3, 6, 12 and 24
Thomas *et al.*, 2007[45]	A (NR)	21	43 (10)	8.5 (1.5)	NR	4 and 6
Tsui *et al.*, 2001[46]	A (18–60)	27	36 (11)	8 (0.6)	Naive	9
Weintrob *et al.*, 2003[47]	C (8–14)	23	12 (1.5)	8 (1)	NR	3.5
Thrailkill *et al.*, 2011[48]	C (8–18)	24	12 (3)	11.5 (2.4)	Naive	6 and 12
Doyle *et al.*, 2004[49]	C (8–21)	32	13 (3)	8.1 (1.2)	Naive	3.7
Nosari *et al.*, 1993[50]	P (NR)	32	26 (2.4)	NR	Naive	9

A, adults; C, children; M, mixed; NR, not reported; P, pregnant women.

TABLE 4 Inclusion and exclusion criteria used in included studies for HbA_{1c} levels and hypoglycaemic events

Study	Inclusion criteria for HbA_{1c} levels (%)	Inclusion/exclusion criteria with regard to hypoglycaemia
Bergenstal *et al.*, 2013 (ASPIRE in-home)[32]	5.8–10	Included if experienced two or more nocturnal hypoglycaemic events during the run in phase. Excluded if experienced more than one episode of severe hypoglycaemia in the previous 6 months
Ly *et al.*, 2013[33]	≤ 8.5	Included those with an impaired awareness of hypoglycaemia (HUS ≥ 4). Mean HUS 6.2 (SD 1.5)
Hirsch *et al.*, 2008[34]	≥ 7.5	There were no exclusions for hypoglycaemia unawareness
O'Connell *et al.*, 2009[35]	≤ 8.5	Excluded those with any co-existent illness that otherwise predisposes to hypoglycaemia (e.g. adrenal insufficiency) or a history of severe hypoglycaemia while using insulin pump therapy
Raccah *et al.*, 2009 (RealTrend)[36]	> 8	NR
Hermanides *et al.*, 2011 (Eurythmics)[37]	≥ 8.2	NR
Lee *et al.*, 2007[38]	≥ 7.5	NR
Peyrot and Rubin, 2009[39]	NR	NR
Bergenstal *et al.*, 2010 (STAR-3)[40]	7.4–9.5	Excluded those with hypoglycaemia unawareness (two or more severe hypoglycaemic episodes without warning of low BG levels within the previous year)
Bolli *et al.*, 2009[41]	6.5–9	Excluded those who had more than two severe hypoglycaemic events in the previous 6 months
DeVries *et al.*, 2002[42]	≥ 8.5	NR
Nosadini *et al.*, 1988[43]	NR	NR
Brinchmann-Hansen *et al.*, 1985 (OSLO)[44]	NR	NR
Thomas *et al.*, 2007[45]	NR	Included those with long-standing T1DM complicated by at least one episode of severe hypoglycaemia within the preceding 6 months
Tsui *et al.*, 2001[46]	NR	Excluded those who had a history of more than two severe hypoglycaemic episodes in the last year
Weintrob *et al.*, 2003[47]	NR	NR
Thrailkill *et al.*, 2011[48]	NR	NR
Doyle *et al.*, 2004[49]	6.5–11	NR
Nosari *et al.*, 1993[50]	NR	NR

HUS, hypoglycaemia unawareness score; NR, not reported.

The two studies looking at the MiniMed Veo system included patients with relatively good glycaemic control at baseline; however, that might have been because those patients had been using an insulin pump for at least 6 months. Other studies, such as Bolli *et al.*,[41] included patients with relatively good glycaemic control at baseline without any previous pump experience. Therefore, there is considerable heterogeneity among the study populations.

Most studies were rated as having a high risk of bias (11 out of 19), four studies were rated as having an unclear risk of bias and another four studies were rated as having a low risk of bias (see *Appendix 2*). The most problematic factor with regard to the risk-of-bias assessment was the lack of blinding (of participants, physicians and outcome assessors) in the included studies. For participants and physicians, it is almost

impossible to perform a trial with true blinding with these types of interventions. Nevertheless, the fact that participants and physicians were not blinded may bias the results, and the outcome assessment for HbA_{1c} measurement could be performed blinded. Selective outcome reporting was assessed as having a high risk of bias in only three trials. Incomplete data reporting was assessed as having a high risk of bias in 12 trials; this was rated as unclear in four trials. Overall, there was a high risk of bias in the included trials.

In the following chapters, we will discuss the results of the included studies by population (i.e. adults, children and pregnant women) and by follow-up time (i.e. 3 months, 6 months and 9 months or more).

Effectiveness of interventions in adults

We found 12 studies that reported data for adults.[32,34,37–46] As can be seen in *Table 5*, the age ranges differed considerably; therefore, we asked a panel of four expert committee members whether or not they thought that the results of these studies could be pooled. Three clinical experts agreed that the studies were similar enough to be pooled, as far as the differences in age ranges were concerned, and the fourth clinical expert did not respond.

TABLE 5 Included studies for adults

Study ID	Veo	Integrated CSII + CGM	CSII+ SMBG	MDI+ SMBG	Mean baseline age, years (SD); age range, years	Mean baseline HbA_{1c}, % (SD)	Previous pump use, months	Follow-up, months
Bergenstal *et al.*, 2013[32]	✓	✓			43 (13); 16–70	7.2 (0.7)	> 6	3
Hirsch *et al.*, 2008[34]		✓	✓		33 (16); 18–72	8.3 (0.6)	> 6	6
Hermanides *et al.*, 2011[37]		✓		✓	38 (11); 18–65	8.6 (0.9)	Naive	6
Lee *et al.*, 2007[38]		✓		✓	NR	9 (0.9)	Naive	3.5
Peyrot and Rubin, 2009[39]		✓		✓	47 (13); NR	8.6 (1)	NR	3.7
Bergenstal *et al.*, 2010[40]		✓		✓	41 (12); 19–70	8.3 (0.5)	Naive	12
Bolli *et al.*, 2009[41]			✓	✓	40 (11); 18–70	7.7 (0.7)	Naive	6
DeVries *et al.*, 2002[42]			✓	✓	37 (10); 18–70	9.4 (1.4)	Naive	3.7
[a]Nosadini *et al.*, 1988[43]			✓	✓	34 (6); NR	NR	NR	12
Brinchmann-Hansen *et al.*, 1985[44]			✓	✓	26 (21); 18–45	8.5 (NR)	NR	3, 6, 12, 24
Thomas *et al.*, 2007[45]			✓	✓	43 (10); NR	8.5 (1.5)	NR	4, 6
Tsui *et al.*, 2001[46]			✓	✓	36 (11); 18–60	8 (0.6)	Naive	9

NR, not reported.
a The study by Nosadini *et al.* (1988)[43] was a three-arm study that compared two different versions of CSII + SMBG with MDI + SMBG.

Veo versus integrated CSII + CGM

One study compared the MiniMed Veo with an integrated CSII + CGM system at 3-month follow-up in adults (ASPIRE in-home).[32] The results of this study, for the head-to-head comparison of the MiniMed Veo system with an integrated CSII + CGM system, are reported in *Table 6*.

No results were found for the MiniMed Veo system versus any other treatment at follow-up of 6 months or more.

Nocturnal hypoglycaemic events occurred 31.8% less frequently in the MiniMed Veo group than in the integrated CSII + CGM group [1.5 (SD 1.0) vs. 2.2 (SD 1.3) events per patient per week, $p < 0.001$]. Similarly, the MiniMed Veo group had significantly lower weekly rates of combined daytime and night-time events than the integrated CSII + CGM group ($p < 0.001$).

The mean area under the curve (AUC) for nocturnal hypoglycaemic events was 37.5% lower in the MiniMed Veo group than in the integrated CSII + CGM group [980 mg/dl (SD 1200 mg/dl) or 54.4 mmol/l (SD 66.6 mmol/l) × minutes vs. 1568 mg/dl (SD 1995 mg/dl) or 87.0 mmol/l (SD 110.7 mmol/l) × minutes; $p < 0.001$]. The mean AUC for daytime and night-time hypoglycaemic events was also significantly lower in the threshold suspend group.

The other outcomes showed no significant differences between groups.

TABLE 6 Results for the MiniMed Veo vs. an integrated CSII + CGM system at 3-month follow-up in adults

Outcome	MiniMed Veo system ($n = 121$)		Integrated CSII + CGM ($n = 126$)		Difference at follow-up
	Baseline	Follow-up	Baseline	Follow-up	
Mean change in HbA_{1c} levels, % (SD)	7.26 (0.71)	7.24 (0.67)	7.21 (0.77)	7.14 (0.77)	0.05 (95% CI –0.05 to 0.15)
Nocturnal hypoglycaemic events per patient per week (glucose < 3.6 mmol/l) (SD)		1.5 (1.0)		2.2 (1.3)	NR; $p < 0.001$
Day and night hypoglycaemic events per patient per week (glucose < 3.6 mmol/l) (SD)		3.3 (2.0)		4.7 (2.7)	NR; $p < 0.001$
Nocturnal hypoglycaemic AUC[a] (SD)		980 (1200)		1568 (1995)	NR; $p < 0.001$
Day and night hypoglycaemic AUC[a] (SD)		798 (965)		1164 (1590)	NR; $p < 0.001$
Meter BG (previous 2 weeks, mg/dl) (SD)	151.4 (24.3)	167.5 (24.7)	151.8 (23.6)	163.9 (32.1)	NS
Insulin use (U per patient per day) (SD)		47.8 (19.40)		46.5 (21.66)	NS
DKA		0		0	No difference
EQ-5D	NR	NR	NR	NR	No difference
Device-related serious AEs		0		0	No difference
AE, death		0		0	No difference

AE, adverse event; AUC, area under the curve; DKA, diabetic ketoacidosis; EQ-5D, European Quality of Life-5 Dimensions scale; NR, not reported; NS, not significant; U, units.

a The AUC is the product of the magnitude and duration of the sensor measured glucose level above or below a specified cut-off level. Higher values for this calculation indicate more numerous, severe or protracted glycaemic events.

Veo versus integrated CSII + CGM, CSII + SMBG and MDI + SMBG

For two outcomes [change in HbA_{1c} levels and diabetic ketoacidosis (DKA)], results of the MiniMed Veo system versus other treatments were available for 3-month follow-up in adults from more than one study,[38,39] which could be combined in indirect comparisons. These two outcomes are reported below.

Change in glycated haemoglobin levels at 3-month follow-up

We found four studies[32,38,39,42] comparing change in HbA_{1c} levels at 3-month follow-up in adults, allowing a comparison of the MiniMed Veo system with an integrated CSII + CGM, CSII + SMBG and MDI + SMBG. *Figure 2* shows the network linking these interventions and *Table 7* shows the results.

The results of these indirect comparisons show that there are no significant differences between the MiniMed Veo system and any other intervention in change in HbA_{1c} levels at 3-month follow-up. Similarly, there are no significant differences between the integrated CSII + CGM system and any other intervention in change in HbA_{1c} levels at 3-month follow-up. The only significant difference found in this analysis was the difference between CSII + SMBG versus MDI + SMBG; in this regard, the results favour CSII + SMBG.

Diabetic ketoacidosis at 3-month follow-up

The same four studies[32,38,39,42] provided data for DKA at 3-month follow-up in adults, allowing a comparison of the MiniMed Veo system with an integrated CSII + CGM system, CSII + SMBG and MDI + SMBG. However, the study that compared the MiniMed Veo system with the integrated CSII + CGM system (ASPIRE in-home)[32] could not be included in the analysis as no events were reported in either arm. The results of the indirect comparisons for DKA are shown in *Table 8*.

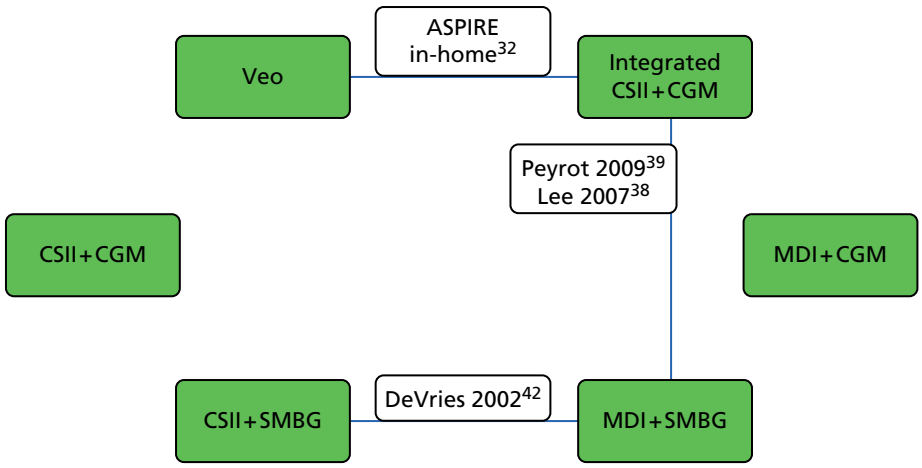

FIGURE 2 Network of studies comparing change in HbA_{1c} levels and DKA at 3-month follow-up in adults. Note: green boxes represent the interventions; lines represent comparisons between interventions at 3-month follow-up; and transparent boxes represent studies in adults.

TABLE 7 Results of the indirect comparisons with regard to change in HbA_{1c} at 3-month follow-up

Intervention	Integrated CSII + CGM, WMD (95% CI)	CSII + SMBG, WMD (95% CI)	MDI + SMBG, WMD (95% CI)
Veo	0.04 (–0.07 to 0.15)	0.41 (–0.31 to 1.13)	–0.43 (–0.95 to 0.10)
Integrated CSII + CGM		0.37 (–0.34 to 1.08)	–0.47 (–0.98 to 0.04)
CSII + SMBG			**–0.84 (–1.33 to –0.35)**

WMD values of < 0 indicate that the results favour the intervention listed in column 1. Differences are significant if the CIs do not include 0 (indicated in bold).

TABLE 8 Results of the indirect comparisons with regard to DKA at 3-month follow-up

Intervention	Integrated CSII + CGM, RR (95% CI)	CSII + SMBG, RR (95% CI)	MDI + SMBG, RR (95% CI)
Veo	No events	No events	No events
Integrated CSII + CGM		0.26 (0.01 to 8.53)	0.32 (0.04 to 2.86)
CSII + SMBG			1.25 (0.08 to 19.22)

RR values of < 1 indicate that the results favour the interventions listed in column 1. Differences are significant if the CIs do not include 1.

The results of these indirect comparisons show that there are no significant differences with between the integrated CSII + CGM system and any other intervention with regard to DKA at 3-month follow-up. The comparison between CSII + SMBG and MDI + SMBG also showed no significant difference.

Integrated CSII + CGM versus CSII + SMBG

One study[34] compared the integrated CSII + CGM system (Paradigm 722 System, Medtronic) with CSII + SMBG (Paradigm 715 Insulin Pump, Medtronic) at 6-month follow-up in adults.

At 6-month follow-up, results for the head-to-head comparison of the integrated CSII + CGM system versus CSII + SMBG were available for one outcome: change in HbA_{1c} levels. Other outcomes were not reported separately for adults. The results for change in HbA_{1c} levels are reported in *Table 9*.

The results for the head-to-head comparison of the integrated CSII + CGM system versus CSII + SMBG at 6-month follow-up in adults showed no significant difference in HbA_{1c} levels between groups.

TABLE 9 Results for the head-to-head comparison of integrated CSII + CGM vs. CSII + SMBG at 6-month follow-up in adults

	Integrated CSII + CGM ($n = 49$)		CSII + SMBG ($n = 49$)		
Outcome	Baseline (%)	Follow-up (%)	Baseline (%)	Follow-up (%)	Difference at follow-up
Change in HbA_{1c} levels (SD)	8.37 (0.6)	7.68 (0.84)	8.30 (0.54)	7.66 (0.67)	–0.0364 (SE 0.1412); $p = 0.80$

SE, standard error.

Integrated CSII + CGM versus MDI + SMBG

Four studies[37–40] compared the integrated CSII + CGM system (MiniMed Paradigm REAL-Time 722 System) with MDI + SMBG in adults. Two of these[38,39] had results at 3 months, one[37] at 6 months and one[40] at 12-month follow-up.

At 3-month follow-up, results for the head-to-head comparison of the integrated CSII + CGM system versus MDI + SMBG were available for the following outcomes: change in HbA_{1c} levels, hypoglycaemic events, DKA and adverse events. These results are reported in *Table 10*.

At 6-month follow-up, results for the head-to-head comparison of the integrated CSII + CGM system versus MDI + SMBG were available for change in HbA_{1c} levels, proportion achieving HbA_{1c} levels of $\leq 7\%$, hypoglycaemic events, hyperglycaemic events, insulin use and quality of life. These results are also reported in *Table 10*, together with the results at 12-month follow-up for change in HbA_{1c} levels, proportion achieving HbA_{1c} levels of $\leq 7\%$, proportion with severe hypoglycaemia, rate of severe hypoglycaemic events, hypoglycaemic AUC, hyperglycaemic AUC, DKA and quality of life.

TABLE 10 Results for the comparison of the integrated CSII + CGM system vs. MDI + SMBG at 3-, 6- and 12-month follow-up in adults

Outcome/study	Integrated CSII + CGM		MDI + SMBG		Difference at follow-up
	Baseline	Follow-up	Baseline	Follow-up	
Three-month follow-up					
Change in HbA_{1c} levels, % (SD)					
Peyrot and Rubin, 2009[39] ($n = 27$)	8.87 (0.89), $n = 14$	7.16 (0.75)	8.32 (1.05), $n = 13$	7.30 (0.92)	–0.69; $p = 0.071$
Lee *et al.*, 2007[38] ($n = 16$)	9.45 (0.55), $n = 8$	7.40 (0.66)	8.58 (1.30), $n = 8$	7.50 (1.01)	–0.97; $p = 0.02$
Hypoglycaemic events (number of patients with events/total number of patients)					
Peyrot and Rubin, 2009[39] ($n = 27$)	NA	0/14	NA	3/13	NS
Lee *et al.*, 2007[38] ($n = 16$)	NA	0/8	NA	1/8	NS
DKA (number of patients with DKA/total number of patients)					
Peyrot and Rubin, 2009[39] ($n = 27$)	NA	0/14	NA	1/13	NS
Lee *et al.*, 2007[38] ($n = 16$)	NA	0/8	NA	1/8	NS
Serious AEs (number of patients with a serious AE/total number of patients)					
Lee *et al.*, 2007[38]	NA	0/8	NA	1/8	NS
Six-month follow-up (Eurythmics[37])	**n = *41***		**n = *36***		
Change in HbA_{1c} levels, % (SD)	8.46 (0.95)	7.23 (0.65)	8.59 (0.82)	8.46 (1.04)	–1.1, 95% CI –1.47 to –0.73
Proportion achieving HbA_{1c} levels of ≤ 7% (number of patients with HbA_{1c} ≤ 7%/total number of patients)	NA	14/41	NA	0/36	$p < 0.001$
Hypoglycaemic events, mean number of events (glucose levels of < 4.0 mmol/l) per day (SD)	NA	0.7 (0.7)	NA	0.6 (0.7)	0.1, 95% CI –0.2 to 0.5
Hyperglycaemic events, mean number of events (glucose levels of > 11.1 mmol/l) per day (SD)	NA	2.1 (0.8)	NA	2.2 (0.7)	–0.2, 95% CI –0.5 to 0.2
Insulin use, total daily dose (SD) in units	NA	46.7 (16.5)	NA	57.8 (18.1)	–11.0, 95% CI –16.1 to –5.9; $p < 0.001$
QoL: SF-36 Health Survey measuring general health, mean score (SD)	55.5 (20.3)	67.7 (21.6)	59.8 (22.3)	63.1 (19.1)	7.9, 95% CI 0.5 to 15.3; $p = 0.04$
Twelve-month follow-up (STAR-3[40])	**n = *169***		**n = *167***		
Change in HbA_{1c} levels, % (SD)	8.3 (0.5)	7.3 (NR)	8.3 (0.5)	7.9 (NR)	–0.6, 95% CI –0.8 to –0.4; $p < 0.001$
Proportion achieving HbA_{1c} levels of ≤ 7% (number of patients with HbA_{1c} ≤ 7%/total number of patients)	NA	57/166	NA	19/163	$p < 0.001$
Severe hypoglycaemia (patients with hypoglycaemic events/total patients)	NA	17/169	NA	13/167	NS
Severe hypoglycaemic event rate (per 100 person-years; HbA_{1c} levels < 50 mg/dl)	NA	15.31/169	NA	17.62/167	$p = 0.66$

TABLE 10 Results for the comparison of the integrated CSII + CGM system vs. MDI + SMBG at 3-, 6- and 12-month follow-up in adults (*continued*)

Outcome/study	Integrated CSII + CGM		MDI + SMBG		Difference at follow-up
	Baseline	Follow-up	Baseline	Follow-up	
Hypoglycaemic AUC (threshold of < 70 mg/dl)	NA	0.25 (0.44)	NA	0.29 (0.55)	$p = 0.63$
Hyperglycaemic AUC (> 250 mg/dl)	NA	3.74 (5.01)	NA	7.38 (8.62)	$p < 0.001$
Patients with DKA	NA	2/169	NA	0/167	NS
QoL	NA	NA	NA	NA	NA
SF-36 General Health	NA	Change: +2.7 (8.07)	NA	Change: –0.3 (7.13)	3 (SD 7.75), 95% CI 1.36 to 4.64
HFS	NA	Change: –9 (16.04)	NA	Change: –2.4 (15.88)	–6.5 (SD 16.0), 95% CI –9.76 to –3.27)

AE, adverse event; HFS, Hypoglycaemia Fear Survey; NA, not applicable; NR, not reported; NS, not significant; QoL, quality of life; SF-36, Short Form questionnaire-36 items.

At 3-month follow-up, results were available from two small RCTs, with 27[39] and 16[38] adult respondents, respectively. With regard to change in HbA_{1c} levels, the results from these RCTs favoured the integrated CSII + CGM system over MDI + SMBG, but this was not significant in one of the trials.[39] There were more hypoglycaemic events, DKA and serious adverse events in the MDI + SMBG groups at 3-month follow-up. None of these results was significant; however, the study sizes were small and the number of events was limited.

At 6-month follow-up, results were available from one small RCT with 77 adult respondents.[37] This trial showed a significant difference in HbA_{1c} change scores favouring the integrated CSII + CGM system, with a significantly higher number of patients achieving HbA_{1c} levels of $\leq 7\%$. Insulin use was significantly lower and quality of life was significantly higher in the integrated CSII + CGM group than in the MDI + SMBG group. The number of hypoglycaemic and hyperglycaemic events showed no differences between groups.

At 12-month follow-up, results were available from one RCT with 336 adult participants.[40] This trial also showed a significant difference in HbA_{1c} change scores in favour of the integrated CSII + CGM system and a significantly higher number of patients achieving HbA_{1c} levels of $\leq 7\%$. Hyperglycaemic AUC was significantly lower in the integrated CSII + CGM group, but hypoglycaemic AUC showed no significant difference. The results suggest that there were no significant differences between groups with regard to severe hypoglycaemia, nor was there any difference in the number of patients with DKA. Quality of life was more significantly improved in the integrated CSII + CGM group than in the MDI + SMBG group. The Hypoglycaemia Fear Survey (HFS) showed that there were significantly more reductions in fear in the integrated CSII + CGM group than in the MDI + SMBG group, for both worries and avoidant behaviour related to hypoglycaemia.

Integrated CSII + CGM versus CSII + SMBG and MDI + SMBG

Results at 3-month follow-up

Proportion of patients with severe hypoglycaemia The results of these indirect comparisons (*Figure 3* and references 38, 39 and 42 therein) suggest that there are no significant differences between the integrated CSII + CGM system and any other intervention with regard to the 'proportion of patients with severe hypoglycaemia' at 3-month follow-up. The comparison between CSII + SMBG and MDI + SMBG also showed no significant difference. These findings are summarised in *Table 11*.

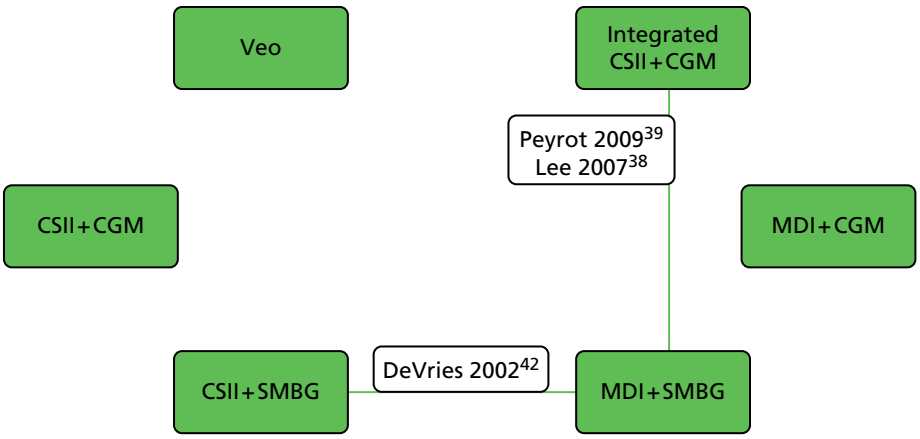

FIGURE 3 Network of studies comparing 'severe hypoglycaemia' at 3-month follow-up in adults.

TABLE 11 Results of the indirect comparisons with regard to the proportion of patients with severe hypoglycaemia at 3-month follow-up in adults

Intervention	CSII + SMBG, RR (95% CI)	MDI + SMBG, RR (95% CI)
Integrated CSII + CGM	0.33 (0.03 to 3.87)	0.19 (0.02 to 1.51)
CSII + SMBG		0.63 (0.17 to 2.31)

RR values of < 1 indicate that the results favour the intervention listed in column 1. Differences are significant if the CIs do not include 1 (these are in bold).

Results at 6-month follow-up

Change in glycated haemoglobin levels The results of these indirect comparisons (*Figure 4* and references 34, 37 and 41 therein) suggest that there are no significant differences between the integrated CSII + CGM system and CSII + SMBG with regard to change in HbA_{1c} levels at 6-month follow-up. The comparison between CSII + SMBG and MDI + SMBG also showed no significant difference. The comparison between the integrated CSII + CGM system and MDI + SMBG did show a significant difference, favouring the integrated CSII + CGM system. These findings are summarised in *Table 12*.

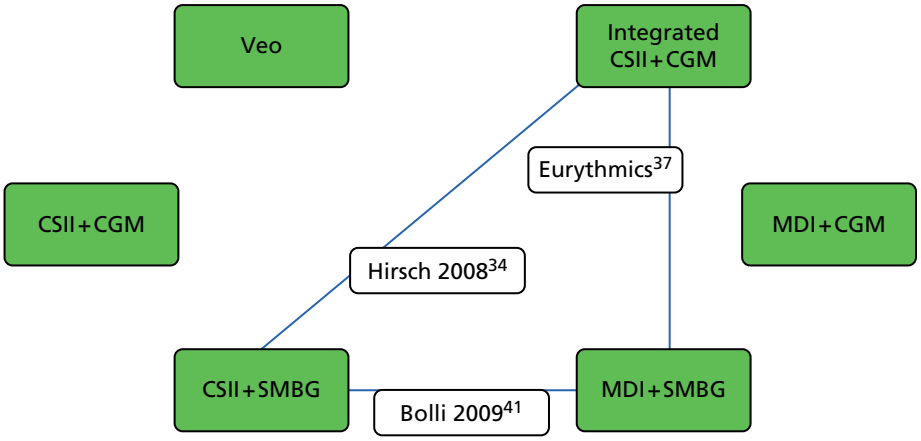

FIGURE 4 Network of studies comparing change in HbA_{1c} levels at 6-month follow-up in adults.

TABLE 12 Results of the indirect comparisons with regard to change in HbA_{1c} levels at 6-month follow-up in adults

Intervention	CSII + SMBG, WMD (95% CI)	MDI + SMBG, WMD (95% CI)
Integrated CSII + CGM	–0.05 (–0.31 to 0.21)	**–1.10 (–1.46 to –0.74)**
CSII + SMBG		–0.10 (–0.52 to 0.32)

WMD values of < 0 indicate that the results favour intervention listed in column 1. Differences are significant if the CIs do not include 0 (these are in bold).

Proportion of patients achieving glycated haemoglobin levels < 7% Results of these indirect comparisons (*Figure 5* and references 34 and 37 therein) suggest that there are no significant differences between the integrated CSII + CGM system and CSII + SMBG with regard to 'HbA_{1c} levels < 7%' at 6-month follow-up. However, the comparison between the integrated CSII + CGM system and MDI + SMBG did show a significant difference in favour of the integrated CSII + CGM system. Similarly, the comparison between CSII + SMBG and MDI + SMBG showed a significant difference in favour of CSII + SMBG. These findings are summarised in *Table 13*.

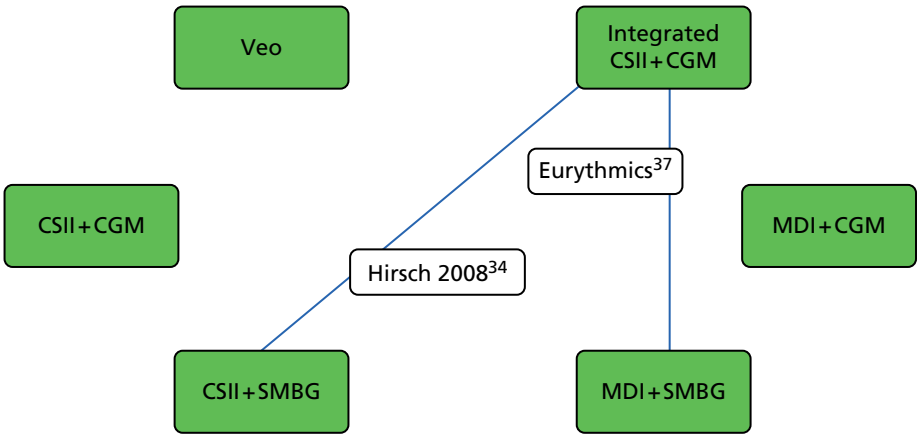

FIGURE 5 Network of studies comparing 'HbA_{1c} levels < 7%' at 6-month follow-up in adults.

TABLE 13 Results of the indirect comparisons with regard to HbA_{1c} levels of < 7% at 6-month follow-up in adults

Intervention	CSII + SMBG, RR (95% CI)	MDI + SMBG, RR (95% CI)
Integrated CSII + CGM	1.45 (0.74 to 2.84)	**25.55 (1.58 to 413.59)**
CSII + SMBG		**17.56 (1.002 to 307.87)**

RR values of > 1 indicate that the results favour the intervention listed in column 1. Differences are significant if the CIs do not include 1 (these are in bold).

Quality of life Different tools were used to measure HRQoL (*Figure 6*). Only those studies using the same questionnaire could be combined in the analysis. Two studies reported results at 6-month follow-up for the Diabetic Treatment Satisfaction Questionnaire (Eurythmics[37] and Bolli *et al.*[41]) using a scale from 0 to 36, with higher scores indicating more satisfaction with treatment. These findings are summarised in *Table 14*. Two studies reported results for the HFS (Eurythmics[37] and Thomas *et al.*[45]); however, these could not be analysed together as one reported only the worry subscale of the HFS, whereas the other reported the total score.

The results of these indirect comparisons show that the integrated CSII + CGM system significantly improved the quality-of-life scores at 6-month follow-up when compared with CSII + SMBG or with MDI + SMBG. There was no significant difference between CSII + SMBG and MDI + SMBG.

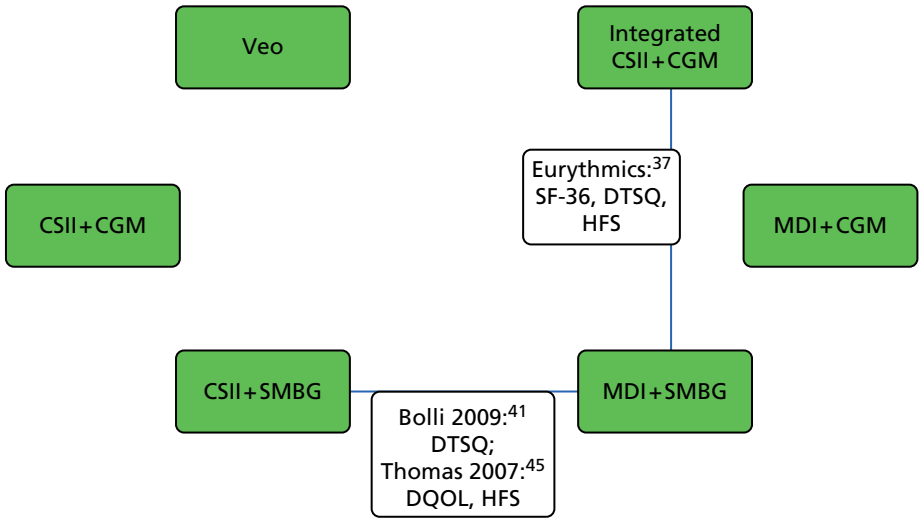

FIGURE 6 Network of studies comparing 'quality of life' at 6-month follow-up in adults. DQOL, Diabetes Quality of Life questionnaire; DTSQ, Diabetic Treatment Satisfaction Questionnaire; SF-36, Short Form questionnaire-36 items.

TABLE 14 Results of the indirect comparisons with regard to quality of life (DTSQ) at 6-month follow-up in adults

Intervention	CSII + SMBG, WMD (95% CI)	MDI + SMBG, WMD (95% CI)
Integrated CSII + CGM	**5.90 (2.22 to 9.58)**	**8.60 (6.28 to 10.92)**
CSII + SMBG		2.70 (–0.16 to 5.56)

DTSQ, Diabetic Treatment Satisfaction Questionnaire.
WMD values of > 0 indicate that the results favour the intervention listed in column 1. Differences are significant if the CIs do not include 0 (these are in bold).

Effectiveness of interventions in children

We found five studies[34,40,47–49] that reported data for children. In addition, there was one study (Ly *et al.*[33]) that included a mixed population of patients between 4 and 50 years old. Approximately 70% of patients were children (< 18 years).

We asked our panel of four expert committee members whether or not they thought that the results of these studies could be pooled, especially whether or not the study by Ly *et al.*[33] (age range of 4 to 50 years, with 70% of participants < 18 years) could be included as if it was a study in children. One clinical expert agreed that the six studies were similar enough, as far as the differences in age ranges were concerned, to be pooled. A second clinical expert agreed that five of the studies were similar enough, as far as the differences in age ranges were concerned, to be pooled, but given that approximately one-third of participants were aged 18–50, it would be difficult to include the Ly *et al.*[33] study in the analysis of the interventions in children (if the adult group had been a younger cohort, e.g. 18–25 years, this expert's conclusion may have been different). The third clinical expert also thought the Ly *et al.*[33] study could not reasonably be included in analyses for either group (children or adults); this third expert also thought that teenage children behave in a different way from pre-teen children and that, therefore, the 8- to 14-year-old cohort may be significantly different and should perhaps have been excluded from analyses. The fourth clinical expert did not respond.

However, the study by Ly *et al.*[33] was the only study looking at the MiniMed Veo system in children; therefore, we will present the results from analyses that included this study as if it was a study in children. In addition, the study by Weintrob *et al.*,[47] with children aged 8 to 14 years old, is the only study with results at 6-month follow-up linking MDI + SMBG to the MiniMed Veo system and the integrated CSII + CGM system; therefore, we included this study in the analyses as well. The results of these analyses should be interpreted with great caution because of the differences in age ranges among the included studies, as shown in *Table 15*.

TABLE 15 Included studies for children

Study	Veo	Integrated CSII + CGM	CSII+ SMBG	MDI+ SMBG	Mean baseline age, years (SD); age range, years	Mean baseline HbA_{1c}, % (SD)	Previous pump use, months	Follow-up, months
Ly *et al.*, 2013[33]	✓		✓		19 (12); 4–50	7.5 (0.8)	> 6	6
Hirsch *et al.*, 2008[34]		✓	✓		33 (16); 12–17	8.7 (0.9)	> 6	6
Bergenstal *et al.*, 2010[40]		✓		✓	12 (3); 7–18	8.3 (0.5)	Naive	12
Weintrob *et al.*, 2003[47]			✓	✓	12 (1.5); 8–14	8 (1)	NR	3.5
Thrailkill *et al.*, 2011[48]			✓	✓	12 (3); 8–18	11.5 (2.4)	Naive	6, 12
Doyle *et al.*, 2004[49]			✓	✓	13 (3); 8–21	8.1 (1.2)	Naive	3.7

NR, not reported.

Veo versus CSII + SMBG

One study[33] compared the MiniMed Veo system with CSII + SMBG at 6-month follow-up in a mixed population of patients between 4 and 50 years old. Results were not reported separately for adults and children. However, approximately 70% of patients were children (< 18 years). As explained above, we have included this study as a study of children. The results of this study are summarised in *Table 16*.

No results were found for the MiniMed Veo system versus any other treatment after 3 months, 9 months or longer follow-up.

As shown in *Table 16*, the only significant difference between treatment groups was the rate of moderate and severe hypoglycaemic events, which favoured the MiniMed Veo system. All other outcomes showed no significant differences between groups.

TABLE 16 Results for the MiniMed Veo system vs. CSII + SMBG at 6-month follow-up in a mixed population (mainly children)

	MiniMed Veo system ($n = 46$)		CSII + SMBG ($n = 49$)		
Outcome	Baseline	Follow-up	Baseline	Follow-up	Difference at follow-up
Change in HbA_{1c} levels, % (95% CI)	7.6 (7.4 to 7.9)	7.5 (7.3 to 7.7)	7.4 (7.2 to 7.6)	7.4 (7.2 to 7.7)	0.07 (–0.2 to 0.3); $p = 0.55$
Number of people with hypoglycaemic events		0/41		6/45	NS
Hypoglycaemic incidence rate[a]		9.5 (95% CI 5.2 to 17.4)		34.2 (95% CI 22.0 to 53.3)	IRR 3.6 (95% CI 1.7 to 7.5); $p < 0.001$
HUS[b]	5.9 (95% CI 5.5 to 6.4)	4.7 (95% CI 4.0 to 5.1)	6.4 (95% CI 5.9 to 6.8)	5.1 (95% CI 4.5 to 5.6)	–0.2 (95% CI –0.9 to 0.5); $p = 0.58$

HUS, Hypoglycaemia Unawareness Score (Clarke questionnaire), higher is worse; IRR, incidence rate ratio; NS, not significant.
a The number of hypoglycaemic events per 100 patient-months.
b The higher the HUS, the higher the level of hypoglycaemia unawareness.

Veo versus integrated CSII + CGM and CSII + SMBG

Results at 6-month follow-up: change in glycated haemoglobin levels

The results of the indirect comparison, shown in *Figure 7* and *Table 17*, demonstrate that there were no significant differences between any of the interventions with regard to changes in HbA_{1c} levels at 6-month follow-up in children.

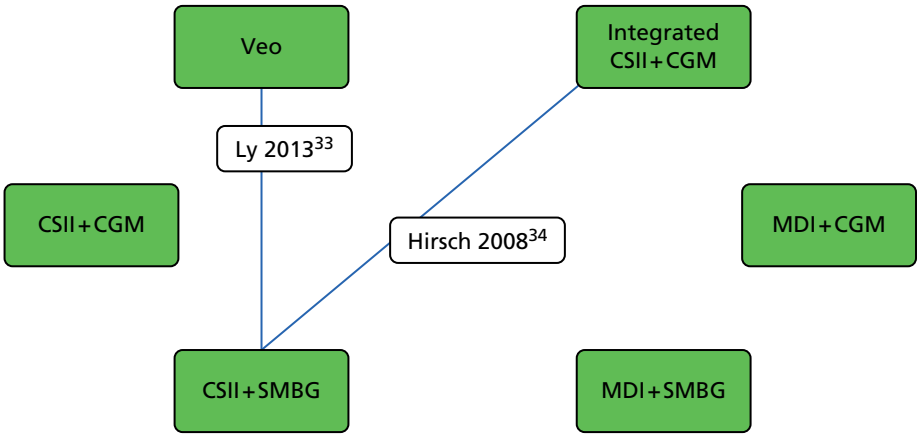

FIGURE 7 Network of studies comparing change in HbA_{1c} levels at 6-month follow-up in children.

TABLE 17 Results of the indirect comparison of changes in HbA_{1c} levels at 6-month follow-up

Intervention	Integrated CSII + CGM, WMD (95% CI)	CSII + SMBG, WMD (95% CI)
Veo	0.38 (–0.16 to 0.92)	–0.04 (–0.26 to 0.18)
Integrated CSII + CGM		–0.42 (–0.92 to 0.08)

WMD values of < 0 indicate that the results favour the interventions listed in column 1. Differences are significant if the CIs do not include 0.

Integrated CSII + CGM versus CSII + SMBG

One study compared the integrated CSII + CGM system with CSII + SMBG at 6-month follow-up in children.[34]

At 6-month follow-up, results for the head-to-head comparison of the integrated CSII + CGM system with CSII + SMBG were available for one outcome: change in HbA_{1c} levels. Other outcomes were not reported separately for children. The results for change in HbA_{1c} levels are reported in *Table 18*.

The results from the head-to-head comparison of the integrated CSII + CGM system with CSII + SMBG at 6-month follow-up in children showed no significant difference in HbA_{1c} levels between groups.

TABLE 18 Results for the integrated CSII + CGM system vs. CSII + SMBG at 6-month follow-up in children

Outcome	Integrated CSII + CGM ($n = 17$)		CSII + SMBG ($n = 23$)		Difference at follow-up
	Baseline	Follow-up	Baseline	Follow-up	
Change in HbA_{1c} levels, % (SD)	8.82 (1.05)	8.02 (1.11)	8.59 (0.80)	8.21 (0.97)	0.4894 (SE 0.2899); $p = 0.10$

Integrated CSII + CGM versus MDI + SMBG

One study compared the integrated CSII + CGM system with MDI + SMBG at 12-month follow-up in 159 children.[40]

At 12-month follow-up, results from the head-to-head comparison of the integrated CSII + CGM system with MDI + SMBG were available for change in HbA_{1c} levels, proportion achieving HbA_{1c} levels of ≤ 7%, proportion with severe hypoglycaemia, rate of severe hypoglycaemic events, hypoglycaemic AUC, hyperglycaemic AUC, DKA and quality of life. These results are reported in *Table 19*.

The trial showed a significant difference in HbA_{1c} change scores in favour of the integrated CSII + CGM system, but no significant difference in the number of children achieving HbA_{1c} levels of ≤ 7%.[40] The hyperglycaemic AUC was significantly lower in the integrated CSII + CGM group, but the hypoglycaemic AUC showed no significant difference. The results for severe hypoglycaemia showed no differences between groups; furthermore, there were no differences in the number of patients with DKA. Quality-of-life scores showed no significant differences between groups. The HFD showed that fear (as indicated by both worry and avoidance behaviour) was significantly reduced in both groups, but there was no difference between groups at 12-month follow-up.

TABLE 19 Results for the integrated CSII + CGM system vs. MDI + SMBG at 12-month follow-up in children

Outcome	Integrated CSII + CGM ($n = 78$)		MDI + SMBG ($n = 81$)		Difference at follow-up
	Baseline	Follow-up	Baseline	Follow-up	
Change in HbA_{1c} levels, % (SD)	8.3 (0.6)	7.9 (NR)	8.3 (0.5)	8.5 (NR)	–0.5 (95% CI –0.8 to –0.2); $p < 0.001$
Proportion achieving HbA_{1c} levels of ≤ 7% (patients with HbA_{1c} level ≤ 7%/total number of patients)		10/78		4/78	$p = 0.15$
Number of people with severe hypoglycaemic events (patients with severe hypoglycaemic events/total number of patients)		4/78		4/81	NS
Severe hypoglycaemic event rate (per 100 person-years; HbA_{1c} levels of < 50 mg/dl)		8.98/78		4.95/81	$p = 0.35$
Hypoglycaemic (< 70 mg/dl) AUC (SD)		0.23 (0.41)		0.25 (0.41)	$p = 0.79$
Hyperglycaemic (> 250 mg/dl) AUC (SD)		9.2 (8.08)		17.64 (14.62)	$p < 0.001$
Patients with DKA		1/78		1/81	NS
QoL					
PedsQL[a] – psychosocial, mean score (SD)	78.38 (14.59)	Change: 3.39	78.76 (10.27)	Change: 3.64	NS
PedsQL[a] – physical, mean score (SD)	86.99 (12.93)	Change: 2.53	88.37 (11.16)	Change: 1.41	NS
HFS[b] – worry, mean score (SD)	28.88 (9.74)	Change: –3.62	26.97 (8.06)	Change: –2.43	NS
HFS[b] – avoidance, mean score (SD)	30.60 (5.43)	Change: –4.01	29.70 (6.04)	Change: –2.25	NS

NR, not reported; NS, not significant; PedsQL, paediatric quality of life measurement tool; QoL, quality of life.
a The higher the PedsQL score, the higher the quality of life.
b The higher the HF score, the higher the quality of life.

Effectiveness of interventions in pregnant women

We found one RCT[50] that reported data for pregnant women (*Table 20*). The study included 32 pregnancies in 31 different women. The number of pregnancies was the unit of analysis. The study compared CSII + SMBG with MDI + SMBG; as these are not the relevant interventions described by NICE, the results will not be further discussed in this chapter. Full results are reported in *Appendix 3*.

TABLE 20 Included studies for pregnant women

Study	Veo	Integrated CSII + CGM	CSII+ SMBG	MDI+ SMBG	Mean baseline age, years (SD years); age range	Mean baseline HbA_{1c}	Previous pump use	Follow-up, months
Nosari *et al.*, 1993[50]			✓	✓	26 (2.4); NR	NR	Naive	9

NR, not reported.

Several non-RCTs (controlled clinical trials and observational studies) were identified; however, none of these looked at the MiniMed Veo system or an integrated CSII + CGM system. One ongoing study was identified; this is reported below (see *Ongoing studies*).

Additional analyses for the economic model

So far, we have adhered to the usual methods of meta-analyses, in accordance with which studies are combined in one analysis only if they compare similar interventions in similar populations at similar follow-up times, using similar outcomes.

We checked with clinical experts/committee members with regard to whether or not they agreed with these intended analyses and there was general agreement on the following points:

- *Age* Studies in children and adults should be analysed separately and studies in mixed age groups (adults and children), if data are not reported separately by age group, should not be included in analyses for children or adults.
- *Follow-up* Studies with results at 3-, 6- or 9-month follow-up should be analysed separately. Results from studies reporting outcomes at 2- to 4-month follow-ups can be pooled with results from studies reporting at 3-month follow-up; results from studies reporting at ≥ 9-month follow-up can be pooled in a ≥ 9-month follow-up group.

In cases in which the clinical experts disagreed with our suggested analyses, the clinical experts were always more cautious. For instance, it was suggested that Ly *et al.*[33] should not be treated as a study in children because one-third of participants were aged 18–50 years; therefore, it would be difficult to include this study with the analysis of children. If the adult age group in this study had been a younger cohort (e.g. 18–25 years) it may have been different. Similarly, teenage children were considered to behave in a different way from pre-teen children; therefore, the study by Weintrob *et al.*[47] (in which participants were aged 8 to 14 years) may be significantly different from the other studies in children (of up to 18 years) and perhaps should be excluded.

However, because of the lack of data, we have included the studies by Ly *et al.*[33] and Weintrob *et al.*[47] in the analyses for children. As a consequence, the results of these analyses are less reliable as a result of clinical heterogeneity between studies.

Despite trying to include as many studies as possible in the analyses for adults, we still have missing results for key comparisons for the economic model. Most importantly, results for comparisons of the MiniMed Veo system and the integrated CSII + CGM system with the comparators CSII + CGM, CSII + SMBG, MDI + CGM and MDI + SMBG are missing for the outcomes change in HbA_{1c} levels and severe hypoglycaemic event rates. As can be seen in *Table 2*, none of the included studies looked at CSII + CGM and MDI + CGM. Therefore, a comparison between these comparators cannot be made. However, it is possible to calculate results for these outcomes (change in HbA_{1c} and severe hypoglycaemic event rates) by comparing the MiniMed Veo system and the integrated CSII + CGM system with CSII + SMBG and with MDI + SMBG in a series of indirect comparisons, if we accept the following assumptions:

- All studies can be pooled, irrespective of length of follow-up (3, 6 or ≥ 9 months).
- Studies in mixed populations (including those of children and adults that do not report separate results by age group) can be pooled in one analysis. This means that we will include O'Connell *et al.* (30 adults and 32 children),[35] RealTrend (81 adults and 51 children)[36] and Hirsch *et al.* (98 adults and 40 children),[34] in the analyses for adults. Ly *et al.*[33] (30 adults and 65 children) will still be excluded from these analyses.
- For event rates, we assumed that if numbers of events were reported, the rate could be derived by assuming that all patients had been observed for the follow-up duration of the trial.

It should be taken into account that the following analyses, including any subsequent analyses, such as the economic model, are based on these assumptions and that the clinical experts advised against using these wide inclusion criteria for pooling studies in one analysis. The results of these analyses are therefore likely to be considerably less reliable because of higher levels of clinical heterogeneity between studies included in these analyses for adults.

Change in glycated haemoglobin levels

The results of the indirect comparison, as shown in *Figure 8* and *Table 21*, demonstrate that there were no significant differences with regard to the change in HbA_{1c} levels in adults (including mixed populations) between the MiniMed Veo system and the integrated CSII + CGM system. Similarly, there were no

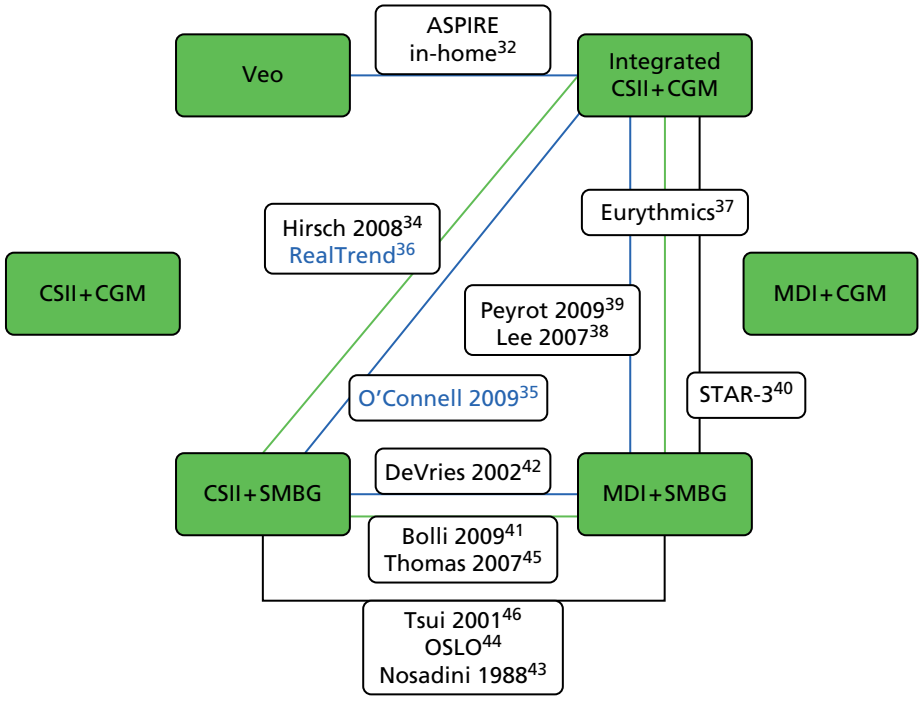

FIGURE 8 Network of studies[32,34–46] comparing change in HbA_{1c} levels at all follow-up times in adults and mixed populations. Green boxes represent the interventions; lines represent comparisons between interventions at different follow-up times (blue line, 3 months; green line, 6 months; black line, ≥ 9 months); and transparent boxes represent studies (blue, mixed population; black, adult population).

TABLE 21 Results of the indirect comparison with regard to change in HbA_{1c} levels at all follow-up times in adults and mixed populations

Intervention	Integrated CSII + CGM, WMD (95% CI)	CSII + SMBG, WMD (95% CI)	MDI + SMBG, WMD (95% CI)
Veo	0.04 (–0.07 to 0.15)	–0.07 (–0.31 to 0.17)	**–0.66 (–1.05 to –0.27)**
Integrated CSII + CGM		–0.11 (–0.32 to 0.10)	**–0.70 (–1.05 to –0.30)**[a]
CSII + SMBG			–0.46 (–1.18 to 0.27)[b]

WMD values of < 0 indicate that the results favour the interventions listed in column 1. Statistically significant differences are those where the 95% CIs do not include 0 (shown in bold).
a This result was from a random-effects analysis as I^2 was 62.5%.
b This result was from a random-effects analysis as I^2 was 80.2%.

significant differences with regard to the change in HbA_{1c} levels in adults (including mixed populations) between the MiniMed Veo system and the integrated CSII + CGM system on the one hand and CSII + SMBG on the other. There was a significant difference in the change in HbA_{1c} levels in adults (including mixed populations) between the MiniMed Veo system and the integrated CSII + CGM system if both systems are compared with MDI + SMBG, favouring the MiniMed Veo system and the integrated CSII + CGM system over MDI + SMBG.

Overall, integrated systems (the MiniMed Veo system and the integrated CSII + CGM system) are superior to SMBG (with CSII or MDIs) in terms of HbA_{1c} levels. However, as reported above, the reliability of the results of these analyses is reduced because of a relatively high level of heterogeneity between the studies included in the analyses. This is particularly true for the comparison between the MiniMed Veo system and CSII + SMBG, which is based not only on an indirect comparison (using data from the ASPIRE in-home trial,[32] O'Connell *et al.*,[35] Hirsch *et al.*[34] and RealTrend[36]), but also on data from 3-month follow-up (ASPIRE in-home[32] and O'Connell *et al.*[35]) combined with data from 6-month follow-up (Hirsch *et al.*[34] and RealTrend[36]), and on data from adults (ASPIRE in-home[32] and Hirsch *et al.*[34]) and mixed populations (O'Connell *et al.*[35] and RealTrend[36]).

Severe hypoglycaemic event rate

The results of the indirect comparison, as shown in *Figure 9* and *Table 22*, show that there were no significant differences in the severe hypoglycaemic event rate in adults (including mixed populations) between the MiniMed Veo system and any of the other treatments. Similarly, there were no significant differences in the change in severe hypoglycaemic event rate between the integrated CSII + CGM system and MDI + SMBG. There was a significant difference in the severe hypoglycaemic event rate between the integrated CSII + CGM system and CSII + SMBG, in favour of CSII + SMBG. However, as reported above, the reliability of the results of these analyses is reduced because of a relatively high level of heterogeneity between the studies included in the analyses. With regard to the significant difference in particular, it is important to point out that this result relies upon the data from three trials with different follow-up times (3 months for O'Connell *et al.*[35] and 6 months for Hirsch *et al.*[34] and RealTrend[36]), and that data from all three trials are from mixed populations, including adults and children.

Overall, the main conclusion regarding the evidence for hypoglycaemic event rate, and change in HbA_{1c} levels, in adults is that the evidence is limited and when all available evidence is combined, the results become highly unreliable.

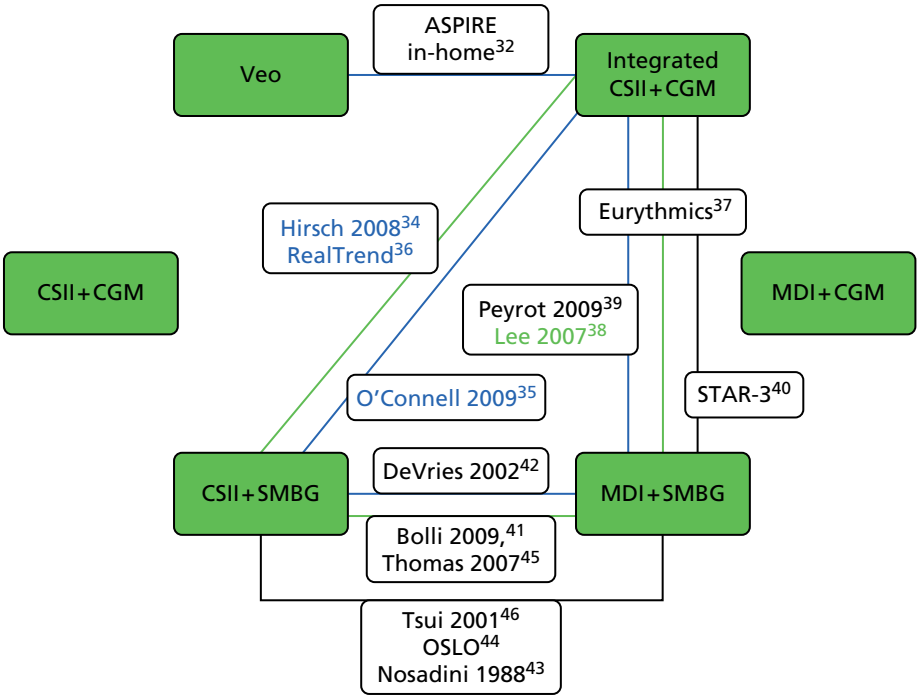

FIGURE 9 Network of studies[32,34–46] comparing severe hypoglycaemic event rate at all follow-up times in adults and mixed populations. Green boxes represent the interventions; lines represent comparisons between interventions at different follow-up times (blue line, 3 months; green line, 6 months; black line, ≥ 9 months); transparent boxes represent studies (blue, mixed population; black, adult population; green, adults and all hypoglycaemic events).

TABLE 22 Results of the indirect comparison for severe hypoglycaemic event rate at all follow-up times in adults and mixed populations

Intervention	Integrated CSII + CGM, rate ratio (95% CI)	CSII + SMBG, rate ratio (95% CI)	MDI + SMBG, rate ratio (95% CI)
Veo	0.12 (0.01 to 2.14)	0.39 (0.02 to 8.40)	0.10 (0.01 to 1.93)
Integrated CSII + CGM		**3.23 (1.10 to 9.49)**	0.86 (0.51 to 1.46)
CSII + SMBG			0.67 (0.38 to 1.20)

Rate ratio values of < 1 indicate that the results favour the intervention listed in column 1. Statistically significant differences are those where the 95% CIs do not include 1 (shown in bold).

Ongoing studies

We found 18 ongoing studies[51–68] – 17 RCTs[51–55,57–68] and one observational study[56] looking at the use of a threshold suspend feature at home with a sensor-augmented insulin pump (SAP) (MiniMed 530G). Most ongoing studies are in children (12 out of 18 studies[51,53,54,56,60–62,64–68]), five are in a general population (adults or adults and children)[52,55,57,59,63] and one study is in pregnant women.[58] Seven studies include the MiniMed Veo system[51,52,54–56,59,64] and four studies include the integrated CSII + CGM system.[55,63,64,66] Details of ongoing studies are reported in *Table 23*.

TABLE 23 Ongoing studies

Study ID	Year	Intervention	RCT	Comment	Age
Lawson *et al.*[51]	2014	Veo vs. CSII + SMBG	Yes	Complex design. Trial uses the Veo system. Patients are randomised to simultaneous initiation of pump and CGM vs. initiation of pump with CGM started 6 months later. Outcomes were measured after 6 and 12 months. Group B is pump + SMBG for 6 months then pump + CGM for the next 6 months	5–18 years
Troub *et al.*[52]	2013	Veo vs. CSII + CGM	Yes		General
Blair *et al.*[53]	2010	CSII + SMBG vs. MDI + SMBG	Yes	CSII compared with MDI regimens in children and young people at diagnosis of T1DM; protocol only	Children
Assistance Publique – Hôpitaux de Paris NCT00949221[54]	2012	Veo vs. CSII + SMBG	Yes	Device: Medtronic's Paradigm 754 Veo monitor with MiniLink REAL-Time transmitter (Conformité Européenne). 3 months and 9 months of SMBG vs. 12 months of using the Veo system	2–18 years
Steno Diabetes Centre NCT01454700[55]	2012	Veo vs. integrated CSII + CGM vs. MDI + SMBG	Yes	CSII plus CGM (Medtronic's MiniMed Paradigm REAL-Time system or Veo) vs. MDIs	General
Medtronic Diabetes NCT02120794[56]	2014	Veo	Obs	Use of threshold suspend feature at home with a SAP [MiniMed 530G (Medtronic)] in children with T1DM over 1 year	2–15 years
Vastra Gotaland Region NCT02092051[57]	2014	MDI + CGM vs. MDI + SMBG	Yes	CGM vs. SMBG in individuals with T1DM treated with MDIs	General
University of British Columbia NCT02064023[58]	2014	CSII + SMBG vs. MDI + SMBG	Yes	Comparison of CSII with MDIs for the treatment of pregestational diabetes during pregnancy (T1DM and T2DM)	Pregnant
Sheffield Teaching Hospitals NHSFT (REPOSE Trial) NCT01616784EUCTR2010-023198–21-GB[59]	2013	Veo vs. CSII + SMBG vs. MDI + SMBG	Yes	CSII (insulin pump) plus DAFNE versus MDI [insulin detemir (Levemir®, Novo Nordisk) and quick-acting insulin] plus DAFNE	> 18 years
Seattle Children's Hospital NCT00875290[60]	2011	CSII + CGM vs. CSII + SMBG	Yes	CSII alone vs. CSII + RTSA in infants with T1DM	0–3 years
Nemours Children's Clinic NCT00357890[61]	2012	CSII + SMBG vs. MDI + SMBG	Yes	MDI vs. CSII in adolescents with newly diagnosed T1DM	12–17 years

continued

TABLE 23 Ongoing studies (*continued*)

Study ID	Year	Intervention	RCT	Comment	Age
Addenbrooke's NHS Trust EUCTR2005-004526-72-GB[62]	2006	CSII + CGM vs. MDI + SMBG	Yes	CSII vs. MDI in preschool-aged children with T1DM	< 18 years
Medtronic Australasia ACTRN12606000049572[63]	2006	Integrated CSII + CGM vs. CSII + SMBG	Yes	MiniMed Paradigm REAL-Time insulin pump and CGM system (MMT-722 pump) vs. pre-trial insulin pump device (no new intervention)	13–39 years
Juvenile Diabetes Research Foundation ACTRN12614000510640[64]	2014	Veo vs. integrated CSII + CGM	Yes	CSII with real-time CGM system and predictive LGS feature (Medtronic's MiniMed 640G) vs. standard SAPT	8–20 years
The Royal Children's Hospital Melbourne ACTRN12610000605099[65]	2010	CSII + SMBG vs. MDI + SMBG	Yes	CSII vs. MDIs in children and adolescents with T1DM	9–16 years
Royal Children's Hospital ACTRN12611000142932[66]	2011	Integrated CSII + CGM vs. CSII + CGM	Yes	Patients' own pump vs. a new integrated pump (unclear which type of monitoring was used with patients' own pumps)	< 18 years
Alder Hey Children's NHS Foundation Trust ISRCTN29255275[67]	2010	CSII + SMBG vs. MDI + SMBG	Yes	CSII vs. MDIs in children with T1DM	1–15 years
University of Schleswig-Holstein NCT01338922[68]	2011	CSII + SMBG vs. MDI + SMBG	Yes	CSII vs. MDIs in children with T1DM	6–16 years

DAFNE, dose adjusted for normal eating; NHSFT, Sheffield Teaching Hospitals NHS Foundation Trust; Obs, observational study; RTSA, real-time sensor augmentation.

Summary of results

In this summary of results, we will describe the results by population (adults, children and pregnant women) and by comparison. First, we will describe comparisons between the MiniMed Veo system and other treatments, then comparisons between the integrated CSII + CGM system and other treatments, and, finally, we will describe the main remaining comparisons.

Nineteen trials were included:[32–50] 12 reported data for adults,[32,34,37–46] six reported data for children[33,34,40,47–49] and one trial reported data for pregnant women.[57] Four trials were in mixed populations (adults and children);[34–36,40] two of these reported data separately for adults and children and are included in the 12 trials for adults and six trials for children.[34,40] Two trials (O'Connell *et al.*[35] and RealTrend[36]) did not report data separately for adults and children. Therefore, the results from these trials were not used in the main analyses. However, the data are reported in the data extraction tables in *Appendix 3* and they are used in the additional analyses for the economic model (see *Additional analyses for the economic model*).

Studies in adults

Twelve studies were included in the analyses for adults.[32,34,37–46] Only one of these studies (Hirsch *et al.*[34]) reported the change in HbA_{1c} levels separately for adults. None of these studies looked at CSII or MDI + CGM. *Table 5* shows an overview of these 12 studies, their comparisons and their baseline data. Further details are reported in *Appendix 3*.

MiniMed Veo system versus the integrated CSII + CGM system

Only one study (ASPIRE in-home[32]) with data for adults ($n = 247$) included the MiniMed Veo system as one of the treatment arms. This study compared the MiniMed Veo system with an integrated CSII + CGM system at 3-month follow-up. The results of this study showed that there was no significant difference in change in HbA_{1c} levels at 3-month follow-up; however, both nocturnal hypoglycaemic event rates and day and night hypoglycaemic event rates were significantly reduced for patients using the MiniMed Veo system. There were no significant differences in any of the other reported outcomes (BG level at follow-up, insulin use, DKA, quality of life or adverse events). Therefore, the conclusion from this trial is that the MiniMed Veo system reduces hypoglycaemic events in adults more than the integrated CSII + CGM system does, without any differences in other outcomes, including the change in HbA_{1c} levels.

MiniMed Veo system versus other treatments

Indirect evidence seems to suggest that that there are no significant differences between the MiniMed Veo system and CSII + SMBG or MDI + SMBG with regard to the change in HbA_{1c} levels at 3-month follow-up.

However, if all studies are combined (see *Additional analyses for the economic model*), the MiniMed Veo system is significantly better than MDI + SMBG in terms of the change in HbA_{1c} levels.

The integrated CSII + CGM system versus other treatments

Five studies compared the integrated CSII + CGM system with other treatments.[34,37–40] One of these compared the integrated CSII + CGM system with CSII + SMBG at 6-month follow-up (Hirsch *et al.*[34]), but this study reported only the change in HbA_{1c} levels separately for adults. The other four studies compared the integrated CSII + CGM system with MDI + SMBG at 3-month follow-up (Lee *et al.*,[38] and Peyrot and Rubin[39]), at 6-month follow-up (Eurythmics[37]) and at 12-month follow-up (STAR-3[40]).

The results of the trial[34] comparing the integrated CSII + CGM system with CSII + SMBG at 6-month follow-up in adults showed no significant difference in HbA_{1c} levels between groups. Other outcomes in this trial were not reported separately for adults.[34] An indirect comparison showed that quality of life was significantly more improved in the integrated CSII + CGM group than in the CSII + CGM group.[37,41]

For the comparison of the integrated CSII + CGM system with MDI + SMBG, the most reliable data, from the largest trial with 12-month follow-up (STAR-3[40]), show that there is a significant difference in the change in HbA_{1c} levels and in the proportion of patients achieving HbA_{1c} levels of $\leq 7\%$, in favour of the integrated CSII + CGM system. With regard to hypoglycaemic event rates, none of the studies showed a significant difference between groups. Similarly, there were no significant differences in DKA between groups. Insulin use was significantly lower in patients using the integrated CSII + CGM system, and quality of life was significantly more improved in the integrated CSII + CGM group than in the CSII + SMBG group. Overall, the results show significant results in favour of the integrated CSII + CGM system over MDI + SMBG with regard to HbA_{1c} levels and quality of life.

Continuous subcutaneous insulin infusion versus multiple daily insulin injections

We found six trials with data for adults comparing CSII + SMBG with MDI + SMBG.[41–46] No trials were found with data for adults comparing the treatments CSII + CGM and MDI + CGM.

In terms of the change in HbA_{1c} levels, only one[42] of the six trials showed a significant difference between CSII + SMBG and MDI + SMBG. DeVries *et al.*[42] found a significant difference in favour of CSII + CGM: at 16 weeks, the mean HbA_{1c} level was 0.84% lower (mean = –0.84%, 95% CI –1.31% to –0.36%) in the CSII + SMBG group than in the MDI + SMBG group. Significance was not reported in the OSLO trial[44] or in Nosadini *et al.*,[43] while the difference between groups was not significant in Bolli *et al.*,[41] Thomas *et al.*[45] or Tsui *et al.*[46]

In terms of the number of severe hypoglycaemic events, three trials found no significant differences between groups (Bolli *et al.*,[41] DeVries *et al.*[42] and Thomas *et al.*[45]), while this was not reported in the other three trials.

Studies in children

Six studies were included in the analyses for children.[33,34,40,47–49] One of these studies (Hirsch *et al.*[34]) reported only the change in HbA_{1c} levels separately for children. None of these studies looked at CSII or MDI + CGM. *Table 15* shows an overview of these six studies, their comparisons and their baseline data. Further details are reported in *Appendix 3*.

MiniMed Veo system versus the integrated CSII + CGM system

None of the studies in children made a direct comparison between the MiniMed Veo system and the integrated CSII + CGM system.

An indirect comparison was possible, using data at 6-month follow-up from Ly *et al.*[33] and Hirsch *et al.*,[34] but only for HbA_{1c} levels, which showed no significant difference between groups.

MiniMed Veo system versus other treatments

One study compared the MiniMed Veo system with CSII + SMBG at 6-month follow-up in a mixed population of patients between 4 and 50 years old (Ly *et al.*[33]). No results were found for the MiniMed Veo system versus any other treatment at 3-month or ≥ 9-month follow-up.

The only significant difference between treatment groups was the rate of moderate and severe hypoglycaemic events, which favoured the MiniMed Veo system. All other outcomes showed no significant differences between groups.

The integrated CSII + CGM system versus other treatments

One study compared the integrated CSII + CGM system with CSII + SMBG at 6-month follow-up in children (Hirsch *et al.*[34]). This trial found no significant difference in HbA_{1c} levels between groups.

One study (STAR-3[40]) compared the integrated CSII + CGM system with MDI + SMBG at 12-month follow-up in children. This trial showed a significant difference in HbA_{1c} change scores in favour of the integrated CSII + CGM system, but no significant difference in the number of children achieving HbA_{1c} levels of ≤ 7%. The hyperglycaemic AUC was significantly lower in the integrated CSII + CGM group, but the hypoglycaemic AUC showed no significant difference between groups. Other outcomes showed no significant differences between groups.

Studies in pregnant women

We found one RCT that reported data for pregnant women.[57] The study included 32 pregnancies in 31 different pregnant women. The number of pregnancies was the unit of analysis. The study compared CSII + SMBG with MDI + SMBG; therefore, the results are not relevant for comparisons with the MiniMed Veo system or the integrated CSII + CGM system.

Chapter 4 Assessment of cost-effectiveness

In this chapter, we explore the cost-effectiveness of integrated insulin pump systems in the management of T1DM in adults in the UK.

Review of the economic evaluations

Search methods

Literature searches were undertaken to identify published economic evaluations of the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system. The search strategy for economic evaluations included a filter designed to identify cost and economic studies in databases that are not health economics specific.

The following databases and resources were searched for relevant economic evaluations and cost studies:

- NHS Economic Evaluation Database (Wiley Online Library): issue 3/July 2014
- Health Economic Evaluations Database (Wiley Online Library): up to 5 September 2014
- MEDLINE (via OvidSP): 1946–2014/August week 4
- MEDLINE In-Process Citations and Daily Update (via OvidSP): up to 5 September 2014
- PubMed (via National Library of Medicine): up to 5 September 2014
- EMBASE (via OvidSP): 1974–2014/week 34
- EconLit (EBSCO*host*): 1969–1 August 2014
- Cost-effectiveness Analysis Registry (www.cearegistry.org): up to 5 September 2014
- Research Papers in Economics (http://repec.org/): up to 5 September 2014.

In addition, economic searches specifically for the MiniMed Paradigm Veo system, and Vibe and G4 PLATINUM CGM system were conducted using the same resources listed above.

The full search strategies are presented in *Appendix 1*.

Relevant studies were then identified in two stages. Titles and abstracts returned by the search strategy were examined independently by two researchers (Maiwenn Al and Isaac Corro Ramos) and screened for possible inclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (Maiwenn Al and Isaac Corro Ramos) examined these independently for inclusion or exclusion, and disagreements were resolved by discussion.

Inclusion criteria

The initial search identified a total of eight abstracts, six of which were of conference abstracts and were thus not included. Both of the full-text papers were identified as relevant to our review. These studies were by Kamble *et al.*[69] and Ly *et al.*[70] The study by Kamble *et al.*[69] evaluated integrated CSII + CGM versus MDI + SMBG in the USA, whereas the study by Ly *et al.*[70] evaluated the MiniMed Paradigm Veo system versus CSII + SMBG in Australia. The first evaluation[69] showed that the integrated CSII + CGM system was not cost-effective compared with MDI + SMBG, despite taking all health effects into account through the IMS Centre for Outcomes Research and Effectiveness diabetes model (IMS CDM) version 8.5 (IMS Health, Danbury, CT, USA). On the other hand, the second study[70] showed that the MiniMed Veo system was cost-effective compared with CSII + SMBG, if only the impact on the reduction of severe hypoglycaemic events was taken into account.

The characteristics of these studies are summarised in *Table 24*.

TABLE 24 Summary of included full-text papers

Study, country	Summary of model	Intervention/ comparator	Patient population; average age; HbA_{1c} levels at baseline	QALYs (intervention; comparator)	Costs (intervention; comparator)	ICER (per QALY gained)	Sensitivity analyses
Kamble *et al.* (2012),[69] USA	• CORE Diabetes Model (Markov model for diabetes, includes a large number of complications) • US health-care perspective • Time horizon: 60 years • Discount rate: 3% for costs and effects • Clinical data from STAR-3 trial[32] • Utilities: mixed, EQ-5D for some complications, direct elicitation for some other complications • Deterministic and probabilistic sensitivity analysis conducted	Integrated CSII + CGM vs. MDI + SMBG	Adults with inadequately controlled T1DM; 41.3 years; 8.3%	10.794; 10.418	For 3-d sensor: US$253,493; US$167,170 For 6-d sensor: US$230,352; US$167,170	For 3-d sensor: US$229,675/QALY For 6-d sensor: US$168,104/QALY	• Deterministic sensitivity analysis indicated that ICER would only substantially reduce (below US$100,000) when assuming only 1 test strip per sensor change with the integrated system or when assuming a 0.0329 utility increment associated with less fear of hypoglycaemia throughout the remaining lifetimes of patients using the integrated system • PSA indicated that, at a willingness-to-pay threshold of US$50,000/QALY, the probability of integrated CSII + CGM being cost-effective was 0%
Ly *et al.* (2014),[70] Australia	• Decision analytical model with only severe hypoglycaemia as event • Australian health-care system perspective • Time horizon: 6 months • No discounting • Clinical data from trial ACTRN1261000002404433 • Utilities: EQ-5D • One-way sensitivity analyses conducted	MiniMed Paradigm Veo system vs. CSII + SMBG	Patients with T1DM who have impaired awareness of hypoglycaemia (subgroup analysis for ≥ 12 years); 18.6 years; 7.5%	Outcome: severe hypoglycaemic events (all patients/patients ≥ 12 years); CSII + CGM + LGS: 0/0; CSII + SMBG: 0.08607/0.1052 Outcome: QALYs (using patients ≥ 12 years); CSII + CGM + LGS: 00.036650; CSII + SMBG: –0.00017	Total costs (intervention costs + other medical costs due to severe hypoglycaemic events) (all patients/patients ≥ 12 years); CSII + CGM + LGS: AU$4382/AU$4432; CSII + SMBG: AU$2867/AU$2929	All patients: NA because utility data were available only for patients ≥ 12 years; patients ≥ 12 years: AU$40,803	Sensitivity analysis indicated that ICER would only substantially increase (above AU$100,000) when the utility values were changed to 0.0075

3-d sensor, a sensor that needs to be replaced every 3 days; 6-d sensor, a sensor that needs to be replaced every 6 days; CORE, Centre for Outcomes Research and Effectiveness; EQ-5D, European Quality of Life-5 Dimensions scale; ICER, incremental cost-effectiveness ratio; NA, not applicable; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Of the six (excluded) conference abstracts, one was an abstract that was later published as a full-text paper[71] and was already included as one of the two selected full-text papers.[69] While we will not formally discuss the conference abstracts,[72–76] their characteristics, as far as they can be found in these abstracts, are presented in *Table 25*.

Quality assessment

A quality appraisal was carried out on the two studies,[69,70] using the Drummond checklist.[77] A summary of the results are provided in *Table 26*.

Results

Study design

Both studies[69,70] were modelling studies, each based primarily on one clinical study. As a result, one of the studies[69] did not explain why the comparator had been chosen. They both stated their research question and the approach to economic evaluation clearly.

In one study,[70] results were presented both as cost per severe hypoglycaemic events avoided (all patients) and as costs per quality-adjusted life-year (QALY) gained (patients of ≥ 12 years of age). A clear rationale was provided [i.e. the European Quality of Life-5 Dimensions scale (EQ-5D) was administered to parents and carers on behalf of children aged < 12 years] with regard to why cost per QALY could only be estimated for patients of ≥ 12 years. The outcomes per severe hypoglycaemic events avoided are unlikely to be informative for decision makers who want to establish the cost-effectiveness from a health-care perspective.

Data

As mentioned above, both studies[69,70] were based on a single clinical study. The current papers describe the details of the study design only briefly, but refer to the papers that specifically present the clinical results. The study[69] based on the IMS CDM did not provide a rationale with regard to why the IMS CDM was chosen. The other study[70] explained the choice of model by stating that this was a trial-based economic evaluation and so costs and effects were not extrapolated beyond the 6-month clinical trial period. This means that the long-term impact of the changes in HbA_{1c} levels seen during the clinical study were not taken into consideration, and only the direct impact of avoiding severe hypoglycaemic events are accounted for.

For the study based on the IMS CDM,[69] all utilities and costs of complications were taken from literature. Hence, in this paper, no information was available with regard to the subjects from whom valuations of quality of life were obtained, and resources for complications were not reported separately from their unit cost. The cost information relating to the technologies and insulin treatment did provide both resource-use and unit costs.

For the 6-month study,[70] all details regarding utilities and resource use were clearly presented. However, once the results were presented, it became clear that an explanation for the calculation of utilities and QALYs was lacking. For example, the paper reported a QALY accumulation of –0.00017 for the standard pump group (CSII + SMBG), which would only be possible if patients had a health state of worse than death. A likely explanation is the definition of QALYs used in the paper, but this was not clarified.

Analysis and interpretation of results

Both studies[69,70] were, in general, performed appropriately; however, the study by Kamble *et al.*[69] did not discuss any issues pertaining to generalisability.

In summary, only one study was found for the integrated CSII + CGM and one for the MiniMed Veo system, both with different comparators and for different countries. The latter study is of limited importance to the current diagnostic appraisal, given its short time horizon of 6 months and its very limited model structure. The study of integrated CSII + CGM by Kamble *et al.*[69] was better, given that all

TABLE 25 Summary of conference abstracts

Study, country	Summary of model	Intervention/ comparator	Patient population; average age; HbA_{1c} levels at baseline	QALYs (intervention; comparator)	Costs (intervention; comparator)	ICER (per QALY gained)	Sensitivity analyses
Gomez *et al.* (2013),[73] Colombia	• CORE Diabetes Model (Markov model for diabetes, includes a large number of complications) • Perspective: not stated • Time horizon: not stated • Discount rate: not stated • Clinical data from trial (no reference) • Utilities: not mentioned but the reduction in the fear of hypoglycaemic events on quality of life was included • Deterministic sensitivity analysis conducted	SAP/comparator not stated	Model population not described, trial population of 217 T1DM patients (average diabetes duration of 14 years); 34 years; 8.97%	QALYs not presented but life-year gain of 3.51	No costs presented	COP44,889,916 (US$24,939) based on only direct costs	Extensive sensitivity analyses showed the robustness of the results
Gomez *et al.* (2014),[72] Colombia	This study is the same as the study above,[73] but reports only on effects, not costs	SAP vs. MDIs	The inputs were taken from a real-life Colombian clinical study of 217 T1DM patients on SAPT	QALYs not presented but life-year gain of 3.51; diabetes complications delayed by 1.74 years			
Lindholm Olinder *et al.* (2014),[74] Sweden	Abstract does not indicate if a model was used; systematic review to establish available evidence on effects of CGM and SAPT, in A, C and P, compared with SMBG	CGM and SAPT vs. SMBG	Patients (A, C and P) with T1DM	No QALYs presented	Calculations of costs demonstrated an increased cost of €3026 for CGM vs. SMBG and €4216 for SAP vs. MDI and SMBG	No ICER presented	

Study, country	Summary of model	Intervention/ comparator	Patient population; average age; HbA_{1c} levels at baseline	QALYs (intervention; comparator)	Costs (intervention; comparator)	ICER (per QALY gained)	Sensitivity analyses
Roze *et al.* (2014),[75] France	• CORE Diabetes Model (Markov model for diabetes, includes a large number of complications) • Perspective: not stated • Time horizon: lifetime • Discount rate: not stated • Effectiveness data from meta-analysis • Reduced fear of hypoglycaemic events in integrated CSII + CGM group accounted for in QALY • Sensitivity analysis conducted	Integrated CSII + CGM vs. CSII (the method for BG monitoring is not stated)	Adults with inadequately controlled T1DM; 36 years; 9%	1.27 QALYs gained	Extra annual costs of €1258 per patient	€27,796	Sensitivity analysis on key drivers confirmed robustness of results under a wide range of assumptions
Roze *et al.* (2014),[76] UK	• CORE Diabetes Model (Markov model for diabetes, includes a large number of complications) • Perspective: not stated • Time horizon: lifetime • Discount rate: not stated • Effectiveness data from meta-analysis and real-life observational study • Reduced fear of hypoglycaemic events in integrated CSII + CGM group accounted for in QALY • Sensitivity analysis conducted	Integrated CSII + CGM vs. CSII (the method for BG monitoring is not stated)	Adults with inadequately controlled T1DM; 27 years; 10%	3.1 QALYs gained	Extra annual costs of £1143 per patient	£16,986	Sensitivity analysis on key drivers confirmed robustness of results under a wide range of assumptions

A, adults; C, children; COP, Columbian Pesos; CORE, Centre for Outcomes Research and Effectiveness; ICER, incremental cost-effectiveness ratio; P, pregnant women; QALY, quality-adjusted life-year.

TABLE 26 Results of the quality assessment of studies, performed using the Drummond checklist (1996)[77]

Criteria	Kamble *et al.* (2012)[69]	Ly *et al.* (2014)[70]
Study design		
1. Was the research question stated?	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No, CEA based on clinical trial so alternative based on that	Yes
5. Were the alternatives being compared clearly described?	Partially; not easy to find if glucose monitoring is CGM or SMBG	Yes
6. Was the form of economic evaluation stated?	Yes	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Justification was given, but doubtful if choice is reasonable
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes; most details in separate paper	Yes; most details in separate paper
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	NA
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	Yes	Yes; however, after seeing QALY outcomes, explanation clearly insufficient
13. Were the details of the subjects from whom valuations were obtained given?	NA; utilities from literature	Yes
14. Were productivity changes (if included) reported separately?	NA	NA
15. Was the relevance of productivity changes to the study question discussed?	NA	NA
16. Were quantities of resources reported separately from their unit cost?	Yes for all treatment related costs; no for complication costs	Yes
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Yes
18. Were currency and price data recorded?	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	Yes	NA

TABLE 26 Results of the quality assessment of studies, performed using the Drummond checklist (1996)[77] (*continued*)

Criteria	Kamble *et al.* (2012)[69]	Ly *et al.* (2014)[70]
20. Were details of any model used given?	Yes	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No justification for why IMS CDM was used in the paper	A justification was given, i.e. the clinical trial was modelled and extrapolation was not considered of interest. Unlikely that only looking at hypoglycaemic events and not long-term complications is of interest for decision makers
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Yes
23. Was the discount rate stated?	Yes	NA
24. Was the choice of rate justified?	Yes	NA
25. Was an explanation given if costs or benefits were not discounted?	NA	Yes
26. Were the details of statistical test(s) and CIs given for stochastic data?	Yes	Yes
27. Was the approach to sensitivity analysis described?	Yes	Yes
28. Was the choice of variables for sensitivity analysis justified?	Yes	No justification given, but choices appear reasonable
29. Were the ranges over which the parameters were varied stated?	Yes	Yes
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Yes
31. Was an incremental analysis reported?	Yes	Yes
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Yes; this highlighted the lack of face validity: QALYs in both arms were 0.036650 and –0.00017, while perfect health would yield 0.5 per arm
33. Was the answer to the study question given?	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	Yes
35. Were conclusions accompanied by the appropriate caveats?	Yes	Not fully; authors did not discuss the impact of the intervention in the trial on HbA_{1c} levels and how that would impact cost-effectiveness
36. Were generalisability issues addressed?	No	Yes

CEA, cost-effectiveness analysis; NA, not applicable; QALY, quality-adjusted life-year.

potentially relevant costs and effects were included. However, IMS Health has now published updated utility values that conform with the NICE standard (i.e. based on EQ-5D)[78] and has also updated the IMS CDM several times. Thus, the value of the Kamble *et al.* paper[69] mostly relates to its use for formulating scenarios and presenting a benchmark against which the validity of outcomes from the de novo cost-effectiveness analysis could be checked.

Model structure and methodology

This section describes the health economic model used to evaluate the cost-effectiveness of the MiniMed Paradigm Veo system (an integrated CGM and insulin pump system with LGS function) and the Vibe and G4 PLATINUM CGM system for the management of T1DM in adults in comparison with (1) CSII + CGM, (2) CSII + SMBG, (3) MDI + CGM and (4) MDI + SMBG.

The IMS CDM[79] was chosen to perform the cost-effectiveness analyses in this assessment. The IMS CDM has been previously used in NICE- and NHS-related projects on T1DM. It is probably the most commonly used model in the literature and it has been validated extensively. It was used to assess the cost-effectiveness of CSII versus MDIs for T1DM patients in a HTA report from 2010.[80] In that report, the IMS CDM was deemed to be inappropriate for health economic outcomes in paediatric and adolescent populations. This was confirmed by the model developers who also mentioned that the model is not appropriate for pregnant women either. Therefore, these two subgroup populations were not included in the cost-effectiveness analyses. The IMS CDM has also been used in the current update of the NICE Guideline on T1DM (NG17).[81] The model's time horizon was set to 80 years. Costs were estimated from the perspective of the NHS in England and Wales. Consequences were expressed in life-years gained and QALYs. All costs and effects were discounted by 3.5%. The uncertainty about model input parameters and the potential impact on the model results were explored through scenario analyses and probabilistic sensitivity analyses.

Model structure

The IMS CDM is an internet-based, interactive simulation model that predicts the long-term health outcomes and costs associated with the management of T1DM and T2DM. It is suitable for running cohort (bootstrap) and individual patient-level simulations. It was first developed by the Centre for Outcomes Research and Effectiveness and details of the first version were published by Palmer *et al.* in 2004.[79] It is widely used in diabetes cost-effectiveness research, both by health technology companies as well as those who pay for such technologies, and it has also been used in previous NICE technology assessments and clinical guidelines.[14,81–85] The model has been extensively validated. Since 1999, it has been examined at Mount Hood conferences, during which health economic models on diabetes are compared with each other in terms of their structure, performance and validity.[86–88] Two major validation papers on the IMS CDM have been published to date.[89,90] The latest one,[90] from 2014, is the basis for the technical model description provided in this report. This description is consistent with the latest version of the model (version 8.5). Given the degree of validation of the model, and in order to be in line with the T1DM NICE guideline,[81] it was deemed important not to use an alternative model or develop a de novo cost-effectiveness model for this evaluation.

The structure of the IMS CDM (from McEwan *et al.*[90]) is shown in *Figure 10*. The IMS CDM comprises 17 interdependent submodels, which represent the most common diabetes-related complications: angina pectoris, myocardial infarction (MI), congestive heart failure (CHF), stroke, peripheral vascular disease (PVD), diabetic retinopathy, cataracts, hypoglycaemia, DKA, nephropathy, neuropathy, foot ulcer/amputation, macular oedema, lactic acidosis (T2DM only), (peripheral) oedema (T2DM only) and depression. A submodel for non-specific mortality is also included. Each of these submodels is a Markov model that includes different health states depicting the severity/stage of the complication. Transition probabilities in between the states of a complication submodel can be dependent on time, demographics, health state, physiological factors and diabetes type.

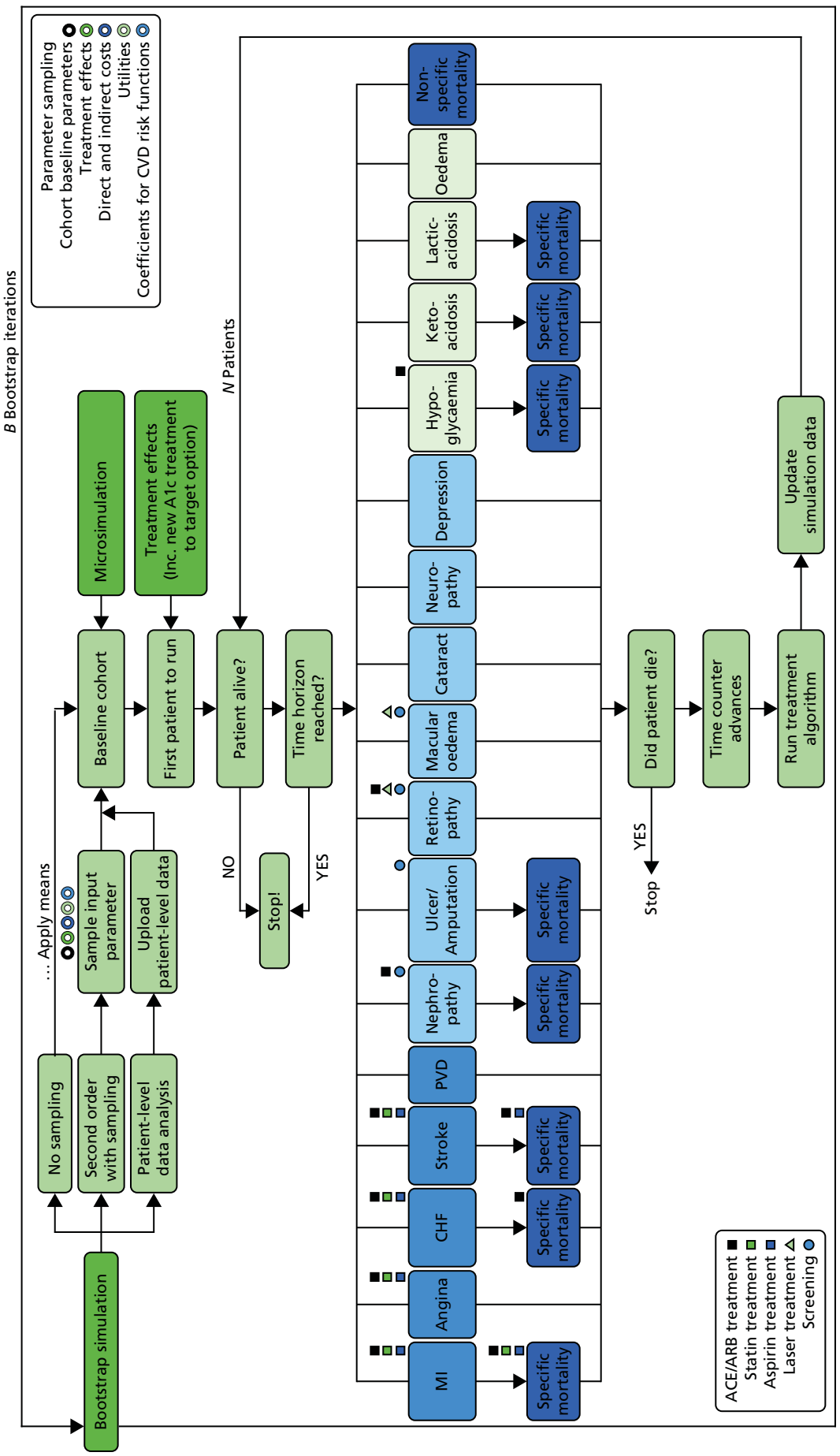

FIGURE 10 IMS CDM model structure. Reprinted from *Value in Health*, 17/6, Phil McEwan, Volker Foos, James L. Palmer, Mark Lamotte, Adam Lloyd, David Grant, Validation of the IMS CORE Diabetes Model, Pages 714–724, Copyright (2014), with permission from Elsevier.[90] ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CHF, congestive heart failure; CVD, cardiovascular disease; Inc., including; MI, myocardial infarction; PVD, peripheral vascular disease.

In addition, the non-parametric bootstrapping approach provides additional information on the uncertainty surrounding the long-term outcomes provided by the model. In this approach, a cohort population (with a size that can be defined by the model user) is created. Each patient in this population is unique in the sense of its baseline characteristics (demographics, existing baseline complications, baseline physiological risk factors and other risk factors, e.g. the number of cigarettes smoked per day). Within the bootstrapping simulation approach, two types of analysis are possible: deterministic and probabilistic. In the deterministic simulation, the continuous input parameters (baseline age, diabetes duration, HbA_{1c} levels, etc.) of each patient in the cohort that is created (e.g. 1000 patients) will be identical, but binary variables will differ (gender, presence of a diabetes-related complication, e.g. MI, etc.). In each iteration, one of the patients in this cohort is sampled with replacement and entered into the simulation (i.e. the complication submodels) until the patient dies. Applied treatment effects, utilities, costs and coefficients of cardiovascular disease (CVD) events will then be identical in each iteration. However, results will differ per iteration because of the differences in the binary input parameters in the baseline cohort and the way a patient progresses through the model (random walk). In the probabilistic simulation, all variables that are subjected to random sampling (i.e. cohort baseline parameters, treatment effects, coefficients of the CVD risk equations, health-state utilities/adverse event disutilities and costs) are randomly assigned at the beginning of the first iteration according to pre-defined probability distributions. Then all the patients in the cohort (e.g. 1000) are processed through the model while the parameters assigned at the start of the iteration are held constant. Those patients will only differ as a result of binary variables and random walk. When the model progresses to the next iteration, parameters are resampled again and the next 1000 patients are progressed though the model while parameters are held constant again. This process is repeated for all the bootstrap iterations.

However, it should be noted that because of computational time requirements, not all parameters in the model are subjected to random sampling. For instance, among the baseline risk factors, cigarette and alcohol consumption per day are not subjected to sampling. The same is true for minor and severe hypoglycaemia/ketoacidosis rates and coefficients from non-CVD-related risk adjustment equations.

Transition probabilities within each submodel (i.e. the annual probability of a change in health state) are dependent on baseline demographic and current physiological patient characteristics [HbA_{1c} levels, body mass index (BMI), etc.], and the existence of other complications and concomitant treatments (e.g. angiotensin-converting enzyme inhibitor, statin or laser). Transition probabilities are further calculated based on established regression or risk adjustment functions from the literature.[91–93] State transitions of a cohort occur simultaneously in each submodel. Therefore, it is possible that a patient will develop multiple complications in 1 year. In the IMS CDM model, diabetes-specific mortality is assumed to be caused by the following complications: MI, stroke, CHF, nephropathy, foot ulcer/amputation, hypoglycaemia, DKA and lactic acidosis. However, non-specific mortality is based on UK life tables.[94] Additional details on the submodels of the IMS CDM are given in *Appendix 5*.

An important limitation of the model is that it is not suitable for modelling long-term outcomes for children or adolescent populations, because the background risk adjustment/risk factor progression equations (such as those based on the Framingham studies)[93,95–97] are all based on adult populations. Hence, we had to limit all our analyses to the adult population.

Model input parameters

This section describes the input parameters used in the model for the base case and how their values were estimated. Six different input parameter databases can be distinguished in the IMS CDM: (1) cohort, (2) economics (including management costs, costs of complications and utilities), (3) treatment effects, (4) treatment costs, (5) other management and (6) clinical. *Table 27* maps the IMS CDM input parameter databases into the conventional model input categories.

TABLE 27 Mapping IMS CDM input parameter databases into conventional input parameter categories

IMS CDM input database	Conventional input parameter category
Cohort database	Demographics (age, diabetes duration, percentage male, racial profile)
	Baseline physiological risk factors (e.g. HbA_{1c} levels, SBP, T-CHOL, BMI, etc.)
	Baseline complications (proportion with MI history, proportion with cataract, etc.)
	Other risk factors (proportion that smoke, alcohol consumption, etc.)
Economics database	Cost and effect discount rates
	Sampling settings for PSA (for costs)
	Management costs (e.g. statin, aspirin, ACEI costs, screening costs for depression, foot ulcer, eye disease, etc.)
	Utilities/utility decrements for all relevant health states and adverse events
	Direct costs for: • Cardiovascular complications (year 1 and ≥ 2 costs for MI, angina, CHF, stroke, etc.) • Renal complications (year 1 and ≥ 2 costs for haemodialysis, renal transplantation, etc.) • Eye diseases/complications (year 1 and ≥ 2 costs for cataract, severe vision loss, etc.) • Foot ulcer/amputation/neuropathy (year 1 and ≥ 2)
	Acute events (severe hypoglycaemia, DKA, etc.)
Treatment database	Effect of the treatment on physiological parameters: • For the first year: change in the baseline value • For the consecutive years: progression approach (e.g. UKPDS,[91,96,98] Framingham[93,95–97] or user-defined clinical tables)
	Adverse events: • Minor and severe hypoglycaemic events • DKA events
	Risk adjustments for concomitant medicines (e.g. ACEIs, statins)
Treatment cost group database	Assigns treatment costs to the treatments for year 1 and afterwards
Management database	Percentage of patients on concomitant medication (e.g. statins, ACEIs)
	Percentage of patients on screening or patient management programmes (e.g. renal disease screening or foot ulcer prevention programme)
	Other: • Risk reductions because of management and sensitivity/specificity of screening tests
Clinical database	Risk adjustments for: • HbA_{1c} • SBP
	Risk multipliers for: • MI • Stroke • Angina • CHF • Ethnicity • Adverse events • Other microvascular complications • Foot ulcer/amputation • Depression • Others

ACEI, angiotensin-converting enzyme inhibitor; PSA, probabilistic sensitivity analysis; SBP, systolic blood pressure; T-CHOL, total cholesterol; UKPDS, UK Prospective Diabetes Study.

Given the degree of validation of the model, only those parameters that needed to be adapted to time (year 2015), place (the UK), population (T1DM patients eligible for a pump) and technologies to be compared were amended in the base case. Furthermore, for the sake of consistency, unless there was thought to be a more appropriate value, we chose to follow the approach from the latest diabetes NICE guideline[81] (which also adopted the IMS CDM). In addition, many of the parameters were also validated by clinical experts. Further details on specific input parameters and their probability distributions are described below.

Baseline population characteristics

If possible, we estimated cohort baseline parameters based on the studies identified in our systematic review to properly reflect our base-case population (i.e. T1DM patients eligible for an insulin pump). In this case, only the study by Bergenstal *et al.*[32] provided reliable information for some patient characteristics. For the characteristics not reported in Bergenstal *et al.*,[32] we used those from the general T1DM population, as in the latest diabetes NICE guideline.[81] The cohort baseline characteristics used in our base-case analysis and their sources can be seen in *Table 28*. For the probabilistic sensitivity analysis (PSA) the input parameters age, duration of diabetes and baseline risk factors, for HbA_{1c} levels, systolic blood pressure (SBP), BMI, total cholesterol and low-density lipoproteins, are sampled from a normal distribution; the means and SDs are given in *Table 28*. Baseline triglyceride and high-density lipoprotein levels are sampled from a gamma distribution with the following parameters: alpha = $mean^2/SD^2$ and beta = $mean/SD^2$.

TABLE 28 Cohort baseline characteristics (base-case analysis)

Parameter	Mean	SD	Source
Patient demographics			
Start age (years)	41.6	12.8	Bergenstal *et al.* (2013)[32]
Duration of diabetes (years)	27.1	12.5	
Proportion male	0.38	NA	
Baseline risk factors			
HbA_{1c} (% points)	7.26	0.71	Bergenstal *et al.* (2013)[32]
SBP (mmHg)	128.27	16.07	National Diabetes Audit[99]
Total cholesterol (mg/dl)	176.50	33.00	Nathan *et al.* (2009)[100]
HDL (mg/dl)	50.25	13.00	
LDL (mg/dl)	109.75	29.00	
Triglycerides (mg/dl)	81.50	41.00	
BMI (kg/m^2)	27.6	15.9	Bergenstal *et al.* (2013)[32]
eGFR ($ml/min/1.73\ m^2$)	77.50	0	Default IMS CDM value[81] (not used in our analyses)
Haemoglobin (g/dl)	14.50	0	
White blood cell count (10^6/ml)	6.80	0	
Heart rate (b.p.m.)	72	0	
Proportion smoker	0.22	NA	National Diabetes Audit[99]
Cigarettes/day	12	NA	*Opinions and Lifestyle Survey, Smoking Habits Amongst Adults, 2012*[101]
Alcohol consumption (oz/week)	9[a]	NA	The WHO's *Global Status Report on Alcohol and Health* (2011)[102]

TABLE 28 Cohort baseline characteristics (base-case analysis) (*continued*)

Parameter	Mean	SD	Source
Racial characteristics			
Proportion white	0.92	NA	National Diabetes Audit[99]
Proportion black	0.03	NA	
Proportion Hispanic	0.05	NA	
Proportion Native American	0	NA	
Proportion Asian/Pacific Islander	0	NA	
Baseline CVD complications			
Proportion MI	0	NA	Assumption
Proportion angina	0.00298[b]	NA	England Health Survey (2011)[103]
Proportion PVD	0	NA	Assumption
Proportion stroke	0.00298[c]	NA	England Health Survey (2011)[103]
Proportion heart failure	0	NA	Assumption
Proportion atrial fibrillation	0	NA	
Proportion left ventricular hypertrophy	0	NA	
Baseline renal complications			
Proportion microalbuminuria	0.181	NA	National Diabetes Audit[99]
Proportion gross proteinuria	0	NA	Assumption
Proportion end-stage renal disease	0	NA	
Baseline retinopathy complications			
Proportion background diabetic retinopathy	0	NA	Assumption
Proportion proliferative diabetic retinopathy	0	NA	
Proportion severe vision loss	0	NA	
Baseline macular oedema			
Proportion macular oedema	0	NA	Assumption
Baseline cataract			
Proportion cataract	0	NA	Assumption
Baseline foot ulcer complications			
Proportion uninfected ulcer	0	NA	Assumption
Proportion infected ulcer	0	NA	
Proportion healed ulcer	0	NA	
Proportion history of amputation	0	NA	
Baseline neuropathy			
Proportion neuropathy	0.049	NA	Nathan *et al.* (2009)[100]
Baseline depression			
Proportion depression	0.21	NA	Hopkins *et al.* (2012)[104]

b.p.m., beats per minute; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable.
a 13.37 litres per year.
b Angina in 25- to 34-year age group.
c Stroke in 25- to 34-year age group.

Costs

The direct costs included in the model are for:

- management (for primary prevention of complications)
- diabetes-related complications
- the treatment of diabetes (this also includes the cost of the pump and/or glucose monitor)
- other hospital costs.

Indirect costs parameters were set to zero in the model as these were not included in our analyses, given the perspective of the NHS. Treatment costs were not included in the PSA because this was not possible using the current version of the IMS CDM, as the model developers argue that the uncertainty around the pharmacy/treatment administration costs is very small.

All other direct costs can be included in the PSA. Although cost parameters are typically sampled from different distributions independently in other economic evaluations, in the IMS CDM all direct costs are multiplied by the same positive factor which is sampled from a log-normal distribution with a mean of 1 and a user-defined coefficient of variation. In line with the latest diabetes NICE guideline,[81] for our analyses we assumed a 20% deviation from the mean as it is assumed that this would represent a reasonable range of variation. Detailed descriptions of all four direct cost categories are given in the following sections.

Disease management unit costs

Management costs include the costs of managing chronic conditions, performing screening procedures, administering concomitant medication, etc. All cost data were sourced from NG17[81] and, if necessary, were further inflated to 2014 prices using the 2013/14 Hospital and Community Health Services (HCHS) index available from the Personal Social Services Research Unit (PSSRU).[105] The management costs used in our analyses can be seen in *Table 29*.

Costs of diabetes-related complications

Both ongoing disease complications and acute events are considered in this section. The costs of ongoing complications are considered per year until the complication is resolved or the patient dies. The costs of acute events are assumed to occur at only the time of the event. The costs of diabetes-related complications were sourced from NICE Guideline NG17[81] and, if necessary, were inflated to 2014 prices using the 2013/14 HCHS index available from the PSSRU.[105] These costs are shown in *Table 30*.

Treatment costs

Sensor-augmented pump therapy

In addition to the cost of the MiniMed Paradigm Veo System and the Vibe and G4 PLATINUM CGM system, a number of consumables are needed. These are cannulas, reservoirs and batteries for the insulin pump and sensors for the CGM device. The prices and expected lifetimes of these devices and consumables were reported by the relevant manufacturers. To estimate the equipment costs associated with these devices, the following assumptions were made:

- insulin pumps have a 4-year lifetime
- cannulas and reservoirs would be replaced every 3 days
- the MiniMed Paradigm Veo requires one Energizer® AAA alkaline battery (Energizer® Holdings, Inc., St Louis, MO, USA) and the battery will be replaced every 8.5 days (the lifetime of the battery is dependent on the quality of the battery, the nature of the pump use, temperature, etc.)
- the Vibe pump operates on one AA battery (lithium batteries are recommended) and the expected battery lifetime is 5 weeks (35 days) (continuous glucose monitor components are supplied with a rechargeable battery and a charger)
- the MiniLink transmitter is replaced each year and the sensors are replaced every 6 days
- the G4 PLATINUM monitor is replaced every 6 months and the sensors are replaced every 7 days.

TABLE 29 Management costs in T1DM patients

Management type	Mean cost per year (£)	Source
ACEIs	18.54[a]	NHS drug tariff (2014)[106]
Statins	38.22[b]	
Aspirin	13.70[c]	
Screening for microalbuminuria	3.12[d]	Lamb *et al.* (2009)[107]
Screening for gross proteinuria	2.94[e]	
Stopping ACEIs because of adverse events	19.96[f]	NHS drug tariff (2014)[106]
Eye screening	35.38	Assumption[g]
Foot screening programme	42.46[h]	*NHS Reference Costs 2012–13*[108]
Non-standard ulcer treatment [e.g. becaplermin (Regranex®, Smith & Nephew)]	0	Default value in IMS CDM[81]
Antidepression treatment and management	494.44	NICE Guideline NG17[81]
Screening for depression	0	Assumption[i]

ACEI, angiotensin-converting enzyme inhibitor.
a Average cost of five generics.
b Atorvastatin (80 mg/day for 28 days).
c After an ischaemic event (75 mg/day for 28 days).
d Weighted: 80% once per year; 20% three times per year; unit cost £2.16.
e Two per year; unit cost £1.42.
f Angiotensin receptor antagonist for 28 days (50 mg/day of losartan potassium or 8 mg/day of candesartan cilexitil).
g Based on annual national cost of £70M for 2 million diabetic screens once per year (Clinical Guideline Development Group of the UK National Screening Committee, December 2013, personal communication).
h Podiatrist outpatient visit.
i Included in cost of antidepression treatment and management.

TABLE 30 Costs of T1DM-related complications

Type of complication	Mean cost (£)	Source
CVD complications		
MI, first year	3731	[a]NICE lipids clinical guideline (CG181)[109,110]
MI, each subsequent year	788	
Angina, first year	6406	
Angina, each subsequent year	288	
CHF, first year	3596	
CHF, each subsequent year	2597	
Stroke, fatal (within 30 days)	1174	
Stroke, non-fatal first year	4170	
Stroke, each subsequent year	155	
PVD, first year	952	
PVD, each subsequent year	529	

continued

TABLE 30 Costs of T1DM-related complications (*continued*)

Type of complication	Mean cost (£)	Source
Renal complications		
Haemodialysis, each year	30,819	NICE peritoneal dialysis clinical guideline (CG125)[111]
Peritoneal dialysis, each year	24,793	
Renal transplant, first year	20,600	
Renal transplant, each subsequent year	7694	
Acute events		
Severe hypoglycaemic event (cost per event)	439	NICE Guideline NG17[81]
Minor hypoglycaemic event (cost per event)	0	
DKA event (cost per event)	0	
Eye disease		
Laser treatment	705	*NHS Reference Costs 2012–13* (BZ24D: non-surgical ophthalmology with interventions)[108]
Cataract operation	1035	Weighted *NHS Reference Costs 2012/13*: non-phacoemulsification cataract surgery, with complication score 0 (BZ03A) and score 1+ (BZ03B)[108]
After cataract operation	81	*NHS Reference Costs 2012–13* (WF01A: non-admitted face-to-face attendance, ophthalmology follow-up)[108]
Blindness, year of onset	5647	NICE glaucoma clinical guideline (CG85)[112,113]
Blindness, each subsequent year	5456	
Neuropathy/foot ulcer/amputation		
Neuropathy, each year	362	MIMS, 2014 (online version):[114] 60 mg of duloxetine (Cymbalta®, Elli Lilly and Co.) daily (first-line treatment in NICE CG96)[115]
Amputation, event based	11,416	NICE lower limb peripheral arterial disease clinical guideline (CG147)[116,117]
Amputation with prosthesis, event based	15,420	
Gangrene treatment	5483	Ghatnekar *et al.* (2002)[118]
Healed ulcer	266	
Infected ulcer	7410	NICE CG147[116,117] and Kerr (2012)[119]
Uninfected ulcer	4115	
Healed ulcer with history of amputation	25,577	NICE lower limb peripheral arterial disease clinical guideline (CG147)[116,117]

MIMS, Monthly Index of Medical Specialties.
a It was assumed that one-third of angina episodes would be unstable and two-thirds would be stable.

Table 31 presents the estimated yearly equipment costs for the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system.

Continuous subcutaneous insulin infusion (stand-alone insulin pumps)

The average price of a stand-alone insulin pump in the UK was sourced from a study from the London New Drugs Group in November 2013.[120] This was inflated to 2014 prices using the 2013/14 HCHS index available from the PSSRU[105] and are shown in *Table 32*. An estimated market share for each brand was calculated based on White *et al.*[121] and data from Diabetes UK.[122] Based on this information, the estimated weighted average price for a stand-alone pump in the UK is £2173.54.

Continuous glucose monitoring (stand alone)

We followed the approach in NICE Guideline NG17[81] and considered the three main CGM technologies available in the UK: Dexcom G4 PLATINUM, Abbott (Chicago, IL) FreeStyle Navigator and Medtronic Guardian®. The items included were receivers, transmitters and sensors. The costs of the three receivers were sourced from NICE Guideline NG17.[81] Transmitter and sensor costs, and usage for the Dexcom G4 and the Medtronic Guardian, were assumed to be the same as for integrated systems (see *Table 31*), since this information was provided by the companies. For the Abbott FreeStyle Navigator, sensor costs (there is no transmitter) and usage were assumed to be the same as reported in NICE Guideline NG17.[81] Finally, a yearly weighted average cost, equal to £3087.75, was estimated based on the estimated market share from White *et al.*[121] and data from Diabetes UK.[122] This information is shown in *Table 33*.

TABLE 31 Equipment costs of MiniMed Paradigm Veo system and Vibe/G4 Platinum CGM system based on 2014 costs

Cost component	MiniMed Paradigm Veo system	Vibe/G4 Platinum CGM system
Insulin pump	£2679	£2800
Insulin pump cannula	£8.70	£9.75
Insulin pump reservoir	£2.68	£2.46
Insulin pump batteries	£0.49[a]	£1.77[b]
Continuous glucose monitor transmitter	£228.70	£335.0
Continuous glucose monitor sensor	£42.05	£46.50
Total device cost	£2961.62	£3195.48
Insulin pump		
Years of use	4	4
Cannula, units/year (days of use)	121.67 (3)	121.67 (3)
Reservoir, units/year (days of use)	121.67 (3)	121.67 (3)
Batteries, units/year (days of use)	42.94 (8.5)	10.42 (35)
Continuous glucose monitor		
Transmitter (years of use)	1	0.5
Sensor, units/year (days of use)	60.83 (6)	52.14 (7)
Total costs		
Total cost per year	£4862.10	£5298.65

a Energizer Classic AAA batteries (4 pack).
b Energizer Ultimate Lithium AA batteries (4 pack).

TABLE 32 Price and market share of stand-alone insulin pumps in the UK

Cost component (all costs net of VAT)	Insulin pump				
	Accu-Chek® Spirit (Roche, Basel)	Dana (SOOIL, Seoul)	Animas Vibe	Medtronic Paradigm	mylife OmniPod (Ypsomed, Burgdorf)
Insulin pump	£2523[a]	£1972[a]	£2831[a]	£2882[a]	£425[a]
Estimated annual non-consumables cost (based on 4 years of life)	£631	£493	£708	£720	
Estimated annual consumables cost	£1324	£1400	£1663	£1282	£3052
Total cost per year	**£1955**	**£1893**	**£2371**	**£2002**	**£3158**
Estimated UK market share (%)[b]	30	3	23	35	9
Average cost per year (based on market shares)			**£2174**		

VAT, value-added tax.
a Quoted price from the London New Drugs Group *Comparative Table of Insulin Pumps* (produced for use within the NHS),[120] inflated to 2014 prices using the 2013/14 HCHS index available from the PSSRU (2014).[105]
b UK market share per brand derived from White *et al.* (2013)[121,122] and Diabetes UK.

TABLE 33 Price and market share of stand-alone CGM devices in the UK in 2014

Continuous glucose monitor component	CGM device		
	Dexcom G4	FreeStyle Navigator	Medtronic Guardian
Receiver cost	£1750	£950	£1059
Transmitter cost	£335	£0	£229
Sensor cost	£47	£48	£42
Total equipment cost	**£2132**	**£998**	**£1330**
Receiver, years of use	5	5	5
Transmitter, years of use	0.5	0	1
Sensor, units/year (days of use)	52.14 (7)	60.83 (6)	60.83 (6)
Total cost/year	**£3445**	**£3110**	**£2999**
Estimated UK market share	15%	20%	65%
Average cost per year (based on market shares)		**£3088**	

Blood glucose tests costs

Blood glucose tests are needed in all interventions and comparators. Each time a BG test is conducted a lancet and a test strip are consumed. The estimated cost of a single BG test (computed as the average of all marketed lancets and test strips) is £0.29 according to NICE Guideline NG17.[81] We assumed that BG meters are supplied free of charge. The number of BG tests required for the different interventions and comparators depend on the method of monitoring glucose, whether it is manual (SMBG) or continuous (CGM). Our systematic review identified only two studies reporting the number of BG tests.[37,40] Based on these studies, we defined, on average, four BG tests per day for both SMBG and CGM for the base case. Based on clinical opinion, this choice seems to be somewhat counterintuitive as a higher number of tests would be expected for SMBG than for CGM. However, we believe that trial values are generally more valid and consistent within our analyses, given that the estimate of effectiveness comes from the trials and there is likely to be a correlation between frequency of monitoring and outcome. Nevertheless, since there was some uncertainty around these values, other options were explored in scenario analyses. Yearly costs associated with SMBG for the base case are shown in *Table 34*.

TABLE 34 Blood glucose test costs

Cost component	CGM and SMBG
Cost of single BG test	£0.29
Number of tests per day	4
Total number of tests per year	1460
Total yearly cost	£423.40

Insulin costs

Both SAP and CSII therapies use short-acting insulin. Based on expert opinion, we assumed the same type and amount of short-acting insulin for both technologies. Following the approach in NICE Guideline NG17,[81] only the cartridges and pre-filled pens were used to calculate the costs of short-acting insulin. For the base case, we assumed 48 units per day of short-acting insulin for pumps, as in Bergenstal *et al.*[32] and NICE Guideline NG17.[81] This choice was validated by clinical experts/committee members. The total insulin costs per year for patients on insulin pumps are shown in *Table 35*.

Based on clinical opinion, we assumed that patients on MDIs would use a regimen with basal (long-acting) insulin once or twice daily, and bolus (short-acting) insulin with meals, three times per day. Furthermore, the conclusion from NICE Guideline NG17[81] is that insulin detemir twice daily is the most cost-effective long-acting insulin regimen for people with T1DM. Therefore, we assumed this for the base case. Based on the information from our clinical experts, we also assumed that the number of insulin units would be split 50 : 50 between basal and bolus. For the base case, we also assumed 48 units per day for MDIs, as in NICE Guideline NG17.[81] Thus, we assumed 24 units per day of long-acting insulin and 24 units per day of short-acting insulin. The unit cost of the needles was assumed to be £0.11 as in NICE Guideline NG17.[81] This was calculated as a weighted average of the prices of the 10 most commonly used needles, according to data from *Prescription Cost Analysis – England, 2012*.[123] The annual cost of needles per patient was then calculated based on a frequency of five injections per day (long-acting twice daily and short-acting insulin three times per day) as mentioned above. The total insulin costs (including the costs of needles) per year for patients on MDIs are shown in *Table 36*.

TABLE 35 Sensor-augmented insulin pump and CSII (short-acting) insulin costs

Short-acting insulin	Cartridges and pens	Unit cost (£)	Cost per unit of insulin (£)[a]	Yearly cost per patient (£)[b]
Insulin aspart (NovoRapid®, Novo Nordisk)	5 × 3-ml cartridges	28.31	0.0188	330.66
	5 × 3-ml FlexPen pre-filled (Novo Nordisk, Bagsværd, Denmark)	30.60	0.0204	357.41
	5 × 3-ml FlexTouch pre-filled (Novo Nordisk, Bagsværd, Denmark)	32.13	0.0214	375.28
Insulin glulisine (Apidra®, Sanofi-Aventis)	5 × 3-ml cartridges	28.30	0.0188	330.54
	5 × 3-ml SoloStar pre-filled (Sanofi-Aventis, Paris, France)	28.30	0.0188	330.54
Insulin lispro (Humalog®, Lilly)	5 × 3-ml cartridges	28.31	0.0188	330.66
	5 × 3-ml KwikPen pre-filled (Eli Lilly, Indianapolis, IN, USA)	29.46	0.0196	344.09
Average insulin costs	NA	29.34	0.0196	342.74

NA, not applicable.
a Unit cost divided by 1500.
b Based on 48 units per day.

TABLE 36 Multiple daily insulin injection (long-acting insulin detemir and short-acting insulin) costs

Cost item	Unit cost (£)	Cost per unit of insulin (£)[a]	Yearly cost per patient (£)
Long-acting insulin detemir	42.00	0.0280	245.28[b]
Short-acting insulin	29.34	0.0196	171.35[b]
Needles	0.11	NA	200.75[c]
Total cost for MDIs			617.38

NA, not applicable.
a Unit cost divided by 1500.
b Based on 24 units per day.
c Based on five injections per day.

There was some uncertainty around the assumption of equal amounts of insulin for pumps and MDIs. Clinical experts have different opinions about this; some experts expect that a lower amount of insulin would be used for pumps than would be used for MDIs (14% lower according to Cummins *et al.*[80]). Therefore, we explored this in a separate scenario.

Other hospital costs

Outpatient care-related costs

Outpatient care-related costs (consultant and diabetic specialised nurse) were estimated based on clinical expert opinion. We assumed that in the first year during pump initiation, there would be seven appointments and three group sessions of 45 minutes each with diabetic specialist nurses in a 6-month period. After the pump initiation period, but still during the first year, we assumed two appointments of 45 minutes with a consultant and two appointments of 45 minutes with a diabetic specialised nurse. Therefore, in total, in the first year, we assumed that there would be nine appointments and three group sessions of 45 minutes with a diabetic specialised nurse, and two appointments of 45 minutes with a consultant. Each subsequent year we assumed that there would be two appointments of 45 minutes with a consultant and two appointments of 45 minutes with a diabetic specialised nurse. For patients on MDIs, we assumed two appointments of 45 minutes with a consultant and two appointments of 45 minutes with a diabetic specialised nurse every year. The NHS outpatient follow-up tariff is £99.[124] Total outpatient costs for the base case are shown in *Table 37*.

Glycated haemoglobin tests costs

The cost and frequency of HbA_{1c} tests were also estimated based on clinical expert opinion. We assumed that, on average, this test would be performed three times a year. The cost of the test is dependent on the hospital, the lab, etc., in which the test is performed. Based on the average of three hospital prices, we assumed £3.14 as the average cost of a HbA_{1c} test.

Summary of treatment and other hospital costs

A summary of treatment-related costs for the six technologies considered in this study is shown in *Table 38*.

TABLE 37 Annual outpatient care-related costs

Year	Insulin pump (£)	MDIs (£)
Year 1	1386.00	396.00
Year 2 or more	396.00	396.00
Average yearly cost (based on a time horizon of 80 years)	408.38	396.00

TABLE 38 Summary of annual treatment-related costs per technology

Technology	Equipment and consumables (£)	Blood glucose tests (£)	Insulin (£)	Outpatient (£)	HbA_{1c} tests (£)	Total (£)
MiniMed Veo system	4862.10	423.40	342.74	408.38	9.42	6046.04
Integrated CSII + CGM (Vibe)	5298.65	423.40	342.74	408.38	9.42	6482.59
CSII + CGM	5261.29	423.40	342.74	408.38	9.42	6445.22
CSII + SMBG	2166.13	423.40	342.74	408.38	9.42	3350.07
MDI + CGM	3288.50	423.40	416.63	396.00	9.42	4533.94
MDI + SMBG	200.75	423.40	416.63	396.00	9.42	1446.20

Utilities

Health benefits were expressed in terms of life-years and QALYs gained. If more than one complication occurs at a time, a multiplicative approach is applied.[125] For the PSA, utility and disutility values are sampled from a beta distribution. Means and SDs are inputs for the IMS CDM; these are parameterized into parameters a and b of the beta distribution as follows: $a = ((\text{mean}^2) \times (1 - \text{mean})/(\text{SD}^2))$; and $b = (\text{mean} \times (1 - \text{mean})/(\text{SD}^2)) - ((\text{mean}^2) \times (1 - \text{mean})/(\text{SD}^2))$. The utilities used in the model are summarised in *Table 39*.

Treatment effects

We used the reduction in HbA_{1c} baseline levels and the number of severe hypoglycaemic events as the outcomes to characterise treatment effectiveness. We considered using the number of minor hypoglycaemic and DKA events as well but not enough reliable data were found to make comparisons.

For HbA_{1c} levels, a baseline value had to be established onto which the treatment effect could be applied [i.e. the value at the start of treatment (time zero)]. The mean baseline value was 7.26% (standard error 0.71%), based on the relevant population, as shown in *Table 28*. Treatment effects were then estimated as the mean reduction from the baseline value, determined from our systematic review. An indirect meta-analysis was conducted to estimate the WMD between the MiniMed Paradigm Veo system and integrated CSII + CGM (used to inform the Vibe and G4 PLATINUM CGM system), CSII + CGM, CSII + SMBG, MDI + CGM and MDI + SMBG. Because of a lack of published clinical data, MDI + CGM had to be excluded from the analysis (see *Figure 8*) and treatment effects of integrated CSII + CGM and non-integrated CSII + CGM were assumed to be identical (see *Figure 8* and *Table 21*). After calculating the change in HbA_{1c} levels from baseline in Bergenstal *et al.*[32] as –0.02, the change in HbA_{1c} levels for other treatments could be found. These values are listed in *Table 40*.

Since there is uncertainty and there are limitations in the indirect meta-analysis (because of heterogeneity and differences in baseline HbA_{1c} levels), to explore the impact of different HbA_{1c} change levels, we analysed a hypothetical situation in which the baseline HbA_{1c} levels do not change after the initiation of treatment in a separate scenario. It should be noted that, in the IMS CDM, the change in HbA_{1c} level is assumed to occur within the first 12 months. After this, an annual progression rate is applied. For the base case we followed the approach in NICE Guideline NG17,[81] in which an annual progression of 0.045% (derived from the DCCT)[92] was used.

For severe hypoglycaemic events, it is not necessary to set a baseline value since the IMS CDM assumes that this is a treatment-specific parameter. Treatment effects were estimated as the rate ratio of event rates per 100 patient-years obtained from our systematic review (see *Figure 9* and *Table 22*). This was then applied to a reference value for integrated CSII + CGM, which was derived from a weighted average (by sample size) of the event rates observed in the CSII + CGM arms of the trials. These values are shown in *Table 41*.

TABLE 39 Utilities per health state

Health state	Mean (dis) utility value	SE	Source
T1DM with no complications	0.814	0.01	Clarke *et al.* (2002)[126]
MI, event year	–0.055	0.01	Beaudet *et al.* (2014)[78]
MI, after event	0.759	0.01	Equal to no complication minus event
Angina	0.695	0.01	Beaudet *et al.* (2014)[78]
Chronic heart failure	0.677	0.01	
Stroke, event year	–0.164	0.01	
Stroke, after event	0.650	0.01	Equal to no complication minus event
PVD	0.724	0.01	Beaudet *et al.* (2014)[78]
Microalbuminuria	0.814	0.01	Equal to no complication
Gross proteinuria	0.737	0.01	Beaudet *et al.* (2014)[78]
Haemodialysis	0.621	0.03	
Peritoneal dialysis	0.581	0.03	
Renal transplant	0.762	0.12	
Background diabetic retinopathy	0.745	0.02	
Background diabetic retinopathy, wrongly treated	0.745	0.02	
Proliferative diabetic retinopathy, laser treated	0.715	0.02	
Proliferative diabetic retinopathy, non-laser treated	0.715	0.02	
Macular oedema	0.745	0.02	
Severe vision loss	0.711	0.01	
Cataract	0.769	0.02	
Neuropathy	0.701	0.01	
Healed ulcer	0.814	0.01	Equal to no complication
Active ulcer	0.615	0.01	Beaudet *et al.* (2014)[78]
Amputation, event year	–0.280	0.01	
Amputation, after event	0.534	0.01	Equal to no complication minus event
Severe hypoglycaemic event	–0.012	0.00	Currie *et al.* (2006)[127]
Minor hypoglycaemic event	0	0.00	Assumption
Fear of hypoglycaemic event	0	0.00	Included in the disutility for severe hypoglycaemic event
DKA event	0	0.00	Assumption
Depression, not treated	0.6059	0.00	Goldney *et al.* (2004)[128]
Depression, treated	0.814	0.00	Equal to no complication

SE, standard error.

TABLE 40 Change in HbA_{1c} levels with respect to baseline for all treatments included in the analysis

Treatment	Mean (SE) change in HbA_{1c} levels compared with baseline, %
MiniMed Veo system	–0.02 (0.04)
Integrated CSII + CGM (Vibe)	–0.06 (0.05)
CSII + SMBG	0.05 (0.12)
MDI + SMBG	0.64 (0.19)
CSII + CGM	–0.06 (0.05)

TABLE 41 Rate per 100 patient-years of severe hypoglycaemic episodes for all treatments included in the analysis

Treatment	Rate per 100 patient-years of severe hypoglycaemic episodes
MiniMed Veo system	1.9584
Integrated CSII + CGM (Vibe)	16.32
CSII + SMBG	5.0215
MDI + SMBG	19.584
CSII + CGM	16.32

For the PSA, treatment effects on HbA_{1c} levels at baseline are sampled from a beta distribution (mean and SD are converted into beta distribution-specific parameters, as explained in *Utilities*). The event rates of severe hypoglycaemic events are fixed in the IMS CDM and therefore they are not included in the PSA. In order to explore the uncertainty of the effects of severe hypoglycaemic episodes on long-term outcomes, several scenarios with different treatment-specific rates were analysed (see *Treatment effects part II: severe hypoglycaemic event rates*).

Disease management parameters

These parameters will determine the proportion of patients that will receive disease management regimens, such as preventative treatments or screening programmes. These parameters and their sources are shown in *Table 42*. With the exception of the proportion on the UK-specific foot ulcer prevention programme, for which we followed the approach in NICE Guideline NG17,[81] the majority of the inputs are the default values from the IMS CDM and were also used in the latest diabetes NICE guideline.[81]

Disease natural history parameters

These are the parameters that will determine the natural course of the disease. These parameters are either transition probabilities, that is the probability of each of the events (e.g. diabetic retinopathy or MI) or the (relative) risk of an event, given a particular risk factor; risk factors are based on physiological measures, such as HbA_{1c} levels, BMI, SBP or characteristics like the presence of microalbuminuria. We considered the same values as in NICE Guideline NG17,[81] most of which were the same as the IMS CDM default values. For that reason, and because the number of parameters is so large that it may distract the reader's attention, we have decided to show these parameters in *Appendix 6*.

It should be noted that one of these parameters is the probability of death from a severe hypoglycaemic event. In line with NICE Guideline NG17,[81] this was assumed to be zero for the base case. However, as deaths due to severe hypoglycaemic events have been reported,[138,139] we expect that this parameter may have an impact on our results, as one of the key features of the MiniMed Paradigm Veo is the LGS function, which was shown to reduce the number of severe hypoglycaemic events, and thus the number of deaths caused by severe hypoglycaemia. Therefore, other options for this mortality rate were explored in additional scenarios.

TABLE 42 Disease management parameters

Parameter	Mean value	Source
Concomitant medication		
Proportion using aspirin for primary prevention	0.456	Minshall *et al.* (2008)[129]
Proportion using aspirin for secondary prevention	0.755	Gerstein *et al.* (2008)[130]
Proportion using statins for primary prevention	0.450	Minshall *et al.* (2008)[129]
Proportion using statins for secondary prevention	0.878	Gerstein *et al.* (2008)[130]
Proportion using ACEIs for primary prevention	0.500	Minshall *et al.* (2008)[129]
Proportion using ACEIs for secondary prevention	0.708	Gerstein *et al.* (2008)[130]
Screening and patient management proportions		
Proportion on foot ulcer prevention programme	0.992	National Diabetes Audit[99]
Proportion screened for eye disease	1.000	No data
Proportion screened for renal disease	1.000	No data
Proportion receiving intensive insulin after MI	0.877	McMullin *et al.* (2004)[131]
Proportion treated with extra ulcer treatment	0.570	Lyon (2008)[132]
Proportion screened for depression with no complications	0.830	Jones and Doebbeling (2007)[133]
Proportion screened for depression with complications	0.830	
Others		
Reduction in incidence of foot ulcers with prevention programme	0.310	O'Meara *et al.* (2000)[134]
Improvement in ulcer healing rate with extra ulcer treatment	1.390	Kantor and Margolis (2001)[135]
Reduction in amputation rate with foot care	0.340	O'Meara *et al.* (2000)[134]
Sensitivity of eye screening	0.920	Lopez-Bastida *et al.* (2007)[136]
Specificity of eye screening	0.960	
Sensitivity of gross proteinuria screening	0.830	Cortes-Sanabria *et al.* (2006)[137]
Sensitivity of microalbuminuria screening	0.830	
Specificity of microalbuminuria screening	0.960	

ACEI, angiotensin-converting enzyme inhibitor.

Sensitivity and scenario analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was used to explore the impact of statistical uncertainties regarding the model's input parameters. PSA is an in-built feature of the IMS CDM, activated if the second order with sampling option is selected.

Probabilistic sensitivity analysis results were presented in the cost-effectiveness plane for all the treatments compared. Cost-effectiveness acceptability curves (CEACs) were used to describe the probability of a treatment being considered cost-effective given a threshold incremental cost-effectiveness ratio (ICER). The probability distributions used in the PSA are described throughout the *Model input parameters* section.

Scenario analyses

Scenario analyses were performed to explore the impact on costs and QALYs of using different assumptions on the baseline population characteristics, on the number of blood tests (finger prick tests) conducted per day, on the amount of insulin used, on the inclusion of HbA_{1c} progression after year 1,

on treatment effects (both in terms of HbA_{1c} level change and in terms of the number of severe hypoglycaemic episodes per treatment), on the inclusion of a non-zero probability of death as a result of hypoglycaemia, on time horizon, on QALY estimation methods, on utility benefits associated with less fear of hypoglycaemia, and on the cost of the stand-alone insulin pump and CGM devices.

Baseline population characteristics

The base case assumed baseline population characteristics, as in the Bergenstal *et al.*[32] In this scenario, we considered the general T1DM population, as used in NICE Guideline NG17.[81] *Table 43* shows the patient characteristics that were changed for this scenario.

Number of blood glucose tests per day

In the base case, we assumed four BG tests (finger prick tests) for interventions containing CGM (the MiniMed Paradigm Veo system, integrated CSII + CGM and stand-alone CSII + CGM) and four BG tests for interventions containing SMBG (CSII + SMBG and MDI + SMBG). This assumption was based on the results from the systematic review, in which no significant differences in the number of tests between the CGM- and SMBG-containing treatments were observed.[32,37]

In the sensitivity analysis, we followed the approach in NICE Guideline NG17 (appendix P of this guideline),[81] and considered two tests per day (for calibration) for CGM-containing treatments and four tests per day for SMBG-containing treatments, since this is considered to be current practice. Moreover, we have included 8 (the most cost-effective frequency in the guideline) and 10 tests per day for SMBG-containing technologies versus 2 tests per day for CGM-containing technologies as scenarios in our analysis. Unlike the latest diabetes NICE guideline scenarios (appendix P of the guideline),[81] we assumed in our analyses that the number of blood tests per day had no impact on the treatment effect, since such an effect (e.g. that more blood tests lead to a greater decrease in HbA_{1c} levels) was not observed in our systematic review. Finally, we also explored a scenario based on the observational study by Lynch *et al.*,[140] which reports an average number of 4.35 BG tests per day for CGM and 7.11 for SMBG. The costs related to BG testing for the complete list of the scenarios conducted are given in *Table 44*.

Amount of insulin per day

For the base case, we assumed equal units of insulin per day for both MDI-containing interventions (MDI + SMBG) and insulin pump-containing interventions (the MiniMed Paradigm Veo system, integrated CSII + CGM, stand-alone CSII + CGM and CSII + SMBG). However, some of the clinical experts mentioned that they would expect a lower amount of insulin to be used for pumps than for MDIs. In addition, Cummins *et al.*[80] report a 14% reduction in insulin use with pumps compared with MDIs. From the findings of our systematic review, this seems to be a reasonable assumption.[37,41,141] Thus, for this scenario, we assumed 48 units per day of short-acting insulin for pump-containing treatments (which is the same as

TABLE 43 Baseline characteristics that change with respect to the base case

Parameter	Mean base case	Mean scenario	SD	Source
Patient demographics				
Start age (years)	41.6	42.98	19.14	Nathan *et al.* (2009)[100]
Duration of diabetes (years)	27.1	16.92	13.31	National Diabetes Audit[99]
Proportion male	0.38	0.567	NA	
Baseline risk factors				
HbA_{1c} (% points)	7.26	8.60	4.00	National Diabetes Audit[99]
BMI (kg/m^2)	28.27	27.09	5.77	

NA, not applicable.

TABLE 44 Number of BG tests and test costs for the additional scenarios

Cost component	CGM	SMBG
Cost of single BG test[81]	0.29	0.29
Scenario 1		
Number of tests per day[81]	2	4
Total number of tests per year (365 days)	730	1460
Total yearly cost (£)	212	423
Scenario 2		
Number of tests per day[81]	2	8
Total number of tests per year (365 days)	730	2920
Total yearly cost (£)	212	847
Scenario 3		
Number of tests per day[81]	2	10
Total number of tests per year (365 days)	730	3650
Total yearly cost (£)	212	1058
Lynch* et al. *(2012)*[140] *scenario		
Number of tests per day	4.35	7.11
Total number of tests per year (365 days)	1588	2595
Total yearly cost (£)	460	753

the insulin use assumption in the base case given in *Table 35*) and 55 units of insulin per day (14% more) for MDI + SMBG treatments. It was also assumed that the insulin used for MDI + SMBG is split 50 : 50 between basal and bolus (27.5 units per day of long-acting insulin and 27.5 units per day of short-acting insulin). The costs pertaining to the insulin use for this scenario analysis are given *Table 45*.

Glycated haemoglobin progression

In the base-case analysis, the IMS CDM default value for the annual progression in HbA_{1c} levels after year 1 was used (0.045%). This value was based on the DCCT.[92] According to NICE Guideline NG17,[81] the Guideline Development Group expects that HbA_{1c} levels in T1DM patients will be more stable than in T2DM patients. Therefore, an alternative assumption of no annual progression in HbA_{1c} levels (0%) was tested to gain insight into the effects of HbA_{1c} progression rate on costs and QALYs gained after year 1.

TABLE 45 Multiple daily insulin injection (long-acting insulin detemir and short-acting insulin) costs based on 55 units per day

Cost item	Unit cost (£)	Cost per unit of insulin (£)[a]	Yearly cost per patient (£)
Long-acting insulin detemir	42.00	0.0280	281[b]
Short-acting insulin	29.34	0.0196	196[b]
Needles	0.11	NA	201[c]
Total cost for MDIs			678

NA, not applicable.
a Unit cost divided by 1500.
b Based on 27.5 units per day.
c Based on five injections per day.

Treatment effects part I: change in glycated haemoglobin levels in the first year

As explained above (see *Treatment effects*), treatment effects were estimated as the mean reduction from the baseline HbA_{1c} value obtained from our systematic review. The baseline HbA_{1c} value was taken from Bergenstal *et al.*[32] This value is lower than the average baseline HbA_{1c} value of patients given in the National Diabetes Audit,[99] which indicates that the patients in the Bergenstal *et al.*[32] study have better glycaemic control. As an alternative scenario, we assumed that the baseline HbA_{1c} value is stable for one year and does not change with any of the treatments (0% change in HbA_{1c} level in the first year).

Treatment effects part II: severe hypoglycaemic event rates

Treatment-specific severe hypoglycaemic event rates were derived from our systematic review, from which it was observed that the MiniMed Paradigm Veo system had fewer reported severe hypoglycaemic events than the other treatments. In the scenario analysis, we elaborate on this observation, and for all treatments other than the MiniMed Paradigm Veo system, we assumed a uniform event rate for severe hypoglycaemia (16.32 events per 100 patient-years) and applied different RR values (1, 0.5, 0.25 and 0.125) for the severe hypoglycaemic event rate for the MiniMed Paradigm Veo system. It should be noted that the value of 16.32 events per 100 patient-years is derived from the indirect comparison, as explained above (see *Treatment effects*), and is the weighted mean for the severe hypoglycaemic event rate for integrated CSII + CGM, which is chosen as a reference treatment in this case because the number of studies ($n = 8$)[32,34–40] that the weighted average rate was based on is highest for integrated CSII + CGM; the Bergenstal *et al.* trial,[32] from which the baseline population characteristics were derived, is one of these eight studies.

In addition, we conducted a scenario analysis in which the higher severe hypoglycaemic episode rate from Hirsch *et al.*[34] was taken as the baseline rate for integrated CSII + CGM, and the RRs from the indirect comparison in *Treatment effects* (base case) were applied for other treatments. Severe hypoglycaemic episode rates (number of events per 100 patient-years) are given in *Table 46* for each scenario.

Non-zero probability of death resulting from severe hypoglycaemia

In the base case, the case fatality rate for severe hypoglycaemia was taken as zero. This assumption is in line with NICE Guideline NG17[81] and systematic review results, since none of the included studies reported a death due to severe hypoglycaemia.

As an extreme scenario, as in NG17,[81] we assumed a case fatality rate of 4.9%, derived from a study by Ben-Ami *et al.*[142] in which five patients were reported to die among 102 patients who had drug-induced hypoglycaemic coma.

TABLE 46 Severe hypoglycaemic episode rates for different scenarios

Intervention	Number of events per 100 patient-years				
	Scenario 1 (RR = 1)	Scenario 2 (RR = 0.5)	Scenario 3 (RR = 0.25)	Scenario 4 (RR = 0.125)	Scenario 5[a]
MDI + SMBG	16.32	16.32	16.32	16.32	38.37
CSII + SMBG	16.32	16.32	16.32	16.32	10.20
CSII + CGM	16.32	16.32	16.32	16.32	33
MiniMed Veo system	16.32	8.16	4.08	2.04	3.96
Integrated CSII + CGM (Vibe)	16.32	16.32	16.32	16.32	33

a Scenario 5 is based on the severe hypoglycaemic event rate described by Hirsch *et al.*[34] for integrated CSII + CGM (Vibe) system and RRs from the indirect treatment comparison.

Quality-adjusted life-year estimation method

In the base case, a multiplicative approach was applied for the QALY estimation. This approach, in which the utility values of multiple events are multiplied to derive an overall utility in cases of multiple events/complications, is considered to be appropriate for this condition because simultaneous complications often do develop.[125] As a scenario analysis, the minimum approach was used as an alternative QALY estimation method; for this approach, the minimum of the multiple health state utility values was applied for patients with a history of multiple events.

Different time horizons

In the base case, a lifetime analysis is achieved by selecting 80 years as the model time horizon. For scenario analyses, a 4-year time horizon (the average lifetime of an insulin pump) was selected and the effect of this time horizon on the results was explored.

Fear of hypoglycaemia unawareness

In the STAR-3 trial,[40] patients using integrated CSII + CGM devices demonstrated more of an improvement compared with baseline values on the 'worry' subscale of the Hypoglycaemia Fear Survey[143] than the MDI group. Subsequently, in Kamble *et al.*,[69] this improvement was translated into a utility increment of 0.0329 using the EQ-5D questionnaire index. As a scenario analysis, we applied this utility increment associated with less fear of hypoglycaemia throughout the remaining lifetimes of patients using integrated devices (the MiniMed Paradigm Veo system and integrated CSII + CGM). This benefit was not applied to non-integrated devices (CSII + CGM, CSII + SMBG and MDI + SMBG), as these devices do not give a warning or activate/stop the release of insulin automatically in response to low BG levels.

Cost of stand-alone insulin pumps and continuous glucose monitoring devices

In the base-case analysis, the yearly device cost (equipment + consumables) of the stand-alone CSII + CGM (£5261.29) was estimated based on the market share obtained from White *et al.*[121,122] As a scenario analysis, we considered the average costs without the market-share weighting. Therefore, in this scenario, the estimated yearly device cost is £2275.80 for the stand-alone insulin pump and £3184.39 for the stand-alone CGM device. Thus, when the other cost items are considered (insulin, BG tests, outpatient costs and HbA_{1c} tests), the average yearly cost (without using any market share assumptions) of the stand-alone CSII + CGM is £6644.13. Hence, the cost of the stand-alone CSII + CGM combination is £198.90 higher than the base-case cost. In a similar manner, the yearly cost of CSII + SMBG is £102.26 higher than the base-case cost. Because of these higher costs, stand-alone CSII + CGM becomes more expensive than integrated CSII + CGM (Vibe) in this scenario. Since both technologies are assumed to have the same efficacy, integrated CSII + CGM (Vibe) will dominate stand-alone CSII + CGM.

Model assumptions

The main assumptions made in our analyses are summarised in *Box 1*.

BOX 1 Main model assumptions

General

1. For the base-case scenario, baseline population characteristics, as in Bergenstal *et al.*,[32] were assumed. In an additional scenario, we considered general T1DM population characteristics as in NICE Guideline NG17.[81]
2. For the costs included in the PSA, 20% deviation from the mean was assumed. This is in line with NICE Guideline NG17.[81]
3. Costs of initiation training for insulin pumps and CGM were covered by outpatient costs. This was based on clinical expert opinion.

Sensor-augmented pump therapy

4. A 4-year lifetime was assumed for insulin pumps.
5. Cannulas and reservoirs would be replaced every 3 days.
6. The MiniMed Paradigm Veo system requires one Energizer AAA alkaline battery. An estimated replacement time of 8.5 days was assumed.
7. The Vibe system pump operates on one AA lithium battery. The expected battery lifetime is 5 weeks (35 days) when used with CGM and 8 weeks when used without CGM.
8. We assumed the same percentage of increase in battery lifetime for the MiniMed Paradigm Veo system when used without CGM.
9. The MiniLink transmitter is replaced each year and the sensors are replaced every 6 days.
10. The G4 PLATINUM monitor is replaced every 6 months and the sensors are replaced every 7 days.

Stand-alone insulin pumps

11. The assumptions made for integrated insulin pumps are also valid for stand-alone insulin pumps.

Stand-alone continuous glucose monitoring

12. Transmitter and sensor costs, and usage for the Dexcom G4 and the Medtronic Guardian were assumed to be the same as for integrated systems. This was mentioned by the relevant companies.
13. For the Abbott FreeStyle Navigator, sensor costs and usage were assumed to be the same as reported in NICE Guideline NG17.[81]

Blood glucose tests

14. For the base case, we assumed, on average, four BG tests per day for both SMBG and CGM.
15. In the sensitivity analysis, we followed the approach in NICE Guideline NG17[81] and considered two tests per day (for calibration) for CGM and four tests per day for SMBG, since this is considered current practice. Moreover, we have included eight tests per day (the most cost-effective frequency according to the guideline) and 10 tests per day for SMBG-containing technologies vs. two tests per day for CGM-containing technologies, as scenarios in our analysis.
16. We also explored a scenario based on the observational study by Lynch *et al.*[140] which reports an average number of 4.35 BG tests per day for CGM and 7.11 for SMBG.
17. We assumed that BG meters are supplied free of charge.

BOX 1 Main model assumptions (*continued*)

Insulin

18. We assumed the same type and amount of short-acting insulin for both integrated and stand-alone insulin pumps. This was based on expert opinion.
19. For the base case, we assumed 48 units per day of short-acting for insulin pumps. This was based on Bergenstal *et al.*[32] and NICE Guideline NG17,[81] and it was validated by clinical experts.
20. Based on clinical opinion, we assumed that patients on MDIs would use a regimen with basal (long-acting) insulin once or twice daily, and bolus (short-acting) insulin with meals, three times per day.
21. NICE Guideline NG17[81] concluded that it is likely that insulin detemir twice daily is the most cost-effective long-acting insulin regimen for people with T1DM. Therefore, we assumed this for the base case.
22. Based on clinical opinion, we also assumed that the amount of daily insulin would split 50 : 50 between basal and bolus.
23. For the base case, we assumed 48 units per day for MDIs, as in NICE Guideline NG17.[81]
24. In an additional scenario, we assumed 48 units per day of short-acting insulin for pumps, as in the base case, and 55 units per day (14% increase as reported in Cummins *et al.*[80]) for MDIs.

Multiple daily insulin injections

25. The unit cost of the needles was assumed to be £0.11 as in NICE Guideline NG17.[81]
26. The annual cost of needles per patient was then calculated based on a frequency of 5 injections per day (long-acting twice daily and short-acting insulin three times per day).

Outpatient care

27. We assumed that, in the first year of pump initiation, there would be seven appointments and three group sessions of 45 minutes each with diabetic specialist nurses in a 6-month period.
28. After the pump initiation period, but still during the first year, we assumed two appointments of 45 minutes with a consultant and two appointments of 45 minutes with a diabetic specialised nurse.
29. Each subsequent year we assumed two appointments of 45 minutes with a consultant and two appointments of 45 minutes with a diabetic specialised nurse.
30. For patients on MDIs, we assumed two appointments of 45 minutes with a consultant and two appointments of 45 minutes with a diabetic specialised nurse every year.

Glycated haemoglobin tests

31. We assumed that, on average, this test would be performed three times a year.
32. The cost of this test depends on the hospital, lab, etc., in which they are performed. Based on the average of three hospital prices, we assumed that the average price for a HbA_{1c} test would be £3.14.

Treatment effects

33. Treatment effects are estimated as the mean reduction from the baseline value from our systematic review. This reduction is assumed to occur for up to 12 months. After this, annual progression occurs. In the base case, we followed NICE Guideline NG17,[81] which chose a T1DM trial, DCCT (annual progression of 0.045%), for the base case and no progression in sensitivity analysis.
34. In the absence of data, treatment effects of integrated CSII + CGM and non-integrated CSII + CGM were assumed to be identical.

Disease natural history

35. The probability of death from severe hypoglycaemic events was assumed to be zero for the base case.[81] Other values were explored in separate scenarios.

Results of cost-effectiveness analyses

Base-case results

The base-case results from the full incremental analysis reported as cost per QALY gained (ICER) per technology for adult T1DM patients are summarised in *Table 47*.

First, it should be noted that since the same treatment effects were assumed for stand-alone and integrated CSII + CGM, the latter is dominated by the former (i.e. effectiveness is the same for the integrated as for the stand-alone technology, but the integrated technology is more expensive, as shown in *Table 38*). As expected, MDI + SMBG is the cheapest treatment but also the one that provides the lowest number of QALYs. The ICER of CSII + SMBG compared with MDI + SMBG is £52,381. MiniMed Paradigm Veo is extendedly dominated by stand-alone CSII + CGM. Essentially, this means that, in a full incremental analysis, where all the interventions and comparators are considered, CSII + CGM is better value for money than MiniMed Veo. This is because, from our systematic review, the decrease in HbA_{1c} levels with respect to baseline was highest for stand-alone CSII + CGM; this decrease in HbA_{1c} levels leads to a decrease in the number of complications that occur over a lifetime to such an extent that it compensates for the higher number of hypoglycaemic events. In any case, the ICER of stand-alone CSII + CGM compared with CSII + SMBG is £660,376. Thus, given the common threshold ICER of £30,000, it is clear that stand-alone CSII + CGM is not cost-effective.

Alternatively, we present the base-case ICERs for the two interventions against every comparator in *Table 48*. Integrated CSII + CGM (Vibe) is dominated by stand-alone CSII + CGM. It should be noted that when the MiniMed Veo system is compared with stand-alone CSII + CGM, the ICER obtained is high (£422,849) but that this results from both negative incremental QALYs and incremental costs (i.e. the ICER is in the south-west quadrant of the cost-effectiveness plane). In this case, the cost savings outweigh the loss in QALYs and therefore the MiniMed Veo system is more cost-effective than stand-alone CSII + CGM.

TABLE 47 Base-case model results (all technologies) probabilistic simulation

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.4146	61,050	–	–	–
CSII + SMBG	11.9756	90,436	0.561	29,386	52,381
MiniMed Veo system	12.0412	138,357	Extendedly dominated[a] by stand-alone CSII + CGM		
CSII + CGM	12.0604	146,476	0.0849	56,039	660,376
Integrated CSII + CGM (Vibe)	12.0604	147,150	Dominated by stand-alone CSII + CGM		

a An extendedly dominated strategy has an ICER higher than that of the next most effective strategy.

TABLE 48 Base-case model results (intervention vs. comparator only) probabilistic simulation

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.6266	77,307	123,375
MiniMed Veo system	CSII + SMBG	0.0656	47,921	730,501
MiniMed Veo system	CSII + CGM	–0.0192	8119	422,849
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.6458	86,100	133,323
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.0849	56,713	668,789
Integrated CSII + CGM (Vibe)	CSII + CGM	0	674	Undefined

This might not be immediately apparent when looking at the full incremental results in *Table 47* because, in this table, the MiniMed Veo system is in position of extended dominance. The lowest ICERs are obtained when the interventions are compared with MDI + SMBG, but these are above £100,000 in the north-east quadrant of the cost-effectiveness plane. When the interventions are compared with CSII + SMBG, the highest ICERs are obtained (around £700,000 in the north-east quadrant of the cost-effectiveness plane). Thus, given the common threshold ICER of £30,000, the interventions are not cost-effective.

In the deterministic simulation, the cost-effectiveness results are very similar except that, in this simulation, MiniMed Veo is not extendedly dominated by stand-alone CSII + CGM. These results are shown in *Table 24*. Although overall cost and QALY estimates are higher than in the probabilistic simulation, the ICERs and the main conclusions from the simulation presented in *Table 49* are similar to the conclusions drawn from the simulation presented in *Table 47*.

The base-case ICERs for the two interventions compared with every comparator in the deterministic simulation are shown in *Table 50*. These results are similar to those presented in *Table 48* and so are the conclusions drawn.

When we looked at the breakdown of the total costs, we observed that treatment costs always represent the largest proportion of the total costs, independently of the treatment chosen. In *Figure 11*, the treatment costs constitute 79% of the total direct costs for the MiniMed Paradigm Veo system, and integrated and stand-alone CSII + CGM. For CSII + SMBG, treatment costs represent 66% of the total costs and for MDI + SMBG this is 41%. For each treatment, the foot ulcer/amputation/neuropathy cost category is the second largest, and eye diseases and renal diseases are the third and fourth largest cost categories, respectively. MDI + SMBG has higher complication incidences (CVD, ulcer, eye disease, etc.), whereas for the other four treatments these complication incidences are similar. Lifetime hypoglycaemic events were least reported for the MiniMed Paradigm Veo system (0.622 severe hypoglycaemic events per patient), and were most reported for MDI + SMBG (5.412 severe hypoglycaemic events per patient).

TABLE 49 Base-case model results (all technologies) deterministic simulation

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	12.1450	62,927	–	–	–
CSII + SMBG	12.7258	93,433	0.5808	30,506	52,524
MiniMed Veo system	12.8087	143,309	0.0829	49,876	601,641
CSII + CGM	12.8223	151,671	0.0136	8,363	614,910
Integrated CSII + CGM (Vibe)	12.8223	152,372	Dominated by CSII + CGM		

TABLE 50 Base-case model results (intervention vs. comparator only) deterministic simulation

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.6637	80,382	121,112
MiniMed Veo system	CSII + SMBG	0.0829	49,876	601,639
MiniMed Veo system	CSII + CGM	–0.0136	–8363	614,910
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.6773	89,445	132,061
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.0965	58,939	610,772
Integrated CSII + CGM (Vibe)	CSII + CGM	0	701	Undefined

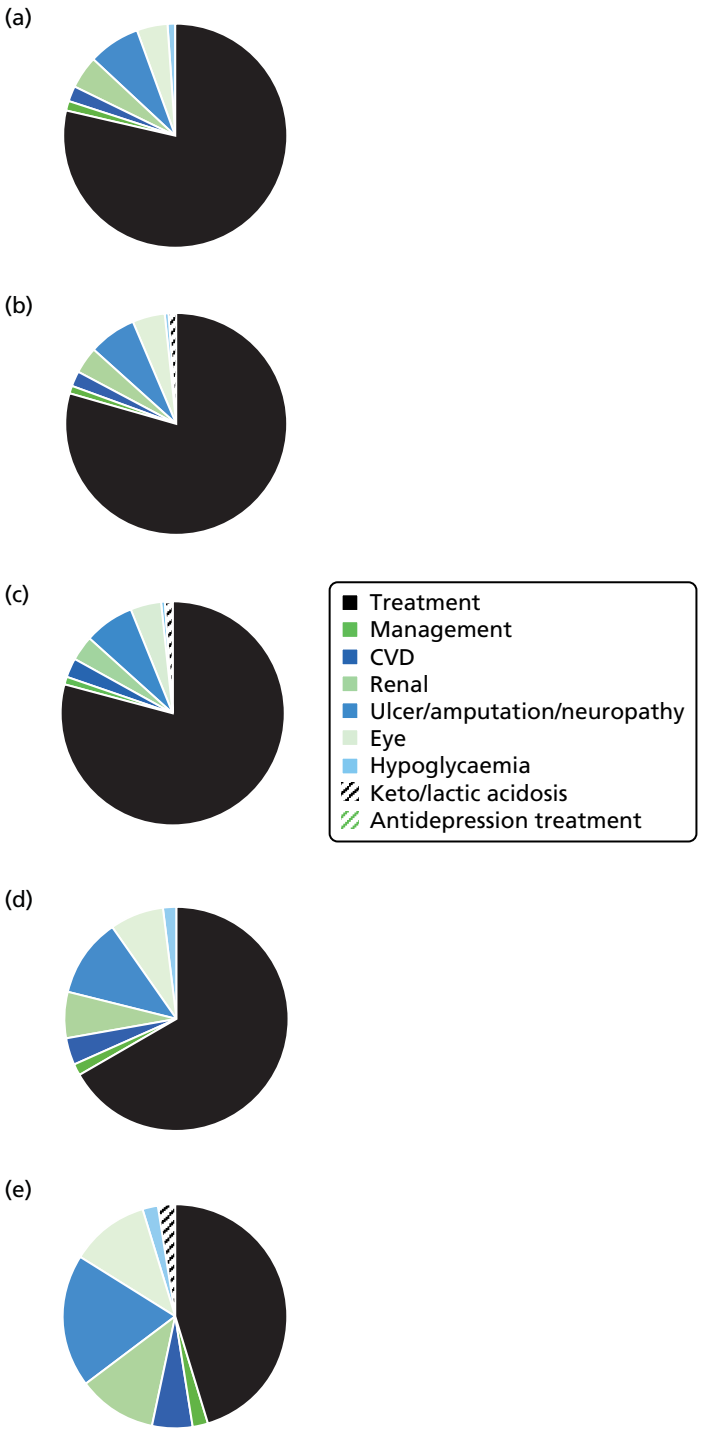

FIGURE 11 Breakdown of costs per treatment: (a) breakdown of MiniMed Veo system costs; (b) breakdown of integrated CSII + CGM costs; (c) breakdown of stand-alone CSII + CGM costs; (d) breakdown of CSII + SMBG costs; and (e) breakdown of MDI + SMBG costs.

Results of the probabilistic sensitivity analyses

Statistical uncertainties in the model were investigated in the PSA. Since we compared five treatments simultaneously, the scatterplot of the PSA outcomes in the cost-effectiveness plane was not very informative (*Figure 12*). Nevertheless, we can observe a clear positive correlation between costs and QALYs and that the treatments including CGM are similarly scattered, showing that they are more expensive but also provide more QALYs.

The CEACs for each treatment are shown in *Figure 13*. These CEACs confirm that only the treatments including SMBG are considered cost-effective. At ceiling ratio values of < £52,381, MDI + SMBG was the treatment with the highest probability of being cost-effective. When that threshold is exceeded, then CSII + SMBG was the treatment with the highest probability of being cost-effective. It should be noted that, for all three treatments including CGM, the cost-effectiveness probability was zero for all the ceiling ratios considered in the analysis. This was expected as the difference in costs between CGM treatments and SMBG treatments was too large to outweigh the additional QALYs gained by using CGM.

Multiple daily insulin injection-unsuitable subgroup

As mentioned in *Chapter 1* (see *Comparators*), insulin pumps are recommended for people with T1DM for whom MDIs are not suitable. Therefore, we questioned the extent to which insulin pumps (especially modern pumps such as the integrated systems) and MDIs are used in similar populations. This seemed a reasonable question in light of the lack of studies found by our systematic review that compared these two treatments. If MDI + SMBG is not considered in the analysis, the ICERs from the full incremental analysis were the same as those reported in *Table 47*, but excluding the first row. It appears that CSII + SMBG is the strategy most likely to be cost-effective, independent of the ceiling ratio value (up to £100,000 per QALY), as shown in *Figure 14*.

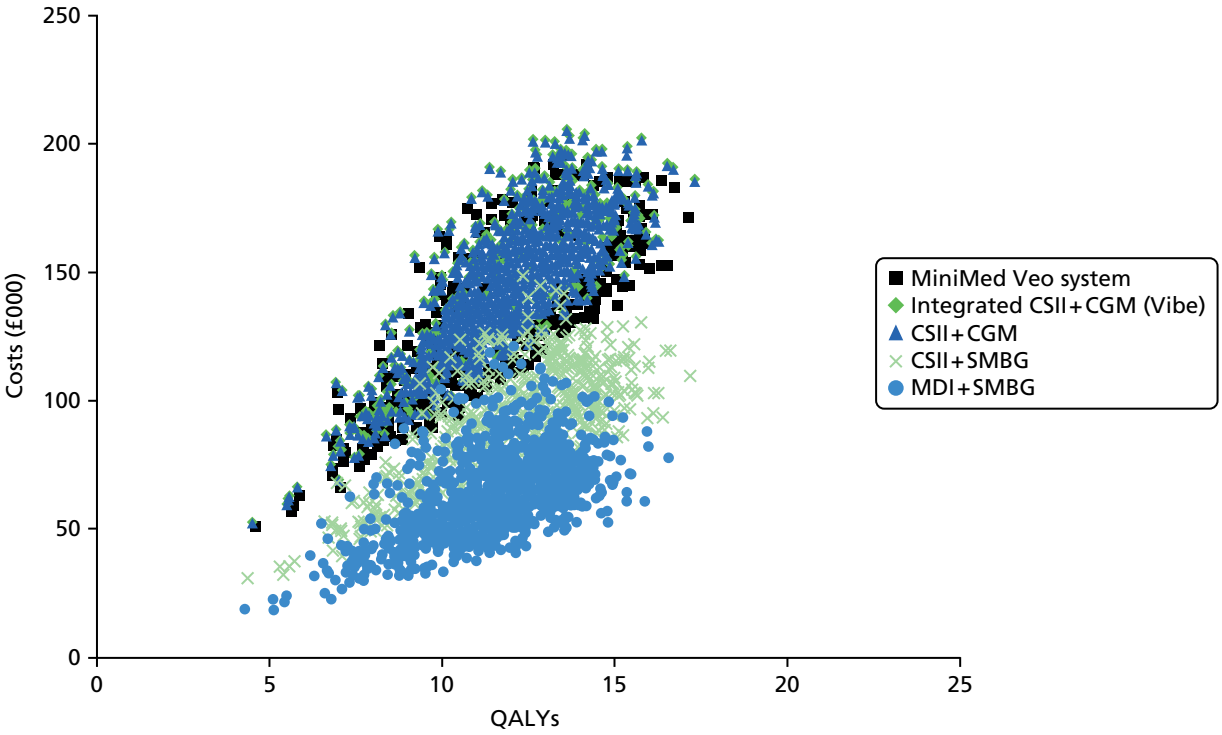

FIGURE 12 Cost-effectiveness plane with PSA outcomes for all treatments in T1DM patients.

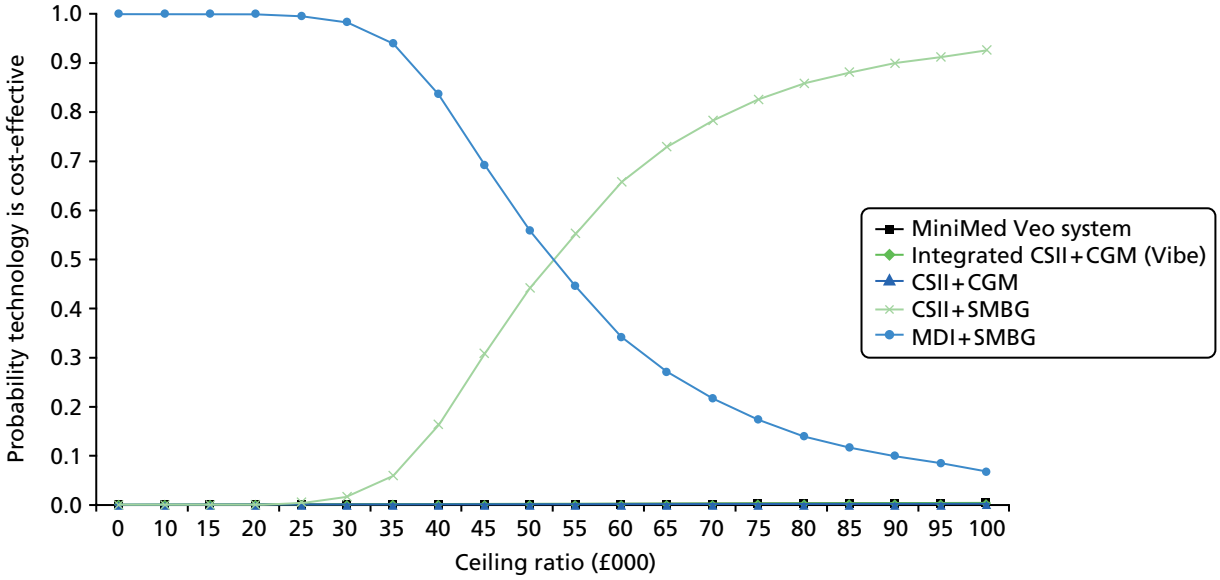

FIGURE 13 Cost-effectiveness acceptability curves for all treatments in T1DM patients.

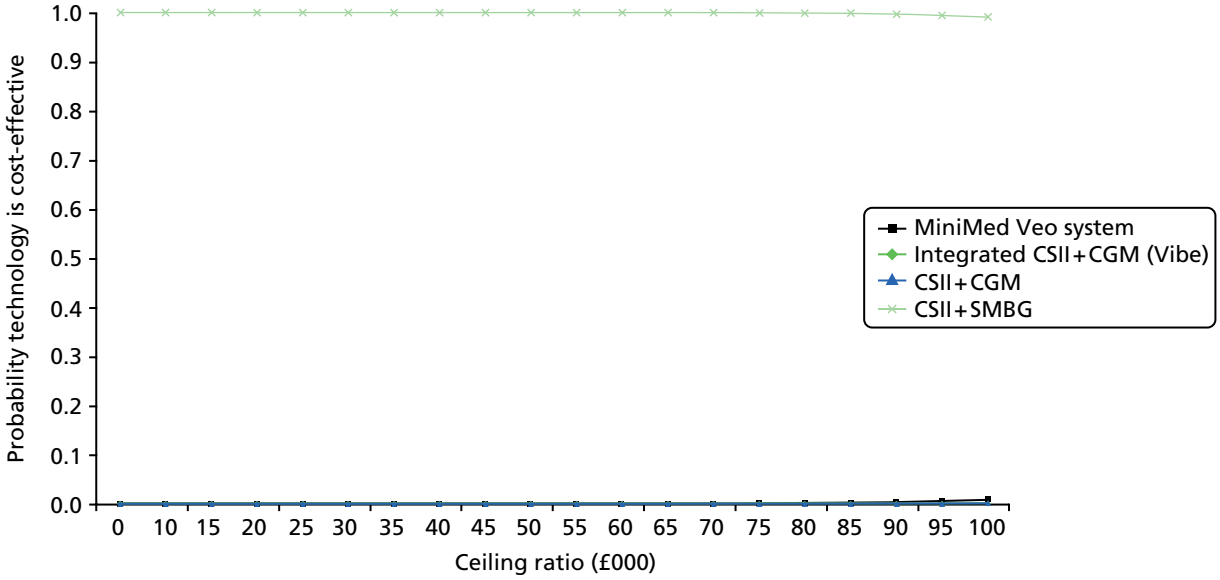

FIGURE 14 Cost-effectiveness acceptability curves for all non-MDI treatments in T1DM patients.

Continuous glucose monitoring-indicated/self-monitoring of blood glucose-unsuitable subgroup

In the analysis for the CGM-indicated/SMBG-unsuitable subgroup, we excluded SMBG-based treatment options from the analysis on the presumption that the most relevant population comprises those who find it difficult to perform SMBG often or adequately enough. In this situation, integrated CSII + CGM (Vibe) is dominated by stand-alone CSII + CGM, as shown in *Table 47* and the only relevant comparison is the MiniMed Veo system with stand-alone CSII + CGM. The ICER is £422,849 (in the south-west quadrant of the cost-effectiveness plane), as shown in *Table 48*. The corresponding CEACs are shown in *Figure 15*. These CEACs indicate that the MiniMed Veo system is the CGM treatment most likely to be cost-effective for all the ceiling ratios considered in the analysis. However, as the ceiling ratio increases, the CEACs for the MiniMed Paradigm Veo system and stand-alone CSII + CGM seem to converge. As expected, the CEAC for integrated CSII + CGM was always zero for all the ceiling ratios considered in the analysis, since this was dominated by the stand-alone combination of CSII and CGM.

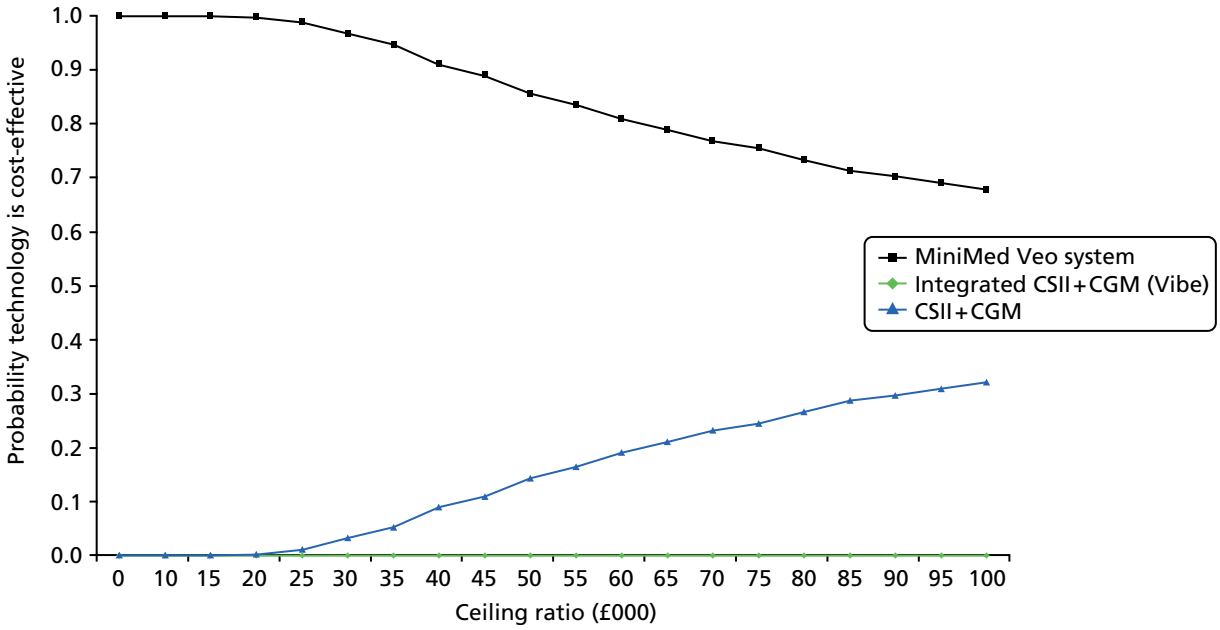

FIGURE 15 Cost-effectiveness acceptability curves for CGM treatments in T1DM patients.

Results of scenario analyses

In the scenarios presented below, only the ICERs from the full incremental analysis are discussed. The ICERs for the two interventions against every comparator are shown in *Appendix 7*.

Baseline population characteristics

In the scenario analysis, in which the baseline population characteristics have been updated in accordance with NICE Guideline NG17,[81] the main results are similar to the base-case results, as shown in *Table 51*.

The intervention with the lowest costs and the lowest gain in QALYs is MDI + SMBG. CSII + SMBG and stand-alone CSII + CGM are on the efficient frontier, with ICERs of £53,588 per QALY and £738,593 per QALY, respectively. Thus, given the common threshold ICER of £30,000, they are not cost-effective. The MiniMed Veo system and integrated CSII + CGM are extendedly dominated and dominated, respectively, by stand-alone CSII + CGM.

Number of blood glucose tests per day

All of the scenarios listed in *Table 44* gave similar results. Compared with the base case, costs were lower in the scenarios for treatments that require fewer than four BG tests per day and, otherwise, were higher. Since all results were similar, in *Table 52* we present only the full incremental cost-effectiveness results of the scenarios with two BG tests per day for CGM-containing treatments and eight BG tests per day for SMBG. Eight tests per day for SMBG represent the most cost-effective frequency, as was shown in NICE Guideline NG17.[81]

TABLE 51 Model results (all technologies) for scenarios with different baseline population characteristics

Interventions	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	9.6117	65,070	–	–	–
CSII + SMBG	10.0991	91,189	0.4874	26,119	53,588
MiniMed Veo system	10.1474	132,149	Extendedly dominated by stand-alone CSII + CGM		
CSII + CGM	10.164	139,157	0.0649	47,967	738,593
Integrated CSII + CGM (Vibe)	10.164	139,733	Dominated by stand-alone CSII + CGM		

TABLE 52 Model results (all technologies) for scenario with two (CGM) vs. eight (SMBG) BG tests per day

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.4146	68,460	–	–	–
CSII + SMBG	11.9756	98,034	0.5610	29,574	£52,717
MiniMed Veo system	12.0412	138,357	Extendedly dominated by CSII + CGM		
CSII + CGM	12.0604	146,476	0.0849	48,441	570,844
Integrated CSII + CGM (Vibe)	12.0604	147,150	Dominated by CSII + CGM		

The intervention with the lowest costs and the lowest gain in QALYs is MDI + SMBG. CSII + SMBG and stand-alone CSII + CGM are on the efficient frontier, with ICERs of £52,717 per QALY and £570,844 per QALY, respectively. Therefore, given the common threshold ICER of £30,000, they are not cost-effective. The MiniMed Veo system and integrated CSII + CGM are extendedly dominated and dominated, respectively, by stand-alone CSII + CGM.

Amount of insulin per day

In this scenario, the costs for MDI + SMBG were higher than in the base case; however, this had a very small impact on the cost-effectiveness results because all QALYs and the costs of the other treatments remained unchanged. Since the main conclusions of the cost-effectiveness analyses were the same in this scenario as in the base case, we have not presented these results in a separate table in this chapter, but these results are shown in *Appendix 7*.

Glycated haemoglobin progression

In this scenario, no HbA_{1c} progression after year 1 was assumed for each treatment. *Table 53* summarises the model results.

The intervention with the lowest costs and the lowest gain in QALYs is MDI + SMBG. CSII + SMBG and stand-alone CSII + CGM are on the efficient frontier, with ICERs of £51,615 per QALY and £683,889 per QALY, respectively. Therefore, they are not cost-effective given the common threshold ICER of £30,000. The MiniMed Veo system and integrated CSII + CGM (Vibe) are extendedly dominated and dominated, respectively, by stand-alone CSII + CGM.

Treatment effects part I: change in glycated haemoglobin levels in the first year

In this scenario analysis, we assumed that the baseline HbA_{1c} value is stabilised for 1 year and that it does not change in any of the treatments (i.e. 0% change in HbA_{1c} levels in the first year). The model results for this scenario are shown in *Table 54*.

The QALY expectations for all treatments are very similar. The minor differences in QALYs can be explained by the differences in severe hypoglycaemic episode rates. It should be noted that although the rate of severe hypoglycaemic events for MDI + SMBG was estimated to be higher than the rate for integrated

TABLE 53 Model results (all technologies) for scenario with no HbA_{1c} progression

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.8715	58,520	–	–	–
CSII + SMBG	12.4558	88,663	0.5843	30,143	51,615
MiniMed Veo system	12.5228	137,739	Extendedly dominated by CSII + CGM		
CSII + CGM	12.5398	146,076	0.0840	57,414	683,889
Integrated CSII + CGM (Vibe)	12.5398	146,767	Dominated by CSII + CGM		

TABLE 54 Cost-effectiveness results when no treatment effect (in terms of change in HbA_{1c} levels) is assumed in the first year (for all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
CSII + CGM	12.0006	146,632	Dominated by MDI + SMBG		
Integrated CSII + CGM (Vibe)	12.0006	147,304	Dominated by MDI + SMBG		
MDI + SMBG	12.0016	56,928	–	–	–
CSII + SMBG	12.0160	90,178	0.0144	33,250	2,309,028
MiniMed Veo system	12.0260	138,538	0.0099	48,360	4,871,356

CSII + CGM (see *Treatment effects*), MDI + SMBG resulted in a slightly higher gain in QALYs which could be due to randomness. CSII + CGM systems were dominated by MDI + SMBG. Furthermore, CSII + SMBG and the MiniMed Veo system are on the efficient frontier but with extremely high ICER values. As can be seen in the resulting CEACs in *Figure 16*, MDI + SMBG was the most cost-effective treatment for all the values of the ceiling ratio considered in the analysis.

Treatment effects part II: severe hypoglycaemic event rates

When we used different RRs (0.125, 0.25, 0.5 and 1) for the severe hypoglycaemic episode rates for the MiniMed Veo system, the results did not deviate significantly from the base case. In all of the scenarios, MDI + SMBG was the lowest cost intervention, the MiniMed Veo system was extendedly dominated by stand-alone CSII + CGM and integrated CSII + CGM was dominated. *Table 55* shows the results for the most extreme scenario, which is obtained if the RR value is 0.125. For this RR, the severe hypoglycaemia rates per 100 patient-years for all interventions are shown in *Table 46*.

Non-zero probability of death caused by severe hypoglycaemia

In this scenario, we assumed a mortality due to severe hypoglycaemia of 4.9%, as derived from Ben-Ami *et al.*[142] The model results are shown in *Table 56*.

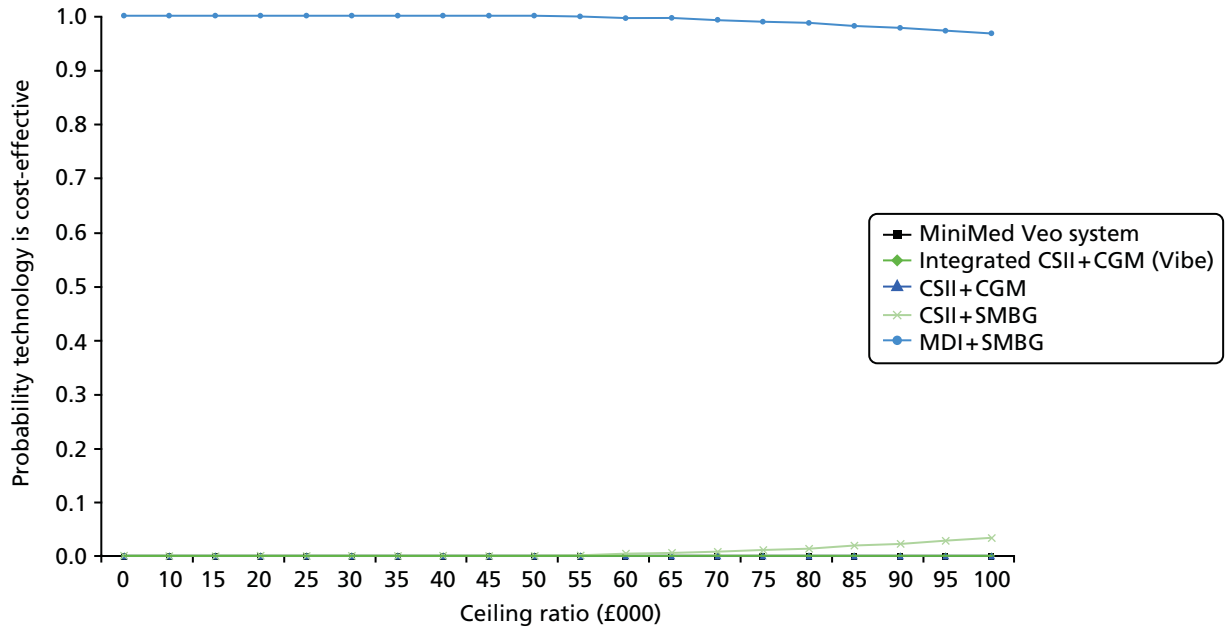

FIGURE 16 Cost-effectiveness acceptability curves for all treatments when there is no HbA_{1c} treatment effect.

TABLE 55 Cost-effectiveness results if a RR of 0.125 is used for the MiniMed Veo system severe hypoglycaemic rate (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.4120	60,812	–	–	–
CSII + SMBG	11.9597	91,195	0.5477	30,383	55,474
MiniMed Veo system	12.0453	138,333	Extendedly dominated by CSII + CGM		
CSII + CGM	12.0604	146,476	0.1007	55,281	549,080
Integrated CSII + CGM (Vibe)	12.0604	147,150	Dominated by CSII + CGM		

TABLE 56 Cost-effectiveness results for the mortality due to severe hypoglycaemia scenario (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.1041	58,510	–	–	–
CSII + CGM	11.7701	142,215	Dominated by CSII + SMBG		
Integrated CSII + CGM (Vibe)	11.7701	142,872	Dominated by CSII + SMBG		
CSII + SMBG	11.8781	89,475	0.774	30,965	40,006
MiniMed Veo system	12.0071	137,801	0.129	8326	374,531

In this scenario, both integrated and stand-alone CSII + CGM were dominated by CSII + SMBG. The ICER of CSII + SMBG compared with MDI + SMBG was £40,006, and the ICER of MiniMed Veo compared with CSII + SMBG was £374,531. Thus, these treatments are not cost-effective given the common threshold ICER of £30,000. Both cost-effectiveness plane scatterplots and CEACs are similar to those for the base-case scenario and therefore they are not shown here. If only the CGM treatments were considered, the probability of the MiniMed Paradigm Veo system being cost-effective was equal to 1 for almost all the values of the ceiling ratio considered in the analysis; this is shown in *Figure 17*.

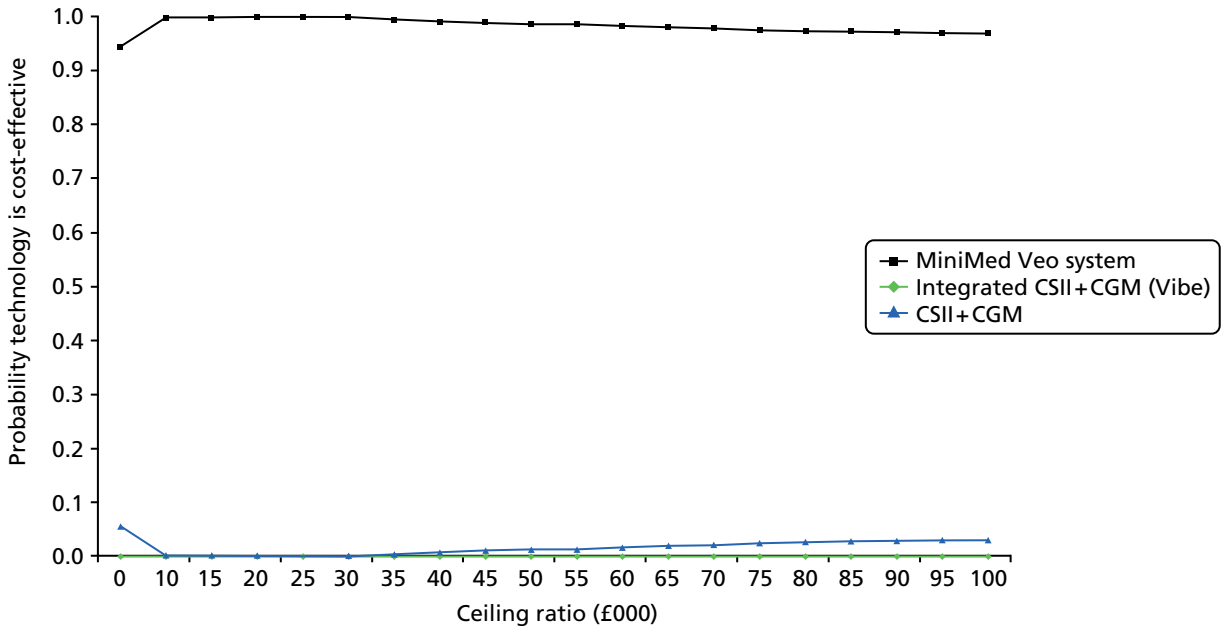

FIGURE 17 Cost-effectiveness acceptability curves for only CGM treatments for the non-zero mortality due to severe hypoglycaemia scenario.

Quality-adjusted life-year estimation method

In this scenario, we assumed the minimum approach as an alternative QALY estimation method, in which the minimum of the multiple health-state utility values was applied for patients with a history of multiple events. The results of this scenario are shown in *Table 57*.

These results are similar to those obtained using the base-case scenario; however, in this scenario, the MiniMed Paradigm Veo system is not extendedly dominated by stand-alone CSII + CGM. All the ICERs are larger than £50,000 and therefore the different treatments are not cost-effective given the common threshold ICER of £30,000.

Different time horizon

In this scenario, we assumed a 4-year time horizon, which corresponds to the average lifetime of an insulin pump. These results are shown in *Table 58*.

We observed that both stand-alone and integrated CSII + CGM are dominated by CSII + SMBG. Although the MiniMed Paradigm Veo system is the treatment with the highest number of QALYs gained, its high cost when compared with CSII + SMBG does not outweigh this gain in QALYs, and results in an ICER of £4,461,063. Therefore, for this scenario also, it is very unlikely that MiniMed Paradigm Veo will be deemed cost-effective, as illustrated by the corresponding CEACs in *Figure 18*.

If only the CGM treatments are considered, the MiniMed Paradigm Veo system is clearly the treatment with the highest probability of being cost-effective, as shown in *Figure 19*.

Fear of hypoglycaemia unawareness

Table 59 shows the results obtained when the utility increment (0.0329) from Kamble *et al.*[69] was used to represent the reduced fear of hypoglycaemia. We applied this utility increment throughout the remaining lifetimes of patients using integrated devices (the MiniMed Paradigm Veo system and integrated CSII + CGM). This benefit was not applied to non-integrated devices (stand-alone CSII + CGM, CSII + SMBG and MDI + SMBG), as these non-integrated devices do not give a warning or activate/stop the release of insulin automatically in response to low BG levels.

TABLE 57 Cost-effectiveness results using the minimum QALY estimation method scenario (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	12.1327	61,050	–	–	–
CSII + SMBG	12.5861	90,436	0.4534	29,386	64,813
MiniMed Veo system	12.6408	138,357	0.0546	47,920	876,987
CSII + CGM	12.6462	146,476	0.0601	56,039	932,305
Integrated CSII + CGM (Vibe)	12.6462	147,150	Dominated by CSII + CGM		

TABLE 58 The 4-year time horizon scenario (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	2.7718	6706	–	–	–
CSII + CGM	2.7882	24,803	Dominated by CSII + SMBG		
Integrated CSII + CGM (Vibe)	2.7886	24,939	Dominated by CSII + SMBG		
CSII + SMBG	2.7906	13,365	0.0188	6659	354,202
MiniMed Paradigm Veo	2.7928	23,144	0.0022	9778	4,461,063

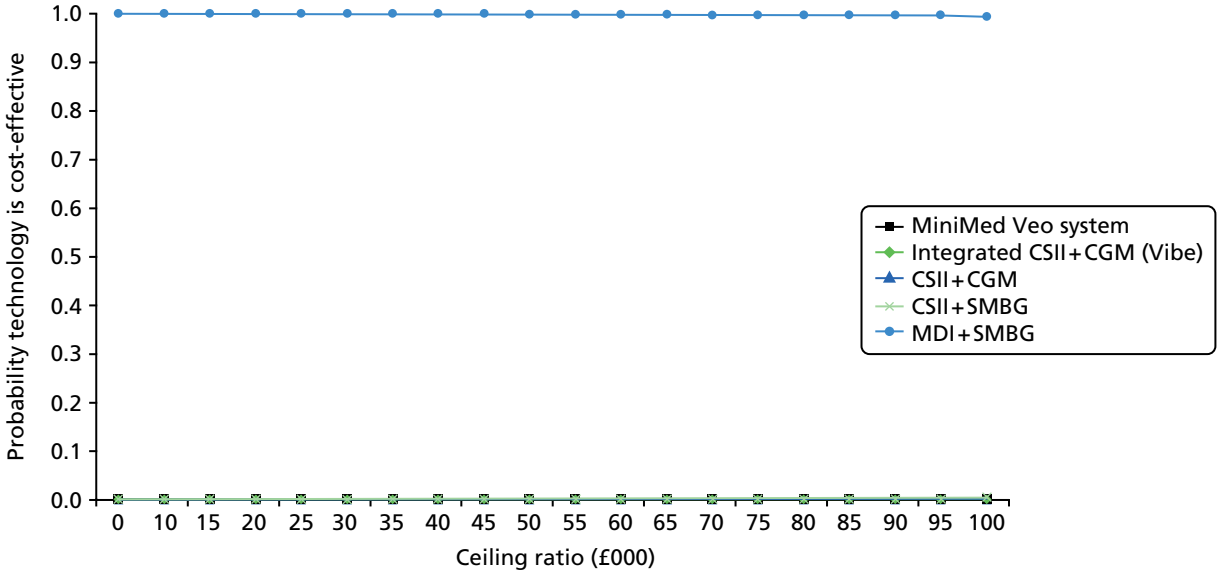

FIGURE 18 Cost-effectiveness acceptability curves for all treatments for the 4-year time horizon scenario.

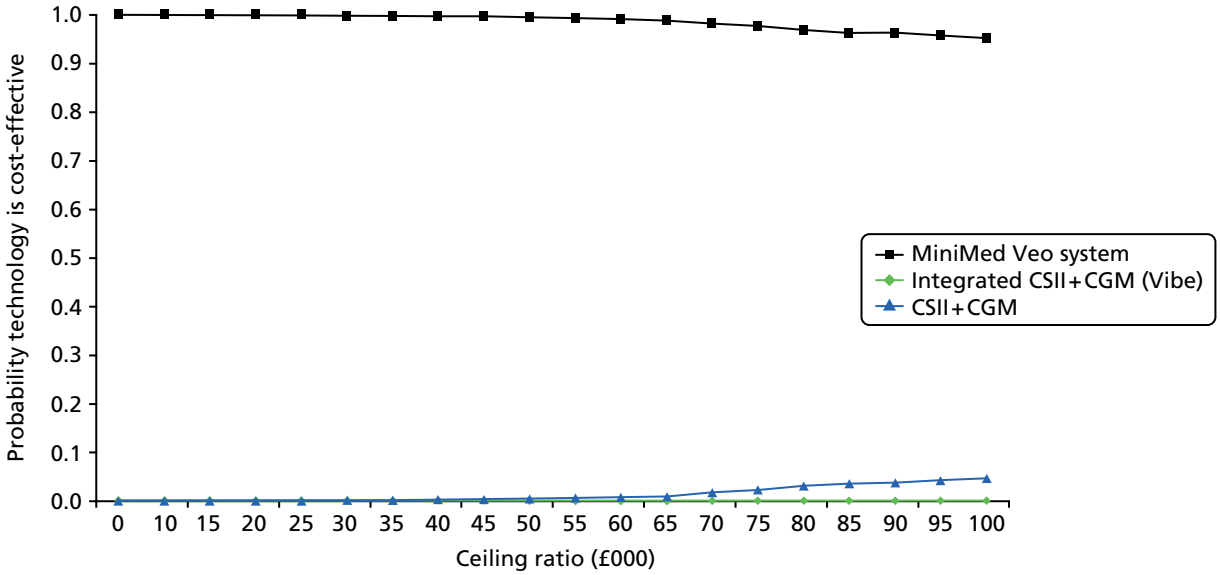

FIGURE 19 Cost-effectiveness acceptability curves for CGM treatments only: 4-year time horizon scenario.

TABLE 59 Cost-effectiveness results for the fear of hypoglycaemia scenario (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.4146	61,050	–	–	–
CSII + SMBG	11.9756	90,436	0.5610	259,386	52,381
CSII + CGM	12.0604	146,476	Extendedly dominated by MiniMed Veo system		
MiniMed Veo system	12.6224	138,357	0.6468	47,920	74,088
Integrated CSII + CGM (Vibe)	12.6429	147,150	0.0205	8792	428,595

For this scenario, the main difference with respect to the base-case scenario is that stand-alone CSII and stand-alone CGM devices is extendedly dominated by the MiniMed Paradigm Veo system, which has an ICER compared with CSII + SMBG of £74,088. Moreover, in this scenario, integrated CSII + CGM is not dominated by the corresponding stand-alone combination, as the utility increment for the integrated system led to a larger number of QALYs accumulated than the non-integrated options. Nevertheless, the ICER of integrated CSII + CGM compared with the MiniMed Paradigm Veo system is still very large (£428,595).

The scatterplot of the PSA outcomes in the CE plane is very similar to the one in the base-case scenario and therefore we decided not to show it here. The CEACs for each treatment are shown in *Figure 20*. These CEACs demonstrate that, compared with the base-case scenario, the probability of being cost-effective for CSII + SMBG starts decreasing at approximately £60,000. As the ceiling ratio increases, the probability of being cost-effective for the MiniMed Paradigm Veo system and integrated CSII + CGM systems also increases. At ceiling ratio values larger than (approximately) £75,000, the MiniMed Paradigm Veo system is the treatment with the highest probability of being cost-effective, followed by integrated CSII + CGM systems, at ceiling ratio values of more than (approximately) £90,000. It should be noted that for stand-alone CSII + CGM, the cost-effectiveness probability was zero for all of the ceiling ratios considered in the analysis.

If only the CGM treatments were considered, we observed similar CEACs (*Figure 21*) to those observed for the base case (see *Figure 14*), but in this scenario the role of integrated and stand-alone CSII + CGM was interchanged in the CEAC.

Cost of stand-alone insulin pumps and continuous glucose monitoring devices

In this scenario, we assumed that the yearly cost of stand-alone CSII + CGM could be estimated from the average costs of the different stand-alone devices, as shown in *Tables 32* and *33*, but without the weighting for market share from White *et al.*[121,122] Therefore, in this scenario, the estimated yearly cost of stand-alone CSII + CGM was £5460. The results from this scenario are shown in *Table 60*.

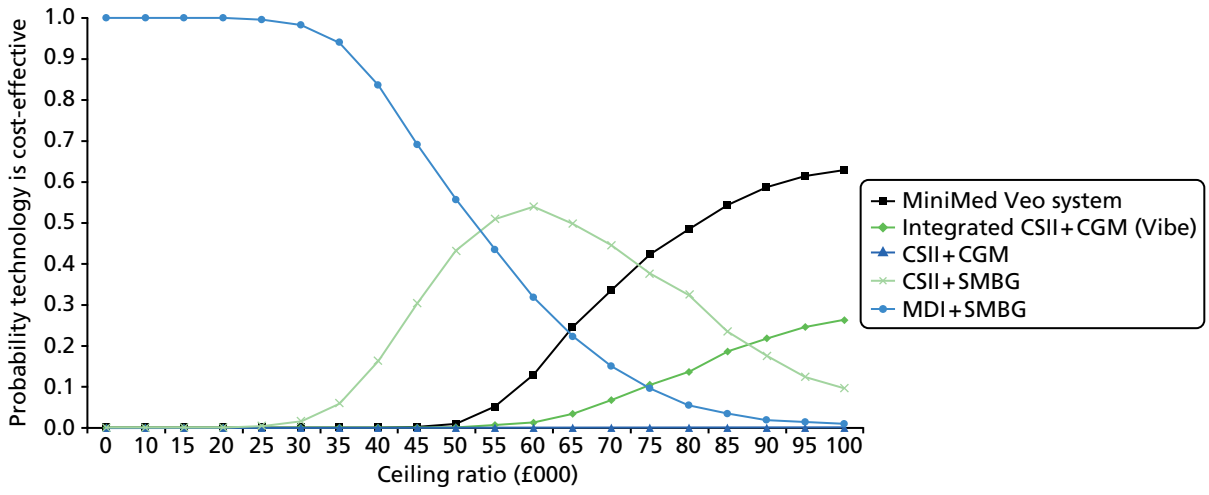

FIGURE 20 Cost-effectiveness acceptability curves for reduced fear of hypoglycaemia scenario.

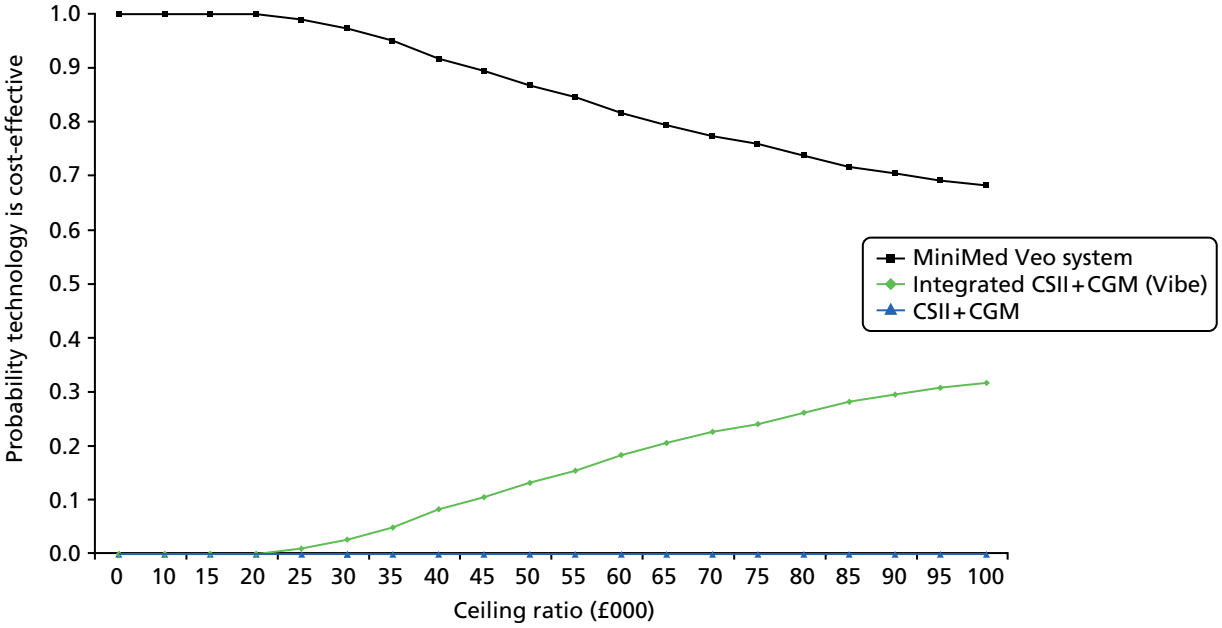

FIGURE 21 Cost-effectiveness acceptability curves for only CGM treatments for the fear of hypoglycaemia scenario.

TABLE 60 Cost-effectiveness results for cost of stand-alone CSII + CGM without market share scenario (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.4146	61,050	–	–	–
CSII + SMBG	11.9756	92,272	0.5610	31,222	55,654
MiniMed Veo system	12.0412	138,357	Extendedly dominated by integrated CSII + CGM		
Integrated CSII + CGM (Vibe)	12.0604	147,150	0.0849	54,878	646,692
CSII + CGM	12.0604	150,063	Dominated by integrated CSII + CGM		

The main difference in these results, with respect to the base-case scenario, was that, as expected, stand-alone CSII + CGM was more expensive than integrated CSII + CGM (Vibe). Since both technologies are assumed to have the same efficacy, integrated CSII + CGM (Vibe) dominated stand-alone CSII + CGM. The CEACs for each treatment are shown in *Figure 22*. These are very similar to those for the base-case scenario. The higher cost of stand-alone CSII + CGM had almost no impact on the cost-effectiveness probability since MDI + SMBG and CSII + SMBG are the only strategies that are considered cost-effective.

If only the CGM treatments were considered, we observed similar CEACs (*Figure 23*) as those observed for the base-case scenario (see *Figure 15*) but, as expected, in this scenario the role of integrated CSII + CGM (Vibe) and stand-alone CSII + CGM was interchanged in the CEAC.

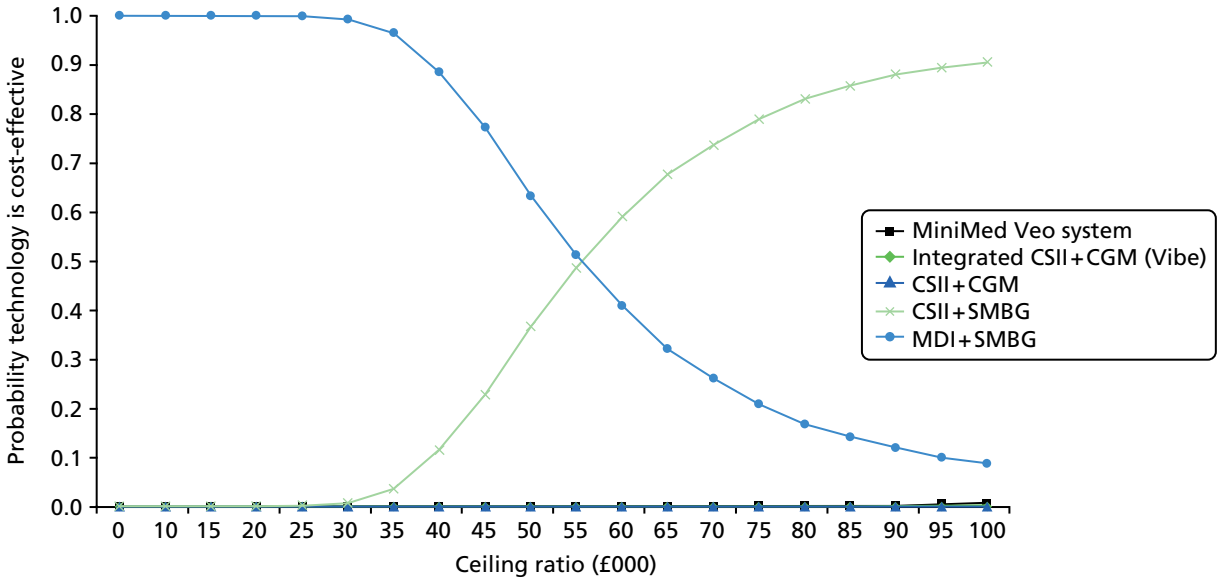

FIGURE 22 Cost-effectiveness acceptability curves for cost of stand-alone CSII and stand-alone CGM devices CGM without market share scenario.

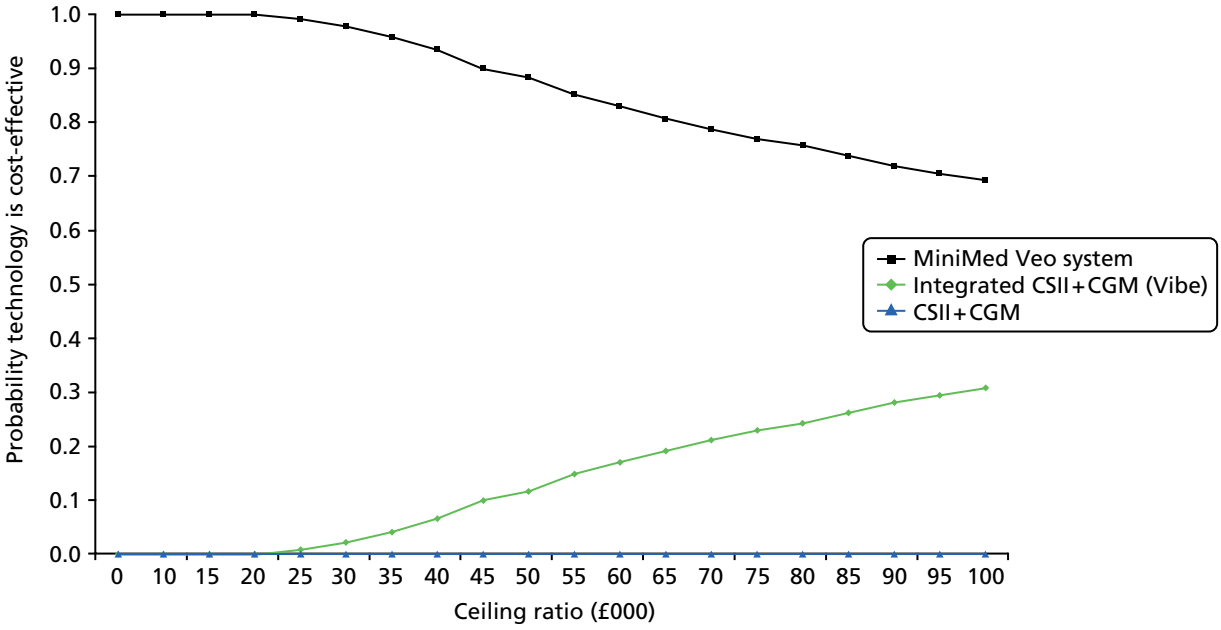

FIGURE 23 Cost-effectiveness acceptability curves for CGM treatments only for the cost of stand-alone CSII and stand-alone CGM devices without market share scenario.

Extension of the health economic analysis to children and adolescents

In addition to the clinical effectiveness limitations with regard to the evidence for children and adolescent patients mentioned in *Chapter 3* (see *Effectiveness of interventions in children*), the model employed to conduct the cost-effectiveness analyses, the IMS CDM, is not suitable for modelling long-term outcomes for children/adolescent populations, mostly because the background risk adjustment/risk factor progression equations are all based on adult populations.

Based on these limitations, it was deemed that there are too many crucial parameters with essentially no evidence specifically for these subgroups. This makes the reliability and validity of the results of conducting an economic evaluation for children and adolescents in this diagnostics assessment programme questionable. An overview of these parameters and reasons for the extreme uncertainty related to children and young adolescent patients is given in the following sections.

We have also reviewed the latest NICE guidelines (see *Health economic analyses of type 1 diabetes for children and adolescent patients in other National Institute for Health and Care Excellence guidelines/ assessment reports*) in order to summarise how they have modelled with regard to children and further emphasise the limitations resulting from a lack of evidence.

Parameters subject to extreme uncertainty in the clinical effectiveness evidence for child and adolescent patients

These are all parameters for treatment effects on both HbA_{1c} levels and hypoglycaemic event rates for all six treatment options (i.e. essentially 12 different parameters).

For the MiniMed Veo system, our systematic review identified only one study in children: Ly *et al.*[33] This study included patients between 4 and 50 years old, 70% of whom were children (4–18 years old). However, data were not reported separately by age group; therefore, we could use only the data for the total population and assume that it would apply to children.

However, our clinical experts advised us not to use this study as a study in children for two main reasons: (1) children behave differently to adults and, therefore, results for children are not the same as those for adults; and (2) pre-teen children behave differently from teenagers and, therefore, the 4- to 12-year-old age group would be different from a 12- to 18-year-old age group and the influence of parents on younger children would have to be taken into account. Indeed, this further subdivision of children essentially implies a doubling of the number of parameters for which there is no evidence of any treatment effect.

The only reason that we presented the data from this study in *Chapter 3* (see *Assessment of clinical effectiveness*) is that, without it, there would have been no evidence at all with regard to the effectiveness of the MiniMed Veo system in children. Therefore, for the MiniMed Veo system (and the assessment of severe hypoglycaemic events), we have data from only one study and this does not properly apply to children.

In addition, we found two trials presenting evidence for the integrated CSII + CGM system versus CSII + SMBG[34] and versus MDI + SMBG,[40] and three trials comparing CSII + SMBG with MDI + SMBG.[47–49]

However, these studies differed with regard to the age groups included (12–17 years,[34] 7–18 years,[40] 8–14 years,[47] 8–18 years[48] and 8–21 years[49]), whether or not patients had pump experience, baseline HbA_{1c} levels (8–11.5%), follow-up times (3, 6 and 12 months), hypoglycaemic status at baseline (in one study, patients with hypoglycaemia unawareness were excluded;[40] in another study, only patients with impaired awareness of hypoglycaemia were included;[33] and other studies had no exclusions[34] or no information[47–49]), and country (Israel,[47] the USA,[34,48,49] and the USA and Canada[40]). None of the studies was performed in the UK. Therefore, there is considerable heterogeneity between the studies, which makes any pooling of results invalid.

Uncertainties around the parameters for disease progression and treatment within the IMS CDM for child and adolescent patients

Several additional modelling uncertainties with regard to using the IMS CDM for children and adolescents have been identified. Indeed, the CDM structure is limited in that it lacks crucial parameters to inform the long-term effects of hypoglycaemia. These uncertainties have been summarised in *Table 61*, along with those regarding the treatment effects on HbA_{1c} levels and hypoglycaemic event rate.

TABLE 61 Uncertainties regarding modelling a children and adolescent population with the IMS CDM

Category of parameter	Parameter	Possibility to include parameter in the current version of IMS CDM	Impact on CE results
Treatment-related adverse events	Long-term consequences of hypoglycaemia in young children are not included in the model, despite them being potentially relevant. Couper *et al.*,[144] for example, indicate that there is greater concern about the consequences of hypoglycaemia in young children, given the rapid growth and development of the brain from birth to 7 years. In children who develop diabetes before 5 years of age, hypoglycaemia-related long-term adverse effects have been found, such as cognitive deficits, particularly in visuospatial tasks and lower IQ scores. In children who develop diabetes after 5 years, this impairment has not been found[145]	No. The model structure is fixed	Long-term costs and QALYs associated with these complications would change. It is not possible to predict in which direction the CE results would change
Costs	1. Disease management costs: whether or not disease management is the same for children and adults is uncertain. Some additional disease management categories can be relevant for children/ adolescents, such as screening/ management of eating disorders and anxiety 2. BG test costs: the frequency of BG tests differs for adults and children 3. Insulin costs: the amount of insulin used differs for adults and children 4. Outpatient care-related costs: unclear how these costs would differ for children. We anticipate additional costs associated with special training for parents 5. HbA_{1c} tests: unclear how these costs would differ for children	Partially (except for categories that only apply to children, if any). These costs could be averaged (together with the costs for the adult population) over the simulation time horizon	Costs 1, 2 and 5: no change in base-case incremental results, as these costs are the same for all treatments (unless there are categories that apply only to children) Cost 3: results would be more favourable towards CSII technologies, as the difference in insulin costs with respect to MDI technologies would increase Cost 4: it is not possible to predict in which direction the CE results would change

TABLE 61 Uncertainties regarding modelling a children and adolescent population with the IMS CDM (*continued*)

Category of parameter	Parameter	Possibility to include parameter in the current version of IMS CDM	Impact on CE results
Utilities	It is uncertain how the different complications can affect quality of life in children compared with adults. If this differs, then at least two different utility values would be needed for each complication We anticipate that utilities associated with severe hypoglycaemic events (including the fear of experiencing it) may be different, in particular for younger children, as hypoglycaemic events can cause serious long-term adverse events (e.g. brain damage)	No. The model only accepts one value per health state as input. Note also that the consequences of hypoglycaemic events in young children are not modelled	It is not possible to predict in which direction the CE results would change
Treatment effects: reduction in baseline HbA_{1c} levels in the first 12 months	In the IMS CDM, the change in HbA_{1c} levels is assumed to occur within the first 12 months. It is uncertain whether or not this is also applicable to children. It may take longer to observe the treatment benefits in children	Partially. The change in HbA_{1c} levels can be an input in the model regardless of age. However, extending the treatment effect beyond 12 months is not possible	It is not possible to predict in which direction the CE results would change
Treatment effects: rate per 100 patient-years of severe hypoglycaemic episodes	The rate of severe hypoglycaemic events differs between children and adults[146]	No. The model only accepts one value as input which is carried over the simulation time horizon	It is not possible to predict in which direction the CE results would change
HbA_{1c} progression after year 1	Annual HbA_{1c} progression in children and adults is different;[146] progression in children has been reported in the literature[147]	Yes. This can be modelled, for example, as in NICE Guideline NG18 for children[148]	It is not possible to predict in which direction the CE results would change
Disease management parameters	It is uncertain whether or not these parameters are the same for adults and children. If these are different then at least two values would be needed for each parameter	No. The model only accepts one value as input	It is not possible to predict in which direction the CE results would change
Disease natural history parameters	It is uncertain whether or not these parameters are the same for adults and children. If these are different then at least two values would be needed for each parameter	No. The model only accepts one value as input	It is not possible to predict in which direction the CE results would change
Transition probabilities/risk equations	All of these probabilities/equations are based on adult data. Therefore, it is uncertain to what extent these parameters are appropriate for modelling child populations. We anticipate that, for example, the reduction of the risk of MI or nephropathy for every 1% reduction in HbA_{1c} levels or every 10 mmHg reduction in SBP would be different for children/younger patients than for adults because of differences in the accumulation of any depreciation with disease duration	No. The model only accepts one value as input	It is not possible to predict in which direction the CE results would change

CE, cost-effectiveness; IQ, intelligence quotient.

Health economic analyses of type 1 diabetes for children and adolescent patients in other National Institute for Health and Care Excellence guidelines/assessment reports

CG15 (2004)[148] *Type 1 Diabetes: Diagnosis and Management of Type 1 Diabetes in Children and Young People*

This guideline was developed for the diagnosis and management of T1DM in adults and children/younger patients. In this guideline, no economic analysis was carried out for children or younger patients.[148] No explicit reasons for not conducting such economic analyses were mentioned in the guideline. In the introduction section of this guideline, it is stated that it was accepted that economic models utilising literature review data should be considered when there are resource implications with recommendations from guidelines, or when clinical effectiveness data from well-conducted studies were presented, or when guideline recommendations signified a policy amendment.

TA151 (2011)[14] *Continuous Subcutaneous Insulin Infusion for the Treatment of Diabetes Mellitus*

No economic analysis was conducted for children in this assessment, because in the technology assessment report, it was stated that the IMS CDM (online software applied for the adult economic analysis) was not created to run with children and could not replicate childrens' long-term outcomes. Therefore, the cost-effectiveness results for children/younger adults for CSII are not modelled in TA151.[80]

NG18 (2015)[148] *Diabetes (Type 1 and Type 2) in Children and Young People: Diagnosis and Management*

This guideline focuses on children and younger patients with T1DM as well as with T2DM.

In this guideline, two cost-effectiveness analyses for T1DM were conducted using the IMS CDM. The first analysis compared MDIs (four or more injections of insulin per day, matching insulin to food – also known as a basal–bolus regimen) with mixed insulin injections (less than four injections of insulin per day and no matching of insulin to food). The second analysis is a 'what if' analysis in which the intervention effects were based on an observational study and explored the possible cost-effectiveness of different frequencies of capillary BG monitoring.

For these analyses, a newly diagnosed cohort (i.e. with a disease duration of 0 years) with a baseline age of 12 years and an average baseline HbA_{1c} value of 11.4% was used. Among the physical risk factors, only HbA_{1c} progression was tailored by the Guideline Development Group (based on clinical advice) to represent progression in children. However, we anticipate that other risk factors and the risk adjustments for children/younger patients should also be adjusted: for example, the reduction of the risk of MI or nephropathy for every 1% reduction in HbA_{1c} levels, or every 10 mmHg reduction in SBP would be different for children/younger patients than for adults because of differences in the accumulation of any depreciation with disease duration. In conclusion, some input parameters of the IMS CDM (such as the baseline HbA_{1c} value and HbA_{1c} progression) were adapted for the child population, but there are many other parameters that cannot be adjusted (see *Table 61*). It should be noted that it is not possible to predict the extent to which these non-adjusted parameters will affect the cost-effectiveness results; therefore, the use of the IMS CDM for these analyses of children/younger populations is questionable. No explicit discussion regarding the use of the IMS CDM in children/adolescents was given in this draft guideline.

Finally, it should also be noted that, in this draft guideline, it was mentioned that the clinical evidence was not sufficiently robust to support a recommendation for the routine use of CGM as a glucose monitoring strategy and therefore modelling was not used to aid recommendations.[81] In this regard, the conclusions of this draft guideline[81] on the lack of clinical evidence are similar to those of our report, which are summarised in *Parameters subject to extreme uncertainty in the clinical effectiveness evidence for children and adolescent patients*.

Conclusion

The limited clinical effectiveness evidence (as discussed in *Chapter 3*, *Effectiveness of interventions in children* and *Parameters subject to extreme uncertainty in the clinical effectiveness evidence for children and adolescent patients*), the limitations of the model (summarised in *Table 61*), and the approaches followed in previous NICE clinical guidelines and assessment reports support our conclusion that it is not possible to conduct a reliable and valid economic evaluation for children/adolescent populations using the IMS CDM.

Chapter 5 Discussion

Statement of principal findings

Clinical effectiveness

Nineteen trials were included, 12 reported data for adults,[32,34,37–46] six reported data for children[33,34,40,47–49] and one trial reported data for pregnant women.[50] Four trials were in mixed populations (adults and children); two of these reported data separately for adults and children and are included in both the 12 trials for adults and the six trials for children.[34,40] Two trials did not report data separately for adults and children (O'Connell *et al.*[35] and RealTrend[36]). Therefore, the results from these trials were not used in the main analyses.

Twelve studies were included in the analyses for adults.[32,34,37–46] The main conclusion from these trials is that the MiniMed Paradigm Veo system reduces hypoglycaemic events in adults in comparison with the integrated CSII + CGM system, without any differences in other outcomes, including change in HbA_{1c} levels. Nocturnal hypoglycemic events occurred 31.8% less frequently in the MiniMed Veo group than in the integrated CSII + CGM group [1.5 events (SD 1.0 event) vs. 2.2 events (SD 1.3 events) per patient per week; $p < 0.001$]. Similarly, the MiniMed Veo group had significantly lower weekly rates of combined daytime and night-time events than the integrated CSII + CGM group ($p < 0.001$). Indirect evidence seems to suggest that that there are no significant differences between the MiniMed Paradigm Veo system and CSII + SMBG or MDI + SMBG with regard to the change in HbA_{1c} levels at 3-month follow-up. However, if all studies are combined (combining different follow-up times and including mixed populations), the MiniMed Paradigm Veo system is significantly better than MDI + SMBG in terms of HbA_{1c} levels.

For the integrated CSII + CGM system (MiniMed Paradigm REAL-Time 722 System) versus other treatments, the results suggest a significant effect in favour of the integrated CSII + CGM system over MDI + SMBG for HbA_{1c} levels, but not if compared with CSII + SMBG, and a significant effect in favour of the integrated CSII + CGM system over MDI + SMBG and CSII + SMBG with regard to quality of life.

With regard to comparisons of CSII and MDIs, only one of the six trials[41–46] showed a significant difference between CSII + SMBG and MDI + SMBG in terms of change in HbA_{1c} levels. DeVries *et al.*[42] found a significant difference in favour of CSII + CGM: at 16 weeks, mean HbA_{1c} levels were 0.84% lower (mean = –0.84%, 95% CI –1.31% to –0.36%) in the CSII + SMBG group than the MDI + SMBG group. No differences were found in any trial with regard to the number of severe hypoglycaemic events.

Six studies were included in the analyses for children.[33,34,40,47–49] None of the studies in children made a direct comparison between the MiniMed Paradigm Veo system and the integrated CSII + CGM system. An indirect comparison was possible, using data from Ly *et al.*[33] and Hirsch *et al.*[34] at 6-month follow-up, but only for HbA_{1c} levels, which showed no significant difference between groups.

One study[33] compared the MiniMed Paradigm Veo system with CSII + SMBG. The only significant difference between treatment groups was the rate of moderate and severe hypoglycaemic events, which favoured the MiniMed Paradigm Veo system.

One study[34] compared the integrated CSII + CGM system with CSII + SMBG; this trial found no significant difference in HbA_{1c} levels between groups. One study[40] compared the integrated CSII + CGM system with MDI + SMBG; this trial found a significant difference in HbA_{1c} change scores in favour of the integrated CSII + CGM system, but no significant difference in the number of children achieving HbA_{1c} levels of $\leq 7\%$. The hyperglycaemic AUC was significantly lower in the integrated CSII + CGM group, but the hypoglycaemic AUC showed no significant difference. Other outcomes showed no significant differences between groups.

For pregnant women, we found only one trial[50] comparing CSII + SMBG with MDI + SMBG, which is not relevant to the decision problem.

Cost-effectiveness

We assessed the cost-effectiveness of the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system compared with stand-alone CSII + CGM, CSII + SMBG, MDI + CGM and MDI + SMBG for the management of T1DM in adults.

In addition to the literature limitations regarding the population subgroups of interest (i.e. children and pregnant women) mentioned above, the model employed to conduct the cost-effectiveness analyses, the IMS CDM, is not suitable for modelling long-term outcomes for child/adolescent or pregnant woman populations, because all of the background risk adjustment/risk factor progression equations are based on adult populations.

The comparator MDI + CGM was not included in the cost-effectiveness analyses as no relevant evidence for this comparator was found in the systematic review. Moreover, in the absence of data comparing the clinical effectiveness of integrated CSII + CGM systems with stand-alone CSII + CGM systems, we assumed, in our analyses, that both technologies would be equally effective, which seems to be plausible. The immediate consequence of this assumption was that stand-alone CSII + CGM systems dominated the integrated CSII + CGM systems since the stand-alone system was cheaper, according to our estimated cost, while being equally effective.

Overall, the cost-effectiveness results suggest that the technologies using SMBG (either with CSII or MDIs) are more likely to be cost-effective, since the higher quality of life provided by the technologies that use CGM does not outweigh their higher costs. This is in line with the findings in the currently updated T1DM guideline,[81] in which CGM was compared with several SMBG setups and was found not to be cost-effective. In particular, the base-case results show that MDI + SMBG is the cheapest treatment, but also the one that provides the lowest number of QALYs. The ICER of CSII + SMBG compared with MDI + SMBG is £52,381. The MiniMed Paradigm Veo system is extendedly dominated by stand-alone CSII + CGM. This is mainly because, according to our systematic review, the decrease in HbA_{1c} levels with respect to baseline was highest for integrated CSII + CGM, and this decrease in HbA_{1c} leads to a decrease in the number of complications that occur over a lifetime to such an extent that it compensates for the higher number of severe hypoglycaemic events. In any case, the ICER of stand-alone CSII + CGM compared with CSII + SMBG was £660,376. Thus, given the common threshold ICER of £30,000, it is clear that stand-alone CSII + CGM would not be cost-effective.

We also considered two additional base-case analyses. Since insulin pumps are recommended for people with T1DM for whom MDIs are not suitable, we excluded MDI-containing technologies from the analysis. In this scenario, the CSII + SMBG appeared to be the strategy most likely to be cost-effective, with a cost-effectiveness probability equal to almost 1 for all of the ceiling ratios considered in the analysis. Following this, we also excluded SMBG treatments from the analysis in order to capture the effect of the LGS function of the MiniMed Paradigm Veo system, which is expected to have an influence on reducing the number of severe hypoglycaemic events, and thus on the number of QALYs gained. In this situation, the only relevant comparison was the MiniMed Veo system versus stand-alone CSII + CGM, since the Vibe and G4 PLATINUM CGM system was dominated by the stand-alone combination of CSII and CGM. The corresponding results showed that when the MiniMed Veo system was compared with stand-alone CSII + CGM, the ICER obtained was high (£422,849). However, this results from both negative incremental QALYs and incremental costs (i.e. the ICER is in the south-west quadrant of the cost-effectiveness plane). In this case, the higher the ICER, the better (i.e. any cost saving could be used on other patients in order to generate QALYs that could 'outweigh' the loss in QALYs). Therefore, at a ceiling ratio of £30,000 per QALY, the MiniMed Veo system would be more cost-effective than stand-alone CSII + CGM. This is demonstrated by the corresponding CEACs, since the MiniMed Paradigm Veo system is the CGM treatment most likely to be cost-effective for all of the ceiling ratios considered in the analysis.

However, as the ceiling ratio increases, the CEACs for the MiniMed Paradigm Veo system and stand-alone CSII + CGM seem to converge. As expected, the PSA showed that, for the Vibe and G4 PLATINUM CGM system, the probability of this system being cost-effective is always zero for all of the ceiling ratios considered in the analysis.

The results of these different scenario analyses did not differ much from the base-case results. The scenario that was most favourable with regard to the MiniMed Paradigm Veo system was the one that considered an additional utility decrement associated with the fear of hypoglycaemia. In this scenario, the ICER of the MiniMed Paradigm Veo system compared with CSII + SMBG was equal to £74,088 (the lowest found in all analyses). However, given the common threshold ICER of £30,000, the MiniMed Paradigm Veo system would not be considered cost-effective. For the Vibe and G4 PLATINUM CGM system, when it was not (extendedly) dominated by other strategies, the lowest ICER obtained was £428,595 when compared with the MiniMed Paradigm Veo system. This was also the case for the scenario in which a utility increment associated with reducing the fear of hypoglycaemia was considered.

Strengths and limitations of the assessment

Clinical effectiveness

Overall, the evidence seems to suggest that the MiniMed Paradigm Veo system reduces hypoglycaemic events in comparison with other treatments, without any differences in other outcomes, including change in HbA_{1c} levels. In addition, we found significant results in favour of the integrated CSII + CGM system in comparison with MDI + SMBG with regard to HbA_{1c} levels and quality of life. However, the evidence base was poor. The quality of included studies was generally low and often there was only one study that compared treatments in a specific population and at a specific follow-up time. In particular, the evidence for the two interventions of interest was limited, with only one study comparing the MiniMed Paradigm Veo system with an integrated CSII + CGM system,[32] and only one study, in a mixed population, comparing the MiniMed Paradigm Veo system with CSII + SMBG.[33] In addition, although several studies included the integrated CSII + CGM system as a treatment arm, it is important to note that none of these studies looked at the Vibe and G4 PLATINUM CGM system; in the included studies, the integrated CSII + CGM system was always a MiniMed Paradigm pump with integrated CGM system (MiniMed Paradigm REAL-Time 722 System). This also means that all of the studies that assessed the effectiveness of the integrated CSII + CGM system were performed in the USA. Overall, only 3[37,41,45] out of the 19 included studies included patients from the UK, and only one of these was completely performed in the UK (Thomas *et al.*).[45] Interactions between patients and health-care providers may show considerable differences in different countries, which will affect patients' behaviour and therefore the effectiveness of insulin pumps and monitors. Therefore, the results from the included studies may not be representative of the UK situation.

Unfortunately, many studies had to be excluded because they compared CSII with MDIs, without specifying the type of monitoring, or CGM with SMBG, without specifying the type of insulin delivery. Two studies[149,150] with 2 × 2 factorial design, including CSII + CGM, CSII + SMBG, MDI + CGM and MDI + SMBG, had to be excluded because the results were reported for only CSII versus MDIs and CGM versus SMBG. One of these studies was in children (Mauras *et al.*[149]) and one was in adults [Little *et al.* (HypoCOMPaSS trial.[150])] These studies were excluded because they could not be classified as one of the relevant comparators defined by NICE and they could not be compared with the MiniMed Paradigm Veo system or an integrated CSII + CGM system.

In addition, we had problems differentiating stand-alone and integrated CSII + CGM interventions because the interventions were often poorly described, making it difficult to be sure which type of intervention was used. Sometimes researchers indicated no differences between these two types of treatments and provided patients in the same treatment arm with stand-alone and integrated CSII + CGM systems (see Beck[151]).

Four of the included studies were in mixed populations (Ly *et al.*[33] used 65 children and 30 adults with an age range of 4–50 years; O'Connell *et al.*[35] used 32 children and 30 adults with an age range of 13–40 years; RealTrend[36] used 51 children and 81 adults with an age range of 2–65 years; and Hirsch *et al.*[34] used 40 children and 98 adults with an age range of 12–72 years). The advice from clinical experts was not to combine results from adults and children and vice versa. Therefore, these studies were, in the first instance, excluded from our analyses. Only if results were reported separately for adults and children were results included in the analyses or if there would have been no data without using a mixed adult/child population study, as in the case of Ly *et al.*,[33] which was used as a study in children to make a comparison between the MiniMed Paradigm Veo system and other treatments.

As reported in *Chapter 1* of this report (see *Comparators*), there is a problem with the comparability of populations in studies evaluating insulin pumps and MDIs. NICE recommended CSII as a potential treatment for children ≥ 12 years and adults, who have disabling hypoglycaemia (including anxiety about hypoglycaemia) when trying to attain $HbA_{1c} < 7.5\%$, or HbA_{1c} is constantly > 8.5%, while undergoing MDIT.[14] In other words, insulin pumps are recommended for people with T1DM for whom MDIs are not suitable. Therefore, it was anticipated that it would be problematic finding studies comparing insulin pumps (especially modern pumps such as the integrated systems) with MDIs in similar populations.

Most studies comparing CSII with MDIs show no difference with regard to HbA_{1c} levels. One trial found a significant difference in the change in HbA_{1c} levels at follow-up (DeVries *et al.*[42]). In this trial, patients with persistent poor control, defined as a mean of all HbA_{1c} levels of ≥ 8.5% in the 6 months before the trial, were included. Partly based on this trial, NICE[14] concluded that CSII would most likely be cost-effective in patients with poorly controlled diabetes. Our current systematic review shows that nothing has changed in the evidence base with regard to CSII versus MDIs. The trial by DeVries *et al.*[42] is still the only trial showing significant differences in HbA_{1c} levels at follow-up between CSII + SMBG and MDI + SMBG. This highlights the problem with identifying the correct population for comparisons between the interventions relevant to this appraisal. For the comparison of the MiniMed Paradigm Veo system with the integrated CSII + CGM system, we have included a general population of T1DM patients. However, if we compare these interventions with CSII + SMBG or MDI + SMBG in general populations, we will obscure the differences that exist between CSII and MDIs in diabetes patients with poor control at baseline.

For the comparison of CSII with MDIs, it is important to differentiate between populations with good HbA_{1c} control at baseline and populations with poor control. However, if we compare the MiniMed Paradigm Veo system with the integrated CSII + CGM system and with CSII + SMBG, all patients will be using a pump and, in most studies comparing different types of pumps, patients will have been using a pump for > 6 months. In such studies, baseline HbA_{1c} levels will be relatively low because of long-term pump use. Therefore, it is difficult to assess how valid comparisons are between those patients and patients involved in trials comparing pump use with MDIs.

Given these problems resulting from the heterogeneity among RCT populations, we did not consider including any further observational studies, as these problems would be even more apparent if results from observational studies were compared.

For pregnant women, we found no studies looking at the MiniMed Paradigm Veo system or the integrated CSII + CGM system.

Cost-effectiveness

An important strength of the current cost-effectiveness evaluation is that we used a well-validated diabetes model (IMS CDM) that has been used for many assessments, including submissions for NICE.[14,81–85] In particular, this model was used to assess the cost-effectiveness of CSII versus MDIs for T1DM patients in a 2010 HTA report[80] and in the current update of the NICE Guideline on T1DM (NG17).[81] Since 1999, the model has been used at Mount Hood conferences, during which health economic models on diabetes are compared with each other in terms of their structure, performance and validity.[86–88] Two major validation

papers on the IMS CDM have been published to date.[89,90] The latest one,[90] from 2014, is the basis for the technical model description provided in this report. This description is consistent with the latest version of the model (version 8.5). Given the degree of validation of the model, and in order to be in line with the currently updated T1DM guideline[81] from which we sourced many input parameters, it was deemed important not to use an alternative model or develop a de novo cost-effectiveness model for this evaluation. The most recent unit cost data were obtained for the analyses, including detailed data on equipment costs obtained from the relevant companies.

Although many of our input parameters are the same as those described in NICE Guideline NG17,[81] we have also considered interventions that were not assessed in the guideline. Furthermore, we have considered a large variety of scenarios and performed PSAs for all of them.

A major limitation of the model is that the IMS CDM is not appropriate for analysing health economic outcomes for paediatric/adolescent populations. This was reported in the 2010 assessment of CSII versus MDIs for T1DM patients[80] and confirmed by the model developers, who also mentioned that the model is not appropriate for pregnant women either. Therefore, these two subgroup populations were not included in the cost-effectiveness analyses.

Another limitation of the IMS CDM is that not all input parameters can be included in a PSA because of the technical constraints of the model. It is likely that the most important parameter not included in the PSA was the rate of severe hypoglycaemic events, as this is considered to be one of the key drivers of the model results, especially with regard to the MiniMed Paradigm Veo system. As a consequence, the uncertainty regarding the ICERs is currently somewhat underestimated. However, the ICERs themselves are not influenced by this limitation.

Another major limitation is the lack of comparability of treatments and clinical trials to estimate the treatment effect for stand-alone CSII + CGM. In the current analysis, we had to assume equal effectiveness of integrated and stand-alone CSII + CGM, thus assuring that stand-alone CSII + CGM would always dominate integrated CSII + CGM. Moreover, it was difficult to determine the extent to which the effect of the LGS function of the MiniMed Paradigm Veo system was captured in the model results. Furthermore, we found no reliable data on minor hypoglycaemic events and DKA events. The impact of these parameters on the cost-effectiveness results is difficult to predict, but we expect them to have less of an impact than the other treatment effect parameters (e.g. reduction in HbA_{1c} levels and rate of severe hypoglycaemic events).

Finally, information was limited for the estimation of the cost of the stand-alone insulin pump. Although we do not expect a large difference in our estimated costs, it may have a major implication for the comparison of stand-alone CSII + CGM versus the integrated Vibe and G4 PLATINUM CGM system, as both are equally effective. Thus, depending on the price, one of these two options will dominate the other.

Uncertainties

Clinical effectiveness

The main uncertainties with regard to clinical effectiveness are the general lack of data (especially for children and pregnant women) and the poor quality of the available data. In addition, there were problems with differentiating interventions (in particular integrated and stand-alone CSII + CGM systems) and with interpreting results from mixed populations (adults and children).

Because of inherent differences in patient characteristics at baseline, it was difficult to compare MDI + SMBG with any of the other interventions in this assessment.

Cost-effectiveness

The uncertainties described for clinical effectiveness also apply to the assessment of cost-effectiveness. In addition, it is uncertain how realistic it is to assume a continuous increase in HbA_{1c} levels over the first year of treatment. It seems likely that, in clinical practice, efforts would be made to keep HbA_{1c} levels as low as possible, so periods of increase may be followed by decreases. It is unclear at this moment what the most realistic scenario will be in the long term.

Chapter 6 Conclusions

Implications for service provision

Overall, the limited evidence seems to suggest that the MiniMed Paradigm Veo system reduces hypoglycaemic events in comparison with other treatments, without any differences in other outcomes, including change in HbA_{1c} levels. In addition, we found significant results in favour of the integrated CSII + CGM system over MDI + SMBG with regard to HbA_{1c} levels and quality of life. However, the evidence base was poor. The quality of included studies was generally low and there was often only one study to compare treatments in a specific population and at a specific follow-up time. In particular, the evidence for the two interventions of interest was limited, with only one study comparing the MiniMed Paradigm Veo system with an integrated CSII + CGM system, and only one study, in a mixed population, comparing the MiniMed Paradigm Veo system with CSII + SMBG.

Cost-effectiveness analyses indicated that MDI + SMBG is the option most likely to be cost-effective, given the current threshold of £30,000 per QALY gained, whereas integrated CSII + CGM systems and MiniMed Paradigm Veo are dominated and extendedly dominated, respectively, by stand-alone CSII + CGM. Scenario analyses, used to assess the potential impact of changing various input parameters, did not alter these conclusions. No cost-effectiveness modelling was conducted for children and pregnant women.

Suggested research priorities

In adults, a trial comparing the MiniMed Paradigm Veo system with CSII + SMBG is warranted. Similarly, a trial comparing the integrated CSII + CGM system with CSII + SMBG is warranted.

In children, a trial comparing the MiniMed Paradigm Veo system with the integrated CSII + CGM system is warranted. Similarly, a trial comparing the integrated CSII + CGM system with CSII + SMBG is warranted.

For pregnant women, trials comparing the MiniMed Paradigm Veo system and the integrated CSII + CGM system with other interventions are warranted.

Future trials should include longer-term follow-up and include EQ-5D (besides more disease-specific quality-of-life questionnaires) at various time points with a view to informing improved cost-effectiveness modelling.

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Contributions of authors

Rob Riemsma was involved in planning and performing this systematic review and interpreting the evidence.

Isaac Corro Ramos was involved in planning and performing the cost-effectiveness analyses and interpreting the results.

Richard Birnie was involved in planning and performing this systematic review and interpreting the evidence.

Nasuh Büyükkaramikli was involved in planning and performing the cost-effectiveness analyses and interpreting the results.

Nigel Armstrong contributed to the planning and interpretation of the cost-effectiveness analyses and the acquisition of input data for modelling.

Steve Ryder contributed to obtaining the input data for the modelling.

Steven Duffy devised and performed the literature searches and provided information support to the project.

Gill Worthy was involved in planning and performing this systematic review and interpreting the evidence.

Maiwenn Al was involved in planning and performing the cost-effectiveness analyses and interpreting the results.

Johan Severens provided senior advice and support to the assessment.

Jos Kleijnen provided senior advice and support to the assessment.

All of the authors were involved in drafting and/or commenting on the report.

Data sharing statement

Study characteristics and results of trials included in the systematic review of the effectiveness of interventions are provided in *Appendix 3*. Details of disease natural history parameters and transition probabilities are provided in *Appendix 7*, and results (full incremental and intervention vs. comparator) of base-case and scenario analyses are provided in *Appendix 8*. All data created during this research are available by request from the authors.

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Appendix 1 Literature search strategies

Clinical effectiveness searches

EMBASE (via OvidSP)

Date range searched: 1974–2014/week 34.

Date searched: 5 September 2014.

Search strategy

1. insulin dependent diabetes mellitus/ (78,607)
2. exp diabetic ketoacidosis/ (7787)
3. (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ti,ab,ot,hw. (49,088)
4. (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ti,ab,ot,hw. (29,355)
5. ((insulin$ adj2 depend$) or insulindepend$).ti,ab,ot,hw. (217,259)
6. (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab,ot,hw. (20,038)
7. (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab,ot,hw. (14,231)
8. hypoglycemia/ or hyperglycemia/ (108,615)
9. (hyperglyc?em$ or hypoglyc?em$).ti,ab,ot. (104,051)
10. ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ti,ab,ot,hw. (126,603)
11. or/1-10 (436,900)
12. (sensor$ adj3 (augment$ or pump$)).ti,ab,hw,ot. (598)
13. SAPT.ti,ab,ot,hw. (114)
14. (minimed or paradigmveo).ti,ab,ot,hw,dm,dv. (727)
15. (paradigm$ adj3 (veo or pump$)).ti,ab,hw,ot,dm,dv. (127)
16. (veo adj3 pump$).ti,ab,ot,hw,dm,dv. (38)
17. ((animas or vibe) adj3 (pump$ or infus$ or system$)).ti,ab,ot,hw,dm,dv. (25)
18. (g4 adj3 platinum).ti,ab,ot,hw,dm,dv. (27)
19. dexcom.ti,ab,ot,hw,dm,dv. (298)
20. or/12-19 (1674)
21. 11 and 20 (1105)
22. insulin pump/ (3425)
23. insulin infusion/ (5096)
24. artificial pancreas/ (1433)
25. (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ti,ab,ot,hw. (17,265)
26. (pump$ adj2 (therap$ or treatment$)).ti,ab,ot,hw. (3171)
27. ((subcutaneous adj2 insulin$) or CSII).ti,ab,ot,hw. (4218)
28. (artificial adj3 (pancreas or beta cell$)).ti,ab,ot,hw. (2050)
29. (closed loop adj3 (pump$ or deliver$ or infus$ or therap$ or treatment$ or system$)).ti,ab,ot,hw. (1941)
30. (accu-chek or cellnovo or dana diabecare or omnipod).ti,ab,ot,hw,dm,dv. (529)
31. ((integrat$ or dual or combined or unified) adj3 (system$ or device$)).ti,ab,ot,hw. (39,256)
32. or/22-31 (62,055)
33. insulin/ and exp injection/ (3392)
34. (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (1188)
35. (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (561)

36. (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (9358)
37. MDI.ti,ab,hw,ot. (3791)
38. (injection adj3 therapy).ti,ab,ot,hw. (4157)
39. ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ti,ab,hw,ot. (1491)
40. (short acting adj3 insulin).ti,ab,hw,ot. (1038)
41. rapid acting adj3 insulin).ti,ab,hw,ot. (864)
42. or/33-41 (22,079)
43. 32 or 42 (81,787)
44. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ (397,683)
45. (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab,ot,hw. (1,636,591)
46. 44 or 45 (1,636,591)
47. 11 and 43 and 46 (3628)
48. 21 or 47 (4491)
49. animal/ (1,574,788)
50. animal experiment/ (1,795,287)
51. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5,694,449)
52. or/49-51 (5,694,449)
53. exp human/ (15,050,997)
54. human experiment/ (328,369)
55. 53 or 54 (15,052,426)
56. 52 not (52 and 55) (4,552,229)
57. (letter or editorial or note).pt. (1,874,995)
58. 48 not (56 or 57) (4185)

The trials filter was based on terms suggested in chapter 6 of the Cochrane Handbook.[152]

MEDLINE (via OvidSP)

Date range searched: 1946–2014/August week 4.

Date searched: 5 September 2014.

Search strategy

1. Diabetes Mellitus, Type 1/ (62,323)
2. Diabetic Ketoacidosis/ (5178)
3. (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ti,ab,ot,hw. (69,580)
4. (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ti,ab,ot,hw. (20,273)
5. ((insulin$ adj2 depend$) or insulindepend$).ti,ab,ot,hw. (30,469)
6. (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab,ot,hw. (13,085)
7. (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab,ot,hw. (9331)
8. Hyperglycemia/ (20,833)
9. Hypoglycemia/ (21,743)
10. (hyperglyc?em$ or hypoglyc?em$).ti,ab,ot. (72,656)
11. ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ti,ab,ot,hw. (94,623)
12. or/1-11 (24,5714)
13. (sensor$ adj3 (augment$ or pump$)).ti,ab,hw,ot. (312)

14. SAPT.ti,ab,ot,hw. (93)
15. (minimed or paradigmveo).ti,ab,ot,hw. (197)
16. (paradigm$ adj3 (veo or pump$)).ti,ab,hw,ot. (34)
17. (veo adj3 pump$).ti,ab,ot,hw. (5)
18. ((animas or vibe) adj3 (pump$ or infus$ or system$)).ti,ab,ot,hw. (7)
19. (g4 adj3 platinum).ti,ab,ot,hw. (3)
20. dexcom.ti,ab,ot,hw. (44)
21. or/13-20 (645)
22. 12 and 21 (297)
23. Insulin Infusion Systems/ (3988)
24. Pancreas, Artificial/ (402)
25. (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ti,ab,ot,hw. (11,972)
26. (pump$ adj2 (therap$ or treatment$)).ti,ab,ot,hw. (1810)
27. ((subcutaneous adj2 insulin$) or CSII).ti,ab,ot,hw. (2474)
28. (artificial adj3 (pancreas or beta cell$)).ti,ab,ot,hw. (1203)
29. (closed loop adj3 (pump$ or deliver$ or infus$ or therap$ or treatment$ or system$)).ti,ab,ot,hw. (1310)
30. (accu-chek or cellnovo or dana diabecare or omnipod).ti,ab,ot,hw. (150)
31. ((integrat$ or dual or combined or unified) adj3 (system$ or device$)).ti,ab,ot,hw. (32,573)
32. or/23-31 (47,787)
33. Insulin/ and Injections, Subcutaneous/ (2134)
34. (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (624)
35. (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (452)
36. (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (6795)
37. MDI.ti,ab,hw,ot. (2372)
38. (injection adj3 therapy).ti,ab,ot,hw. (2858)
39. ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ti,ab,hw,ot. (1015)
40. (short acting adj3 insulin).ti,ab,hw,ot. (466)
41. (rapid acting adj3 insulin).ti,ab,hw,ot. (468)
42. or/33-41 (15,196)
43. 32 or 42 (61,325)
44. randomized controlled trial.pt. (387,461)
45. controlled clinical trial.pt. (89,748)
46. randomized.ab. (283,558)
47. placebo.ab. (150,467)
48. randomly.ab. (200,457)
49. trial.ab. (294,684)
50. groups.ab. (1,279,172)
51. or/44-50 (1,878,983)
52. exp Animals/ not (exp Animals/ and Humans/) (4,007,023)
53. 51 not 52 (1,535,840)
54. 12 and 43 and 53 (2750)
55. 22 not 52 (291)
56. 54 or 55 (2966)

Based on trials filter from box 6.4.c of the Cochrane Handbook.[152]

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily Update (via OvidSP)

Date searched: 5 September 2014.

Search strategy

1. Diabetes Mellitus, Type 1/ (36)
2. Diabetic Ketoacidosis/ (3)
3. (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ti,ab,ot,hw. (2614)
4. (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ti,ab,ot,hw. (1105)
5. ((insulin$ adj2 depend$) or insulindepend$).ti,ab,ot,hw. (701)
6. (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab,ot,hw. (884)
7. (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab,ot,hw. (430)
8. Hyperglycemia/ (20)
9. Hypoglycemia/ (10)
10. (hyperglyc?em$ or hypoglyc?em$).ti,ab,ot. (5462)
11. ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ti,ab,ot,hw. (7457)
12. or/1-11 (14909)
13. (sensor$ adj3 (augment$ or pump$)).ti,ab,hw,ot. (59)
14. SAPT.ti,ab,ot,hw. (83)
15. (minimed or paradigmveo).ti,ab,ot,hw. (13)
16. (paradigm$ adj3 (veo or pump$)).ti,ab,hw,ot. (4)
17. (veo adj3 pump$).ti,ab,ot,hw. (1)
18. ((animas or vibe) adj3 (pump$ or infus$ or system$)).ti,ab,ot,hw. (0)
19. (g4 adj3 platinum).ti,ab,ot,hw. (3)
20. dexcom.ti,ab,ot,hw. (7)
21. or/13-20 (164)
22. 12 and 21 (40)
23. Insulin Infusion Systems/ (2)
24. Pancreas, Artificial/ (2)
25. (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ti,ab,ot,hw. (504)
26. (pump$ adj2 (therap$ or treatment$)).ti,ab,ot,hw. (189)
27. ((subcutaneous adj2 insulin$) or CSII).ti,ab,ot,hw. (172)
28. (artificial adj3 (pancreas or beta cell$)).ti,ab,ot,hw. (61)
29. (closed loop adj3 (pump$ or deliver$ or infus$ or therap$ or treatment$ or system$)).ti,ab,ot,hw. (343)
30. (accu-chek or cellnovo or dana diabecare or omnipod).ti,ab,ot,hw. (16)
31. ((integrat$ or dual or combined or unified) adj3 (system$ or device$)).ti,ab,ot,hw. (4137)
32. or/23-31 (5154)
33. Insulin/ and Injections, Subcutaneous/ (3)
34. (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (66)
35. (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (9)
36. (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (492)
37. MDI.ti,ab,hw,ot. (161)
38. (injection adj3 therapy).ti,ab,ot,hw. (206)
39. ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ti,ab,hw,ot. (51)
40. (short acting adj3 insulin).ti,ab,hw,ot. (29)
41. (rapid acting adj3 insulin).ti,ab,hw,ot. (59)
42. or/33-41 (937)
43. 32 or 42 (6014)
44. randomized controlled trial.pt. (809)

45. controlled clinical trial.pt. (53)
46. randomized.ab. (24,330)
47. placebo.ab. (8979)
48. randomly.ab. (21,647)
49. trial.ab. (25,986)
50. groups.ab. (122,705)
51. or/44-50 (163,158)
52. exp Animals/ not (exp Animals/ and Humans/) (1565)
53. 51 not 52 (162,926)
54. 12 and 43 and 53 (178)
55. 22 not 52 (40)
56. 54 or 55 (203)

Based on trials filter from box 6.4.c of the Cochrane Handbook.[152]

PubMed (via the National Library of Medicine)

URL: www.ncbi.nlm.nih.gov/pubmed/

Date range searched: from inception until 5 September 2014.

Date searched: 5 September 2014.

Search strategy

#63 Search (#61 and #62) (99)
#62 Search (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) (1,815,003)
#61 Search (#57 not #60) (1862)
#60 Search ((#58 not (#58 and #59))) (2,730,690)
#59 Search human*[tiab] (2,017,079)
#58 Search (rat[tiab] or rats[tiab] or mouse[tiab] or mice[tiab] or murine[tiab] or rodent[tiab] or rodents [tiab] or hamster[tiab] or hamsters[tiab] or pig[tiab] or pigs[tiab] or porcine[tiab] or rabbit[tiab] or rabbits [tiab] or animal[tiab] or animals[tiab] or dogs[tiab] or dog[tiab] or cats[tiab] or cow[tiab] or bovine[tiab] or sheep[tiab] or ovine[tiab] or monkey[tiab] or monkeys[tiab]) (3,335,539)
#57 Search (#30 or #56) (1967)
#56 Search (#20 and #54 and #55) (1778)
#55 Search (#38 or #46) (19531)
#54 Search (#47 or #48 or #49 or #50 or #51 or #52 or #53) (2,074,509)
#53 Search groups [tiab] (1,413,274)
#52 Search trial [tiab] (369,610)
#51 Search randomly [tiab] (219,790)
#50 Search placebo [tiab] (160,018)
#49 Search randomized [tiab] (324,067)
#48 Search controlled clinical trial [pt] (87,768)
#47 Search randomized controlled trial [pt] (371,691)
#46 Search (#39 or #40 or #41 or #42 or #43 or #44 or #45) (9426)
#45 Search ("short acting insulin"[tiab] OR "rapid acting insulin"[tiab]) (810)
#44 Search (basal*[tiab] AND bolus[tiab] AND (injection*[tiab] OR regime*[tiab] OR routine*[tiab] OR system*[tiab])) (1549)
#43 Search "injection therapy"[tiab] (2098)
#42 Search MDI[tiab] (2524)
#41 Search "multiple injection"[tiab] or "multiple injections"[tiab] or "multiple insulin"[tiab] or "multiple regime"[tiab] or "multiple regimes"[tiab] or "multiple routine"[tiab] or "multiple routines"[tiab] (2414)

#40 Search "multiple dose injection"[tiab] or "multiple dose injections"[tiab] or "multiple dose insulin"[tiab] or "multiple dose regime"[tiab] or "multiple dose regimes"[tiab] or "multiple dose routine"[tiab] or "multiple dose routines"[tiab] (48)
#39 Search "multiple daily injection"[tiab] or "multiple daily injections"[tiab] or "multiple daily insulin"[tiab] or "multiple daily regime"[tiab] or "multiple daily regimes"[tiab] or "multiple daily routine"[tiab] or "multiple daily routines"[tiab] (603)
#38 Search (#31 or #32 or #33 or #34 or #35 or #36 or #37) (10,964)
#37 Search "integrated system"[tiab] or "integrated systems"[tiab] "integrated device"[tiab] or "integrated devices"[tiab] or "dual system"[tiab] or "dual systems"[tiab] or "dual device"[tiab] or "dual devices"[tiab] or "combined system"[tiab] or "combined systems"[tiab] or "combined device"[tiab] or "combined devices"[tiab] or "unified system"[tiab] or "unified systems"[tiab] or "unified device"[tiab] or "unified devices"[tiab] (1317)
#36 Search (accu-chek[tiab] or cellnovo[tiab] or "dana diabecare"[tiab] or omnipod[tiab]) (159)
#35 Search "closed loop pump"[tiab] or "closed loop pumps"[tiab] or "closed loop delivery"[tiab] or "closed loop infusion"[tiab] or "closed loop infusions"[tiab] or "closed loop therapy"[tiab] or "closed loop treatment"[tiab] or "closed loop treatments"[tiab] or "closed loop system"[tiab] or "closed loop systems"[tiab] (812)
#34 Search "artificial pancreas"[tiab] or "artificial beta cell"[tiab] (822)
#33 Search "subcutaneous insulin"[tiab] or CSII[tiab] (2385)
#32 Search "pump therapy"[tiab] or "pump therapies"[tiab] or "pump treatment"[tiab] or "pump treatments"[tiab] (920)
#31 Search "insulin pump"[tiab] or "insulin pumps"[tiab] or "insulin infusion"[tiab] or "insulin infuse"[tiab] or "insulin infused"[tiab] or "insulin deliver"[tiab] or "insulin delivery"[tiab] (7485)
#30 Search (#20 and #29) (273)
#29 Search (#21 or #22 or #23 or #25 or #26 or #27 or #28) (928)
#28 Search dexcom (54)
#27 Search (animas or vibe) AND (pump* or infus* or system*) (81)
#26 Search "veo pump" or "veo pumps" (15)
#25 Search (paradigm* AND (veo or pump*)) (350)
#23 Search minimed or paradigmveo (216)
#22 Search SAPT[tiab] (184)
#21 Search "sensor augmented"[tiab] or "sensor augment"[tiab] or "sensor pump"[tiab] or "pump sensor"[tiab] or "sensor pumps"[tiab] (91)
#20 Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19) (126,788)
#19 Search "high glycohemoglobin"[tiab] or "higher glycohemoglobin"[tiab] or "low glycohemoglobin"[tiab] or "lower glycohemoglobin"[tiab] or "increase glycohemoglobin"[tiab] or "increased glycohemoglobin"[tiab] or "increases glycohemoglobin"[tiab] or "decrease glycohemoglobin"[tiab] or "decreasedcglycohemoglobin"[tiab] or "decreases glycohemoglobin"[tiab] or "deficient glycohemoglobin"[tiab] or "sufficient glycohemoglobin"[tiab] or "insufficient glycohemoglobin"[tiab] or "reduce glycohemoglobin"[tiab] or "reduced glycohemoglobin"[tiab] or "glycohemoglobin reduction"[tiab] or "fallen glycohemoglobin"[tiab] or "falling glycohemoglobin"[tiab] or "glycohemoglobin threshold"[tiab] or "safe glycohemoglobin"[tiab] (17)
#18 Search "high haemoglobin"[tiab] or "higher haemoglobin"[tiab] or "low haemoglobin"[tiab] or "lower haemoglobin"[tiab] or "increase haemoglobin"[tiab] or "increased haemoglobin"[tiab] or "increases haemoglobin"[tiab] or "decrease haemoglobin"[tiab] or "decreasedchaemoglobin"[tiab] or "decreases haemoglobin"[tiab] or "deficient haemoglobin"[tiab] or "sufficient haemoglobin"[tiab] or "insufficient haemoglobin"[tiab] or "reduce haemoglobin"[tiab] or "reduced haemoglobin"[tiab] or "haemoglobin reduction"[tiab] or "fallen haemoglobin"[tiab] or "falling haemoglobin"[tiab] or "haemoglobin threshold"[tiab] or "safe haemoglobin"[tiab] (1110)

#17 Search "high hemoglobin"[tiab] or "higher hemoglobin"[tiab] or "low hemoglobin"[tiab] or "lower hemoglobin"[tiab] or "increase hemoglobin"[tiab] or "increased hemoglobin"[tiab] or "increases hemoglobin"[tiab] or "decrease hemoglobin"[tiab] or "decreasedchemoglobin"[tiab] or "decreases hemoglobin"[tiab] or "deficient hemoglobin"[tiab] or "sufficient hemoglobin"[tiab] or "insufficient hemoglobin"[tiab] or "reduce hemoglobin"[tiab] or "reduced hemoglobin"[tiab] or "hemoglobin reduction"[tiab] or "fallen hemoglobin"[tiab] or "falling hemoglobin"[tiab] or "hemoglobin threshold"[tiab] or "safe hemoglobin"[tiab] (3476)

#16 Search "high a1c"[tiab] or "higher a1c"[tiab] or "low a1c"[tiab] or "lower a1c"[tiab] or "increase a1c"[tiab] or "increased a1c"[tiab] or "increases a1c"[tiab] or "decrease a1c"[tiab] or "decreasedca1c"[tiab] or "decreases a1c"[tiab] or "deficient a1c"[tiab] or "sufficient a1c"[tiab] or "insufficient a1c"[tiab] or "reduce a1c"[tiab] or "reduced a1c"[tiab] or "a1c reduction"[tiab] or "fallen a1c"[tiab] or "falling a1c"[tiab] or "a1c threshold"[tiab] or "safe a1c"[tiab] (291)

#15 Search (("high hba1"[tiab] or "higher hba1"[tiab] or "low hba1"[tiab] or "lower hba1"[tiab] or "increase hba1"[tiab] or "increased hba1"[tiab] or "increases hba1"[tiab] or "decrease hba1"[tiab] or "decreasedchba1"[tiab] or "decreases hba1"[tiab] or "deficient hba1"[tiab] or "sufficient hba1"[tiab] or "insufficient hba1"[tiab] or "reduce hba1"[tiab] or "reduced hba1"[tiab] or "hba1 reduction"[tiab] or "fallen hba1"[tiab] or "falling hba1"[tiab] or "hba1 threshold"[tiab] or "safe hba1"[tiab])) (76)

#14 Search "high hb a1"[tiab] or "higher hb a1"[tiab] or "low hb a1"[tiab] or "lower hb a1"[tiab] or "increase hb a1"[tiab] or "increased hb a1"[tiab] or "increases hb a1"[tiab] or "decrease hb a1"[tiab] or "decreasedchb a1"[tiab] or "decreases hb a1"[tiab] or "deficient hb a1"[tiab] or "sufficient hb a1"[tiab] or "insufficient hb a1"[tiab] or "reduce hb a1"[tiab] or "reduced hb a1"[tiab] or "hb a1 reduction"[tiab] or "fallen hb a1"[tiab] or "falling hb a1"[tiab] or "hb a1 threshold"[tiab] or "safe hb a1"[tiab] (0)

#13 Search "high hba1c"[tiab] or "higher hba1c"[tiab] or "low hba1c"[tiab] or "lower hba1c"[tiab] or "increase hba1c"[tiab] or "increased hba1c"[tiab] or "increases hba1c"[tiab] or "decrease hba1c"[tiab] or "decreasedchba1c"[tiab] or "decreases hba1c"[tiab] or "deficient hba1c"[tiab] or "sufficient hba1c"[tiab] or "insufficient hba1c"[tiab] or "reduce hba1c"[tiab] or "reduced hba1c"[tiab] or "hba1c reduction"[tiab] or "fallen hba1c"[tiab] or "falling hba1c"[tiab] or "hba1c threshold"[tiab] or "safe hba1c"[tiab] (1271)

#12 Search "high sugar"[tiab] or "higher sugar"[tiab] or "low sugar"[tiab] or "lower sugar"[tiab] or "increase sugar"[tiab] or "increased sugar"[tiab] or "increases sugar"[tiab] or "decrease sugar"[tiab] or "decreasedcsugar"[tiab] or "decreases sugar"[tiab] or "deficient sugar"[tiab] or "sufficient sugar"[tiab] or "insufficient sugar"[tiab] or "reduce sugar"[tiab] or "reduced sugar"[tiab] or "sugar reduction"[tiab] or "fallen sugar"[tiab] or "falling sugar"[tiab] or "sugar threshold"[tiab] or "safe sugar"[tiab] (1539)

#11 Search ("high glucose"[tiab] or "higher glucose"[tiab] or "low glucose"[tiab] or "lower glucose"[tiab] or "increase glucose"[tiab] or "increased glucose"[tiab] or "increases glucose"[tiab] or "decrease glucose"[tiab] or "decreasedcglucose"[tiab] or "decreases glucose"[tiab] or "deficient glucose"[tiab] or "sufficient glucose"[tiab] or "insufficient glucose"[tiab] or "reduce glucose"[tiab] or "reduced glucose"[tiab] or "glucose reduction"[tiab] or "fallen glucose"[tiab] or "falling glucose"[tiab] or "glucose threshold"[tiab] or "safe glucose"[tiab]) (16,645)

#10 Search (hyperglycemia[tiab] or hypoglycaemia[tiab] or hyperglycemic[tiab] or hypoglycaemic[tiab]) (44,267)

#9 Search ketoacidosis[tiab] or acidoketosis[tiab] or "keto acidosis"[tiab] or ketoacidemia[tiab] or ketosis[tiab] (7293)

#8 Search dm1[tiab] or "dm 1"[tiab] or t1dm[tiab] or "t1 dm"[tiab] or t1d[tiab] or iddm[tiab] (13,131)

#7 Search "insulin dependent"[tiab] or insulindepend*[tiab] (27,550)

#6 Search "brittle diabetic"[tiab] or "diabetic juvenile"[tiab] or "diabetic pediatric"[tiab] or "diabetic paediatric"[tiab] or "diabetic early"[tiab] or "diabetic labile"[tiab] or "diabetic acidosis"[tiab] or "diabetic sudden onset"[tiab] (348)

#5 Search "diabetic brittle"[tiab] or "juvenile diabetic"[tiab] or "pediatric diabetic"[tiab] or "paediatric diabetic"[tiab] or "early diabetic"[tiab] or "labile diabetic"[tiab] or "acidosis diabetic"[tiab] or "sudden onset diabetic"[tiab] (1122)

#4 Search "brittle diabetes"[tiab] or "diabetes juvenile"[tiab] or "diabetes pediatric"[tiab] or "diabetes paediatric"[tiab] or "diabetes early"[tiab] or "diabetes ketosis"[tiab] or "diabetes labile"[tiab] or "diabetes acidosis"[tiab] or "diabetes sudden onset"[tiab] (264)
#3 Search "diabetes brittle"[tiab] or "juvenile diabetes"[tiab] or "pediatric diabetes"[tiab] or "paediatric diabetes"[tiab] or "early diabetes"[tiab] or "ketosis diabetes"[tiab] or "labile diabetes"[tiab] or "acidosis diabetes"[tiab] or "sudden onset diabetes"[tiab] (2238)
#2 Search "diabetic type 1"[tiab] OR "type 1 diabetic"[tiab] OR "diabetic type i"[tiab] OR "type i diabetic"[tiab] OR "diabetic type1"[tiab] OR "type1 diabetic"[tiab] OR "diabetic typei"[tiab] OR "typei diabetic"[tiab] (6044)
#1 Search (("diabetes type 1"[tiab] OR "type 1 diabetes"[tiab] OR "diabetes type i"[tiab] OR "type i diabetes"[tiab] OR "diabetes type1"[tiab] OR "type1 diabetes"[tiab] OR "diabetes typei"[tiab] OR "typei diabetes"[tiab])) (28,884)

Cochrane Database of Systematic Reviews (via Wiley Online Library), Cochrane Central Register of Controlled Trials (via Wiley Online Library), Database of Abstracts of Reviews of Effects (via Wiley Online Library) and Health Technology Assessment Database (via Wiley Online Library)

Cochrane Database of Systematic Reviews: issue 9 of 12, September 2014.

Cochrane Central Register of Controlled Trials: issue 8 of 12, August 2014.

Database of Abstracts of Reviews of Effects: issue 3 of 4, July 2014.

Health Technology Assessment Database: issue 3 of 4, July 2014.

Date searched: 5 September 2014.

Search strategy

#1 MeSH descriptor: [Diabetic Mellitus, Type 1] this term only
#2 MeSH descriptor: [Diabetic Ketoacidosis] this term only
#3 (diabet* near/3 (typ* next 1 or typ* next i or type1 or typei or typ* next one)):ti,ab,kw
#4 (diabet* near/3 (britt* or juvenil* or pediatric or paediatric or early or keto* or labil* or acidos* or autoimmun* or auto next immun* or sudden next onset)):ti,ab,kw
#5 ((insulin* near/2 depend*) or insulindepend*):ti,ab,kw
#6 (dm1 or dm next 1 or dmt1 or dm next t1 or t1dm or t1 next dm or t1d or iddm):ti,ab,kw
#7 (ketoacidosis or acidoketosis or keto next acidosis or ketoacidemia or ketosis):ti,ab,kw
#8 MeSH descriptor: [Hyperglycemia] this term only
#9 MeSH descriptor: [Hypoglycemia] this term only
#10 (hyperglyc?em* or hypoglyc?em*):ti,ab,kw
#11 ((high or higher or low or lower or increas* or decreas* or deficien* or sufficien* or insufficien* or reduce* or reduction* or fluctuat* or fallen or falling or threshold or safe) near/3 (glucose* or sugar* or hba1c or hb next a1 or hba1 or a1c or h?emoglob* or glycoh?emoglob*)):ti,ab,kw
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 (sensor* near/3 (augment* or pump*))
#14 SAPT:ti,ab,kw
#15 minimed or paradigmveo
#16 (paradigm* near/3 (veo or pump*))
#17 (veo near/3 pump*)
#18 ((animas or vibe) near/3 (pump* or infus* or system*))
#19 dexcom
#20 #13 or #14 or #15 or #16 or #17 or #18 or #19

#21 MeSH descriptor: [Insulin Infusion Systems] this term only
#22 MeSH descriptor: [Pancreas, Artificial] this term only
#23 (insulin* near/3 (pump* or infus* or deliver* or catheter*)):ti,ab,kw
#24 (pump* near/2 (therap* or treatment*)):ti,ab,kw
#25 ((subcutaneous near/2 insulin*) or CSII):ti,ab,kw
#26 (artificial near/3 (pancreas or beta next cell*)):ti,ab,kw
#27 (closed next loop near/3 (pump* or deliver* or infus* or therap* or treatment* or system*)):ti,ab,kw
#28 accu-chek or cellnovo or dana next diabecare or omnipod
#29 ((integrat* or dual or combined or unified) near/3 (system* or device*)):ti,ab,kw
#30 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31 MeSH descriptor: [Insulin] this term only
#32 MeSH descriptor: [Injections, Subcutaneous] this term only
#33 #31 and #32
#34 "multiple daily" near/3 (inject* or insulin* or regime* or routine*):ti,ab,kw
#35 "multiple dose" near/3 (inject* or insulin* or regime* or routine*):ti,ab,kw
#36 multiple near/3 (inject* or insulin* or regime* or routine*):ti,ab,kw
#37 MDI:ti,ab,kw
#38 injection near/3 therapy:ti,ab,kw
#39 (basal* and bolus) near/3 (inject* or regime* or routine* or system*):ti,ab,kw
#40 ("short acting" near/3 insulin) or ("rapid acting" near/3 insulin):ti,ab,kw
#41 #34 or #35 or #36 or #37 or #38 or #39 or #40
#42 #12 and (#20 or #30 or #41)

Cochrane Database of Systematic Reviews: 14.

Database of Abstracts of Reviews of Effects: 25.

Cochrane Central Register of Controlled Trials: 1910.

HTA: 19.

Science Citation Index Expanded (Web of Science)

Date range searched: 1988–29 August 2014.

Date searched: 5 September 2014.

Search strategy

40 4,012 #38 not #39
39 3,123,359 TS=(rat or rats or mouse or mice or murine or hamster or hamsters or animal or animals or dogs or dog or pig or pigs or cats or bovine or cow or sheep or ovine or porcine or monkey)
38 5,027 #37 OR #18
37 4,914 #36 AND #33 AND #8
36 4,219,275 #35 OR #34
35 4,185,460 TS=((clinic* SAME trial*) OR (placebo* OR random* OR control* OR prospectiv*))
34 194,182 TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))
33 126,955 #32 OR #26
32 11,323 #31 OR #30 OR #29 OR #28 OR #27
31 837 TS=("short acting" NEAR/3 insulin) or TS=("rapid acting" NEAR/3 insulin)
30 5,207 TS=(injection NEAR/3 therapy)
29 4,652 TS=MDI

28 332 TS=("multiple dose" NEAR/3 (inject* or insulin* or regime* or routine*))
27 774 TS=("multiple daily" NEAR/3 (inject* or insulin* or regime* or routine*))
26 116,578 #19 or #20 or #21 or #22 or #23 or #24 or #25
25 91,258 TS=((integrat* or dual or combined or unified) NEAR/3 (system* or device*))
24 165 TS=(accu-chek or cellnovo or "dana diabecare" or omnipod)
23 11,130 TS=("closed loop" NEAR/3 (pump* or deliver* or infus* or therap* or treatment* or system*))
22 851 TS=(artificial NEAR/3 (pancreas or "beta cell*"))
21 3,017 TS=((subcutaneous NEAR/2 insulin*) or CSII)
20 3,696 TS=(pump* NEAR/2 (therap* or treatment*))
19 10,301 TS=(insulin* NEAR/3 (pump* or infus* or deliver* or catheter*))
18 260 #8 and #17
17 1,375 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
16 38 TS=dexcom
15 7 TS=(g4 NEAR/3 platinum)
14 13 TS=((animas or vibe) NEAR/3 (pump* or infus* or system*))
13 4 TS=(veo NEAR/3 pump*)
12 38 TS=(paradigm* NEAR/3 (veo or pump*))
11 154 TS=(minimed or paradigmveo)
10 396 TS=SAPT
9 765 TS=(sensor* NEAR/3 (augment* or pump*))
8 226,312 #1 or #2 or #3 or #4 or #5 or #6 or #7
7 109,659 TS=((high or higher or low or lower or increas* or decreas* or deficien* or sufficien* or insufficien* or reduce* or reduction* or fluctuat* or fallen or falling or threshold or safe) NEAR/3 (glucose* or sugar* or hba1c or "hb a1" or hba1 or a1c or hemoglob* or glycohemoglob* or haemoglob* or glycohaemoglob*))
6 68,183 TS=(hyperglycem* or hypoglycem* or hyperglycaem* or hypoglycaem*)
5 5,944 TS=(ketoacidosis or acidoketosis or "keto acidosis" or ketoacidemia or ketosis)
4 17,145 TS=(dm1 or "dm 1" or dmt1 or "dm t1" or t1dm or "t1 dm" or t1d or iddm)
3 25,575 TS=((insulin* NEAR/2 depend*) or insulindepend*)
2 17,654 TS=(diabet* NEAR/3 (britt* or juvenil* or pediatric or paediatric or early or keto* or labil* or acidos* or autoimmun* or "auto immun*" or "sudden onset"))
1 40,584 TS=(diabet* NEAR/3 ("typ* 1" or "typ* i" or type1 or typei or "typ* one"))

Latin American and Caribbean Health Sciences Literature (LILACS)

URL: http://lilacs.bvsalud.org/en/

Date range searched: 1982–5 September 2014.

Date searched: 5 September 2014.

Search strategy

((MH:C18.452.394.750.124 or MH:C18.452.076.176.652.500 or MH:C18.452.394.952 or MH: C18.452.394.984 or "diabetes type 1" or "diabetes type i" or "diabetes type1" or "diabetes typei" or "diabetes type one" or "type 1 diabetes" or "type I diabetes" or "type1 diabetes" or "typei diabetes" or "type one diabetes" or "diabetes tipo 1" or "diabetes tipo i" or "diabetes tipo1" or "diabetes tipoi" or "tipo 1 diabetes" or "tipo I diabetes" or "tipo1 diabetes" or "tipoi diabetes" or "brittle diabetes" or "juvenile diabetes" or "pediatric diabetes" or "paediatric diabetes" or "early diabetes" or "labile diabetes" or "autoimmune diabetes" or "auto immune diabetes" or "sudden onset diabetes" or "diabetes autoimune" or "diabetes inestable" or "diabetes instável" or "insulin dependent" or insulindependent or "insulin dependiente" or insulinodependiente or "insulin dependente" or insulinodependente or dm1 or "dm 1" or dmt1 or "dm t1" or t1dm or "t1 dm" or t1d or iddm or dmid or ketoacidosis or acidoketosis or "keto acidosis" or ketoacidemia or ketosis or cetoacidosis or cetoacidose or hyperglycem$ or hyperglycaem$ or hiperglucem$ or hiperglicem$ or hypoglycem$ or hypoglycaem$ or hipoglucem$ or hipoglicem$) AND (MH:E02.319.300.508 or "insulin pump" or "insulin pumps" or "insulin infusion" or "insulin infusions" or "insulin delivery" or "insulin catheter" or "insulin catheters" or "pump therapy" or "pump therapies" or "pump treatment" or "pump treatments" or "insulina sistemas" or "sistemas insulina" or "insulina infusion" or "infusion insulina" or "insulina infusions" or "infusion insulinas" or "infusão de insulina" or "subcutaneous insulin" or CSII or "artificial pancreas" or "artificial beta cell" or "célula beta artificial" or "páncreas endocrino artificial" or "integrated system" or "integrated systems" or "integrated devices" or "dual system" or "dual systems" or "dual devices" or "combined system" or "combined systems" or "combined devices" or "unified system" or "unified systems" or "unified devices" or (MH: D06.472.699.587.200.500.625 and MH; E02.319.267.530.620) or "multiple daily injection" or "multiple daily injections" or "multiple daily insulin" or "multiple dose injection" or "multiple dose injections" or "multiple injection" or "multiple injections" or MDI or "injection therapy" or "inyecciones terapia" or "injeções terapia" or "short acting insulin" or "rapid acting insulin")) or ("sensor augmented pump" or "sensor augmented pumps" or "sensor augmented insulin" or SAPT or minimed or paradigmveo or "paradigm veo" or "paradigm pump" or "veo pump" or "veo pumps" or "animas pump" or "animas pumps" "animas system" or "vibe pump" or "vibe pumps" or "vibe system" or dexcom)

Retrieved: 58.

NIHR Project Portfolio and NIHR Journals Library

NIHR Project Portfolio URL: www.nets.nihr.ac.uk/projects/

NIHR Journals Library URL: www.journalslibrary.nihr.ac.uk/

Date range searched: from inception until 5 September 2014.

Date searched: 5 September 2014.

Search terms	NIHR Project Portfolio	NIHR Journals Library
"sensor augmented pump"	0	0
"sensor augmented pumps"	0	0
"sensor augmented insulin"	0	0
SAPT	0	0
minimed	1	6
paradigmveo	0	0
"paradigm veo"	0	0
"veo pump"	0	0
"veo pumps"	0	0
animas	0	4
vibe	0	0
dexcom	0	1
"insulin pump"	5	14
"insulin pumps"	5	12
"continuous subcutaneous insulin infusion"	4	17*
[Journals Library limit: ICD-10; E10-E14 Diabetes mellitus*]		
"artificial pancreas"	0	2
"multiple daily injection"	3	7
"multiple daily injections"	3	11
Total	21 (14 duplicates)	72 (47 duplicates)
Total after removal of duplicates	**32 (61 duplicates)**	

PROSPERO

URL: www.crd.york.ac.uk/prospero/

Date range searched: up to 5 September 2014.

Date searched: 5 September 2014.

Search: combine phrase/terms with 'OR'; five search boxes in 'All fields'.

Terms searched	Records
sensor augmented pump* OR sensor augmented insulin* OR SAPT OR minimed OR paradigmveo	2
paradigm veo OR veo pump* OR animas OR vibe OR dexcom	0
insulin pump* OR insulin infusion* OR insulin therapy OR subcutaneous insulin OR CSII	14 (1 duplicate)
artificial pancreas	0
multiple daily injection* OR multiple daily insulin*	1
MDI [review title]	0
Total	17 (2 duplicates)
Total after removal of duplicates	**15**

US Food and Drug Administration

URL: www.fda.gov/ (includes links to approval/summary of safety and effectiveness).

Date range searched: from inception up to 5 September 2014.

Date searched: 5 September 2014.

Search strategy for medical devices

Search terms	Records
minimed	6
animas	5
Vibe	0
"g4 platinum"	3
"multiple daily injection"	0
"multiple daily injections"	0
"multiple daily insulin"	1
Total	**15**

Medicines and Healthcare Products Regulatory Agency

URL: www.mhra.gov.uk

Date range searched: from inception up to 5 September 2014.

Date searched: 5 September 2014.

Search strategy

Search terms	Records
minimed	7
Animas + insulin + pump	16
Animas + vibe	5
"g4 platinum"	2
"multiple daily injection"	0
"multiple daily injections"	0
"multiple daily insulin"	0
Total	**30**[a]

a Results almost entirely field safety notices.

National Institutes of Health (US) ClinicalTrials.gov

URL: http://clinicaltrials.gov/ct2/search/advanced

Date range searched: from inception up to 2 September 2014.

Date searched: 2 September 2014.

Advanced search option.

Search strategy

Search terms	Results
Search terms: ("sensor augmented pump" OR "sensor augmented insulin" OR SAPT OR minimed or paradigmveo OR paradigm* OR veo OR animas OR vibe OR dexcom OR "G4 platinum") Conditions: Type 1 Diabetes Mellitus OR Hyperglycemia OR Hypoglycemia	84
Search terms: "insulin pump" OR "insulin pumps" OR "insulin infusion" OR "insulin delivery" OR "pump therapy" OR "subcutaneous insulin" OR CSII OR "artificial pancreas" OR "artificial beta cell" Conditions: Type 1 Diabetes Mellitus OR Hyperglycemia OR Hypoglycemia	454
Search terms: "closed loop" OR accu-chek OR cellnovo OR "dana diabecare" OR omnipod Conditions: Type 1 Diabetes Mellitus OR Hyperglycemia OR Hypoglycemia	136
Search terms: "integrated system" OR "integrated device" OR "integrated systems" OR "integrated devices" OR "dual system" OR "dual device" OR "dual systems" OR "dual devices" OR "combined system" OR "combined device" OR "combined systems" OR "combined devices" Conditions: Type 1 Diabetes Mellitus OR Hyperglycemia OR Hypoglycemia	1

Search terms	Results
Search terms: "multiple daily injection" OR "multiple daily injections" OR "multiple daily insulin" OR "multiple dose injection" OR "multiple dose injections"	42
Conditions: Type 1 Diabetes Mellitus OR Hyperglycemia OR Hypoglycemia	
Search terms: MDI OR "multiple dose insulin" OR "multiple injection" OR "multiple injections" OR "multiple insulin" OR "injection therapy"	46
Conditions: Type 1 Diabetes Mellitus OR Hyperglycemia OR Hypoglycemia	
Total	763
Total after removal of duplicates	**496**

meta*Register of Controlled Trials*

URL: www.controlled-trials.com/

Date range searched: from inception up to 5 September 2014.

Date searched: 5 September 2014.

National Institutes of Health (US) Clinical Trials register option not ticked as already searched separately.

Search strategy

Search terms	Results
("sensor augmented pump" OR "sensor augmented insulin" OR SAPT OR minimed or paradigmveo OR paradigm* OR veo OR animas OR vibe OR dexcom OR "G4 platinum") AND (Diabetes OR Hyperglycemia OR Hypoglycemia)	2
("insulin pump" OR "insulin pumps" OR "insulin infusion" OR "insulin delivery" OR "pump therapy" OR "subcutaneous insulin" OR CSII OR "artificial pancreas" OR "artificial beta cell") AND (Diabetes OR Hyperglycemia OR Hypoglycemia)	4
("closed loop" OR accu-chek OR cellnovo OR "dana diabecare" OR omnipod) AND (Diabetes OR Hyperglycemia OR Hypoglycemia)	0
("integrated system" OR "integrated device" OR "integrated systems" OR "integrated devices") AND (Diabetes OR Hyperglycemia OR Hypoglycemia)	0
("dual system" OR "dual device" OR "dual systems" OR "dual devices" OR "combined system" OR "combined device" OR "combined systems" OR "combined devices") AND (Diabetes OR Hyperglycemia OR Hypoglycemia)	0
("multiple daily injection" OR "multiple daily injections" OR "multiple daily insulin" OR "multiple dose injection" OR "multiple dose injections") AND (Diabetes OR Hyperglycemia OR Hypoglycemia)	0
(MDI OR "multiple dose insulin" OR "multiple injection" OR "multiple injections" OR "multiple insulin" OR "injection therapy") AND (Diabetes OR Hyperglycemia OR Hypoglycemia)	3
Total	9
Total after removal of duplicates	**7**

WHO International Clinical Trials Register Platform

URL: www.who.int/ictrp/en/

Date range searched: from inception up to 5 September 2014.

Date searched: 5 September 2014.

Standard search option.

Search strategy

Search terms	Results
sensor augmented pump* OR SAPT OR minimed OR paradigmveo OR paradigm veo OR animas vibe OR dexcom OR G4 platinum	70 for 65 trials
type 1 diabetes mellitus AND insulin pump* OR insulin infusion* OR pump therapy OR subcutaneous insulin* OR CSII OR artificial pancreas	317 for 297 trials
type 1 diabetes mellitus AND closed loop* OR accu-chek OR cellnovo OR dana diabecare OR omnipod	115 for 115 trials
type 1 diabetes mellitus AND integrated system* OR integrated device* OR dual system* OR dual device*	1
type 1 diabetes mellitus AND multiple daily injection* OR multiple dose injection* OR multiple daily insulin* OR multiple injection*	75 for 50 trials
type 1 diabetes mellitus AND MDI OR multiple insulin OR injection therapy	95 for 78 trials
Total	606
Total after removal of duplicates	**475**

Diabetes UK Professional Conference

URL: www.diabetes.org.uk/diabetes-uk-professional-conference/

Date range searched: 2010–14.

Date searched: 10 September 2014.

Abstracts were not available from the Diabetes UK website; proceedings were published in the journal Diabetic Medicine. It was not possible to search the proceedings from the Diabetic Medicine search screen. Available PDFs were scanned for 2014 and 2013. Previous conference proceedings (2010, 2011 and 2012) were only available for purchase online, so could not be scanned.

Abstracts of the Diabetes UK Professional Conference 2014

Abstracts of the Diabetes UK Professional Conference 2014, Arena and Convention Centre, Liverpool, UK, 5–7 March 2014. *Diabet Med* 2014;**31**(Suppl. 1):1–184. URL: http://onlinelibrary.wiley.com/doi/10.1111/dme.2014.31.issue-s1/issuetoc (accessed 10 September 2014).

Basic and clinical science posters.

Clinical care and other categories posters.

Hypoglycaemia.

Children, young people and emerging adulthood.

Abstracts of the Diabetes UK Professional Conference 2013

Abstracts of the Diabetes UK Professional Conference 2013. Manchester, UK, 13–15 March 2013. *Diabet Med* 2013;**30**(Suppl. 1):1–213, E1–10. URL: http://onlinelibrary.wiley.com/doi/10.1111/dme.2013.30.issue-s1/issuetoc (accessed 10 September 2014).

Basic and clinical science posters.

Clinical care and other categories posters.

Abstracts of Diabetes UK Professional Conference 2012

Abstracts of Diabetes UK Professional Conference 2012. Glasgow, UK, 7–9 March 2012. *Diabet Med* 2012;**29**(Suppl. 1):1–187. URL: http://onlinelibrary.wiley.com/doi/10.1111/dme.2012.29.issue-s1/issuetoc (accessed 10 September 2014).

Not available online. Purchase access only.

Abstracts of Diabetes UK Professional Conference 2011

Abstracts of Diabetes UK Annual Professional Conference 2011. London, UK, 30 March 30–1 April 2011. *Diabet Med* 2011;**28**(Suppl. 1):1–214. URL: http://onlinelibrary.wiley.com/doi/10.1111/dme.2012.29.issue-s1/issuetoc (accessed 10 September 2014).

Not available online. Purchase access only.

Abstracts of Diabetes UK Professional Conference 2010

Abstracts of Diabetes UK Annual Professional Conference. Liverpool, UK. 3–5 March 2010. *Diabet Med* 2010;**27**(Suppl. 1):1–188. URL: http://onlinelibrary.wiley.com/doi/10.1111/dme.2010.27.issue-s1/issuetoc (accessed 10 September 2014).

Not available online. Purchase access only.

Search results

Terms scanned	Abstracts identified
sensor augmented	2014 = 0
	2013 = 1
SAPT	2014 = 0
	2013 = 0
minimed	2014 = 0
	2013 = 0
paradigmveo	2014 = 0
	2013 = 0
paradigm veo	2014 = 0
	2013 = 0
animas	2014 = 0
	2013 = 0
dexcom	2014 = 0
	2013 = 0
Total	**1**

European Association for the Study of Diabetes annual meeting

URL: www.easd.org

Date searched: 10 September 2014.

Advanced search

Session type = ALL Keyword = ALL.

Searched in presentation title and abstract body.

Meetings searched

The 50th European Association for the Study of Diabetes (EASD) Annual Meeting, 15–19 September 2014, Vienna, Austria.

The 49th EASD Annual Meeting, 23–27 September 2013, Barcelona, Spain (URL: www.abstractsonline.com/plan/start.aspx?mkey={7E87E03A-5554-4497-B245-98ADF263043C}).

The 48th EASD Annual Meeting, 1–5 October 2012, Berlin, Germany (URL: www.abstractsonline.com/plan/ViewSession.aspx?mID=1668&skey=8e40db00-2d48-40da-891e-e4c9db8d9378&mKey={2DBFCAF7-1539-42D5-8DDA-0A94ABB089E8}).

The 47th EASD Annual Meeting, 12–16 September 2011, Lisbon, Portugal (URL: www.abstractsonline.com/plan/start.aspx?mkey={BAFB2746-B0DD-4110-8588-E385FAF957B7}).

The 46th EASD Meeting. 20–24 September 2010, Stockholm, Sweden (URL: www.abstractsonline.com/plan/AdvancedSearch.aspx?mkey={10A86782-07E4-4A2D-9100-F660E5D752A9}).

The 45th EASD Meeting. 29 September-2 October 2009, Vienna, Austria (URL: www.abstractsonline.com/plan/start.aspx?mkey={B3E385FB-2CC7-4F7C-8766-2F743C19F069}).

Search results

Terms	Hits in title	Hits in abstract body
"sensor augmented pump"	2013 = 0	2013 = 0
	2012 = 0	2012 = 1
	2011 = 1	2011 = 0
	2010 = 0	2010 = 2
	2009 = 1	
"sensor augmented pumps"	2013 = 0	2013 = 0
	2012 = 0	2012 = 0
	2011 = 0	2011 = 0
	2010 = 0	2010 = 0
	2009 = 0	

Terms	Hits in title	Hits in abstract body
SAPT	2013 = 0	2013 = 0
	2012 = 0	2012 = 0
	2011 = 0	2011 = 0
	2010 = 0	2010 = 0
	2009 = 0	
minimed	2013 = 0	2013 = 5
	2012 = 0	2012 = 5
	2011 = 0	2011 = 2
	2010 = 0	2010 = 5
	2009 = 0	
paradigmveo	2013 = 0	2013 = 0
	2012 = 0	2012 = 0
	2011 = 0	2011 = 0
	2010 = 0	2010 = 0
	2009 = 0	
"paradigm veo"	2013 = 0	2013 = 0
	2012 = 0	2012 = 0
	2011 = 0	2011 = 2
	2010 = 0	2010 = 0
	2009 = 0	
"veo pump"	2013 = 0	2013 = 0
	2012 = 0	2012 = 0
	2011 = 0	2011 = 0
	2010 = 0	2010 = 0
	2009 = 0	
animas	2013 = 0	2013 = 0
	2012 = 0	2012 = 1
	2011 = 0	2011 = 2
	2010 = 0	2010 = 3
	2009 = 0	

APPENDIX 1

Terms	Hits in title	Hits in abstract body
vibe	2013 = 0	2013 = 0
	2012 = 0	2012 = 0
	2011 = 0	2011 = 1
	2010 = 0	2010 = 0
	2009 = 0	
dexcom	2013 = 0	2013 = 4
	2012 = 1	2012 = 7
	2011 = 0	2011 = 1
	2010 = 0	2010 = 2
	2009 = 0	
"insulin pump"	2013 = 7	2013 = 18
	2012 = 8	2012 = 20
	2011 = 8	2011 = 18
	2010 = 5	2010 = 16
	2009 = 3	
"insulin pumps"	2013 = 4	2013 = 8
	2012 = 0	2012 = 6
	2011 = 0	2011 = 6
	2010 = 0	2010 = 5
	2009 = 2	
"continuous subcutaneous insulin infusion"	2013 = 3	2013 = 8
	2012 = 1	2012 = 8
	2011 = 4	2011 = 11
	2010 = 7	2010 = 13
	2009 = 6	
CSII	2013 = 3	2013 = 15
	2012 = 2	2012 = 23
	2011 = 2	2011 = 17
	2010 = 3	2010 = 20
	2009 = 4	

Terms	Hits in title	Hits in abstract body
"artificial pancreas"	2013 = 2	2013 = 5
	2012 = 3	2012 = 7
	2011 = 0	2011 = 3
	2010 = 0	2010 = 1
	2009 = 0	
"multiple daily injection"	2013 = 1	2013 = 6
	2012 = 0	2012 = 1
	2011 = 0	2011 = 2
	2010 = 4	2010 = 6
	2009 = 0	
"multiple daily injections"	2013 = 0	2013 = 7
	2012 = 0	2012 = 2
	2011 = 0	2011 = 6
	2010 = 2	2010 = 7
	2009 = 3	
MDI	2013 = 0	2013 = 13
	2012 = 2	2012 = 12
	2011 = 1	2011 = 8
	2010 = 0	2010 = 13
	2009 = 1	
Total	94	354
Overall total	448	
Overall total after removal of duplicates	**196**	

American Diabetes Association Scientific Sessions

URL: www.diabetes.org/

Date searched: 10 September 2014.

Sessions searched

74th American Diabetes Association Scientific Sessions, 13–17 June 2014, San Francisco, CA (URL: www.abstractsonline.com/plan/start.aspx?mkey={40FC5C61-819A-4D1B-AABA-3705F7D0EA76}).

73rd American Diabetes Association Scientific Sessions, 21–25 June 2013, Chicago, IL (URL: www.abstractsonline.com/plan/start.aspx?mkey={89918D6D-3018-4EA9-9D4F-711F98A7AE5D}).

72nd American Diabetes Association Scientific Sessions, 8–12 June 2012, Philadelphia, PA (URL: www.abstractsonline.com/plan/start.aspx?mkey={0F70410F-8DF3-49F5-A63D-3165359F5371}).

Search results

Terms	Hits in abstract title
"sensor augmented pump"	2014 = 0
	2013 = 0
	2012 = 0
"sensor augmented pumps"	2014 = 0
	2013 = 0
	2012 = 0
SAPT	2014 = 0
	2013 = 0
	2012 = 0
minimed	2014 = 0
	2013 = 2
	2012 = 0
paradigmveo	2014 = 0
	2013 = 0
	2012 = 0
"paradigm veo"	2014 = 0
	2013 = 0
	2012 = 0
"veo pump"	2014 = 0
	2013 = 0
	2012 = 0
animas	2014 = 0
	2013 = 0
	2012 = 0
vibe	2014 = 0
	2013 = 0
	2012 = 0
dexcom	2014 = 1
	2013 = 0
	2012 = 1

Terms	Hits in abstract title
"insulin pump"	2014 = 16
	2013 = 7
	2012 = 12
"insulin pumps"	2014 = 6
	2013 = 0
	2012 = 1
"continuous subcutaneous insulin infusion"	2014 = 5
	2013 = 6
	2012 = 3
CSII	2014 = 8
	2013 = 7
	2012 = 5
"artificial pancreas"	2014 = 13
	2013 = 7
	2012 = 4
"multiple daily injection"	2014 = 1
	2013 = 0
	2012 = 0
"multiple daily injections"	2014 = 1
	2013 = 0
	2012 = 0
MDI	2014 = 2
	2013 = 6
	2012 = 1
Total	115
Total after removal of duplicates	**91**

Cost-effectiveness searches

NHS Economic Evaluation Database (via Wiley Online Library)

Issue searched: 3 of 4, July 2014.

Date searched: 5 September 2014.

Search strategy

#1 MeSH descriptor: [Diabetes Mellitus, Type 1] this term only
#2 MeSH descriptor: [Diabetic Ketoacidosis] this term only
#3 (diabet* near/3 (typ* next 1 or typ* next i or type1 or typei or typ* next one)):ti,ab,kw
#4 (diabet* near/3 (britt* or juvenil* or pediatric or paediatric or early or keto* or labil* or acidos* or autoimmun* or auto next immun* or sudden next onset)):ti,ab,kw
#5 ((insulin* near/2 depend*) or insulindepend*):ti,ab,kw
#6 (dm1 or dm next 1 or dmt1 or dm next t1 or t1dm or t1 next dm or t1d or iddm):ti,ab,kw
#7 (ketoacidosis or acidoketosis or keto next acidosis or ketoacidemia or ketosis):ti,ab,kw
#8 MeSH descriptor: [Hyperglycemia] this term only
#9 MeSH descriptor: [Hypoglycemia] this term only
#10 (hyperglyc?em* or hypoglyc?em*):ti,ab,kw
#11 ((high or higher or low or lower or increas* or decreas* or deficien* or sufficien* or insufficien* or reduce* or reduction* or fluctuat* or fallen or falling or threshold or safe) near/3 (glucose* or sugar* or hba1c or hb next a1 or hba1 or a1c or h?emoglob* or glycoh?emoglob*)):ti,ab,kw
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 (sensor* near/3 (augment* or pump*))
#14 SAPT:ti,ab,kw
#15 minimed or paradigmveo
#16 (paradigm* near/3 (veo or pump*))
#17 (veo near/3 pump*)
#18 ((animas or vibe) near/3 (pump* or infus* or system*))
#19 dexcom
#20 #13 or #14 or #15 or #16 or #17 or #18 or #19
#21 MeSH descriptor: [Insulin Infusion Systems] this term only
#22 MeSH descriptor: [Pancreas, Artificial] this term only
#23 (insulin* near/3 (pump* or infus* or deliver* or catheter*)):ti,ab,kw
#24 (pump* near/2 (therap* or treatment*)):ti,ab,kw
#25 ((subcutaneous near/2 insulin*) or CSII):ti,ab,kw
#26 (artificial near/3 (pancreas or beta next cell*)):ti,ab,kw
#27 (closed next loop near/3 (pump* or deliver* or infus* or therap* or treatment* or system*)):ti,ab,kw
#28 accu-chek or cellnovo or dana next diabecare or omnipod
#29 ((integrat* or dual or combined or unified) near/3 (system* or device*)):ti,ab,kw
#30 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31 MeSH descriptor: [Insulin] this term only
#32 MeSH descriptor: [Injections, Subcutaneous] this term only
#33 #31 and #32
#34 "multiple daily" near/3 (inject* or insulin* or regime* or routine*):ti,ab,kw
#35 "multiple dose" near/3 (inject* or insulin* or regime* or routine*):ti,ab,kw
#36 multiple near/3 (inject* or insulin* or regime* or routine*):ti,ab,kw
#37 MDI:ti,ab,kw
#38 injection near/3 therapy:ti,ab,kw

#39 (basal* and bolus) near/3 (inject* or regime* or routine* or system*):ti,ab,kw
#40 ("short acting" near/3 insulin) or ("rapid acting" near/3 insulin):ti,ab,kw
#41 #34 or #35 or #36 or #37 or #38 or #39 or #40
#42 #12 and (#20 or #30 or #41)

NHS Economic Evaluation Database (NHS EED) records retrieved: 16 records.

Health Economic Evaluations Database (via Wiley Online Library)

Date range searched: from inception up to 5 September 2014.

Date searched: 5 September 2014.

Search strategy

AX='sensor augmented' or sensor-augmented or SAPT (1)

AX=minimed or paradigmveo or 'paradigm veo' or 'paradigm pump' or 'veo pump' or 'animas pump' or 'animas infusion' or 'vibe pump' or 'vibe infusion' or 'g4 platinum' or dexcom (0)

CS=1 or 2 (1)

AX=diabetes or dm1 or 'dm 1' or dmt1 or 'dm t1' or t1dm or 't1 dm' or t1d or iddm (2289)

AX=ketoacidosis or acidoketosis or 'keto acidosis' or ketoacidemia or ketosis (28)

AX=hyperglycemia or hypoglycemia or hyperglycaemia or hypoglycaemia (146)

CS=4 or 5 or 6 (2321)

AX='insulin pump' or 'insulin pumps' or 'insulin infusion' or 'insulin infusions' or 'insulin delivery' (46)

AX='pump therapy' or 'subcutaneous insulin' or CSII or 'artificial pancreas' or 'artificial beta-cell' (41)

AX='closed loop' or accu-chek or cellnovo or 'dana diabecare' or omnipod (1)

AX='integrated system' or 'integrated systems' or 'integrated device' or 'integrated devices' or 'dual system' or 'dual systems' or 'dual device' or 'dual devices' (7)

AX='multiple daily injection' or 'multiple daily injections' or 'multiple daily insulin' or 'multiple dose injection' or 'multiple dose injections' or 'multiple dose insulin' or AX='multiple injection' or 'multiple injections' or 'multiple insulin' OR MDI (45)

CS=8 or 9 or 10 or 11 or 12 (86)

CS=7 and 12 (52)

CS=3 or 14 (52)

EMBASE (via OvidSP)

Date range searched: 1974–2014/week 34.

Date searched: 5 September 2014.

Search strategy

1. insulin dependent diabetes mellitus/ (78,607)
2. exp diabetic ketoacidosis/ (7787)
3. (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ti,ab,ot,hw. (49,088)
4. (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ti,ab,ot,hw. (29,355)
5. ((insulin$ adj2 depend$) or insulindepend$).ti,ab,ot,hw. (217,259)
6. (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab,ot,hw. (20,038)
7. (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab,ot,hw. (14,231)
8. hypoglycemia/ or hyperglycemia/ (108,615)
9. (hyperglyc?em$ or hypoglyc?em$).ti,ab,ot. (104,051)
10. ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ti,ab,ot,hw. (126,603)
11. or/1-10 (436,900)
12. (sensor$ adj3 (augment$ or pump$)).ti,ab,hw,ot. (598)
13. SAPT.ti,ab,ot,hw. (114)
14. (minimed or paradigmveo).ti,ab,ot,hw,dm,dv. (727)
15. (paradigm$ adj3 (veo or pump$)).ti,ab,hw,ot,dm,dv. (127)
16. (veo adj3 pump$).ti,ab,ot,hw,dm,dv. (38)
17. ((animas or vibe) adj3 (pump$ or infus$ or system$)).ti,ab,ot,hw,dm,dv. (25)
18. (g4 adj3 platinum).ti,ab,ot,hw,dm,dv. (27)
19. dexcom.ti,ab,ot,hw,dm,dv. (298)
20. or/12-19 (1674)
21. insulin pump/ (3425)
22. insulin infusion/ (5096)
23. artificial pancreas/ (1433)
24. (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ti,ab,ot,hw. (17,265)
25. (pump$ adj2 (therap$ or treatment$)).ti,ab,ot,hw. (3171)
26. ((subcutaneous adj2 insulin$) or CSII).ti,ab,ot,hw. (4218)
27. (artificial adj3 (pancreas or beta cell$)).ti,ab,ot,hw. (2050)
28. (closed loop adj3 (pump$ or deliver$ or infus$ or therap$ or treatment$ or system$)).ti,ab,ot,hw. (1941)
29. (accu-chek or cellnovo or dana diabecare or omnipod).ti,ab,ot,hw,dm,dv. (529)
30. ((integrat$ or dual or combined or unified) adj3 (system$ or device$)).ti,ab,ot,hw. (39,256)
31. or/21-30 (62,055)
32. insulin/ and exp injection/ (3392)
33. (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (1188)
34. (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (561)
35. (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (9358)
36. MDI.ti,ab,hw,ot. (3791)
37. (injection adj3 therapy).ti,ab,ot,hw. (4157)
38. ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ti,ab,hw,ot. (1491)
39. (short acting adj3 insulin).ti,ab,hw,ot. (1038)
40. (rapid acting adj3 insulin).ti,ab,hw,ot. (864)
41. or/32-40 (22,079)
42. 20 or 31 or 41 (82,594)
43. 11 and 42 (18,536)

44. health-economics/ (33,789)
45. exp economic-evaluation/ (214,699)
46. exp health-care-cost/ (207,493)
47. exp pharmacoeconomics/ (168,062)
48. or/44-47 (484,055)
49. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (620,526)
50. (expenditure$ not energy).ti,ab. (24,446)
51. (value adj2 money).ti,ab. (1422)
52. budget$.ti,ab. (24,740)
53. or/49-52 (645,088)
54. 48 or 53 (918,375)
55. letter.pt. (853,934)
56. editorial.pt. (454,769)
57. note.pt. (566,292)
58. or/55-57 (1,874,995)
59. 54 not 58 (830,092)
60. (metabolic adj cost).ti,ab. (913)
61. ((energy or oxygen) adj cost).ti,ab. (3189)
62. ((energy or oxygen) adj expenditure).ti,ab. (20,605)
63. or/60-62 (23,877)
64. 59 not 63 (824,949)
65. exp animal/ (19,314,568)
66. exp animal-experiment/ (1,798,176)
67. nonhuman/ (4,359,920)
68. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (4,850,843)
69. or/65-68 (20,707,342)
70. exp human/ (15,050,997)
71. exp human-experiment/ (328,369)
72. 70 or 71 (15,052,426)
73. 69 not (69 and 72) (5,655,873)
74. 64 not 73 (761,307)
75. 43 and 74 (1027)

The economics terms were based on the following costs filter:

Centre for Reviews and Dissemination. Search strategies: NHS EED EMBASE using OvidSP (economics filter). York: Centre for Reviews and Dissemination; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase (accessed 2 June 2014).

MEDLINE (via OvidSP)

Date range searched: 1946–2014/August week 4.

Date searched: 5 September 2014.

1. Diabetes Mellitus, Type 1/ (62,323)
2. Diabetic Ketoacidosis/ (5178)
3. (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ti,ab,ot,hw. (69,580)
4. (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ti,ab,ot,hw. (20,273)
5. ((insulin$ adj2 depend$) or insulindepend$).ti,ab,ot,hw. (30469)
6. (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab,ot,hw. (13,085)
7. (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab,ot,hw. (9331)
8. Hyperglycemia/ (20,833)
9. Hypoglycemia/ (21,743)
10. (hyperglyc?em$ or hypoglyc?em$).ti,ab,ot. (72,656)
11. ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ti,ab,ot,hw. (94,623)
12. or/1-11 (245,714)
13. (sensor$ adj3 (augment$ or pump$)).ti,ab,hw,ot. (312)
14. SAPT.ti,ab,ot,hw. (93)
15. (minimed or paradigmveo).ti,ab,ot,hw. (197)
16. (paradigm$ adj3 (veo or pump$)).ti,ab,hw,ot. (34)
17. (veo adj3 pump$).ti,ab,ot,hw. (5)
18. ((animas or vibe) adj3 (pump$ or infus$ or system$)).ti,ab,ot,hw. (7)
19. (g4 adj3 platinum).ti,ab,ot,hw. (3)
20. dexcom.ti,ab,ot,hw. (44)
21. or/13-20 (645)
22. Insulin Infusion Systems/ (3988)
23. Pancreas, Artificial/ (402)
24. (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ti,ab,ot,hw. (11,972)
25. (pump$ adj2 (therap$ or treatment$)).ti,ab,ot,hw. (1810)
26. ((subcutaneous adj2 insulin$) or CSII).ti,ab,ot,hw. (2474)
27. (artificial adj3 (pancreas or beta cell$)).ti,ab,ot,hw. (1203)
28. (closed loop adj3 (pump$ or deliver$ or infus$ or therap$ or treatment$ or system$)).ti,ab,ot,hw. (1310)
29. (accu-chek or cellnovo or dana diabecare or omnipod).ti,ab,ot,hw. (150)
30. ((integrat$ or dual or combined or unified) adj3 (system$ or device$)).ti,ab,ot,hw. (32,573)
31. or/22-30 (47,787)
32. Insulin/ and Injections, Subcutaneous/ (2134)
33. (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (624)
34. (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (452)
35. (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (6795)
36. MDI.ti,ab,hw,ot. (2372)
37. (injection adj3 therapy).ti,ab,ot,hw. (2858)
38. ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ti,ab,hw,ot. (1015)
39. (short acting adj3 insulin).ti,ab,hw,ot. (466)
40. (rapid acting adj3 insulin).ti,ab,hw,ot. (468)
41. or/32-40 (15,196)
42. 21 or 31 or 41 (61,753)
43. 12 and 42 (10,730)
44. economics/ (27,125)
45. exp "costs and cost analysis"/ (184,746)

46. economics, dental/ (1867)
47. exp "economics, hospital"/ (19,806)
48. economics, medical/ (8680)
49. economics, nursing/ (3985)
50. economics, pharmaceutical/ (2574)
51. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (431,861)
52. (expenditure$ not energy).ti,ab. (17,649)
53. (value adj1 money).ti,ab. (23)
54. budget$.ti,ab. (17,373)
55. or/44-54 (557,969)
56. ((energy or oxygen) adj cost).ti,ab. (2704)
57. (metabolic adj cost).ti,ab. (788)
58. ((energy or oxygen) adj expenditure).ti,ab. (16,809)
59. or/56-58 (19,580)
60. 55 not 59 (553,698)
61. letter.pt. (826,900)
62. editorial.pt. (346,911)
63. historical article.pt. (306,574)
64. or/61-63 (1,465,388)
65. 60 not 64 (525,046)
66. 43 and 65 (327)

The economics terms were based on the following costs filter:

Centre for Reviews and Dissemination. Search strategies: NHS EED MEDLINE using OvidSP (economics filter). York: Centre for Reviews and Dissemination; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline (accessed 2 June 2014).

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily Update (via OvidSP); 4 September 2014

Date searched: 5 September 2014.

Search strategy

1. Diabetes Mellitus, Type 1/ (36)
2. Diabetic Ketoacidosis/ (3)
3. (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ti,ab,ot,hw. (2614)
4. (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ti,ab,ot,hw. (1105)
5. ((insulin$ adj2 depend$) or insulindepend$).ti,ab,ot,hw. (701)
6. (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab,ot,hw. (884)
7. (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab,ot,hw. (430)
8. Hyperglycemia/ (20)
9. Hypoglycemia/ (10)
10. (hyperglyc?em$ or hypoglyc?em$).ti,ab,ot. (5462)
11. ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ti,ab,ot,hw. (7457)
12. or/1-11 (14909)
13. (sensor$ adj3 (augment$ or pump$)).ti,ab,hw,ot. (59)
14. SAPT.ti,ab,ot,hw. (83)
15. (minimed or paradigmveo).ti,ab,ot,hw. (13)

16. (paradigm$ adj3 (veo or pump$)).ti,ab,hw,ot. (4)
17. (veo adj3 pump$).ti,ab,ot,hw. (1)
18. ((animas or vibe) adj3 (pump$ or infus$ or system$)).ti,ab,ot,hw. (0)
19. (g4 adj3 platinum).ti,ab,ot,hw. (3)
20. dexcom.ti,ab,ot,hw. (7)
21. or/13-20 (164)
22. Insulin Infusion Systems/ (2)
23. Pancreas, Artificial/ (2)
24. (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ti,ab,ot,hw. (504)
25. (pump$ adj2 (therap$ or treatment$)).ti,ab,ot,hw. (189)
26. ((subcutaneous adj2 insulin$) or CSII).ti,ab,ot,hw. (172)
27. (artificial adj3 (pancreas or beta cell$)).ti,ab,ot,hw. (61)
28. (closed loop adj3 (pump$ or deliver$ or infus$ or therap$ or treatment$ or system$)).ti,ab,ot,hw. (343)
29. (accu-chek or cellnovo or dana diabecare or omnipod).ti,ab,ot,hw. (16)
30. ((integrat$ or dual or combined or unified) adj3 (system$ or device$)).ti,ab,ot,hw. (4137)
31. or/22-30 (5154)
32. Insulin/ and Injections, Subcutaneous/ (3)
33. (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (66)
34. (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (9)
35. (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,ot,hw. (492)
36. MDI.ti,ab,hw,ot. (161)
37. (injection adj3 therapy).ti,ab,ot,hw. (206)
38. ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ti,ab,hw,ot. (51)
39. (short acting adj3 insulin).ti,ab,hw,ot. (29)
40. (rapid acting adj3 insulin).ti,ab,hw,ot. (59)
41. or/32-40 (937)
42. 21 or 31 or 41 (6140)
43. 12 and 42 (543)
44. economics/ (0)
45. exp "costs and cost analysis"/ (103)
46. economics, dental/ (0)
47. exp "economics, hospital"/ (10)
48. economics, medical/ (0)
49. economics, nursing/ (0)
50. economics, pharmaceutical/ (0)
51. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (51,540)
52. (expenditure$ not energy).ti,ab. (1501)
53. (value adj1 money).ti,ab. (5)
54. budget$.ti,ab. (2211)
55. or/44-54 (53,783)
56. ((energy or oxygen) adj cost).ti,ab. (294)
57. (metabolic adj cost).ti,ab. (80)
58. ((energy or oxygen) adj expenditure).ti,ab. (1183)
59. or/56-58 (1507)
60. 55 not 59 (53,348)
61. letter.pt. (30,310)
62. editorial.pt. (18,730)
63. historical article.pt. (112)
64. or/61-63 (49,132)
65. 60 not 64 (52,805)
66. 43 and 65 (35)

The economics terms were based on the following costs filter:

Centre for Reviews and Dissemination. Search strategies: NHS EED MEDLINE using OvidSP (economics filter). York: Centre for Reviews and Dissemination; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline (accessed 2 June 2014).

PubMed (via the National Library of Medicine)

URL: www.ncbi.nlm.nih.gov/pubmed/

Date range searched: from inception up to 5 September 2014.

Date searched: 5 September 2014.

Search strategy

#59	**Search (#57 and #58)**	**20**
#58	Search (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])	18,150,03
#57	Search (#46 and #56)	188
#56	Search (#51 not #55)	498,516
#55	Search (#52 or #53 or #54)	20,445
#54	Search "energy expenditure"[tiab] or "oxygen expenditure"[tiab]	17,356
#53	Search "metabolic cost"[tiab]	879
#52	Search "energy cost"[tiab] or "oxygen cost"[tiab]	2972
#51	Search (#47 or #48 or #49 or #50)	503,197
#50	Search budget*[tiab]	19,728
#49	Search "value for money"	928
#48	Search (expenditure*[tiab] not energy[tiab])	19,130
#47	Search (economic*[tiab] or cost[tiab] or costs[tiab] or costly[tiab] or costing[tiab] or price[tiab] or prices [tiab] or pricing[tiab] or pharmacoeconomic*[tiab])	482,242
#46	Search (#20 and #45)	5237
#45	Search (#28 or #36 or #44)	20,242
#44	Search (#37 or #38 or #39 or #40 or #41 or #42 or #43)	9426
#43	Search ("short acting insulin"[tiab] OR "rapid acting insulin"[tiab])	810
#42	Search (basal*[tiab] AND bolus[tiab] AND (injection*[tiab] OR regime*[tiab] OR routine*[tiab] OR system*[tiab]))	1549
#41	Search "injection therapy"[tiab]	2098
#40	Search MDI[tiab]	2524
#39	Search "multiple injection"[tiab] or "multiple injections"[tiab] or "multiple insulin"[tiab] or "multiple regime"[tiab] or "multiple regimes"[tiab] or "multiple routine"[tiab] or "multiple routines"[tiab]	2414
#38	Search "multiple dose injection"[tiab] or "multiple dose injections"[tiab] or "multiple dose insulin"[tiab] or "multiple dose regime"[tiab] or "multiple dose regimes"[tiab] or "multiple dose routine"[tiab] or "multiple dose routines"[tiab]	48
#37	Search "multiple daily injection"[tiab] or "multiple daily injections"[tiab] or "multiple daily insulin"[tiab] or "multiple daily regime"[tiab] or "multiple daily regimes"[tiab] or "multiple daily routine"[tiab] or "multiple daily routines"[tiab]	603
#36	Search (#29 or #30 or #31 or #32 or #33 or #34 or #35)	10,964

#35	Search "integrated system"[tiab] or "integrated systems"[tiab] "integrated device"[tiab] or "integrated devices"[tiab] or "dual system"[tiab] or "dual systems"[tiab] or "dual device"[tiab] or "dual devices"[tiab] or "combined system"[tiab] or "combined systems"[tiab] or "combined device"[tiab] or "combined devices"[tiab] or "unified system"[tiab] or "unified systems"[tiab] or "unified device"[tiab] or "unified devices"[tiab]	1317
#34	Search (accu-chek[tiab] or cellnovo[tiab] or "dana diabecare"[tiab] or omnipod[tiab])	159
#33	Search "closed loop pump"[tiab] or "closed loop pumps"[tiab] or "closed loop delivery"[tiab] or "closed loop infusion"[tiab] or "closed loop infusions"[tiab] or "closed loop therapy"[tiab] or "closed loop treatment"[tiab] or "closed loop treatments"[tiab] or "closed loop system"[tiab] or "closed loop systems"[tiab]	812
#32	Search "artificial pancreas"[tiab] or "artificial beta cell"[tiab]	822
#31	Search "subcutaneous insulin"[tiab] or CSII[tiab]	2385
#30	Search "pump therapy"[tiab] or "pump therapies"[tiab] or "pump treatment"[tiab] or "pump treatments"[tiab]	920
#29	Search "insulin pump"[tiab] or "insulin pumps"[tiab] or "insulin infusion"[tiab] or "insulin infuse"[tiab] or "insulin infused"[tiab] or "insulin deliver"[tiab] or "insulin delivery"[tiab]	7485
#28	Search (#21 or #22 or #23 or #24 or #25 or #26 or #27)	928
#27	Search dexcom	54
#26	Search (animas or vibe) AND (pump* or infus* or system*)	81
#25	Search "veo pump" or "veo pumps"	15
#24	Search ((paradigm* AND (veo or pump*)))	350
#23	Search minimed or paradigmveo	216
#22	Search SAPT[tiab]	184
#21	Search "sensor augmented"[tiab] or "sensor augment"[tiab] or "sensor pump"[tiab] or "pump sensor"[tiab] or "sensor pumps"[tiab]	91
#20	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19)	126,838
#19	Search "high glycohemoglobin"[tiab] or "higher glycohemoglobin"[tiab] or "low glycohemoglobin"[tiab] or "lower glycohemoglobin"[tiab] or "increase glycohemoglobin"[tiab] or "increased glycohemoglobin"[tiab] or "increases glycohemoglobin"[tiab] or "decrease glycohemoglobin"[tiab] or "decreased glycohemoglobin"[tiab] or "decreases glycohemoglobin"[tiab] or "deficient glycohemoglobin"[tiab] or "sufficient glycohemoglobin"[tiab] or "insufficient glycohemoglobin"[tiab] or "reduce glycohemoglobin"[tiab] or "reduced glycohemoglobin"[tiab] or "glycohemoglobin reduction"[tiab] or "fallen glycohemoglobin"[tiab] or "falling glycohemoglobin"[tiab] or "glycohemoglobin threshold"[tiab] or "safe glycohemoglobin"[tiab]	17
#18	Search ("high haemoglobin"[tiab] or "higher haemoglobin"[tiab] or "low haemoglobin"[tiab] or "lower haemoglobin"[tiab] or "increase haemoglobin"[tiab] or "increased haemoglobin"[tiab] or "increases haemoglobin"[tiab] or "decrease haemoglobin"[tiab] or "decreased haemoglobin"[tiab] or "decreases haemoglobin"[tiab] or "deficient haemoglobin"[tiab] or "sufficient haemoglobin"[tiab] or "insufficient haemoglobin"[tiab] or "reduce haemoglobin"[tiab] or "reduced haemoglobin"[tiab] or "haemoglobin reduction"[tiab] or "fallen haemoglobin"[tiab] or "falling haemoglobin"[tiab] or "haemoglobin threshold"[tiab] or "safe haemoglobin"[tiab])	1161
#17	Search "high hemoglobin"[tiab] or "higher hemoglobin"[tiab] or "low hemoglobin"[tiab] or "lower hemoglobin"[tiab] or "increase hemoglobin"[tiab] or "increased hemoglobin"[tiab] or "increases hemoglobin"[tiab] or "decrease hemoglobin"[tiab] or "decreasedchemoglobin"[tiab] or "decreases hemoglobin"[tiab] or "deficient hemoglobin"[tiab] or "sufficient hemoglobin"[tiab] or "insufficient hemoglobin"[tiab] or "reduce hemoglobin"[tiab] or "reduced hemoglobin"[tiab] or "hemoglobin reduction"[tiab] or "fallen hemoglobin"[tiab] or "falling hemoglobin"[tiab] or "hemoglobin threshold"[tiab] or "safe hemoglobin"[tiab]	3476
#16	Search "high a1c"[tiab] or "higher a1c"[tiab] or "low a1c"[tiab] or "lower a1c"[tiab] or "increase a1c"[tiab] or "increased a1c"[tiab] or "increases a1c"[tiab] or "decrease a1c"[tiab] or "decreasedca1c"[tiab] or "decreases a1c"[tiab] or "deficient a1c"[tiab] or "sufficient a1c"[tiab] or "insufficient a1c"[tiab] or "reduce a1c"[tiab] or "reduced a1c"[tiab] or "a1c reduction"[tiab] or "fallen a1c"[tiab] or "falling a1c"[tiab] or "a1c threshold"[tiab] or "safe a1c"[tiab]	291

#15	Search (((“high hba1”[tiab] or “higher hba1”[tiab] or “low hba1”[tiab] or “lower hba1”[tiab] or “increase hba1”[tiab] or “increased hba1”[tiab] or “increases hba1”[tiab] or “decrease hba1”[tiab] or “decreasedchba1”[tiab] or “decreases hba1”[tiab] or “deficient hba1”[tiab] or “sufficient hba1”[tiab] or “insufficient hba1”[tiab] or “reduce hba1”[tiab] or “reduced hba1”[tiab] or “hba1 reduction”[tiab] or “fallen hba1”[tiab] or “falling hba1”[tiab] or “hba1 threshold”[tiab] or “safe hba1”[tiab])))	76
#14	Search “high hb a1”[tiab] or “higher hb a1”[tiab] or “low hb a1”[tiab] or “lower hb a1”[tiab] or “increase hb a1”[tiab] or “increased hb a1”[tiab] or “increases hb a1”[tiab] or “decrease hb a1”[tiab] or “decreasedchb a1”[tiab] or “decreases hb a1”[tiab] or “deficient hb a1”[tiab] or “sufficient hb a1”[tiab] or “insufficient hb a1”[tiab] or “reduce hb a1”[tiab] or “reduced hb a1”[tiab] or “hb a1 reduction”[tiab] or “fallen hb a1”[tiab] or “falling hb a1”[tiab] or “hb a1 threshold”[tiab] or “safe hb a1”[tiab]	0
#13	Search “high hba1c”[tiab] or “higher hba1c”[tiab] or “low hba1c”[tiab] or “lower hba1c”[tiab] or “increase hba1c”[tiab] or “increased hba1c”[tiab] or “increases hba1c”[tiab] or “decrease hba1c”[tiab] or “decreasedchba1c”[tiab] or “decreases hba1c”[tiab] or “deficient hba1c”[tiab] or “sufficient hba1c”[tiab] or “insufficient hba1c”[tiab] or “reduce hba1c”[tiab] or “reduced hba1c”[tiab] or “hba1c reduction”[tiab] or “fallen hba1c”[tiab] or “falling hba1c”[tiab] or “hba1c threshold”[tiab] or “safe hba1c”[tiab]	1271
#12	Search “high sugar”[tiab] or “higher sugar”[tiab] or “low sugar”[tiab] or “lower sugar”[tiab] or “increase sugar”[tiab] or “increased sugar”[tiab] or “increases sugar”[tiab] or “decrease sugar”[tiab] or “decreasedcsugar”[tiab] or “decreases sugar”[tiab] or “deficient sugar”[tiab] or “sufficient sugar”[tiab] or “insufficient sugar”[tiab] or “reduce sugar”[tiab] or “reduced sugar”[tiab] or “sugar reduction”[tiab] or “fallen sugar”[tiab] or “falling sugar”[tiab] or “sugar threshold”[tiab] or “safe sugar”[tiab]	1539
#11	Search (“high glucose”[tiab] or “higher glucose”[tiab] or “low glucose”[tiab] or “lower glucose”[tiab] or “increase glucose”[tiab] or “increased glucose”[tiab] or “increases glucose”[tiab] or “decrease glucose”[tiab] or “decreasedcglucose”[tiab] or “decreases glucose”[tiab] or “deficient glucose”[tiab] or “sufficient glucose”[tiab] or “insufficient glucose”[tiab] or “reduce glucose”[tiab] or “reduced glucose”[tiab] or “glucose reduction”[tiab] or “fallen glucose”[tiab] or “falling glucose”[tiab] or “glucose threshold”[tiab] or “safe glucose”[tiab])	16,645
#10	Search (hyperglycemia[tiab] or hypoglycaemia[tiab] or hyperglycemic[tiab] or hypoglycaemic[tiab])	44,267
#9	Search ketoacidosis[tiab] or acidoketosis[tiab] or “keto acidosis”[tiab] or ketoacidemia[tiab] or ketosis [tiab]	7293
#8	Search dm1[tiab] or “dm 1”[tiab] or t1dm[tiab] or “t1 dm”[tiab] or t1d[tiab] or iddm[tiab]	13,131
#7	Search “insulin dependent”[tiab] or insulindepend*[tiab]	27,550
#6	Search “brittle diabetic”[tiab] or “diabetic juvenile”[tiab] or “diabetic pediatric”[tiab] or “diabetic paediatric”[tiab] or “diabetic early”[tiab] or “diabetic labile”[tiab] or “diabetic acidosis”[tiab] or “diabetic sudden onset”[tiab]	348
#5	Search “diabetic brittle”[tiab] or “juvenile diabetic”[tiab] or “pediatric diabetic”[tiab] or “paediatric diabetic”[tiab] or “early diabetic”[tiab] or “labile diabetic”[tiab] or “acidosis diabetic”[tiab] or “sudden onset diabetic”[tiab]	1122
#4	Search “brittle diabetes”[tiab] or “diabetes juvenile”[tiab] or “diabetes pediatric”[tiab] or “diabetes paediatric”[tiab] or “diabetes early”[tiab] or “diabetes ketosis”[tiab] or “diabetes labile”[tiab] or “diabetes acidosis”[tiab] or “diabetes sudden onset”[tiab]	264
#3	Search “diabetes brittle”[tiab] or “juvenile diabetes”[tiab] or “pediatric diabetes”[tiab] or “paediatric diabetes”[tiab] or “early diabetes”[tiab] or “ketosis diabetes”[tiab] or “labile diabetes”[tiab] or “acidosis diabetes”[tiab] or “sudden onset diabetes”[tiab]	2238
#2	Search “diabetic type 1”[tiab] OR “type 1 diabetic”[tiab] OR “diabetic type i”[tiab] OR “type i diabetic”[tiab] OR “diabetic type1”[tiab] OR “type1 diabetic”[tiab] OR “diabetic typei”[tiab] OR “typei diabetic”[tiab]	6044
#1	Search (((“diabetes type 1”[tiab] OR “type 1 diabetes”[tiab] OR “diabetes type i”[tiab] OR “type i diabetes”[tiab] OR “diabetes type1”[tiab] OR “type1 diabetes”[tiab] OR “diabetes typei”[tiab] OR “typei diabetes”[tiab])))	28,884

The economics terms were based on the following costs filter:
Centre for Reviews and Dissemination. Search strategies: NHS EED MEDLINE using OvidSP (economics filter). York: Centre for Reviews and Dissemination; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline (accessed 2 June 2014).

American Economic Association's electronic bibliography EconLit (via EBSCOhost)

Date range searched: 1969 to 1 August 2014.

Date searched: 5 September 2014.

Search strategy

S28 S7 AND S27 (1)
S27 (S11 OR S19 OR S26) (2379)
S26 S20 OR S21 OR S22 OR S23 OR S24 OR S25 (174)
S25 TI ("short acting" N3 insulin or "rapid acting" N3 insulin) or AB ("short acting" N3 insulin or "rapid acting" N3 insulin (0)
S24 TI (((basal* and bolus) N3 injection*) or ((basal* and bolus) N3 regime*) or ((basal* and bolus) N3 routine*) or ((basal* and bolus) N3 system*)) or AB (((basal* and bolus) N3 injection*) or ((basal* and bolus) N3 regime*) or ((basal* and bolus) N3 routine*) or ((basal* and bolus) N3 system*)) (0)
S23 TI (MDI or injection N3 therapy) or AB (MDI or injection N3 therapy) (11)
S22 TI (multiple N3 inject* or multiple N3 insulin* or multiple N3 regime* or multiple N3 routine*) or AB (multiple N3 inject* or multiple N3 insulin* or multiple N3 regime* or multiple N3 routine*) (163)
S21 TI ("multiple dose" N3 inject* or "multiple dose" N3 insulin* or "multiple dose" N3 regime* or "multiple dose" N3 routine*) or AB ("multiple dose" N3 inject* or "multiple dose" N3 insulin* or "multiple dose" N3 regime* or "multiple dose" N3 routine*) (0)
S20 TI ("multiple daily" N3 inject* or "multiple daily" N3 insulin* or "multiple daily" N3 regime* or "multiple daily" N3 routine*) or AB ("multiple daily" N3 inject* or "multiple daily" N3 insulin* or "multiple daily" N3 regime* or "multiple daily" N3 routine*) (0)
S19 S12 or S13 or S14 or S15 or S16 or S17 or S18 (2,206)
S18 TI (integrat* N3 system* or integrat* N3 device* or dual N3 system* or dual N3 device* or combined N3 system* or combined N3 device* or unified N3 system* or unified N3 device) or AB (integrat* N3 system* or integrat* N3 device* or dual N3 system* or dual N3 device* or combined N3 system* or combined N3 device* or unified N3 system* or unified N3 device) (2,187)
S17 TI (accu-chek or cellnovo or "dana diabecare" or omnipod) or AB (accu-chek or cellnovo or "dana diabecare" or omnipod) (0)
S16 TI ("closed loop" N3 pump* or "closed loop" N3 deliver* or "closed loop" N3 infus* or "closed loop" N3 therap* or "closed loop" N3 treatment* or "closed loop" N3 system*) or AB ("closed loop" N3 pump* or "closed loop" N3 deliver* or "closed loop" N3 infus* or "closed loop" N3 therap* or "closed loop" N3 treatment* or "closed loop" N3 system*) (18)
S15 TI (artificial N3 pancreas or artificial N3 "beta cell*" or artificial N2 beta-cell*) or AB (artificial N3 pancreas or artificial N3 "beta cell*" or artificial N3 beta-cell*) (0)
S14 TI (subcutaneous N2 insulin* or CSII) or AB (subcutaneous N2 insulin* or CSII (2)
S13 TI (pump* N3 therap* or pump* N3 treatment*) or AB (pump* N3 therap* or pump* N3 treatment*) (1)
S12 TI (insulin* N3 pump* or insulin* N3 infus* or insulin* N3 deliver* or insulin N3 catheter*) or AB (insulin* N3 pump* or insulin* N3 infus* or insulin* N3 deliver* or insulin N3 catheter*) (1)
S11 S8 or S9 or S10 (0)
S10 TI (animas N3 pump* or animas N3 infus* or animas N3 system* or vibe N3 pump* or vibe N3 infus* or vibe N3 system* or g4 N3 platinum or dexcom) or AB (animas N3 pump* or animas N3 infus* or animas N3 system* or vibe N3 pump* or vibe N3 infus* or vibe N3 system* or g4 N3 platinum or dexcom) (0)

S9 TI (minimed or paradigmveo or paradigm* N3 veo or paradigm* N3 pump* or veo N3 pump*) or AB (minimed or paradigmveo or paradigm* N3 veo or paradigm* N3 pump* or veo N3 pump*) (0)
S8 TI (sensor* N3 augment* or sensor* N3 pump* or sensor-augment* or SAPT) or AB (sensor* N3 augment* or sensor* N3 pump* or sensor-augment* or SAPT) (0)
S7 S1 or S2 or S3 or S4 or S5 or S6 (26)
S6 TI (hyperglycem* or hypoglycem* or hyperglycaem* or hypoglycaem*) or AB (hyperglycem* or hypoglycem* or hyperglycaem* or hypoglycaem*) (5)
S5 TI (ketoacidosis or acidoketosis or "keto acidosis" or ketoacidemia or ketosis) or AB (ketoacidosis or acidoketosis or "keto acidosis" or ketoacidemia or ketosis) (0)
S4 TI (dm1 or "dm 1" or dmt1 or "dm t1" or t1dm or "t1 dm" or t1d or iddm) or AB (dm1 or "dm 1" or dmt1 or "dm t1" or t1dm or "t1 dm" or t1d or iddm) (2)
S3 TI (insulin* N2 depend* or insulindepend*) or AB (insulin* N2 depend* or insulindepend*) (5)
S2 TI (diabet* N3 britt* or diabet* N3 juvenil* or diabet* N3 pediatric or diabet* N3 paediatric or diabet* N3 early or diabet* N3 keto* or diabet* N3 labil* or diabet* N3 acidos* or diabet* N3 autoimmun* or diabet* N3 "auto immune*" or diabet* N3 "sudden onset") or AB (diabet* N3 britt* or diabet* N3 juvenil* or diabet* N3 pediatric or diabet* N3 paediatric or diabet* N3 early or diabet* N3 keto* or diabet* N3 labil* or diabet* N3 acidos* or diabet* N3 autoimmun* or diabet* N3 "auto immune*" or di ... (2)
S1 TI (diabet* N3 "typ* 1" or diabet* N3 "typ* i" or diabet* N3 type1 or diabet* N3 typei or diabet* N3 "typ* one") or AB (diabet* N3 "typ* 1" or diabet* N3 "typ* i" or diabet* N3 type1 or diabet* N3 typei or diabet* N3 "typ* one") (14)

Cost-effectiveness Analysis Registry

URL: www.cearegistry.org

Date range searched: from inception up to 5 September 2014.

Date searched: 5 September 2014.

Seven records retrieved.

Search strategy

sensor augmented

sensor-augmented

SAPT

minimed

paradigmveo

paradigm veo

paradigm-veo

veo pump

animas

vibe pump

vibe infusion

vibe system

vibe systems

g4 platinum

dexcom

insulin pump

insulin pumps

insulin infusion

insulin delivery

pump therapy

pump treatment

pump treatments

subcutaneous insulin

CSII

artificial pancreas

artificial beta cell

artificial beta-cell

closed loop

integrated system

integrated systems

integrated device

integrated devices

multiple daily injection

multiple daily injections

multiple dose injection

multiple dose injections

multiple daily insulin

multiple dose insulin

multiple injection

multiple injections

MDI

injection therapy

basal bolus

short acting insulin

rapid acting insulin

RePEc Research Papers in Economics

URL: http://repec.org/

Date range searched: from inception up to 5 September 2014.

Date searched: 5 September 2014.

IDEAS search interface.

Search strategy

("diabetes mellitus type 1" | "diabetes type 1" | "diabetes mellitus type1" | "diabetes type1" | "diabetes mellitus type I" | "diabetes type I" | "diabetes mellitus typeI" | "diabetes typeI" | "diabetes mellitus type one" | "diabetes type one" | dm1 | "dm 1" | dmt1 | "dm t1" | t1dm | "t1 dm" | t1d | iddm | ketoacidosis) + ("sensor augmented" | sensor-augmented | SAPT | minimed | paradigmveo | "paradigm veo" | "paradigm pump" | "veo pump" | animas | vibe | "g4 platinum" | dexcom)

Records retrieved: 0.

("brittle diabetes" | "juvenile diabetes" | "pediatric diabetes" | "paediatric diabetes" | "early diabetes" | "autoimmune diabetes" | "auto immune diabetes" | "sudden onset diabetes") + ("sensor augmented" | sensor-augmented | SAPT | minimed | paradigmveo | "paradigm veo" | "paradigm pump" | "veo pump" | animas | vibe | "g4 platinum" | dexcom)

Records retrieved: 0.

(hyperglycemia | hypoglycemia | hyperglycaemia | hypoglycaemia) + ("sensor augmented" | sensor-augmented | SAPT | minimed | paradigmveo | "paradigm veo" | "paradigm pump" | "veo pump" | animas | vibe | "g4 platinum" | dexcom)

Records retrieved: 0.

("diabetes mellitus type 1" | "diabetes type 1" | "diabetes mellitus type1" | "diabetes type1" | "diabetes mellitus type I" | "diabetes type I" | "diabetes mellitus typeI" | "diabetes typeI" | "diabetes mellitus type one" | "diabetes type one" | dm1 | "dm 1" | dmt1 | "dm t1" | t1dm | "t1 dm" | t1d | iddm | ketoacidosis) + ("insulin pump" | "insulin pumps" | "insulin infusion" | "insulin delivery" | "pump therapy" | "pump treatment" | "pump treatments")

Records retrieved: 1.

("diabetes mellitus type 1" | "diabetes type 1" | "diabetes mellitus type1" | "diabetes type1" | "diabetes mellitus type I" | "diabetes type I" | "diabetes mellitus typeI" | "diabetes typeI" | "diabetes mellitus type one" | "diabetes type one" | dm1 | "dm 1" | dmt1 | "dm t1" | t1dm | "t1 dm" | t1d | iddm | ketoacidosis) + ("subcutaneous insulin" | CSII | "artificial pancreas" | "artificial beta cell" | "artificial beta-cell" | "artificial beta cells" | "artificial beta-cells" | "closed loop" | closed-loop | "integrated system" | "integrated systems | "dual system" | "dual systems" | "integrated device" | "integrated devices | "dual device" | "dual devices")

Records retrieved: 11.

("brittle diabetes" | "juvenile diabetes" | "pediatric diabetes" | "paediatric diabetes" | "early diabetes" | "autoimmune diabetes" | "auto immune diabetes" | "sudden onset diabetes") + ("insulin pump" | "insulin pumps" | "insulin infusion" | "insulin delivery" | "pump therapy" | "pump treatment" | "pump treatments")

Records retrieved: 0.

("brittle diabetes" | "juvenile diabetes" | "pediatric diabetes" | "paediatric diabetes" | "early diabetes" | "autoimmune diabetes" | "auto immune diabetes" | "sudden onset diabetes") + ("subcutaneous insulin" | CSII | "artificial pancreas" | "artificial beta cell" | "artificial beta-cell" | "artificial beta cells" | "artificial beta-cells" | "closed loop" | closed-loop | "integrated system" | "integrated systems | "dual system" | "dual systems" | "integrated device" | "integrated devices | "dual device" | "dual devices")

Records retrieved: 0.

(hyperglycemia | hypoglycemia | hyperglycaemia | hypoglycaemia) + ("insulin pump" | "insulin pumps" | "insulin infusion" | "insulin delivery" | "pump therapy" | "pump treatment" | "pump treatments")

Records retrieved: 0.

(hyperglycemia | hypoglycemia | hyperglycaemia | hypoglycaemia) + ("subcutaneous insulin" | CSII | "artificial pancreas" | "artificial beta cell" | "artificial beta-cell" | "artificial beta cells" | "artificial beta-cells" | "closed loop" | closed-loop | "integrated system" | "integrated systems | "dual system" | "dual systems" | "integrated device" | "integrated devices | "dual device" | "dual devices")

Records retrieved: 0.

("diabetes mellitus type 1" | "diabetes type 1" | "diabetes mellitus type1" | "diabetes type1" | "diabetes mellitus type I" | "diabetes type I" | "diabetes mellitus typeI" | "diabetes typeI" | "diabetes mellitus type one" | "diabetes type one" | dm1 | "dm 1" | dmt1 | "dm t1" | t1dm | "t1 dm" | t1d | iddm | ketoacidosis) + ("multiple daily injection" | "multiple daily injections" | "multiple dose injection" | "multiple dose injections" | "multiple daily insulin" | "multiple dose insulin" | "multiple injection" | "multiple injections" | MDI | "injection therapy" | "basal bolus" | basal-bolus | basalbolus | "short acting insulin" | "rapid acting insulin")

Records retrieved: 11.

("brittle diabetes" | "juvenile diabetes" | "pediatric diabetes" | "paediatric diabetes" | "early diabetes" | "autoimmune diabetes" | "auto immune diabetes" | "sudden onset diabetes") + ("multiple daily injection" | "multiple daily injections" | "multiple dose injection" | "multiple dose injections" | "multiple daily insulin" | "multiple dose insulin" | "multiple injection" | "multiple injections" | MDI | "injection therapy" | "basal bolus" | basal-bolus | basalbolus | "short acting insulin" | "rapid acting insulin")

Records retrieved: 0.

(hyperglycemia | hypoglycemia | hyperglycaemia | hypoglycaemia) + ("multiple daily injection" | "multiple daily injections" | "multiple dose injection" | "multiple dose injections" | "multiple daily insulin" | "multiple dose insulin" | "multiple injection" | "multiple injections" | MDI | "injection therapy" | "basal bolus" | basal-bolus | basalbolus | "short acting insulin" | "rapid acting insulin")

Records retrieved: 1.

Records retrieved in total: 24.

Records retrieved after removal of duplicates: 11.

Key:

| OR

+ AND

" " phrase search

Specific economic searches (MiniMed and Animas Vibe only)

NHS Economic Evaluation Database (via Wiley Online Library)

Issue searched: 3 of 4, July 2014.

Date searched: 2 October 2014.

Search strategy

#1 (sensor* near/3 (augment* or pump*))
#2 SAPT:ti,ab,kw
#3 minimed or paradigmveo
#4 (paradigm* near/3 (veo or pump*))
#5 (veo near/3 pump*)
#6 ((animas or vibe) near/3 (pump* or infus* or system*))
#7 dexcom
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

NHS EED: 4.

Health Economic Evaluations Database (via Wiley Online Library)

Date range searched: from inception up to 2 October 2014.

Date searched: 2 October 2014.

Search strategy

AX='sensor augmented' or sensor-augmented or SAPT (1)

AX=minimed or paradigmveo or 'paradigm veo' or 'paradigm pump' or 'veo pump' or 'animas pump' or 'animas infusion' or 'vibe pump' or 'vibe infusion' or 'g4 platinum' or dexcom (0)

CS=1 or 2 (1)

EMBASE (via OvidSP)

Date range searched: 1974–2014/week 39.

Date searched: 2 October 2014.

Search strategy

1. insulin dependent diabetes mellitus/ (79,725)
2. exp diabetic ketoacidosis/ (7880)
3. (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ti,ab,ot,hw. (50,200)
4. (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ti,ab,ot,hw. (29,720)
5. ((insulin$ adj2 depend$) or insulindepend$).ti,ab,ot,hw. (221,115)
6. (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab,ot,hw. (20,641)
7. (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab,ot,hw. (14,385)
8. hypoglycemia/ or hyperglycemia/ (110,120)
9. (hyperglyc?em$ or hypoglyc?em$).ti,ab,ot. (105,704)
10. ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ti,ab,ot,hw. (128,520)
11. or/1-10 (442,805)
12. (sensor$ adj3 (augment$ or pump$)).ti,ab,hw,ot. (611)
13. SAPT.ti,ab,ot,hw. (114)
14. (minimed or paradigmveo).ti,ab,ot,hw,dm,dv. (746)
15. (paradigm$ adj3 (veo or pump$)).ti,ab,hw,ot,dm,dv. (134)
16. (veo adj3 pump$).ti,ab,ot,hw,dm,dv. (41)
17. ((animas or vibe) adj3 (pump$ or infus$ or system$)).ti,ab,ot,hw,dm,dv. (29)
18. (g4 adj3 platinum).ti,ab,ot,hw,dm,dv. (29)
19. dexcom.ti,ab,ot,hw,dm,dv. (314)
20. or/12-19 (1730)
21. 11 and 20 (1156)
22. health-economics/ (33,844)
23. exp economic-evaluation/ (215,823)
24. exp health-care-cost/ (208,556)
25. exp pharmacoeconomics/ (168,747)
26. or/22-25 (486,347)
27. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (625,347)
28. (expenditure$ not energy).ti,ab. (24,608)
29. (value adj2 money).ti,ab. (1430)

30. budget$.ti,ab. (24,869)
31. or/27-30 (650,042)
32. 26 or 31 (924,348)
33. letter.pt. (856,710)
34. editorial.pt. (456,641)
35. note.pt. (570,035)
36. or/33-35 (1,883,386)
37. 32 not 36 (835,648)
38. (metabolic adj cost).ti,ab. (924)
39. ((energy or oxygen) adj cost).ti,ab. (3207)
40. ((energy or oxygen) adj expenditure).ti,ab. (20,769)
41. or/38-40 (24,065)
42. 37 not 41 (830,473)
43. exp animal/ (19,415,638)
44. exp animal-experiment/ (1,804,426)
45. nonhuman/ (4,376,931)
46. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (4,869,940)
47. or/43-46 (20,812,704)
48. exp human/ (15,138,243)
49. exp human-experiment/ (329,281)
50. 48 or 49 (15,139,672)
51. 47 not (47 and 50) (5,673,989)
52. 42 not 51 (766,321)
53. 21 and 52 (73)

The economics terms were based on the following costs filter:

Centre for Reviews and Dissemination. Search strategies: NHS EED EMBASE using OvidSP (economics filter). York: Centre for Reviews and Dissemination; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase (accessed 2 June 2014).

MEDLINE (via OvidSP)

Date range searched: 1946–2014/September week 4.

Date searched: 2 October 2014.

Search strategy

1. Diabetes Mellitus, Type 1/ (62,498)
2. Diabetic Ketoacidosis/ (5186)
3. (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ti,ab,ot,hw. (69,786)
4. (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ti,ab,ot,hw. (20,339)
5. ((insulin$ adj2 depend$) or insulindepend$).ti,ab,ot,hw. (30,496)
6. (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab,ot,hw. (13,154)
7. (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab,ot,hw. (9345)
8. Hyperglycemia/ (20,917)
9. Hypoglycemia/ (21,796)
10. (hyperglyc?em$ or hypoglyc?em$).ti,ab,ot. (72,929)
11. ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ti,ab,ot,hw. (95,034)

12. or/1-11 (246,558)
13. (sensor$ adj3 (augment$ or pump$)).ti,ab,hw,ot. (313)
14. SAPT.ti,ab,ot,hw. (93)
15. (minimed or paradigmveo).ti,ab,ot,hw. (198)
16. (paradigm$ adj3 (veo or pump$)).ti,ab,hw,ot. (34)
17. (veo adj3 pump$).ti,ab,ot,hw. (5)
18. ((animas or vibe) adj3 (pump$ or infus$ or system$)).ti,ab,ot,hw. (7)
19. (g4 adj3 platinum).ti,ab,ot,hw. (4)
20. dexcom.ti,ab,ot,hw. (45)
21. or/13-20 (648)
22. 12 and 21 (300)
23. economics/ (27,132)
24. exp "costs and cost analysis"/ (185,352)
25. economics, dental/ (1867)
26. exp "economics, hospital"/ (19,852)
27. economics, medical/ (8682)
28. economics, nursing/ (3987)
29. economics, pharmaceutical/ (2577)
30. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (434,246)
31. (expenditure$ not energy).ti,ab. (17,736)
32. (value adj1 money).ti,ab. (23)
33. budget$.ti,ab. (17,453)
34. or/23-33 (560,640)
35. ((energy or oxygen) adj cost).ti,ab. (2713)
36. (metabolic adj cost).ti,ab. (793)
37. ((energy or oxygen) adj expenditure).ti,ab. (16,876)
38. or/35-37 (19,659)
39. 34 not 38 (556,354)
40. letter.pt. (829,485)
41. editorial.pt. (348,438)
42. historical article.pt. (307,377)
43. or/40-42 (1,470,234)
44. 39 not 43 (527,602)
45. 22 and 44 (8)

The economics terms were based on the following costs filter:

Centre for Reviews and Dissemination. Search strategies: NHS EED MEDLINE using OvidSP (economics filter). York: Centre for Reviews and Dissemination; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline (accessed 2 June 2014).

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily Update (via OvidSP)

Date searched: 2 October 2014.

Search strategy

1. Diabetes Mellitus, Type 1/ (64)
2. Diabetic Ketoacidosis/ (5)
3. (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ti,ab,ot,hw. (2660)
4. (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ti,ab,ot,hw. (1112)

5. ((insulin$ adj2 depend$) or insulindepend$).ti,ab,ot,hw. (712)
6. (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab,ot,hw. (879)
7. (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab,ot,hw. (440)
8. Hyperglycemia/ (32)
9. Hypoglycemia/ (27)
10. (hyperglyc?em$ or hypoglyc?em$).ti,ab,ot. (5503)
11. ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ti,ab,ot,hw. (7549)
12. or/1-11 (15,088)
13. (sensor$ adj3 (augment$ or pump$)).ti,ab,hw,ot. (61)
14. SAPT.ti,ab,ot,hw. (86)
15. (minimed or paradigmveo).ti,ab,ot,hw. (12)
16. (paradigm$ adj3 (veo or pump$)).ti,ab,hw,ot. (4)
17. (veo adj3 pump$).ti,ab,ot,hw. (1)
18. ((animas or vibe) adj3 (pump$ or infus$ or system$)).ti,ab,ot,hw. (0)
19. (g4 adj3 platinum).ti,ab,ot,hw. (3)
20. dexcom.ti,ab,ot,hw. (7)
21. or/13-20 (167)
22. 12 and 21 (39)
23. economics/ (3)
24. exp "costs and cost analysis"/ (243)
25. economics, dental/ (0)
26. exp "economics, hospital"/ (22)
27. economics, medical/ (3)
28. economics, nursing/ (3)
29. economics, pharmaceutical/ (1)
30. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (52,040)
31. (expenditure$ not energy).ti,ab. (1513)
32. (value adj1 money).ti,ab. (5)
33. budget$.ti,ab. (2216)
34. or/23-33 (54,328)
35. ((energy or oxygen) adj cost).ti,ab. (303)
36. (metabolic adj cost).ti,ab. (83)
37. ((energy or oxygen) adj expenditure).ti,ab. (1206)
38. or/35-37 (1538)
39. 34 not 38 (53,879)
40. letter.pt. (30,601)
41. editorial.pt. (18,927)
42. historical article.pt. (188)
43. or/40-42 (49,699)
44. 39 not 43 (53,316)
45. 22 and 44 (3)

The economics terms were based on the following costs filter:

Centre for Reviews and Dissemination. Search strategies: NHS EED MEDLINE using OvidSP (economics filter). York: Centre for Reviews and Dissemination; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline (accessed 2 June 2014).

PubMed (via National Library of Medicine)

URL: www.ncbi.nlm.nih.gov/pubmed/

Date range searched: from inception up to 5 September 2014.

Date searched: 5 September 2014.

Search strategy

#42	**Search (#41 and #42)**	**0**
#41	Search (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])	18,267,75
#40	Search (#35 not #39)	501,673
#39	Search ((#36 or #37 or #38))	20,549
#38	Search "energy expenditure"[tiab] or "oxygen expenditure"[tiab]	17,441
#37	Search "metabolic cost"[tiab]	888
#36	Search "energy cost"[tiab] or "oxygen cost"[tiab]	2986
#35	Search ((#31 or #32 or #33 or #34))	506,382
#34	Search budget*[tiab]	19,827
#33	Search "value for money"	934
#32	Search (expenditure*[tiab] not energy[tiab])	19,227
#31	Search (economic*[tiab] or cost[tiab] or costs[tiab] or costly[tiab] or costing[tiab] or price[tiab] or prices [tiab] or pricing[tiab] or pharmacoeconomic*[tiab])	485,328
#30	Search (#20 and #29)	276
#29	Search (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28)	937
#28	Search "g4 platinum"	10
#27	Search dexcom	56
#26	Search (animas or vibe) AND (pump* or infus* or system*)	81
#25	Search "veo pump" or "veo pumps"	15
#24	Search ((paradigm* AND (veo or pump*)))	354
#23	Search minimed or paradigmveo	217
#22	Search SAPT[tiab]	187
#21	Search "sensor augmented"[tiab] or "sensor augment"[tiab] or "sensor pump"[tiab] or "pump sensor"[tiab] or "sensor pumps"[tiab]	92
#20	Search ((#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19))	127,385
#19	Search "high glycohemoglobin"[tiab] or "higher glycohemoglobin"[tiab] or "low glycohemoglobin"[tiab] or "lower glycohemoglobin"[tiab] or "increase glycohemoglobin"[tiab] or "increased glycohemoglobin"[tiab] or "increases glycohemoglobin"[tiab] or "decrease glycohemoglobin"[tiab] or "decreased glycohemoglobin"[tiab] or "decreases glycohemoglobin"[tiab] or "deficient glycohemoglobin"[tiab] or "sufficient glycohemoglobin"[tiab] or "insufficient glycohemoglobin"[tiab] or "reduce glycohemoglobin"[tiab] or "reduced glycohemoglobin"[tiab] or "glycohemoglobin reduction"[tiab] or "fallen glycohemoglobin"[tiab] or "falling glycohemoglobin"[tiab] or "glycohemoglobin threshold"[tiab] or "safe glycohemoglobin"[tiab]	17

#18	Search ("high haemoglobin"[tiab] or "higher haemoglobin"[tiab] or "low haemoglobin"[tiab] or "lower haemoglobin"[tiab] or "increase haemoglobin"[tiab] or "increased haemoglobin"[tiab] or "increases haemoglobin"[tiab] or "decrease haemoglobin"[tiab] or "decreased haemoglobin"[tiab] or "decreases haemoglobin"[tiab] or "deficient haemoglobin"[tiab] or "sufficient haemoglobin"[tiab] or "insufficient haemoglobin"[tiab] or "reduce haemoglobin"[tiab] or "reduced haemoglobin"[tiab] or "haemoglobin reduction"[tiab] or "fallen haemoglobin"[tiab] or "falling haemoglobin"[tiab] or "haemoglobin threshold"[tiab] or "safe haemoglobin"[tiab])	1167
#17	Search "high hemoglobin"[tiab] or "higher hemoglobin"[tiab] or "low hemoglobin"[tiab] or "lower hemoglobin"[tiab] or "increase hemoglobin"[tiab] or "increased hemoglobin"[tiab] or "increases hemoglobin"[tiab] or "decrease hemoglobin"[tiab] or "decreasedchemoglobin"[tiab] or "decreases hemoglobin"[tiab] or "deficient hemoglobin"[tiab] or "sufficient hemoglobin"[tiab] or "insufficient hemoglobin"[tiab] or "reduce hemoglobin"[tiab] or "reduced hemoglobin"[tiab] or "hemoglobin reduction"[tiab] or "fallen hemoglobin"[tiab] or "falling hemoglobin"[tiab] or "hemoglobin threshold"[tiab] or "safe hemoglobin"[tiab]	3497
#16	Search "high a1c"[tiab] or "higher a1c"[tiab] or "low a1c"[tiab] or "lower a1c"[tiab] or "increase a1c"[tiab] or "increased a1c"[tiab] or "increases a1c"[tiab] or "decrease a1c"[tiab] or "decreasedca1c"[tiab] or "decreases a1c"[tiab] or "deficient a1c"[tiab] or "sufficient a1c"[tiab] or "insufficient a1c"[tiab] or "reduce a1c"[tiab] or "reduced a1c"[tiab] or "a1c reduction"[tiab] or "fallen a1c"[tiab] or "falling a1c"[tiab] or "a1c threshold"[tiab] or "safe a1c"[tiab]	294
#15	Search ((((("high hba1"[tiab] or "higher hba1"[tiab] or "low hba1"[tiab] or "lower hba1"[tiab] or "increase hba1"[tiab] or "increased hba1"[tiab] or "increases hba1"[tiab] or "decrease hba1"[tiab] or "decreasedchba1"[tiab] or "decreases hba1"[tiab] or "deficient hba1"[tiab] or "sufficient hba1"[tiab] or "insufficient hba1"[tiab] or "reduce hba1"[tiab] or "reduced hba1"[tiab] or "hba1 reduction"[tiab] or "fallen hba1"[tiab] or "falling hba1"[tiab] or "hba1 threshold"[tiab] or "safe hba1"[tiab]))))	76
#14	Search "high hb a1"[tiab] or "higher hb a1"[tiab] or "low hb a1"[tiab] or "lower hb a1"[tiab] or "increase hb a1"[tiab] or "increased hb a1"[tiab] or "increases hb a1"[tiab] or "decrease hb a1"[tiab] or "decreasedchb a1"[tiab] or "decreases hb a1"[tiab] or "deficient hb a1"[tiab] or "sufficient hb a1"[tiab] or "insufficient hb a1"[tiab] or "reduce hb a1"[tiab] or "reduced hb a1"[tiab] or "hb a1 reduction"[tiab] or "fallen hb a1"[tiab] or "falling hb a1"[tiab] or "hb a1 threshold"[tiab] or "safe hb a1"[tiab]	0
#13	Search "high hba1c"[tiab] or "higher hba1c"[tiab] or "low hba1c"[tiab] or "lower hba1c"[tiab] or "increase hba1c"[tiab] or "increased hba1c"[tiab] or "increases hba1c"[tiab] or "decrease hba1c"[tiab] or "decreasedchba1c"[tiab] or "decreases hba1c"[tiab] or "deficient hba1c"[tiab] or "sufficient hba1c"[tiab] or "insufficient hba1c"[tiab] or "reduce hba1c"[tiab] or "reduced hba1c"[tiab] or "hba1c reduction"[tiab] or "fallen hba1c"[tiab] or "falling hba1c"[tiab] or "hba1c threshold"[tiab] or "safe hba1c"[tiab]	1287
#12	Search "high sugar"[tiab] or "higher sugar"[tiab] or "low sugar"[tiab] or "lower sugar"[tiab] or "increase sugar"[tiab] or "increased sugar"[tiab] or "increases sugar"[tiab] or "decrease sugar"[tiab] or "decreasedcsugar"[tiab] or "decreases sugar"[tiab] or "deficient sugar"[tiab] or "sufficient sugar"[tiab] or "insufficient sugar"[tiab] or "reduce sugar"[tiab] or "reduced sugar"[tiab] or "sugar reduction"[tiab] or "fallen sugar"[tiab] or "falling sugar"[tiab] or "sugar threshold"[tiab] or "safe sugar"[tiab]	1551
#11	Search ("high glucose"[tiab] or "higher glucose"[tiab] or "low glucose"[tiab] or "lower glucose"[tiab] or "increase glucose"[tiab] or "increased glucose"[tiab] or "increases glucose"[tiab] or "decrease glucose"[tiab] or "decreasedcglucose"[tiab] or "decreases glucose"[tiab] or "deficient glucose"[tiab] or "sufficient glucose"[tiab] or "insufficient glucose"[tiab] or "reduce glucose"[tiab] or "reduced glucose"[tiab] or "glucose reduction"[tiab] or "fallen glucose"[tiab] or "falling glucose"[tiab] or "glucose threshold"[tiab] or "safe glucose"[tiab])	16,743
#10	Search (hyperglycemia[tiab] or hypoglycaemia[tiab] or hyperglycemic[tiab] or hypoglycaemic[tiab])	44,476
#9	Search ketoacidosis[tiab] or acidoketosis[tiab] or "keto acidosis"[tiab] or ketoacidemia[tiab] or ketosis [tiab]	7314
#8	Search dm1[tiab] or "dm 1"[tiab] or t1dm[tiab] or "t1 dm"[tiab] or t1d[tiab] or iddm[tiab]	13,200
#7	Search "insulin dependent"[tiab] or insulindepend*[tiab]	27,576
#6	Search "brittle diabetic"[tiab] or "diabetic juvenile"[tiab] or "diabetic pediatric"[tiab] or "diabetic paediatric"[tiab] or "diabetic early"[tiab] or "diabetic labile"[tiab] or "diabetic acidosis"[tiab] or "diabetic sudden onset"[tiab]	348
#5	Search "diabetic brittle"[tiab] or "juvenile diabetic"[tiab] or "pediatric diabetic"[tiab] or "paediatric diabetic"[tiab] or "early diabetic"[tiab] or "labile diabetic"[tiab] or "acidosis diabetic"[tiab] or "sudden onset diabetic"[tiab]	1125

#4	Search "brittle diabetes"[tiab] or "diabetes juvenile"[tiab] or "diabetes pediatric"[tiab] or "diabetes paediatric"[tiab] or "diabetes early"[tiab] or "diabetes ketosis"[tiab] or "diabetes labile"[tiab] or "diabetes acidosis"[tiab] or "diabetes sudden onset"[tiab]	264
#3	Search "diabetes brittle"[tiab] or "juvenile diabetes"[tiab] or "pediatric diabetes"[tiab] or "paediatric diabetes"[tiab] or "early diabetes"[tiab] or "ketosis diabetes"[tiab] or "labile diabetes"[tiab] or "acidosis diabetes"[tiab] or "sudden onset diabetes"[tiab]	2243
#2	Search "diabetic type 1"[tiab] OR "type 1 diabetic"[tiab] OR "diabetic type i"[tiab] OR "type i diabetic"[tiab] OR "diabetic type1"[tiab] OR "type1 diabetic"[tiab] OR "diabetic typei"[tiab] OR "typei diabetic"[tiab]	6061
#1	Search ((((("diabetes type 1"[tiab] OR "type 1 diabetes"[tiab] OR "diabetes type i"[tiab] OR "type i diabetes"[tiab] OR "diabetes type1"[tiab] OR "type1 diabetes"[tiab] OR "diabetes typei"[tiab] OR "typei diabetes"[tiab]))))	29,036

The economics terms were based on the following costs filter:

Centre for Reviews and Dissemination. Search strategies: NHS EED MEDLINE using OvidSP (economics filter). York: Centre for Reviews and Dissemination; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline (accessed 2 June 2014).

American Economic Association's electronic bibliography EconLit (via EBSCOhost)

Date range searched: 1969–2014.

Date searched: 2 October 2014.

Search strategy

S4 S1 or S2 or S3 (0)

S3 TI (animas N3 pump* or animas N3 infus* or animas N3 system* or vibe N3 pump* or vibe N3 infus* or vibe N3 system* or g4 N3 platinum or dexcom) or AB (animas N3 pump* or animas N3 infus* or animas N3 system* or vibe N3 pump* or vibe N3 infus* or vibe N3 system* or g4 N3 platinum or dexcom) (0)

S2 TI (minimed or paradigmveo or paradigm* N3 veo or paradigm* N3 pump* or veo N3 pump*) or AB (minimed or paradigmveo or paradigm* N3 veo or paradigm* N3 pump* or veo N3 pump*) (0)

S1 TI (sensor* N3 augment* or sensor* N3 pump* or sensor-augment* or SAPT) or AB (sensor* N3 augment* or sensor* N3 pump* or sensor-augment* or SAPT) (0)

Cost-effectiveness Analysis Registry

URL: www.cearegistry.org

Date range searched: from inception up to 5 September 2014.

Date searched: 2 October 2014.

1 record retrieved.

Search strategy

sensor augmented

sensor-augmented

SAPT

minimed

paradigmveo

paradigm veo

paradigm-veo

veo pump

animas

vibe pump

vibe infusion

vibe system

vibe systems

g4 platinum

dexcom

RePEc:Research Papers in Economics

URL: http://repec.org/

Date range searched: from inception up to 2 October 2014.

Date searched: 2 October 2014.

IDEAS search interface.

Search strategy

("diabetes mellitus type 1" | "diabetes type 1" | "diabetes mellitus type1" | "diabetes type1" | "diabetes mellitus type I" | "diabetes type I" | "diabetes mellitus typeI" | "diabetes typeI" | "diabetes mellitus type one" | "diabetes type one" | dm1 | "dm 1" | dmt1 | "dm t1" | t1dm | "t1 dm" | t1d | iddm | ketoacidosis) + ("sensor augmented" | sensor-augmented | SAPT | minimed | paradigmveo | "paradigm veo" | "paradigm pump" | "veo pump" | animas | vibe | "g4 platinum" | dexcom)

Records retrieved: 0.

("brittle diabetes" | "juvenile diabetes" | "pediatric diabetes" | "paediatric diabetes" | "early diabetes" | "autoimmune diabetes" | "auto immune diabetes" | "sudden onset diabetes") + ("sensor augmented" | sensor-augmented | SAPT | minimed | paradigmveo | "paradigm veo" | "paradigm pump" | "veo pump" | animas | vibe | "g4 platinum" | dexcom)

Records retrieved: 0.

(hyperglycemia | hypoglycemia | hyperglycaemia | hypoglycaemia) + ("sensor augmented" | sensor-augmented | SAPT | minimed | paradigmveo | "paradigm veo" | "paradigm pump" | "veo pump" | animas | vibe | "g4 platinum" | dexcom)

Records retrieved: 0.

Records retrieved in total: 0.

Key:

| OR

+ AND

" " phrase search

Appendix 2 List of excluded studies with rationale

The following table lists the studies that were excluded at the full-paper screening stage of the review, along with the reasons for their exclusion.

TABLE 62 Summary of reasons for exclusion of excluded studies at full-paper screening stage

Reason for exclusion	Number of excluded studies
Population	8
Intervention	86
Outcomes	109
Study design	206
Systematic review/meta-analysis	36
Background	3
Duplicate	5
Not found	29
Total	**482**

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion

Excluded study	Reason for exclusion
Conference: 11th Annual Diabetes Technology Meeting San Francisco, CA, USA, 27–29 October 2011. *J Diabetes Sci Technol* 2012;**6**:453–A202	Study design
Conference: 4th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). London, UK, 16–19 February 2011. *Diabetes Technol Ther* 2011;**13**:S1–108	Study design
Abraham M, Davey R, Paramalingam N, Keenan B, Ambler G, Fairchild J, *et al.* Prevention of hypoglycaemia with predictive low glucose management system: comparison of hypoglyclaemia induction with exercise and subcutaneous bolus. *Diabetes Technol Ther* 2014;**16**:A43. Conference: 7th International Conference on Advanced Technologies and Treatments for Diabetes, (ATTD). Vienna, Austria, 5–8 February 2014	Study design
Conference: 7th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Vienna, Austria, 5–8 February 2014. *Diabetes Technol Ther* 2014;**16**:A1–162	Study design
ACTRN12607000198426. *The Australian Sensor-Augmented Pump Algorithm Study*. 2007. URL: www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12607000198426 (accessed 11 January 2016)	Study design
ACTRN12614000035628. *The Performance of an Artificial Pancreas at Home in People with Type 1 Diabetes*. 2014. URL: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12614000035628 (accessed 11 January 2016)	Study design
ACTRN12614000482662. *Closed Loop Insulin Delivery and Glucose Control for Type 1 Diabetes, Seven Days and Nights, Hospital to Home*. 2014. URL: www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=366247 (accessed 11 January 2016)	Study design
Agrawal P, Kannard B, Shin J, Huang S, Welsh JB, Kaufman FR. Improvement in glycemic parameters with use of the low glucose suspend feature of the veo insulin pump. Diabetes 2012;**61**:A229–30. Conference: 72nd Scientific Sessions of the American Diabetes Association. Philadelphia, PA, USA, 8–12 June 2012	Study design

continued

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Agrawal P, Welsh JB, Kannard B, Askari S, Yang Q, Kaufman FR. Usage and effectiveness of the low glucose suspend feature of the Medtronic Paradigm Veo insulin pump. *J Diabetes Sci Technol* 2011;**5**:1137–41	Outcomes
Agrawal P, Welsh JB, Kaufman FR. Use of the low glucose suspend (LGS) feature results in significant reduction in hypoglycemia in pediatric and adult patients with type 1 diabetes. *Pediatr Diabetes* 2012;**13**:116. Conference: 38th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Istanbul, Turkey, 10–13 October 2012	Study design
Alemzadeh R, Palma-Sisto P, Parton E, Holzum M, Kichler J. Insulin pump therapy attenuated glycemic instability without improving glycemic control in a one-year study of preschool children with type 1 diabetes. *Diabetes* 2006;**55**:A97. Paper presented at 66th Annual Meeting of the American Diabetes Association. Washington, DC, USA, 9–13 June 2006	Not found
Alemzadeh R, Palma-Sisto P, Parton EA, Holzum MK. Continuous subcutaneous insulin infusion and multiple dose of insulin regimen display similar patterns of blood glucose excursions in pediatric type 1 diabetes. *Diabetes Technol Ther* 2005;**7**:587–96	Study design
Allen TJ, Cao Z, Youssef S, Hulthen UL, Cooper ME. High-dose intravenous insulin infusion versus intensive insulin treatment in newly diagnosed IDDM. *Diabetes* 1997;**46**:1612–18	Population
Ambrosino JM, Weinzimer SA, Steffen AT, Ruedy K. Short-term psychosocial impact of sensor-augmented pump therapy within three months of diagnosis of type 1 diabetes. *Diabetes* 2012;**61**:A586. Conference: 72nd Scientific Sessions of the American Diabetes Association Philadelphia, PA, USA, 8–12 June 2012	Outcomes
Conference: 72nd Scientific Sessions of the American Diabetes Association Philadelphia, PA, USA, 8–12 June 2012. *Diabetes* 2012;**61**:A1–722	Study design
Arias P, Kerner W, Zier H, Navascues I, Pfeiffer EF. Incidence of hypoglycemic episodes in diabetic patients under continuous subcutaneous insulin infusion and intensified conventional insulin treatment: assessment by means of semiambulatory 24-hour continuous blood glucose monitoring. *Diabetes Care* 1985;**8**:134–40	Study design
Bailey TS, Weiss R, Bode BW, Garg S, Ahmann AJ, Welsh JB, *et al.* Hypoglycemia reduction and changes in A1C in the aspire in-home study. *Diabetes* 2014;**63**:A60. Conference: 74th Scientific Sessions of the American Diabetes Association San Francisco, CA, USA, 13–17 June 2014	Outcomes
Bak JF, Nielsen OH, Pedersen O, Beck-Nielsen H. Multiple insulin injections using a pen injector versus insulin pump treatment in young diabetic patients. *Diabetes Res* 1987;**6**:155–8	Outcomes
Bangstad HJ, Kofoed-Enevoldsen A, Dahl-Jorgensen K, Hanssen KF. Glomerular charge selectivity and the influence of improved blood glucose control in type 1 (insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia* 1992;**35**:1165–9	Population
Bangstad HJ, Osterby R, Dahl-Jorgensen K, Berg KJ, Hartmann A, Hanssen KF. Improvement of blood glucose control in IDDM patients retards the progression of morphological changes in early diabetic nephropathy. *Diabetologia* 1994;**37**:483–90	Study design
Barcelo-Rico F, Luis Diez J, Vehi J, Ampudia-Blasco FJ, Rossetti P, Bondia J. Evaluation of a local-model-based calibration algorithm for continuous glucose monitoring in subjects with type 1 diabetes. *J Diabetes Sci Technol* 2013;**7**:A5. Conference: 12th Annual Diabetes Technology Meeting. Bethesda, MD, USA, 8–10 November 2012	Study design
Battelino T, Conget I, Olsen B, Schutz-Fuhrmann I, Hommel E, Hoogma R, *et al.* The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 2012;**55**:3155–62	Outcomes
Battelino T, Conget I, Olsen B, Schutz-Fuhrmann I, Hommel E, Hoogma R, *et al.* The SWITCH study: continuous glucose monitoring in type 1 diabetes. *Pediatr Diabetes* 2011;**12**:30. Conference: 37th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Miami Beach, FL, USA, 19–22 October 2011	Outcomes
Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* 2011;**34**:795–800	Study design

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Beck RW, Raghinaru D, Wadwa RP, Chase HP, Maahs DM, Buckingham BA, In Home Closed Loop Study Group. Frequency of morning ketosis after overnight insulin suspension using an automated nocturnal predictive low glucose suspend system. *Diabetes Care* 2014;**37**:1224–9	Study design
Beck RW. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009;**32**:1378–83	Intervention
Bell PM, Hayes JR, Hadden DR. A comparison of continuous subcutaneous insulin infusion (CSII) and conventional therapy in insulin dependent diabetes mellitus (IDDM). *Ir J Med Sci* 1984;**153**:116	Intervention
Berg TJ, Nourooz-Zadeh J, Wolff SP, Tritschler HJ, Bangstad HJ, Hanssen KF. Hydroperoxides in plasma are reduced by intensified insulin treatment. A randomized controlled study of IDDM patients with microalbuminuria. *Diabetes Care* 1998;**21**:1295–300	Intervention
Bergenstal RM, Dupre J, Lawson PM, Rizza RA, Rubenstein AH. Observations on C-peptide and free insulin in the blood during continuous subcutaneous insulin infusion and conventional insulin therapy. *Diabetes* 1985;**34**(Suppl. 3):31–6	Intervention
Bergenstal RM, Lee SW, Welsh JB, Shin J, Kaufman FR. Prevention of hypoglycemia in the aspire in-home study. *Diabetes Technol Ther* 2014;**16**:A107. Conference: 7th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Vienna, Austria, 5–8 February 2014	Outcomes
Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, *et al.* Sensor-augmented pump therapy for A1C reduction (STAR 3) study: results from the 6-month continuation phase. *Diabetes Care* 2011;**34**:2403–5	Study design
Bergenstal RM. Sensor-augmented insulin-pump therapy in type 1 diabetes. REPLY. *N Engl J Med* 2010;**363**:2071	Study design
Berhe T, Innocenti M. Insulin pump therapy as a routine care for children with type 1 diabetes: improvement in glycemic control using insulin pump therapy with intermittent higher basal rate in adolescents with type 1 diabetes who have a previous history of poor glyaemic control (HbA_{1c} > 10%). *Diabetes* 2008;**57**:A748. Paper presented at 68th Annual Meeting of the American Diabetes Association. San Francisco, USA, 6–10 June 2008	Not found
Blair J, Gregory JW, Peak M. Insulin delivery by multiple daily injections or continuous subcutaneous insulin infusion in childhood: addressing the evidence gap. *Practical Diabetes* 2012;**29**:47–8	Study design
Blue Cross Blue Shield Association. Artificial pancreas device systems. *Technol Eval Cent Assess Program* 2014;**28**:122	Systematic review/meta-analysis
Bode B, Gross K, Rikalo N, Schwartz S, Wahl T, Page C, *et al.* Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: the guardian continuous monitoring system. *Diabetes Technol Ther* 2004;**6**:105–13	Study design
Bode B, Lee SW, Kaufman FR. Predictors of hypoglycemia during the run-in period of the aspire-2 study. *Diabetes Technol Ther* 2013;**15**:A35. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Paris, France, 27 February–2 March 2013	Outcomes
Bode B, Shelmet J, Gooch B, Hassman DR, Liang J, Smedegaard JK, *et al.* Patient perception and use of an insulin injector/glucose monitor combined device. *Diabetes Educ* 2004;**30**:301–9	Outcomes
Bode BW, Lee SW, Kaufman FR. Predictors of nocturnal hypoglycemia during the run-in period of the ASPIRE-2 study. *Diabetes* 2013;**62**:A252. Conference: 73rd Scientific Sessions of the American Diabetes Association. Chicago, IL USA, 21–25 June 2013	Outcomes
Bode BW, Steed RD, Davidson PC. Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. *Diabetes Care* 1996;**19**:324–7	Study design
Bode BW, Steed RD, Schleusener DS, Strange P. Switch to multiple daily injections with insulin glargine and insulin lispro from continuous subcutaneous insulin infusion with insulin lispro: a randomized, open-label study using a continuous glucose monitoring system. *Endocr Pract* 2005;**11**:157–64	Study design

continued

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Bolli GB, Capani F, Home PD, Kerr D, Thomas R, Torlone E, *et al.* Comparison of a multiple daily injection regimen with once-daily insulin glargine basal insulin and mealtime lispro, to continuous subcutaneous insulin infusion: a randomised, open, parallel study. *Diabetes* 2004;**53**:A107–8. Paper presented at 64th Annual Meeting of the American Diabetes Association. Orlando, USA, 4–8 June 2004	Intervention
Bonfanti R, Meschi F, Viscardi M, Rigamonti A, Biffi V, Frontino G, *et al.* Insulin pump therapy versus multiple injections in young children with diabetes: comparison of long-term efficacy. *Pediatr Diabetes* 2010;**11**:100. Conference: 36th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Buenos Aires, Argentina, 27–30 October 2010	Study design
Bonfanti R, Meschi F, Viscardi M, Rigamonti A, Biffi V, Frontino G, *et al.* Long-term efficacy of insulin pump therapy in young children with diabetes. *Diabetologia* 2010;**53**:S372. Conference: 46th Annual Meeting of the European Association for the Study of Diabetes (EASD). Stockholm, Sweden, 20–24 September 2010	Study design
Bonnemaison E, Hasselmann C, Dieckmann K, Perdereau S, Marques C, Faure N, *et al.* Observational study: continuous glucose monitoring in children under 7 years old. *Pediatr Diabetes* 2011;**12**:132. Conference: 37th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Miami Beach, FL, USA, 19–22 October 2011	Study design
Boston University, Massachusetts General Hospital, Juvenile Diabetes Research Foundation. *Closed-loop Glucose Control for Automated Management of Type 1 Diabetes*. NCT00811317 2010. URL: https://clinicaltrials.gov/ct2/show/NCT00811317 (accessed 12 November 2015)	Intervention
Botta RM, Sinagra D, Angelico MC, Bompiani GD. [Comparison of intensified traditional insulin therapy and micropump therapy in pregnant women with type 1 diabetes mellitus.] *Minerva Med* 1986;**77**:657–61	Not found
Bragd J, Adamson U, Lins PE, Von Dobeln A, Oskarsson P. Basal insulin substitution with glargine or CSII in adult type I diabetes patients: a randomized controlled trial. *Diabetes* 2009;**58**:A60–1. Paper presented at 69th Annual Meeting of the American Diabetes Association. New Orleans, USA, 5–9 June 2009	Not found
Bratina N. The switch study: the impact of continuous glucose monitoring on health care resource utilization. *Diabetes Technol Ther* 2013;**15**:A3. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Paris, France, 27 February 2013–2 March 2013	Outcomes
Brazg R, Garg S, Bailey T, Buckingham B, Slover R, Klonoff D, *et al*. Interim analysis of an in-clinic, randomized, crossover study to assess efficacy of the low glucose suspend feature of the Paradigm Veo system with hypoglycemic induction from exercise. *J Diabetes Sci Technol* 2012;**6**:A19. Conference: 11th Annual Diabetes Technology Meeting. San Francisco, CA, USA, 27–29 October 2011	Study design
Brazg RL, Bailey TS, Garg S, Buckingham BA, Slover RH, Klonoff DC, *et al*. The ASPIRE study: design and methods of an in-clinic crossover trial on the efficacy of automatic insulin pump suspension in exercise-induced hypoglycemia. *J Diabetes Sci Technol* 2011;**5**:1466–71	Study design
Brinchmann-Hansen O, Dahl-Jorgensen K, Hanssen KF, Sandvik L. The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps, and conventional insulin therapy. *Arch Ophthalmol* 1988;**106**:1242–6	Outcomes
Bruttomesso D, Bonomo M, Costa S, Dal Pos M, Di Cianni G, Pellicano F, *et al*. Type 1 diabetes control and pregnancy outcomes in women treated with continuous subcutaneous insulin infusion (CSII) or with insulin glargine and multiple daily injections of rapid-acting insulin analogues (glargine-MDI). *Diabetes Metab* 2011;**37**:426–31	Study design
Bruttomesso D, Crazzolara D, Maran A, Costa S, Dal Pos M, Girelli A, *et al*. In type 1 diabetic patients with good glycaemic control, blood glucose variability is lower during continuous subcutaneous insulin infusion than during multiple daily injections with insulin glargine. *Diabet Med* 2008;**25**:326–32	Intervention

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Buckingham B, Beck RW, Ruedy KJ, Cheng P, Kollman C, Weinzimer SA, *et al*. Effectiveness of early intensive therapy on beta-cell preservation in type 1 diabetes. *Diabetes Care* 2013;**36**:4030–5	Intervention
Buckingham B, Nakamura K, Benassi K, Realsen J, Liljenquist D, Chase P. Effectiveness and safety study of the prototype 4th generation seven day continuous glucose monitoring system in youth with type 1 diabetes mellitus. Paper presented at 47th Annual Meeting of the European Association for the Study of Diabetes (EASD). Lisbon, Portugal, 12–16 September 2011	Study design
Buckingham B, Ruedy K, Chase HP, Weinzimer S, DiMeglio L, Russell W, *et al*. Does intensive metabolic control at the onset of diabetes followed by one year of sensor augmented pump therapy improve C-peptide levels one year post diagnosis? *Diabetes Technol Ther* 2013;**15**:A137. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Paris, France, 27 February–2 March 2013	Study design
Buckingham BA, Cameron F, Calhoun P, Maahs DM, Wilson DM, Chase HP, *et al*. Outpatient safety assessment of an in-home predictive low-glucose suspend system with type 1 diabetes subjects at elevated risk of nocturnal hypoglycemia. *Diabetes Technol Ther* 2013;**15**:622–7	Study design
Buckingham BA, Cheng P, Beck RW, Kollman C, Ruedy K, Weinzimer SA, *et al*. Relationship of glycemic control and c-peptide levels 2 years following diagnosis of T1D. *Diabetes* 2014;**63**:A392. Conference: 74th Scientific Sessions of the American Diabetes Association San Francisco, CA, USA, 13–17 June 2014	Outcomes
Buckingham BA, Tanner JP. Factors predictive of continuous glucose monitoring (CGM) use and benefit in the JDRF CGM RCT. *Diabetes* 2009;**58**. Conference: 69th Annual Meeting of the American Diabetes Association. New Orleans, LA, USA, 5–9 June 2009	Study design
Bukara-Radujkovic G, Zdravkovic D, Lakic S. Short-term use of continuous glucose monitoring system adds to glycemic control in young type 1 diabetes mellitus patients in the long run: a clinical trial. *Vojnosanit Pregl* 2011;**68**:650–4	Study design
Burkart W, Hanker JP, Schneider HP. Complications and fetal outcome in diabetic pregnancy. Intensified conventional versus insulin pump therapy. *Gynecol Obstet Invest* 1988;**26**:104–12	Population
Buse JB, Kudva YC, Guthrie RA, Laffel L, Battelino T, Shin J, *et al*. Assessment of glycemic variability and CD40 ligand in the STAR 3 study. *Diabetes* 2011;**60**:A252. Conference: 71st Scientific Sessions of the American Diabetes Association. San Diego, CA, USA, 24–28 June 2011	Outcomes
Butcher B, Jones T. *Safety, Efficacy and Quality of Life Associated with Continuous Glucose Monitoring in People with Diabetes*. PROSPERO: CRD42014013270; 2014. URL: www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013270 (accessed 16 November 2015)	Systematic review/ meta-analysis
Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* 2012;**6**:CD007543	Study design
Cander S, Oz Gul O, Deligonul A, Un OK, Kiyici S, Tuncel E, *et al*. Weight gain in type 1 diabetic patients with insulin pump therapy. *Obesity Rev* 2011;**12**:214. Conference: 18th European Congress on Obesity (ECO). Istanbul, Turkey, 25–28 May 2011	Outcomes
Capel I, Rigla M, Garcia-Saez G, Rodriguez-Herrero A, Pons B, Subias D, *et al.* Artificial pancreas using a personalized rule-based controller achieves overnight normoglycemia in patients with type 1 diabetes. *Diabetes Technol Ther* 2014;**16**:172–9	Study design
Carta Q, Meriggi E, Trossarelli GF, Catella G, Dal Molin V, Menato G, *et al.* Continuous subcutaneous insulin infusion versus intensive conventional insulin therapy in type I and type II diabetic pregnancy. *Diabetes Metab* 1986;**12**:121–9	Not found
Centre d'Etudes et de Recherche pour l'Intensification du Traitement du D, Abbott. *Are the Continuous Glucose Monitoring Systems Able to Improve Long Term Glycaemic Control in Type 1 Diabetic Patients?* NCT00726440 2012. URL: https://clinicaltrials.gov/ct2/show/NCT00726440 (accessed 12 November 2015)	Outcomes
Chase HP, Beck R, Tamborlane W, Buckingham B, Mauras N, Tsalikian E, *et al.* A randomized multicenter trial comparing the GlucoWatch Biographer with standard glucose monitoring in children with type 1 diabetes. *Diabetes Care* 2005;**28**:1101–6	Study design

continued

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Chase HP, Beck RW, Xing D, Tamborlane WV, Coffey J, Fox LA, *et al.* Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the juvenile diabetes research foundation continuous glucose monitoring randomized trial. *Diabetes Technol Ther* 2010;**12**:507–15	Intervention
Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R, *et al*. Continuous subcutaneous glucose monitoring in children with type 1 diabetes. *Pediatrics* 2001;**107**:222–6	Intervention
Chase HP. A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. *Diabetes Technol Ther* 2014;**16**:A2. Conference: 7th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Vienna, Austria, 5–8 February 2014	Study design
Chatelais L, Voinot C, Robine A, Gatelais F, Dufresne S, Bouhours-Nouet N, *et al*. Continuous subcutaneous insulin infusion in type 1 diabetic adolescents with poor glycemic control under multiple daily injections: 1-year evaluation of HbA_{1c} and acceptability. *Horm Res* 2009;**72**:182. Paper presented at LWPES/ESPE 8th Joint Meeting Global Care in Pediatric Endocrinology in collaboration with APEG, APPES, JSPE and SLEP. New York, NY, USA, 9–12 September 2009	Study design
Chen R, Yogev Y, Weissman-Brenner A, Ben-Haroush A, Hod M. Level of glycemic control and pregnancy outcome in type-1 diabetes: a comparison between multiple daily injections (MDI) and continuous subcutaneous insulin infusions (CSII). *Diabetes* 2007;**56**:A703. Paper presented at 67th Annual Meeting of the American Diabetes Association. Chicago, USA, 22–26 June 2007	Not found
Chen R, Yogev Y, Weissman-Brenner A, Haroush AB, Hod M. Level of glycemic control and pregnancy outcome in type-1 diabetes: a comparison between multiple daily injections (MDI) and continuous subcutaneous insulin infusions (CSII). *Am J Obstet Gynecol* 2006;**195**:S132. Paper presented at 27th Annual Meeting of the Society of Maternal Fetal Medicine. San Francisco, USA, 5–10 February 2007	Study design
Chen Y, Ben-Haroush A, Weismann-Brenner A, Melamed N, Hod M, Yogev Y. Level of glycemic control and pregnancy outcome in type 1 diabetes: a comparison between multiple daily insulin injections and continuous subcutaneous insulin infusions. *Am J Obstet Gynecol* 2007;**197**:e1–5. [Erratum published in *Am J Obstet Gynecol* 2008;**198**:610]	Study design
Chevremont A, Collet-Gaudillat C, Duvezin-Caubet P, Franc S, Gouet D, Jan P, *et al.* [Insulin pump Paradigm Veo with automated insulin suspension function: results of a pilot study in type 1 diabetic patients at high hypoglycemic risk.] *Medecine des Maladies Metaboliques* 2012;**6**:531–8	Study design
Chiasson JL, Ducros F, Poliquin-Hamet M, Lopez D, Lecavalier L, Hamet P. Continuous subcutaneous insulin infusion (Mill-Hill Infuser) versus multiple injections (Medi-Jector) in the treatment of insulin-dependent diabetes mellitus and the effect of metabolic control on microangiopathy. *Diabetes Care* 1984;**7**:331–7	Study design
Chico A, Saigi I, Garcia-Patterson A, Santos MD, Adelantado JM, Ginovart G, *et al*. Glycemic control and perinatal outcomes of pregnancies complicated by type 1 diabetes: influence of continuous subcutaneous insulin infusion and lispro insulin. *Diabetes Technol Ther* 2010;**12**:937–45	Study design
Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. *Diabetes Care* 2003;**26**:1153–7	Population
Choudhary P, Shin J, Wang Y, Evans ML, Hammond PJ, Kerr D, *et al*. Insulin pump therapy with automated insulin suspension in response to hypoglycemia: reduction in nocturnal hypoglycemia in those at greatest risk. *Diabetes Care* 2011;**34**:2023–5	Study design
Christensen CK, Christiansen JS, Christensen T, Hermansen K, Mogensen CE. The effect of six months continuous subcutaneous insulin infusion on kidney function and size in insulin-dependent diabetics. *Diabet Med* 1986;**3**:29–32	Not found
Christensen CK, Christiansen JS, Schmitz A, Christensen T, Hermansen K, Mogensen CE. Effect of continuous subcutaneous insulin infusion on kidney function and size in IDDM patients: a 2 year controlled study. *J Diabet Complications* 1987;**1**:91–5	Intervention

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Christiansen JS, Ingerslev J, Bernvil SS, Christensen CK, Hermansen K, Schmitz A. Near normoglycemia for 1 year has no effect on platelet reactivity, factor VIII, and von Willebrand factor in insulin-dependent diabetes mellitus: a controlled trial. *J Diabet Complications* 1987;**1**:100–6	Intervention
Churchill JN, Ruppe RL, Smaldone A. Use of continuous insulin infusion pumps in young children with type 1 diabetes: a systematic review. *J Pediatr Health Care* 2009;**23**:173–9	Systematic review/ meta-analysis
Ciavarella A, Vannini P, Flammini M, Bacci L, Forlani G, Borgnino LC. Effect of long-term near-normoglycemia on the progression of diabetic nephropathy. *Diabetes Metab* 1985;**11**:3–8	Not found
Cinar A, Turksoy K, Quinn L, Littlejohn E. An integrated hypoglycemia early alarm and adaptive control system for artificial pancreas. *Diabetes Technol Ther* 2014;**16**:A103. Paper presented at 7th International Conference on Advanced Technologies & Treatments for Diabetes. Vienna, Austria, 5–8 February 2014	Study design
Clarke WL, Anderson S, Breton M, Patek S, Kashmer L, Kovatchev B. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: the Virginia experience. *J Diabetes Sci Technol* 2009;**3**:1031–8	Study design
Cobry E, Chase HP, Burdick P, McFann K, Yetzer H, Scrimgeour L. Use of CoZmonitor in youth with type 1 diabetes. *Pediatr Diabetes* 2008;**9**:148–51	Study design
Cohen D, Weintrob N, Benzaquen H, Galatzer A, Fayman G, Phillip M. Continuous subcutaneous insulin infusion versus multiple daily injections in adolescents with type I diabetes mellitus: a randomized open crossover trial. *J Pediatr Endocrinol* 2003;**16**:1047–50	Intervention
Cohen N, Minshall ME, Sharon-Nash L, Zakrzewska K, Valentine WJ, Palmer AJ. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin: economic comparison in adult and adolescent type 1 diabetes mellitus in Australia. *Pharmacoeconomics* 2007;**25**:881–97	Outcomes
Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. *Health Technol Assess* 2004;**8**(43)	Systematic review/ meta-analysis
Conget I, Battelino T, Gimenez M, Gough H, Castaneda J, Bolinder J, *et al.* The SWITCH study (sensing with insulin pump therapy to control HbA_{1c}): design and methods of a randomized controlled crossover trial on sensor-augmented insulin pump efficacy in type 1 diabetes suboptimally controlled with pump therapy. *Diabetes Technol Ther* 2011;**13**:49–54	Study design
Conget I, Battelino T, Gimenez M, Gough H, Castaneda J, Bolinder J. The SWITCH study (Sensing with insulin pump therapy to control HbA_{1c}). Design and methods of a randomized controlled cross-over trial on sensor-augmented insulin pump efficacy in type 1 diabetes suboptimally controlled with pump therapy. *Pediatr Diabetes* 2010;**11**:105. Conference: 36th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Buenos Aires, Argentina, 27–30 October 2010	Outcomes
Cooke D, Hurel SJ, Casbard A, Steed L, Walker S, Meredith S, *et al.* Randomized controlled trial to assess the impact of continuous glucose monitoring on HbA_{1c} in insulin-treated diabetes (MITRE Study). *Diabet Med* 2009;**26**:540–7	Study design
Corabian P, Guo B, Harstall C, Chuck A, Yan C. *Insulin Pump Therapy for Type 1 Diabetes*. Edmonton, AB: Institute of Health Economics, 2012	Systematic review/ meta-analysis
Cordua S, Secher AL, Ringholm L, Damm P, Mathiesen ER. Real-time continuous glucose monitoring during labour and delivery in women with type 1 diabetes – observations from a randomized controlled trial. *Diabet Med* 2013;**30**:1374–81	Intervention
Cosson E, Hamo Tchatchouang E, Dufaitre Patouraux L, Attali JR, Pariès J, Schaepelynck-Bélicar P. Multicentre, randomised, controlled study of the impact of continuous sub cutaneous glucose monitoring (GlucoDay) on glycaemic control in type 1 and type 2 diabetes patients. *Diabetes Metab* 2009;**35**:312–18	Study design
Coustan DR, Reece EA, Sherwin RS, Rudolf MC, Bates SE, Sockin SM, *et al.* A randomized clinical trial of the insulin pump vs intensive conventional therapy in diabetic pregnancies. *JAMA* 1986;**255**:631–6	Intervention

continued

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Crepaldi C, Nosadini R, Bruttomesso D, Fioretto P, Fedele D, Segato T, *et al.* The effect of continuous insulin infusion as compared with conventional insulin therapy in the evolution of diabetic retinal ischaemia. Two years report. *Diabetes Nutr Metab Clin Exp* 1989;**2**:209–18	Intervention
Cummins E, Royle P, Snaith A, Greene A, Robertson L, McIntyre L, *et al. Clinical and Cost-effectiveness of Continuous Subcutaneous Infusion for Diabetes: Updating Review. A Technology Assessment Report Commissioned by the HTA Programme on behalf of NICE*. HTA reference 06/61. London: NICE; 2007. URL: www.nice.org.uk/guidance/ta151/resources/diabetes-insulin-pump-therapy-assessment-report2 (accessed 8 July 2014)	Systematic review/ meta-analysis
Cummins E, Royle P, Snaith A, Greene A, Robertson L, McIntyre L, *et al.* Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technol Assess* 2010;**14**(11)	Systematic review/ meta-analysis
Cyganek K, Hebda-Szydło A, Katra B, Klupa T, Kaim I, Skupien J, *et al.* Efficacy and safety of continuous subcutaneous insulin infusion therapy in pregnancy complicated by type 1 diabetes. Paper presented at 45th Annual Meeting of the European Association for the Study of Diabetes (EASD). Vienna, Austria, 30 September–2 October 2009	Study design
Cyganek K, Hebda-Szydlo A, Katra B, Skupien J, Klupa T, Janas I, *et al.* Glycemic control and selected pregnancy outcomes in type 1 diabetes women on continuous subcutaneous insulin infusion and multiple daily injections: the significance of pregnancy planning. *Diabetes Technol Ther* 2010;**12**:41–7	Outcomes
Cyganek K, Hebda-Szydlo A, Katra B, Skupien J, Klupa T, Janas I, *et al.* Pregnancy planning improves glycemic control and pregnancy outcomes in type 1 diabetes women on CSII and MDI. *Eur J Clin Invest* 2010;**40**:8. Paper presented at 44th Annual Scientific Meeting of the European Society for Clinical Investigation. Bari, Italy, 24–27 February 2010	Study design
Cypryk K, Kosinski M, Kaminska P, Kozdraj T, Lewinski A. Diabetes control and pregnancy outcomes in women with type 1 diabetes treated during pregnancy with continuous subcutaneous insulin infusion or multiple daily insulin injections. *Pol Arch Med Wewn* 2008;**118**:339–44	Study design
Dahl-Jorgensen K, Hanssen KF, Aagenaes O, Larsen S. [New methods for subcutaneous insulin administration. A year's experience with the insulin pump and multiple insulin injection therapy.] *Tidsskr Nor Laegeforen* 1984;**104**:856–61	Not found
Dahl-Jorgensen K, Hanssen KF, Kierulf P, Bjoro T, Sandvik L, Aagenaes O. Reduction of urinary albumin excretion after 4 years of continuous subcutaneous insulin infusion in insulin-dependent diabetes mellitus. The Oslo Study. *Acta Endocrinol* 1988;**117**:19–25	Outcomes
Dahl-Jorgensen K. Blood glucose control and progression of diabetic neuropathy: eight years results from the Oslo study. *Diabetologia* 1992;**35**:A15. Paper presented at 28th Annual Meeting of the European Association for the Study of Diabetes (EASD). Prague, Czech Republic, 8–11 September 1992	Not found
Dahl-Jorgensen K. Near-normoglycemia and late diabetic complications. The Oslo Study. *Acta Endocrinol* 1987;**284**:1–38	Not found
Damiano ER, McKeon K, El-Khatib FH, Zheng H, Nathan DM, Russell SJ. A comparative effectiveness analysis of three continuous glucose monitors: the Navigator, G4 Platinum, and Enlite [published online ahead of print 21 April 2014]. *J Diabetes Sci Technol* 2014	Intervention
Danne T, Kordonouri O, Holder M, Haberland H, Golembowski S, Remus K, *et al.* [LGS system cuts hypoglycaemia excursion frequency in children on SAP therapy.] *Diabetes Stoffwechsel Herz* 2012;**21**:157–63	Study design
Danne T, Kordonouri O, Holder M, Haberland H, Golembowski S, Remus K, *et al.* Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy. *Diabetes Technol Ther* 2011;**13**:1129–34	Study design
Danne T, Kordonouri O, Remus K, Blasig S, Holder M, Wadien T, *et al.* The Low Glucose Suspend (LGS) function in sensor-augmented pump therapy prevents hypoglycaemia in children. *Diabetes* 2011;**60**:A41. Conference: 71st Scientific Sessions of the American Diabetes Association. San Diego, CA, USA, 24–28 June 2011	Study design

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Danne T, Kordonouri O, Remus K, Holder M, Wadien T, Haberland H, *et al.* Prevention of hypoglycaemia by using low glucose suspend (LGS) function in sensor-augmented pump therapy. *Diabetes Technol Ther* 2011;**13**:217. Conference: 4th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). London, UK, 16–19 February 2011	Study design
Danne T. Predictive low glucose management with sensor augmented CSII in response to exercise. *Diabetes Technol Ther* 2014;**16**:A2. Conference: 7th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Vienna, Austria, 5–8 February 2014	Study design
Daskalaki E, Norgaard K, Prountzou A, Zuger T, Diem P, Mougiakakou S. Alarm system for the early warning of hypo- and hyperglycemic events based on online adaptive models. *Diabetes Technol Ther* 2013;**15**:A77–8. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Paris, France, 27 February–2 March 2013	Study design
Dauber A, Corcia L, Safer J, Agus MSD, Einis S, Steil GM. Closed-loop insulin therapy improves glycemic control in children aged > 7 years. *Diabetes Technol Ther* 2014;**16**(Suppl. 1):23–4	Study design
Davies AG, Price DA, Houlton CA, Burn JL, Fielding BA, Postlethwaite RJ. Continuous subcutaneous insulin infusion in diabetes mellitus. A year's prospective trial. *Arch Dis Child* 1984;**59**:1027–33	Intervention
Davis EA, Siafarikas A, Ratnam N, Loveday J, Baker V, Marangou D, *et al.* The initiation of intensive pump therapy at diagnosis of type 1 diabetes mellitus in adolescents: a randomised trial. *Diabetes* 2007;**56**:A53. Paper presented at the 67th Annual Meeting of the American Diabetes Association. Chicago, IL, USA, 22–26 June 2007	Intervention
de Beaufort CE, Bruining GJ, Aarsen RS, den Boer NC, Grose WF. Does continuous subcutaneous insulin infusion (CSII) prolong the remission phase of insulin-dependent diabetic children? Preliminary findings of a randomized prospective study. *Neth J Med* 1985;**28**(Suppl. 1):53–4	Not found
de Beaufort CE, Houtzagers CM, Bruining GJ, Aarsen RS, den Boer NC, Grose WF, *et al.* Continuous subcutaneous insulin infusion (CSII) versus conventional injection therapy in newly diagnosed diabetic children: two-year follow-up of a randomized, prospective trial. *Diabet Med* 1989;**6**:766–71	Not found
De Bock MI, Dart J, George CE, Abraham M, Cooper M, Paramalingam N, *et al.* Performance of a predictive insulin pump suspension algorithm for prevention of overnight hypoglycaemia. *Diabetes* 2014;**63**:A240–1. Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA, USA, 13–17 June 2014	Study design
De Portu S, Castaneda J, Hommel E, Olsen BS, Battelino T, Conget I, *et al.* The switch study: the impact of continuous glucose monitoring on health care resource utilization. *Value Health* 2012;**15**:A357. Conference: ISPOR 15th Annual European Congress. Berlin, Germany, 3–7 November 2012	Outcomes
Deiss D, Bolinder J, Riveline JP, Battelino T, Bosi E, Tubiana-Rufi N, Kerr D, Phillip M. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care* 2006;**29**:2730–2	Intervention
Deiss D, Hartmann R, Schmidt J, Kordonouri O. Results of a randomized controlled cross-over trial on the effect of continuous subcutaneous glucose monitoring (CGMS) on glycemic control in children and adolescents with type 1 diabetes. *Exp Clin Endocrinol Diabetes* 2006;**114**:63–7	Intervention
DeLuca FC, Timoshin A, Bamji N, Ferraro G, Himel A, Noto J, *et al.* The effect of insulin pump therapy on the diabetes control of children and adolescents with IDDM-1. *Pediatr Res* 2004;**55**:136A. Paper presented at the Annual Meeting of the Pediatric Academic Societies, 4 May 2004, San Francisco, USA.	Study design
Derosa G, Maffioli P, D'Angelo A, Salvadeo SAT, Ferrari I, Fogari E, *et al.* Effects of insulin therapy with continuous subcutaneous insulin infusion (CSII) in diabetic patients: comparison with multi-daily insulin injections therapy (MDI). *Endocr J* 2009;**56**:571–8	Population
DeSalvo DJ, Keith-Hynes P, Peyser T, Place J, Caswell K, Wilson DM, *et al.* Remote glucose monitoring in cAMP setting reduces the risk of prolonged nocturnal hypoglycemia. *Diabetes Technol Ther* 2014;**16**:1–7	Study design

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TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
DeVries JH. Health-economic comparison of continuous subcutaneous insulin infusion with multiple daily injection for the treatment of type 1 diabetes in the UK (letter). *Diabet Med* 2006;**23**:709	Outcomes
DexCom Inc. *Effectiveness and Safety Study of the DexCom™ G4 Continuous Glucose Monitoring System in Children and Adolescents With Type 1 Diabetes Mellitus*. NCT01185496 2011. URL: https://clinicaltrials.gov/ct2/show/NCT01185496 (accessed 12 November 2015)	Outcomes
DexCom Inc. *Efficacy of Continuous Glucose Monitoring in Subjects With Type 1 Diabetes Mellitus on Multiple Daily Injections (MDI) or Continuous Subcutaneous Insulin Infusion (CSII) Therapy*. NCT01104142 2010. URL: https://clinicaltrials.gov/ct2/show/NCT01104142 (accessed 12 November 2015)	Study design
Diabetes Research in Children Network Study Group, Weinzimer S, Xing D, Tansey M, Fiallo-Scharer R, Mauras N, *et al.* Prolonged use of continuous glucose monitors in children with type 1 diabetes on continuous subcutaneous insulin infusion or intensive multiple-daily injection therapy. *Pediatr Diabetes* 2009;**10**:91–6	Study design
The Kroc Collaborative Study Group. Diabetic retinopathy after two years of intensified insulin treatment. Follow-up of the Kroc Collaborative Study. *JAMA* 1988;**260**:37–41	Intervention
DiMeglio LA, Pottorff TM, Boyd SR, France L, Fineberg N, Eugster EA. A randomized, controlled study of insulin pump therapy in diabetic preschoolers. *J Pediatr* 2004;**145**:380–4	Intervention
Edelmann E, Walter H, Biermann E, Schleicher E, Bachmann W, Mehnert H. Sustained normoglycemia and remission phase in newly diagnosed type I diabetic subjects. Comparison between continuous subcutaneous insulin infusion and conventional therapy during a one year follow-up. *Horm Metab Res* 1987;**19**:419–21	Intervention
Elleri D, Allen JM, Nodale M, Wilinska ME, Acerini CL, Dunger DB, *et al.* Suspended insulin infusion during overnight closed-loop glucose control in children and adolescents with type 1 diabetes. *Diabet Med* 2010;**27**:480–4	Study design
Ellery B, Mundy L, Hiller JE. *Closed-Loop Insulin Delivery System ('Artificial Pancreas') for Management of Hypoglycaemia in Type 1 Diabetics*. Adelaide, SA: Adelaide Health Technology Assessment on behalf of National Horizon Scanning Unit; 2010	Systematic review/ meta-analysis
Emelyanov A, Kuraeva T, Peterkova V. CSII with real time continuous glucose monitoring versus traditional CSII: the comparative results. *Pediatr Diabetes* 2009;**10**:101. Conference: 35th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Ljubljana, Slovenia, 2–5 September 2009	Study design
Emelyanov A, Kuraeva T, Peterkova V. CSII with real time continuous glucose monitoring vs. traditional CSII: two year comparative results. *Hormone Res Paediatr* 2010;**74**:57. Conference: 49th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE). Prague, Czech Republic, 22–25 September 2010	Study design
Enander R, Adolfsson P, Bergdahl T, Forsander G, Gundevall C, Karlsson AK, *et al.* Intensive subcutaneous insulin therapy and intravenous insulin infusion at onset of T1DM preserve beta-cell function equally well in children. *Diabetes* 2011;**60**:A336. Conference: 71st Scientific Sessions of the American Diabetes Association San Diego, CA, USA. 24–28 June 2011	Intervention
Enander R, Bergdahl T, Adolfsson P, Forsander G, Gundevall C, Karlsson AK, *et al.* Intensive subcutaneous insulin therapy and intravenous insulin infusion at onset of diabetes preserve beta-cell function equally well in children. *Pediatr Diabetes* 2011;**12**:69–70. Conference: 37th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes, ISPAD Miami Beach, FL, USA, 19–22 October 2011	Intervention
Erasmus Medical Center. *Comparison Between Insulin Pump Treatment and Multiple Daily Insulin Injections in Diabetic Type 1 Children*. NCT00462371 2007. URL: https://clinicaltrials.gov/ct2/show/NCT00462371 (accessed 12 November 2015)	Outcomes
Esvant A, Guilhem I, Jouve A, Leguerrier AM, Poirier JY. Real-time continuous monitoring in brittle diabetes: a 6-month observational study. *Diabetes Technol Ther* 2013;**15**:A61. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes, ATTD 2013 Paris, France 27 February–2 March 2013	Study design

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). *Randomized Trial to Assess Efficacy and Safety of Continuous Glucose Monitoring in Children 4-< 10 Years With T1DM*. NCT00760526 2014. URL: https://clinicaltrials.gov/ct2/show/NCT00760526 (accessed 12 November 2015)	Outcomes
Farrar D, Tuffnell DJ, West J. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. *Cochrane Database Syst Rev* 2007;**3**:CD005542	Systematic review/ meta-analysis
Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Clinical review: hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. *J Clin Endocrinol Metab* 2009;**94**:729–40	Systematic review/ meta-analysis
Feldt-Rasmussen B, Mathiesen ER, Jensen T, Lauritzen T, Deckert T. Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetic patients: an update of the Steno studies. *Diabetologia* 1991;**34**:164–70	Intervention
Fendler W, Baranowska AI, Mianowska B, Szadkowska A, Mlynarski W. Three-year comparison of subcutaneous insulin pump treatment with multi-daily injections on HbA_{1c}, its variability and hospital burden of children with type 1 diabetes. *Acta Diabetol* 2012;**49**:363–70	Intervention
Fiallo-Scharer R. Eight-point glucose testing versus the continuous glucose monitoring system in evaluation of glycemic control in type 1 diabetes. *J Clin Endocrinol Metab* 2005;**90**:3387–91	Intervention
Flores d'Arcais A, Morandi F, Beccaria L, Meschi F, Chiumello G. Metabolic control in newly diagnosed type 1 diabetic children. Effect of continuous subcutaneous infusion. *Horm Res* 1984;**19**:65–9	Intervention
Fortwaengler K, Rautenberg T, Caruso A. Short term health-economic outcomes of continuous subcutaneous insulin infusion (CSII) in type 1 diabetes: a cost comparison analysis. *Value Health* 2012;**15**:A350. Conference: ISPOR 15th Annual European Congress. Berlin, Germany, 3–7 November 2012	Outcomes
Fox L, Englert K, Mauras N. Effects of continuous subcutaneous insulin infusion (CSII) in adolescents with newly-diagnosed type 1 diabetes (T1D) on insulin resistance and s-cell function: a pilot study. *Diabetes* 2009;**58**:S1–700. Conference: 69th Annual Meeting of the American Diabetes Association. New Orleans, LA, USA, 5–9 June 2009	Intervention
Fox LA, Buckloh LM, Smith S, Wysocki T, Mauras N. A randomized trial of insulin pump therapy in toddlers and preschool age children with type 1 diabetes (DM1). *Pediatr Res* 2004;**55**:136A. Paper presented at the Annual Meeting of the Pediatric Academic Societies. San Francisco, USA, 4 May 2004	Intervention
Fox LA, Buckloh LM, Smith SD, Wysocki T, Mauras N. A randomized controlled trial of insulin pump therapy in young children with type 1 diabetes. *Diabetes Care* 2005;**28**:1277–81	Study design
Fox LA, Wilkinson K, Buckloh L, Wysocki T, Mauras N. A randomized trial of insulin pump therapy in preschool age children with type 1 diabetes mellitus: preliminary results. *Diabetes* 2002;**51**(Suppl. 2):A426. Paper presented at the 62nd Annual Meeting of the American Diabetes Association. San Francisco, CA, USA, 14–18 June 2002	Outcomes
Frandsen CSS, Kristensen PL, Beck-Nielsen H, Nørgaard K, Perrild H, Christiansen JS, *et al.* Patients with Type 1 Diabetes Treated with Insulin Pumps do not Experience a Reduced Risk of Severe Hypoglycaemia in a Real Life Setting. Paper presented at the 49th Annual Meeting of the European Association for the Study of Diabetes (EASD). Barcelona, Spain, 23–27 September 2013	Study design
Frias JP, Gottlieb PA, Mackenzie T, Chillara B, Ashley M, Garg SK. Better glycemic control and less severe hypoglycemia in pregnant women with type 1 diabetes treated with continuous subcutaneous insulin infusion. *Diabetes* 2002;**51**(Suppl. 2):A431. Paper presented at the 62nd Annual Meeting of the American Diabetes Association. San Francisco, CA, USA, 14–18 June 2002	Study design

continued

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Gane J, White B, Christie D, Viner R. Systematic review and meta-analysis of insulin pump therapy in children and adolescents with type 1 diabetes. *Arch Dis in Child* 2010;**95**:A94. Conference: Royal College of Paediatrics and Child Health Annual Conference (RCPCH). Coventry, UK, 20–22 April 2010	Systematic review/ meta-analysis
Garg S, Bode BW, Bergenstal R, Klonoff DC, Mao M, Weiss R, *et al.* Characteristics and predictors of nocturnal hypoglycemia in the run-in phase of the aspire in-home study. *Diabetes* 2014;**63**:A242. Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA, USA, 13–17 June 2014	Outcomes
Garg S, Brazg RL, Bailey TS, Buckingham BA, Klonoff DC, Shin J, *et al.* Automatic insulin pump suspension for induced hypoglycemia: the ASPIRE study. *Diabetes* 2012;**61**:A59. Conference: 72nd Scientific Sessions of the American Diabetes Association. Philadelphia, PA, USA, 8–12 June 2012	Study design
Garg S, Brazg RL, Bailey TS, Buckingham BA, Klonoff DC, Shin J, *et al.* The order effect of the in-clinic ASPIRE study: hypoglycemia begets hypoglycemia. *Diabetes* 2012;**61**:A58–9. Conference: 72nd Scientific Sessions of the American Diabetes Association. Philadelphia, PA, USA, 8–12 June 2012	Study design
Garg S, Brazg RL, Bailey TS, Buckingham BA, Slover RH, Klonoff DC, *et al.* Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study. *Diabetes Technol Ther* 2012;**14**:205–9	Outcomes
Garg S, Brazg RL, Bailey TS, Buckingham BA, Slover RH, Klonoff DC, *et al.* Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study. *Diabetes Technol Ther* 2013;**15**(Suppl. 1):17–18	Study design
Garg S, Ellis SL, Beatson C, Gottlieb P, Gutin R, Bookout T, *et al.* Improved glycaemic control in intensively treated subjects with type 1 diabetes using Accu-Chek* advisor insulin guidance software. *Diabetologia* 2007;**50**(Suppl. 1):116–17. Paper presented at the 43rd Annual Meeting of the European Association for the Study of Diabetes (EASD). Amsterdam, the Netherlands, 18–21 September 2007	Intervention
Garg SK, Brazg RL, Bailey TS, Buckingham BA, Klonoff DC, Shin J, *et al.* Reduction of hypoglycaemia with insulin pump suspension and role of antecedent hypoglycaemia on future hypoglycaemic inductions: ASPIRE study. *Diabetologia* 2012;**55**:S258–9. Conference: 48th Annual Meeting of the European Association for the Study of Diabetes (EASD). Berlin, Germany, 1–5 October 2012	Study design
Garg SK, Brazg RL, Bailey TS, Buckingham BA, Slover RH, Klonoff DC, *et al.* Hypoglycemia begets hypoglycemia: the order effect in the ASPIRE in-clinic study. *Diabetes Technol Ther* 2014;**16**:125–30	Study design
Garg SK, Crew LB, Moser EG, Voelmle MK, Beatson CR. Effect of continuous glucose monitoring on glycemic control in subjects with type 1 diabetes (T1D) delivering insulin via pump or multiple daily injections (MDI): a prospective study. *Diabetes* 2010;**59**:A33–4. Paper presented at the 70th Annual Meeting of the American Diabetes Association. Orlando, USA, 25–29 June 2010	Study design
Garg SK, Voelmle MK, Beatson CR, Miller HA, Crew LB, Freson BJ, *et al.* Use of continuous glucose monitoring in subjects with type 1 diabetes on multiple daily injections versus continuous subcutaneous insulin infusion therapy: a prospective 6-month study. *Diabetes Care* 2011;**34**:574–9	Study design
Garg SK, Weiss R, Shah A, Mao M, Kaufman FR. Change in A1c and reduction in hypoglycemia with threshold suspend in the aspire in-home study. *Diabetes Technol Ther* 2014;**16**:A107. Conference: 7th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Vienna, Austria, 5–8 February 2014	Outcomes
Giacomet AC. [Efficacy of the monitoring of the glycemias and insulin pump in the control of diabetes mellitus type I.] *Rev AMRIGS* 1984;**28**:303–9	Not found
Gimenez M, Conget I, Nicolau J, Pericot A, Levy I. Outcome of pregnancy in women with type 1 diabetes intensively treated with continuous subcutaneous insulin infusion or conventional therapy. A case–control study. *Acta Diabetol* 2007;**44**:34–7	Study design
Goicolea I, Hernández I, Fombellida J, Vázquez JA. Evolution of GFR and other renal function parameters in insulin-dependent diabetic patients treated with subcutaneous insulin infusion. Comparison against an optimized standard therapy: 1 year follow-up effects. *An Med Internal* 1988;**5**:169–72	Not found

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Goicolea Opacua I, Hernandez Colau I, Vazquez Garcia JA. [Comparative study between the subcutaneous continuous insulin infusion pump and optimized conventional treatment. Effects at 6 months.] *Rev Clin Esp* 1986;**179**:3–7	Intervention
Golden SH, Brown T, Yeh HC, Maruthur N, Ranasinghe P, Berger Z, *et al. Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2012. Report No: 12-EHC036-EF. URL: www.ncbi.nlm.nih.gov/books/NBK99217/ (accessed 16 November 2015)	Systematic review/ meta-analysis
Gomez A, Alfonso-Cristancho R, Prieto-Salamanca D, Valencia JE, Lynch P, Roze S. Health economic benefits of sensor augmented insulin pump therapy in Colombia. *Value Health* 2013;**16**:A690. Conference: ISPOR 4th Latin America Conference. Buenos Aires, Argentina, 12–14 September 2013	Outcomes
Gonzalez-Romero S, Gonzalez-Molero I, Fernandez-Abellan M, Dominguez-Lopez ME, Ruiz-de-Adana S, Olveira G, *et al.* Continuous subcutaneous insulin infusion versus multiple daily injections in pregnant women with type 1 diabetes. *Diabetes Technol Ther* 2010;**12**:263–9	Study design
Gottlieb PA, Crew LB, Moser EG, Voelmle MK, Beatson CR, Gutin RS, *et al.* Effects of continuous glucose monitoring on glycaemic control in subjects with type 1 diabetes delivering insulin via pump or multiple daily injections: a prospective study. *Diabetologia* 2010;**53**:S25. Conference: 46th Annual Meeting of the European Association for the Study of Diabetes (EASD). Stockholm, Sweden, 20–24 September 2010	Study design
Gough H, Castaneda J, Hommel E, Olsen BS, Battelino T, Conget I, *et al.* The switch study: the impact of continuous glucose monitoring on quality of life and treatment satisfaction. *Value Health* 2012;**15**:A359. Conference: ISPOR 15th Annual European Congress. Berlin, Germany, 3–7 November 2012	Outcomes
Greene SA, Smith MA, Baum JD. Clinical application of insulin pumps in the management of insulin dependent diabetes. *Arch Dis Child* 1983;**58**:578–81	Study design
Guerci B, Meyer L, Delbachian I, Kolopp M, Ziegler O, Drouin P. Blood glucose control on Sunday in IDDM patients: intensified conventional insulin therapy versus continuous subcutaneous insulin infusion. *Diabetes Res Clin Pract* 1998;**40**:175–80	Outcomes
Guilmin-Crepon S, Scornet E, Couque N, Sulmont V, Salmon AS, Le Tallec C, *et al.* Could clinical parameters at initiation of continuous glucose monitoring (CGM) predict efficacy on HbA_{1c} in type 1 diabetes (T1D) pediatric patients at 3 months? Preliminary results in a prospective study of 141 patients (Start-In!). *Pediatr Diabetes* 2012;**13**:117. Conference: 38th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Istanbul, Turkey, 10–13 October 2012	Study design
Haakens K, Hanssen KF, Dahl-Jorgensen K, Vaaler S, Aagenaes O, Mosand R. Continuous subcutaneous insulin infusion (CSII), multiple injections (MI) and conventional insulin therapy (CT) in self-selecting insulin-dependent diabetic patients. A comparison of metabolic control, acute complications and patient preferences. *J Intern Med* 1990;**228**:457–64	Study design
Haardt MJ, Selam JL, Slama G, Bethoux JP, Dorange C, Mace B, *et al.* A cost–benefit comparison of intensive diabetes management with implantable pumps versus multiple subcutaneous injections in patients with type I diabetes. *Diabetes Care* 1994;**17**:847–51	Study design
Haidar A, Legault L, Dallaire M, Alkhateeb A, Coriati A, Messier V, *et al.* Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial. *CMAJ* 2013;**185**:297–305	Study design
Halvorson M, Carpenter S, Kaiserman K, Kaufman FR. A pilot trial in pediatrics with the sensor-augmented pump: combining real-time continuous glucose monitoring with the insulin pump. *J Pediatr* 2007;**150**:103–5	Study design
Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. The Study Group for the Development of Pump Therapy in Diabetes. *Diabetes Care* 2000;**23**:1232–5	Outcomes

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TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Hanas R, Lindholm Olinder A, Olsson PO, Johansson UB, Jacobson S, Heintz E, *et al.* CSII and SAP valuable tools in the treatment of diabetes; a Swedish health technology assesment. *Diabetes Technol Ther* 2014;**16**:A56. Conference: 7th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Vienna, Austria, 5–8 February 2014	Systematic review/ meta-analysis
Hanssen KF, Dahl-Jorgensen K, Brinchmann-Hansen O. The influence of strict control on diabetic complications. *Acta Endocrinol* 1985;**272**(Suppl.):57–60	Not found
Haugstvedt A, Wentzel-Larsen T, Graue M, Sovik O, Rokne B. Fear of hypoglycaemia in mothers and fathers of children with type 1 diabetes is associated with poor glycaemic control and parental emotional distress: a population-based study. *Diabet Med* 2010;**27**:72–8	Study design
Hayes Inc. *MiniMed paradigm REAL-Time Closed-Loop Continuous Insulin Infusion and Blood Glucose Monitoring System (Medtronic MiniMed Inc.)*. Hayes, Inc; 2010. URL: www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=32010000975 (accessed 2 February 2015)	Systematic review/ meta-analysis
Health Quality Ontario. Continuous glucose monitoring for patients with diabetes: an evidence-based analysis. *Ont Health Technol Assess Ser* 2011;**11**:1–29	Systematic review/ meta-analysis
Health Quality Ontario. Continuous subcutaneous insulin infusion (CSII) pumps for type 1 and type 2 adult diabetic populations: an evidence-based analysis. *Ont Health Technol Assess Ser* 2009;**9**:1–58	Systematic review/ meta-analysis
Helve E, Koivisto VA, Lehtonen A, Pelkonen R, Huttunen JK, Nikkila EA. A crossover comparison of continuous insulin infusion and conventional injection treatment of type I diabetes. *Acta Med Scand* 1987;**221**:385–93	Intervention
Helve E, Laatikainen L, Merenmies L, Koivisto VA. Continuous insulin infusion therapy and retinopathy in patients with type I diabetes. *Acta Endocrinol* 1987;**115**:313–19	Not found
Hermanides J, DeVries JH. Sensor-augmented insulin pump more effective than multiple daily insulin injections for reducing HbA_{1c} in people with poorly controlled type 1 diabetes. *Evid Based Med* 2011;**16**:46–8	Study design
Hermanides J, Norgaard K, Bruttomesso D, Mathieu C, Frid A, Dayan CM, *et al.* Sensor augmented pump therapy substantially lowers HbA_{1c}; a randomized controlled trial. *Diabetologia* 2009;**52**:S43. Conference: 45th EASD Annual Meeting of the European Association for the Study of Diabetes. Vienna, Austria, 30 September–2 October 2009	Study design
Hermanns N, Kulzer B, Gulde C, Eberle H, Pradler E, Patzelt-Bath A, *et al.* Short-term effects on patient satisfaction of continuous glucose monitoring with the glucoday with real-time and retrospective access to glucose values: a crossover study. *Diabetes Technol Ther* 2009;**11**:275–81	Study design
Hermansen K, Moller A, Christensen CK, Christiansen JS, Schmitz O, Orskov H, *et al.* Diurnal plasma profiles of metabolite and hormone concentration in insulin-dependent diabetic patients during conventional insulin treatment and continuous subcutaneous insulin infusion. A controlled study. *Acta Endocrinol* 1987;**114**:433–9	Not found
Hermansen K, Schmitz O, Boye N, Christensen CK, Christiansen JS, Alberti KG, *et al.* Glucagon responses to intravenous arginine and oral glucose in insulin-dependent diabetic patients during six months conventional or continuous subcutaneous insulin infusion. *Metabolism* 1988;**37**:640–4	Intervention
Hiéronimus S, Cupelli C, Bongain A, Durand-Réville M, Berthier F, Fénichel P. [Pregnancy in type 1 diabetes: insulin pump versus intensified conventional therapy.] *Gynecol Obstet Fertil* 2005;**33**:389–94	Study design
Hirsch IB, Bode BW, Garg S, Lane WS, Sussman A, Hu P, *et al.* Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. *Diabetes Care* 2005;**28**:533–8	Study design
Hoeks L, Greven WL, de Valk HW. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. *Diabet Med* 2011;**28**:386–94	Systematic review/ meta-analysis
Hoffmann-La R. *A Study Comparing Continuous Subcutaneous Insulin Infusion With Multiple Daily Injections With Insulin Lispro and Glargine*. NCT00468754; 2014. URL: https://clinicaltrials.gov/ct2/show/NCT00468754 (accessed 12 November 2015)	Outcomes

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Hoffmann-La R. *European, Open-label, Prospective, Multinational, Multicenter Study in Adult Subjects With Type 1 or Type 2 Diabetes Previously on MDI or CSII Therapy. Subjects Home Setting is Considered Routine Practice*. NCT02105103; 2014. URL: https://clinicaltrials.gov/ct2/show/NCT02105103 (accessed 12 November 2015)	Study design
Holder M, Kordonouri O, Haberland H, Golembowski S, Zierow S, Remus K, *et al.* The low glucose suspend function in sensor-augmented pump therapy prevents hypoglycaemia in children. *Diabetologia* 2011;**54**:S400. Conference: 47th Annual Meeting of the European Association for the Study of Diabetes (EASD). Lisbon, Portugal, 12–16 September 2011	Study design
Hollander AS, White NH. Continuous subcutaneous insulin infusion (CSII) reduces severe hypoglycemia (SH) in children with type 1 diabetes mellitus (T1DM) without compromising overall glycemic control. *Pediatr Res* 2000;**47**:132A. Paper presented at the Pediatric Academic Societies and the American Academy of Pediatrics joint meeting. Boston, USA, 12–16 May 2000	Study design
Home PD, Capaldo B, Burrin JM, Worth R, Alberti KG. A crossover comparison of continuous subcutaneous insulin infusion (CSII) against multiple insulin injections in insulin-dependent diabetic subjects: improved control with CSII. *Diabetes Care* 1982;**5**:466–71	Study design
Hommel E, Olsen B, Battelino T, Conget I, Schutz-Fuhrmann I, Hoogma R, *et al.* Impact of continuous glucose monitoring on quality of life, treatment satisfaction, and use of medical care resources: analyses from the SWITCH study. *Acta Diabetol* 2014;**51**:845–51	Outcomes
Hoogma R, Hoekstra JB, Michels BP, Levi M. Comparison between multiple daily insulin injection therapy (MDI) and continuous subcutaneous insulin infusion therapy (CSII), results of the five nations study. *Diabetes Res Clin Pract* 2006;**74**:S144–7. Paper presented at International Symposium on New Technologies for Insulin Replacement. Assisi, Italy, 28 April–1 May 2005	Study design
Hoogma R, Spijker AJM, van Doorn-Scheele M, van Doorn TT, Michels RPJ, van Doorn RG, *et al.* Quality of life and metabolic control in patients with diabetes mellitus type I treated by continuous subcutaneous insulin infusion or multiple daily insulin injections. *Neth J Med* 2004;**62**:383–7	Study design
Hoogma RP, Hammond PJ, Gomis R, Kerr D, Bruttomesso D, Bouter KP, *et al.* Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. *Diabet Med* 2006;**23**:141–7	Intervention
Hovorka R, Allen JM, Elleri D, Chassin LJ, Harris J, Xing D, *et al.* Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet* 2010;**375**:743–51	Study design
Hovorka R, Elleri D, Thabit H, Allen JM, Leelarathna L, El-Khairi R, *et al.* Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. *Diabetes Care* 2014;**37**:1204–11	Study design
Huang ES, O'Grady M, Basu A, Winn A, John P, Lee J, *et al.* The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. *Diabetes Care* 2010;**33**:1269–74	Outcomes
Husted SE, Nielsen HK, Bak JF, Beck-Nielsen H. Antithrombin III activity, von Willebrand factor antigen and platelet function in young diabetic patients treated with multiple insulin injections versus insulin pump treatment. *Eur J Clin Invest* 1989;**19**:90–4	Outcomes
Ignatova N, Arbatskaya N, Melnikova E. Continuous subcutaneous insulin infusion (CSII) reduces the rate of hypoglycaemic episodes throughout pregnancy. *Diabetologia* 2007;**50**(Suppl. 1):383–4	Outcomes
In Home Closed Loop Study Group. *Outpatient Reduction of Nocturnal Hypoglycemia by Using Predictive Algorithms and Pump Suspension in Children*. NCT01823341; 2014. URL: https://clinicaltrials.gov/ct2/show/NCT01823341 (accessed 12 November 2015)	Study design
In Home Closed Loop Study Group. *An Outpatient Pump Shutoff Pilot Feasibility and Safety Study*. NCT01736930; 2014. URL: https://clinicaltrials.gov/ct2/show/NCT01736930 (accessed 12 November 2015)	Study design
In Home Closed Loop Study Group. *Outpatient Pump Shutoff Pilot Feasibility and Efficacy Study*. NCT01591681; 2014. URL: https://clinicaltrials.gov/ct2/show/NCT01591681 (accessed 12 November 2015)	Study design

continued

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Indiana University, Juvenile Diabetes Research Foundation. *Prospective Study of the Impact of Insulin Pump Therapy in Young Children With Type 1 Diabetes*. NCT00727220; 2012. URL: https://clinicaltrials.gov/ct2/show/NCT00727220 (accessed 12 November 2015)	Study design
ISRCTN01687353. *Standardized Procedure for the Assessment of New-to-Market Continuous Glucose Monitoring Systems*. 2012. URL: www.controlled-trials.com/ISRCTN01687353 (accessed 11 January 2016)	Study design
ISRCTN05450731. *Paediatric Onset Study to Assess the Efficacy of Insulin Pump Therapy using the MiniMed Paradigm® REAL-Time System during the First Year of Diabetes in Children and Adolescents with Type 1 Diabetes*. 2008. URL: www.controlled-trials.com/ISRCTN05450731 (accessed 11 January 2016)	Study design
ISRCTN28387915. *Utility of Continuous Glucose Monitoring (CGMS) in Children with Type 1 Diabetes on Intensive Treatment Regimens*. URL: www.controlled-trials.com/ISRCTN28387915 (accessed 11 January 2016)	Outcomes
ISRCTN33678610. *A Randomised Controlled Trial (RCT) to Compare Minimally Invasive Glucose Monitoring Devices to Conventional Monitoring in the Management of Insulin Treated Diabetes Mellitus.* URL: www.controlled-trials.com/ISRCTN33678610 (accessed 11 January 2016)	Study design
ISRCTN33678610. *A Randomised Controlled Trial (RCT) to Compare Minimally Invasive Glucose Monitoring Devices to Conventional Monitoring in the Management of Insulin Treated Diabetes Mellitus.* 2003. URL: www.controlled-trials.com/ISRCTN33678610 (accessed 11 January 2016)	Intervention
ISRCTN37153662. *Comparison Between Continuous Subcutaneous Insulin Infusion with Multiple Basal Lispro Infusion Rates and Multiple Daily Insulin Injection with Lispro And Glargine*. 2007. URL: www.controlled-trials.com/ISRCTN37153662 (accessed 11 January 2016)	Intervention
ISRCTN52164803. *Prevention of Recurrent Severe Hypoglycaemia: Optimised Multiple Daily Insulin Injection (MDI) versus Continuous Subcutaneous Insulin Infusion (CSII) with or without Adjunctive Real-Time Continuous Glucose Monitoring*. 2009. URL: www.controlled-trials.com/ISRCTN52164803 (accessed 11 January 2016)	Outcomes
ISRCTN62034905. *Comparison of Two Artificial Pancreas Systems for Closed Loop Blood Glucose Control Versus Open Loop Control in Patients with Type 1 Diabetes*. 2011. URL: www.controlled-trials.com/ISRCTN62034905 (accessed 11 January 2016)	Study design
ISRCTN64351161. *Comparison in Metabolic Control and Treatment Satisfaction with Continuous Subcutaneous Insulin Infusion and Multiple Daily Injections in Children at Onset of Type 1 Diabetes Mellitus.* 2007. URL: www.controlled-trials.com/ISRCTN64351161 (accessed 11 January 2016)	Outcomes
ISRCTN77773974. *A Randomised Study of Continuous Subcutaneous Insulin Infusion (CSII) Therapy Compared to Conventional Bolus Insulin Treatment in Preschool Aged Children with Type 1 Diabetes*. URL: www.controlled-trials.com/ISRCTN77773974 (accessed 11 January 2016)	Outcomes
Jakisch BI, Wagner VM, Heidtmann B, Lepler R, Holterhus PM, Kapellen TM, *et al.* Comparison of continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) in paediatric type 1 diabetes: a multicentre matched-pair cohort analysis over 3 years. *Diabet Med* 2008;**25**:80–5	Study design
JDRF Artificial Pancreas Project. *Randomized Study of Real-Time Continuous Glucose Monitors (RT-CGM) in the Management of Type 1 Diabetes.* NCT00406133; 2010. URL: https://clinicaltrials.gov/ct2/show/NCT00406133 (accessed 12 November 2015)	Outcomes
Jeha GS, Karaviti LP, Anderson B, Smith EOB, Donaldson S, McGirk TS, *et al.* Insulin pump therapy in preschool children with type 1 diabetes mellitus improves glycemic control and decreases glucose excursions and the risk of hypoglycemia. *Diabetes Technol Ther* 2005;**7**:876–84	Study design
Jeitler K, Horvath K, Berghold A, Gratzer TW, Neeser K, Pieber TR, *et al.* Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia* 2008;**51**:941–51	Systematic review/ meta-analysis
Jenkins AJ, Krishnamurthy B, Best JD, Cameron FJ, Colman PG, Hamblin PS, *et al.* An algorithm guiding patient responses to real-time-continuous glucose monitoring improves quality of life. *Diabetes Technol Ther* 2011;**13**:105–9	Intervention

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Jennings AM, Lewis KS, Murdoch S, Talbot JF, Bradley C, Ward JD. Randomized trial comparing continuous subcutaneous insulin infusion and conventional insulin therapy in type II diabetic patients poorly controlled with sulfonylureas. *Diabetes Care* 1991;**14**:738–44	Population
Jiang L, Jiang S, Ma Y, Zhang M, Feng X. *Real-time Continuous Glucose Monitoring vs. Conventional Glucose Monitoring in Critically Ill Patients*. PROSPERO: CRD42014013488; 2014. URL: www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013488 (accessed 16 November 2015)	Systematic review/ meta-analysis
Jimenez M, Hernaez R, Conget I, Alonso A, Yago G, Pericot A, *et al.* Metabolic control, maternal and perinatal outcomes in type 1 diabetic pregnancies intensively treated with conventional insulin therapy vs. continuous subcutaneous insulin infusion. *Diabetologia* 2005;**48**(Suppl. 1):A315. Paper presented at 41st Annual Meeting of the European Association for the Study of Diabetes (EASD). Athens, Greece, 10–15 September 2005	Study design
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Group, Beck RW, Lawrence JM, Laffel L, Wysocki T, Xing D, *et al.* Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial. *Diabetes Care* 2010;**33**:2175–7	Intervention
Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, *et al.* Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;**359**:1464–76	Intervention
Kamble S, Perry BM, Shafiroff J, Schulman KA, Reed SD. The cost-effectiveness of initiating sensor-augmented pump therapy versus multiple daily injections of insulin in adults with type 1 diabetes: evaluating a technology in evolution. *Value Health* 2011;**14**:A82. Conference: 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Baltimore, MD, USA, 21–25 May 2011	Outcomes
Kamble S, Schulman KA, Reed SD. Cost-effectiveness of sensor-augmented pump therapy in adults with type 1 diabetes in the USA. *Value Health* 2012;**15**:632–8	Outcomes
Kamble S, Weinfurt KP, Perry BM, Schulman KA, Reed SD. Patient time and indirect costs associated with sensor-augmented insulin pump therapy in type 1 diabetes. *Value Health* 2011;**14**:A824. Conference: 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Baltimore, MD, USA, 21–25 May 2011	Outcomes
Kamble S, Weinfurt KP, Schulman KA, Reed SD. Patient time costs associated with sensor-augmented insulin pump therapy for type 1 diabetes: results from the STAR 3 randomized trial. *Med Decis Making* 2013;**33**:215–24	Outcomes
Kapellen T, Kordonouri O, Pankowska E, Rami B, Coutant R, Hartmann R, *et al.* Sensor-augmented pump therapy from the onset of type 1 diabetes in children and adolescents – results of the Pediatric ONSET Study after 12 months of treatment. *Horm Res Paediatr* 2010;**74**:58. Conference: 49th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE). Prague, Czech Republic, 22–25 September 2010	Study design
Kaufman F, Shin J, Yang Q. Differences in measures of glycemic variability between the multiple daily injection therapy and sensor-augmented pump therapy groups in the star 3 study. *Diabetes Technol Ther* 2011;**13**:186. Conference: 4th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). London, UK, 16–19 February 2011	Outcomes
Kaufman FR, Agrawal P, Askari S, Kannard B, Welsh JB. Effectiveness of the low glucose suspend feature of the medtronic paradigm Veo insulin pump in children and adolescents. *Pediatr Diabetes* 2011;**12**:30–31. Conference: 37th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Miami Beach, FL, USA, 19–22 October 2011	Study design
Kaufman FR, Agrawal P, Lee SW, Kannard B. Characterization of the low glucose suspend feature of the medtronic minimed paradigm veo insulin pump system and events preceding its activation. *Diabetes* 2011;**60**:A249. Conference: 71st Scientific Sessions of the American Diabetes Association. San Diego, CA, USA, 24–28 June 2011	Study design
Kaufman FR, Austin J, Neinstein A, Jeng L, Halvorson M, Devoe DJ, *et al.* Nocturnal hypoglycemia detected with the continuous glucose monitoring system in pediatric patients with type 1 diabetes. *J Pediatr* 2002;**141**:625–30	Study design

continued

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P. A pilot study of the continuous glucose monitoring system: clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. *Diabetes Care* 2001;**24**:2030–4	Study design
Kaufman FR, Halvorson M, Kim C, Pitukcheewanont P. Use of insulin pump therapy at nighttime only for children 7–10 years of age with type 1 diabetes. *Diabetes Care* 2000;**23**:579–82	Study design
Keenan DB, Cartaya R, Mastrototaro JJ. Accuracy of a new real-time continuous glucose monitoring algorithm. *J Diabetes Sci Technol* 2010;**4**:111–18	Study design
Keenan DB, Mastrototaro JJ, Zisser H, Cooper KA, Raghavendhar G, Lee SW, *et al.* Accuracy of the Enlite 6-day glucose sensor with guardian and Veo calibration algorithms. *Diabetes Technol Ther* 2012;**14**:225–31	Study design
Kernaghan D, Farrell T, Hammond P, Owen P. Fetal growth in women managed with insulin pump therapy compared to conventional insulin. *Eur J Obstet Gynecol Reprod Biol* 2008;**137**:47–9	Intervention
Khalil S, Wright T, Field A, Hand J, Dyer P, Karamat MA. Does continuous subcutaneous insulin infusion (CSII) provide an effective method of controlling diabetes in pregnant women with type 1 diabetes? *Diabet Med* 2013;**30**(Suppl. 1):170. Paper presented at Diabetes UK Professional Conference. Manchester, UK, 13–15 March 2013	Study design
King Abdullah International Medical Research Centre. *Incidence of Hypoglycemia During Ramadan in Patients With Type 1 Diabetes on Insulin Pump Versus Multi Dose Injection*. NCT01941238; 2013. URL: https://clinicaltrials.gov/ct2/show/NCT01941238 (accessed 12 November 2015)	Study design
Kordonouri O, Hartmann R, Lauterborn R, Barnekow C, Hoeffe J, Deiss D. Age-specific advantages of continuous subcutaneous insulin infusion as compared with multiple daily injections in pediatric patients: one-year follow-up comparison by matched-pair analysis. *Diabetes Care* 2006;**29**:133–4	Intervention
Kordonouri O, Hartmann R, Pankowska E, Rami B, Kapellen T, Coutant R, *et al.* Follow-up of patients with sensor-augmented pump therapy during the first year of diabetes-pediatric onset study. *Pediatr Diabetes* 2011;**12**:29. Conference: 37th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Miami Beach, FL, USA, 19–22 October 2011	Study design
Kordonouri O, Hartmann R, Pankowska E, Rami B, Kapellen T, Coutant R, *et al.* Sensor augmented pump therapy from onset of type 1 diabetes: late follow-up results of the Pediatric ONSET Study. *Diabetologia* 2011;**54**:S41. Conference: 47th Annual Meeting of the European Association for the Study of Diabetes (EASD). Lisbon, Portugal, 12–16 September 2011	Study design
Kordonouri O, Hartmann R, Pankowska E, Rami B, Kapellen T, Coutant R, *et al.* Sensor augmented pump therapy from onset of type 1 diabetes: late follow-up results of the Pediatric Onset Study. *Pediatr Diabetes* 2012;**13**:515–18	Study design
Kordonouri O, Pankowska E, Rami B, Kapellen T, Coutant R, Hartmann R, *et al.* Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: results of the Paediatric Onset Study (ONSET) after 12 months of treatment. *Diabetologia* 2010;**53**:2487–95	Study design
Kordonouri O. Pumps and sensors from the onset of diabetes. *Pediatr Diabetes* 2010;**11**:6. Conference: 36th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Buenos Aires, Argentina, 27–30 October 2010	Study design
Kovatchev BP. Safety and efficacy of outpatient closed-loop control – results from randomized crossover trials of a wearable artificial pancreas. Paper presented at 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA, USA, 13–17 June 2014	Study design
Kracht T, Kordonouri O, Datz N, Scarabello C, Walte K, Blaesig S, *et al.* Reducing glycaemic variability and HbA_{1c} with the Dexcom Seven.2 continuous glucose monitoring system in children and young adults with type 1 diabetes (T1D). *Pediatr Diabetes* 2009;**10**:104. Conference: 35th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Ljubljana, Slovenia, 2–5 September 2009	Intervention
Kruger J, Brennan A. The cost of type 1 diabetes mellitus in the United Kingdom: a review of cost-of-illness studies. *Eur J Health Econ* 2013;**14**:887–99	Outcomes

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Laatikainen L, Teramo K, Hieta-Heikurainen H, Koivisto V, Pelkonen R. A controlled study of the influence of continuous subcutaneous insulin infusion treatment on diabetic retinopathy during pregnancy. *Acta Med Scand* 1987;**221**:367–76	Intervention
Laffel L, Buckingham B, Chase P, Bailey T, Liljenquist D, Daniels M, *et al.* Performance of a continuous glucose monitoring system (CGM) and CGM glucose ranges in youth ages 2–17 yr old. *Pediatr Diabetes* 2013;**14**:47–48. Conference: 39th Annual Conference of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Gothenburg, Sweden, 16–19 October 2013	Intervention
Lagarde WH, Barrows FP, Davenport ML, Kang M, Guess HA, Calikoglu AS. Continuous subtaneous glucose monitoring in children with type 1 diabetes mellitus: a single-blind, randomized, controlled trial. *Pediatr Diabetes* 2006;**7**:159–64	Outcomes
Laguna AJ, Rossetti P, Ampudia-Blasco FJ, Vehi J, Bondia J. Postprandial performance of Dexcom SEVEN PLUS and Medtronic Paradigm Veo: modeling and statistical analysis. *Biomed Signal Process Control* 2014;**10**:322–31	Study design
Lange K, Coutant R, Danne T, Kapellen T, Pankowska E, Rami B, *et al.* High quality of life in children and psychological wellbeing in mothers 12 month after diabetes onset: results of the paediatric onset-trial of sensor-enhanced CSII. *Pediatr Diabetes* 2010;**11**:101. Conference: 36th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Buenos Aires, Argentina, 27–30 October 2010	Study design
Langeland LB, Salvesen O, Selle H, Carlsen SM, Fougner KJ. Short-term continuous glucose monitoring: effects on glucose and treatment satisfaction in patients with type 1 diabetes mellitus; a randomized controlled trial. *Int J Clin Pract* 2012;**66**:741–7	Study design
Langendam M, Luijf YM, Hooft L, DeVries JH, Mudde AH, Scholten RJPM. Continuous glucose monitoring systems for type 1 diabetes mellitus. *Cochrane Database Syst Rev* 2012; **1**:CD008101	Systematic review/ meta-analysis
Lapolla A, Dalfra MG, Masin M, Bruttomesso D, Piva I, Crepaldi C, *et al.* Analysis of outcome of pregnancy in type 1 diabetics treated with insulin pump or conventional insulin therapy. *Acta Diabetol* 2003;**40**:143–9	Study design
Lauritzen T, Frost-Larsen K, Larsen HW, Deckert T. Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. *Diabetes* 1985;**34**(Suppl. 3):74–9	Intervention
Lawson ML, Bradley B, McAssey K, Clarson C, Kirsch S, Curtis JR, *et al.* Timing of initiation of continuous glucose monitoring in established pediatric diabetes: recruitment and baseline characteristics in the CGM time trial. *Diabetes Technol Ther* 2014;**16**:A73–4. Conference: 7th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Vienna, Austria, 5–8 February 2014	Outcomes
Lawson ML, Olivier P, Huot C, Richardson C, Nakhla M, Romain J. Simultaneous vs. delayed initiation of Real-Time Continuous Glucose Monitoring (RT-CGM) in children and adolescents with established type 1 diabetes starting insulin pump therapy: a pilot study. *Pediatr Diabetes* 2011;**12**:126–7. Conference: 37th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Miami Beach, FL, USA, 19–22 October 2011	Outcomes
Lawson ML, Richardson C, Muileboom J, Evans K, Landry A, Cormack L. Development of a standardized approach to initiating continuous glucose monitoring in amulticentre pediatric study. *Diabetes Technol Ther* 2014;**16**:A73. Conference: 7th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Vienna, Austria, 5–8 February 2014	Outcomes
Lawson P, Home PD, Bergenstal R. Observations on blood lipid and intermediary metabolite concentrations during conventional insulin treatment or CSII. *Diabetes* 1985;**34**(Suppl. 3):27–30	Intervention
Lebenthal Y, Lazar L, Benzaquen H, Shalitin S, Phillip M. Patient perceptions of using OmniPod System compared with conventional insulin pumps in young adults with type 1 diabetes. *Pediatr Diabetes* 2011;**12**:131–2. Conference: 37th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Miami Beach, FL, USA, 19–22 October 2011	Intervention

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TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Lebenthal Y, Lazar L, Benzaquen H, Shalitin S, Phillip M. Patient perceptions of using the OmniPod system compared with conventional insulin pumps in young adults with type 1 diabetes. *Diabetes Technol Ther* 2012;**14**:411–17	Intervention
Lecavalier L, Havrankova J, Hamet P, Chiasson JL. Effects of continuous subcutaneous insulin infusion versus multiple injections on insulin receptors in insulin-dependent diabetics. *Diabetes Care* 1987;**10**:300–5	Study design
Lee SW, Welsh JB, Green JB, Joyce C, Tamborlane WV, Kaufman FR. Successful transitions from MDI therapy to sensor-augmented pump therapy in the STAR 3 study: system settings and behaviours. *Diabetologia* 2011;**54**:S395–6. Conference: 47th Annual Meeting of the European Association for the Study of Diabetes (EASD). Lisbon, Portugal, 12–16 September 2011	Outcomes
Leelarathna L, Little SA, Walkinshaw E, Tan HK, Lubina-Solomon A, Kumareswaran K, *et al.* Restoration of self-awareness of hypoglycemia in adults with long-standing type 1 diabetes: hyperinsulinemic-hypoglycemic clamp substudy results from the HypoCOMPaSS trial. *Diabetes Care* 2013;**36**:4063–70	Study design
Legacy Health System, Juvenile Diabetes Research Foundation. *Sensor-Augmented Insulin Delivery: Insulin Plus Glucagon Versus Insulin Alone*. 2011. URL: http://ClinicalTrials.gov/show/NCT00797823 (accessed 23 February 2016)	Study design
Lepore G, Dodesini AR, Nosari I, Trevisan R. Both continuous subcutaneous insulin infusion and a multiple daily insulin injection regimen with glargine as basal insulin are equally better than traditional multiple daily insulin injection treatment. *Diabetes Care* 2003;**26**:1321–2	Study design
Lepore G, Dodesini AR, Nosari I, Trevisan R. Effect of continuous subcutaneous insulin infusion vs. multiple daily insulin injection with glargine as basal insulin: an open parallel long-term study. *Diabetes Nutr Metab* 2004;**17**:84–9	Not found
Leveno KJ, Fortunato SJ, Raskin P, Williams ML, Whalley PJ. Continuous subcutaneous insulin infusion during pregnancy. *Diabetes Res Clin Pract* 1988;**4**:257–68	Intervention
Li A, Tsang CH. *The Effectiveness of Continuous Subcutaneous Insulin Infusion on Quality of Life of Families and Glycaemic Control Among Children with Type 1 Diabetes: A Systematic Review*. PROSPERO: CRD42012002029; 2012. URL: www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002029 (accessed 16 November 2015)	Systematic review/meta-analysis
Li XL. Multiple daily injections versus insulin pump therapy in patients with type 1 diabetes mellitus: a meta analysis. *J Clin Rehabil Tissue Engineering Res* 2010;**14**:8722–5	Systematic review/meta-analysis
Lindholm Olinder A, Hanas R, Heintz E, Jacobson S, Johansson UB, Olsson PO, *et al.* CGM and SAP are valuable tools in the treatment of diabetes; a swedish health technology assessment. *Diabetes Technol Ther* 2014;**16**:A74. Conference: 7th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Vienna, Austria, 5–8 February 2014	Systematic review/meta-analysis
Liouri E, Koutsovasilis A, Kounenou K, Kamaratos A, Koukouli M-P, Nikolaou A, *et al.* Intensified insulin therapy vs CSII: the influence on family cohesion and adaptability of type 1 diabetics. Paper presented at 45th EASD Annual Meeting of the European Association for the Study of Diabetes. Vienna, Austria, 30 September–2 October 2009	Outcomes
Little S, Chadwick T, Choudhary P, Brennand C, Stickland J, Barendse S, *et al.* Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (the Hypo COMPaSS trial). *BMC Endocr Disord* 2012;**12**:33	Outcomes
Little SA, Leelarathna L, Walkinshaw E, Kai Tan H, Chapple O, Barendse S, *et al.* A definitive multicenter RCT to restore hypoglycemia awareness and prevent recurrent severe hypoglycemia in adults with long- standing type 1 diabetes: Results from the hypocompass trial. *Diabetes* 2013;**62**:A98. Conference: 73rd Scientific Sessions of the American Diabetes Association. Chicago, IL, USA, 21–25 June 2013	Outcomes
Little SA, Leelarathna L, Walkinshaw E, Tan HK, Chapple O, Lubina-Solomon A, *et al.* Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 × 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). *Diabetes Care* 2014;**37**:2114–22	Outcomes

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Littlejohn E, Turksoy K, Quinn LT, Cinar A. Integrated multivariable artificial pancreas control systems work as well as operator controlled systems. Paper presented at 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA, USA, 13–17 June 2014	Intervention
Litton J, Rice A, Friedman N, Oden J, Lee MM, Freemark M. Insulin pump therapy in toddlers and preschool children with type 1 diabetes mellitus. *J Pediatr* 2002;**141**:490–5	Study design
Logtenberg SJ, Kleefstra N, Groenier KH, Gans RO, Bilo HJ. Use of short-term real-time continuous glucose monitoring in type 1 diabetes patients on continuous intraperitoneal insulin infusion: a feasibility study. *Diabetes Technol Ther* 2009;**11**:293–9	Intervention
Ludvigsson J, Hanas R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. *Pediatrics* 2003;**111**:933–8	Intervention
Luijf YM, De Vries JH, Mader JK, Doll W, Place J, Renard E, *et al.* Accuracy and reliability of current continuous glucose monitoring systems: a direct comparison. *J Diabetes Sci Technol* 2013;**7**:A83. Conference: 12th Annual Diabetes Technology Meeting. Bethesda, MD, USA, 8–10 November 2012	Outcomes
Luijf YM, DeVries JH, Mader JK, Doll W, Place J, Renard E, *et al.* Accuracy and reliability of current CGM systems: a direct comparison. *Diabetes Technol Ther* 2013;**15**:A13–14. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Paris, France, 27 February–2 March 2013	Outcomes
Luijf YM, DeVries JH, Zwinderman K, Leelarathna L, Nodale M, Caldwell K, *et al.* Day and night closed-loop control in adults with type 1 diabetes: a comparison of two closed-loop algorithms driving continuous subcutaneous insulin infusion versus patient self-management. *Diabetes Care* 2013;**36**:3882–7	Study design
Luijf YM, Mader JK, Doll W, Pieber T, Farret A, Place J, *et al.* Accuracy and reliability of continuous glucose monitoring systems: a head-to-head comparison. *Diabetes Technol Ther* 2013;**15**:721–6	Study design
Ly TT, Keenan DB, Spital G, Roy A, Grosman B, Cantwell M, *et al.* Portable glucose control with daytime treat-to-range and overnight proportionalintegral-derivative control in adolescents with type 1 diabetes. *Diabetes Technol Ther* 2013;**15**:A14. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Paris, France, 27 February–2 March 2013	Outcomes
Ly TT, Nicholas JA, Davis EA, Jones TW. Initial experience of automated low glucose insulin suspension using the medtronic paradigm veo system. *Diabetes* 2011;**60**:A112. Conference: 71st Scientific Sessions of the American Diabetes Association. San Diego, CA, USA, 24–28 June 2011	Study design
Ly TT, Nicholas JA, Retterath A, Davis EA, Jones TW. Analysis of glucose responses to automated insulin suspension with sensor-augmented pump therapy. *Diabetes Care* 2012;**35**:1462–5	Outcomes
Maahs DM, Calhoun P, Buckingham BA, Chase HP, Hramiak I, Lum J, *et al.* A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. *Diabetes Care* 2014;**37**:1885–91	Study design
Maahs DM, Chase HP, Westfall E, Slover R, Huang S, Shin JJ, *et al.* The effects of lowering nighttime and breakfast glucose levels with sensor-augmented pump therapy on hemoglobin A1c levels in type 1 diabetes. *Diabetes Technol Ther* 2014;**16**:284–91	Study design
Maiorino MI, Bellastella G, Petrizzo M, Improta MR, Brancario C, Castaldo F, *et al.* Treatment satisfaction and glycemic control in young type 1 diabetic patients in transition from pediatric health care: CSII versus MDI. *Endocrine* 2014;**46**:256–62	Study design
Manfrini S, Crino A, Fredrickson L, Pozzilli P. CSII versus intensive insulin therapy at onset of type 1 diabetes: the IMDIAB 8 two-year randomised trial. *Diabetes* 2002;**51**(Suppl. 2):A4. Paper presented at 62nd Annual Meeting of the American Diabetes Association. San Francisco, CA, USA, 14–18 Jun 2002	Study design

continued

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Maran A, Crazzolara D, Nicoletti M, Costa S, dal Pos M, Tiengo A, *et al.* A randomized crossover study to compare continuous subcutaneous insulin infusion (CSII) with multiple daily injection (MDI) in type 1 diabetic patients previously treated with CSII. *Diabetologia* 2005;**48**(Suppl. 1):A328. Paper presented at 41st Annual Meeting of the European Association for the Study of Diabetes (EASD). Athens, Greece, 10–15 September 2005	Outcomes
Mauras N, Beck R, Xing D, Ruedy K, Buckingham B, Tansey M, *et al.* A randomized controlled trial (RCT) to assess the efficacy and safety of real-time continuous glucose monitoring (CGM) in the management of type 1 diabetes (T1D) in young children. *Pediatr Diabetes* 2011;**12**:30. Conference: 37th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Miami Beach, FL, USA, 19–22 October 2011	Intervention
Mauras N, Beck R, Xing D, Ruedy K, Buckingham B, Tansey M, *et al.* A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to < 10 years. *Diabetes Technol Ther* 2013;**15**(Suppl. 1):S14–15	Study design
Mauras N, Beck R, Xing DY, Ruedy K, Buckingham B, Tansey M, *et al.* A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to < 10 years. *Diabetes Care* 2012;**35**:204–10	Study design
McCoy R, Smith S. Insulin pumps with a sensor and threshold-suspend reduced nocturnal hypoglycemia in type 1 diabetes. *Ann Intern Med* 2013;**159**:JC7	Study design
McCoy R. Insulin pumps with a sensor and threshold-suspend reduced nocturnal hypoglycemia in type 1 diabetes. *Ann Intern Med* 2013;**159**:JC7	Study design
Medtronic Diabetes. *Feasibility Study for Training Pump Naive Subjects To Use The Paradigm® System And Evaluate Effectiveness*. NCT00530023; 2011. URL: https://clinicaltrials.gov/ct2/show/NCT00530023 (accessed 12 November 2015)	Intervention
Medtronic. *SWITCH – Sensing With Insulin Pump Therapy to Control HbA_{1c}*. 2010. URL: http://ClinicalTrials.gov/show/NCT00598663 (accessed 16 November 2015)	Study design
Melki V, Hanaire-Broutin H, Bessieres-Lacombe S, Tauber JP. CSII versus MDI in IDDM patients treated with insulin lispro: results of a randomised, cross-over trial. *Diabetologia* 1999;**42**(Suppl. 1):A17. Paper presented at 35th Annual meeting of the European Association for the Study of Diabetes. Brussels, Belgium, 28 September–2 October 1999	Outcomes
Mello G, Biagioni S, Ottanelli S, Nardini C, Tredici Z, Serena C, *et al.* Continuous subcutaneous insulin infusion (CSII) versus multiple daily injections (MDI) of rapid-acting insulin analogues and detemir in type 1 diabetic (T1D) pregnant women. *J Matern Fetal Neonatal Med* 2014;**28**:276–80	Study design
Mello G, Parretti E, Tondi F, Riviello C, Borri P, Scarselli G. Impact of two treatment regimens with insulin lispro in post-prandial glucose excursion patterns and fetal fat mass growth in type 1 diabetic pregnant women. *Am J Obstet Gynecol* 2005;**193**(Suppl. 6):S36. Paper presented at 26th Annual Meeting of the Society for Maternal–Fetal Medicine: the Pregnancy Meeting, 30 January–4 February 2006, Miami, FL, USA	Outcomes
Meschi F, Beccaria L, Vanini R, Szulc M, Chiumello G. Short-term subcutaneous insulin infusion in diabetic children. Comparison with three daily insulin injections. *Acta Diabetol Lat* 1982;**19**(4371–5)	Not found
Meyer L, Boullu-Sanchis S, Boeckler P, Sibenaler A, Treger M, Pinget M, *et al.* Comparison of glycemic control in 3 groups of type 1 diabetic patients treated with multiinjections and lispro (MDI), continuous subcutaneous insulin infusion with lispro (CSII) or continuous peritoneal insulin infusion (CPII): data of continuous subcutaneous glucose sensing (CGMS). *Diabetes* 2002;**51**(Suppl. 2):A124–5. Paper presented at 62nd Annual Meeting of the American Diabetes Association. San Francisco, CA, USA, 14–18 June 2002	Study design
Micossi P, Raggi U, Dosio F. Open-loop device microjet MC 2 improves unstable diabetes, lowers the daily insulin requirement and reduces the excursions of plasma free insulin levels: comparison with a traditional intensive treatment. *J Endocrinol Invest* 1983;**6**:189–94	Intervention
Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev* 2010; **1**:CD005103	Systematic review/ meta-analysis

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Moller A, Rasmussen L, Ledet T, Christiansen JS, Christensen CK, Mogensen CE, *et al.* Lipoprotein changes during continuous subcutaneous insulin infusion in insulin-dependent diabetic patients. *Scand J Clin Lab Invest* 1986;**46**:471–5	Intervention
Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. *Acta Diabetol* 2010;**47**(Suppl. 1):77–81	Systematic review/meta-analysis
Monnier LH, Rodier M, Gancel A, Crastes de Paulet P, Colette C, Piperno M, *et al.* Plasma lipid fatty acids and platelet function during continuous subcutaneous insulin infusion in type I diabetes. *Diabetes Metab* 1987;**13**:210–16	Intervention
Moreno-Fernandez J, Gomez FJ, Gazquez M, Pedroche M, Garcia-Manzanares A, Tenias JM, *et al.* Real-time continuous glucose monitoring or continuous subcutaneous insulin infusion, what goes first? Results of a pilot study. *Diabetes Technol Ther* 2013;**15**:596–600	Study design
Mukhopadhyay A, Farrell T, Fraser RB, Ola B. Continuous subcutaneous insulin infusion vs. intensive conventional insulin therapy in pregnant diabetic women: a systematic review and metaanalysis of randomized, controlled trials. *Am J Obstet Gynecol* 2007;**197**:447–56	Systematic review/ meta-analysis
Murphy HR, Kumareswaran K, Elleri D, Allen JM, Caldwell K, Biagioni M, *et al.* Safety and efficacy of 24-h closed-loop insulin delivery in well-controlled pregnant women with type 1 diabetes: a randomized crossover case series. *Diabetes Care* 2011;**34**:2527–9. [Erratum appears in *Diabetes Care* 2012;**35**:191]	Study design
Myers SJ, Uhrinak AN, Kaufman FR, Lee SW, Yusi J, Huang S, *et al.* Retrospective analysis of events preceding low glucose suspend activation in pediatric subjects on the Paradigm Veo system. *J Diabetes Sci Technol* 2012;**6**:A125. Conference: 11th Annual Diabetes Technology Meeting. San Francisco, CA, USA, 27–29 October 2011	Study design
Nabhan ZM, Kreher NC, Greene DM, Eugster EA, Kronenberger W, DiMeglio LA. A randomized prospective study of insulin pump vs. insulin injection therapy in very young children with type 1 diabetes: 12-month glycemic, BMI, and neurocognitive outcomes. *Pediatr Diabetes* 2009;**10**:202–8	Intervention
Nahata L. Insulin therapy in pediatric patients with type I diabetes: continuous subcutaneous insulin infusion versus multiple daily injections. *Clin Pediatr (Phila)* 2006;**45**:503–8	Study design
Nathan DM, Lou P, Avruch J. Intensive conventional and insulin pump therapies in adult type I diabetes. A crossover study. *Ann Intern Med* 1982;**97**:31–6	Study design
Nemours Children's Clinic. *Insulin Pump Therapy in Adolescents With Newly Diagnosed Type 1 Diabetes (T1D)*. NCT00357890; 2006. URL: https://clinicaltrials.gov/ct2/show/NCT00357890 (accessed 12 November 2015)	Population
JRDF Artificial Pancreas Project. *Randomized Study of Real-Time Continuous Glucose Monitors (RT-CGM) in the Management of Type 1 Diabetes*. NCT00406133; 2006. URL: https://clinicaltrials.gov/ct2/show/NCT00406133 (accessed 12 November 2015)	Outcomes
Erasmus Medical Center. *Comparison Between Insulin Pump Treatment and Multiple Daily Insulin Injections in Diabetic Type 1 Children*. NCT00462371; 2007. URL: https://clinicaltrials.gov/ct2/show/NCT00462371 (accessed 12 November 2015)	Outcomes
Hoffman-La Roche. *A Study Comparing Continuous Subcutaneous Insulin Infusion With Multiple Daily Injections With Insulin Lispro and Glargine*. NCT00468754; 2007. URL: https://clinicaltrials.gov/ct2/show/NCT00468754 (accessed 12 November 2015)	Outcomes
Medtronic Diabetes. *Feasibility Study for Training Pump Naive Subjects To Use The Paradigm® System And Evaluate Effectiveness*. NCT00530023; 2007. URL: https://clinicaltrials.gov/ct2/show/NCT00530023 (accessed 12 November 2015)	Duplicate
Novo Nordisk A/S. *Efficacy and Safety of Insulin Aspart in MDI or CSII in Children Below 7 Years of Age With Type 1 Diabetes*. NCT00571935; 2007. URL: https://clinicaltrials.gov/ct2/show/NCT00571935 (accessed 12 November 2015)	Outcomes

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TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Arkansas Children's Hospital Research Institute. *Preservation of Pancreatic Beta Cell Function Through Insulin Pump Therapy*. NCT00574405; 2007. URL: https://clinicaltrials.gov/ct2/show/NCT00574405 (accessed 12 November 2015)	Outcomes
Medtronic. *SWITCH – Sensing With Insulin Pump Therapy to Control HbA_{1c}*. NCT00598663; 2007. URL: https://clinicaltrials.gov/ct2/show/NCT00598663 (accessed 12 November 2015)	Study design
Boston University. *Closed-loop Glucose Control for Automated Management of Type 1 Diabetes*. NCT00811317; 2008. URL: https://clinicaltrials.gov/ct2/show/NCT00811317 (accessed 12 November 2015)	Intervention
Seattle Children's Hospital. *The Effectiveness of Continuous Glucose Monitoring in Diabetes Treatment for Infants and Young Children*. NCT00875290; 2009. URL: https://clinicaltrials.gov/ct2/show/NCT00875290 (accessed 12 November 2015)	Duplicate
DexCom Inc. *Effectiveness and Safety Study of the DexCom™ G4 Continuous Glucose Monitoring System in Children and Adolescents With Type 1 Diabetes Mellitus*. NCT01185496; 2010. URL: https://clinicaltrials.gov/ct2/show/NCT01185496 (accessed 12 November 2015)	Study design
Steen Andersen. *Effect of CSII and CGM on Progression of Late Diabetic Complications*. NCT01454700; 2011. URL: https://clinicaltrials.gov/ct2/show/NCT01454700 (accessed 12 November 2015)	Duplicate
In Home Closed Loop Study Group. *Outpatient Pump Shutoff Pilot Feasibility and Efficacy Study*. NCT01591681; 2012. URL: https://clinicaltrials.gov/ct2/show/NCT01591681 (accessed 12 November 2015)	Study design
DexCom Inc. *Effectiveness and Safety of the Dexcom™ G4 Continuous Glucose Monitoring System in Pediatric Subjects With Diabetes Mellitus*. NCT01667185; 2012. URL: https://clinicaltrials.gov/ct2/show/NCT01667185 (accessed 12 November 2015)	Study design
In Home Closed Loop Study Group. *An Outpatient Pump Shutoff Pilot Feasibility and Safety Study*. NCT01736930; 2012. URL: https://clinicaltrials.gov/ct2/show/NCT01736930 (accessed 12 November 2015)	Study design
In Home Closed Loop Study Group. *Outpatient Reduction of Nocturnal Hypoglycemia by Using Predictive Algorithms and Pump Suspension in Children*. NCT01823341; 2013. URL: https://clinicaltrials.gov/ct2/show/NCT01823341 (accessed 12 November 2015)	Study design
Medtronic Diabetes. *Post Approval Study of the Threshold Suspend Feature With the Medtronic MiniMed® 530G Insulin Pump*. NCT02003898; 2013. URL: https://clinicaltrials.gov/ct2/show/NCT02003898 (accessed 12 November 2015)	Study design
Vastra Gotaland Region. *CGM Treatment in Patients With Type 1 Diabetes Treated With Insulin Injections*. NCT02092051; 2014. URL: https://clinicaltrials.gov/ct2/show/NCT02092051 (accessed 12 November 2015)	Duplicate
Medtronic Diabetes. *Threshold Suspend in Pediatrics at Home*. NCT02120794; 2014. URL: https://clinicaltrials.gov/ct2/show/NCT02120794 (accessed 12 November 2015)	Duplicate
University Hospital, Montpellier. *Hybrid Artificial Pancreas in Home Setting*. NCT02153190; 2014. URL: https://clinicaltrials.gov/ct2/show/NCT02153190 (accessed 12 November 2015)	Intervention
University of Ljubljana, Faculty of Medicine. *Prevention of Hypoglycaemia With Predictive Insulin Suspend Using Sensor Augmented Insulin Pump in Children*. NCT02179281; 2014. URL: https://clinicaltrials.gov/ct2/show/NCT02179281 (accessed 12 November 2015)	Study design
Neeser K, Kocher S, Weber C, Heister F. CSII compared to MDI: a health economic analysis in the German health care setting. *Value Health* 2009;**12**:A407. Conference: ISPOR 12th Annual European Congress. Paris, France, 24–27 October 2009	Outcomes
Neff K, McCarthy A, Forde R, Foley M, Coulter-Smith S, Daly S, *et al.* Intensive glycaemic control in type 1 diabetic pregnancy: a comparison of continuous subcutaneous insulin infusion and multiple daily injection therapy. *Diabetologia* 2010;**53**(Suppl. 1):S433. Paper presented at 46th Annual Meeting of the European Association for the Study of Diabetes (EASD). Stockholm, Sweden, 20–24 September 2010	Study design
Nemours Children's Clinic. *Insulin Pump Therapy in Adolescents With Newly Diagnosed Type 1 Diabetes (T1D)*. NCT00357890; 2012. URL: https://clinicaltrials.gov/ct2/show/NCT00357890 (accessed 12 November 2015)	Population

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
New J, Ajjan R, Pfeiffer AFH, Freckmann G. Impact of alarm functions with real time continuous glucose monitoring (CGM). *Diabetes Technol Ther* 2013;**15**:A8–9. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Paris, France, 27 February–2 March 2013	Outcomes
Newman SP, Cooke D, Casbard A, Walker S, Meredith S, Nunn A, *et al.* A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). *Health Technol Assess* 2009;**13**(28)	Intervention
Neylon OM, O'Connell MA, Donath S, Cameron FJ. Can integrated technology improve self-care behavior in youth with type 1 diabetes? A randomized crossover trial of automated pump function. *Pediatr Diabetes* 2013;**14**:46. Conference: 39th Annual Conference of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Gothenburg, Sweden, 16–19 October 2013	Outcomes
Ng Tang Fui S, Pickup JC, Bending JJ, Collins AC, Keen H, Dalton N. Hypoglycemia and counterregulation in insulin-dependent diabetic patients: a comparison of continuous subcutaneous insulin infusion and conventional insulin injection therapy. *Diabetes Care* 1986;**9**:221–7	Study design
Nimri R, Miller S, Muller I, Atlas E, Fogel A, Bratina N, *et al.* The home use of MD-logic closed-loop system during the nights significantly improves daytime glycemic control in subjects with type 1 diabetes. *Diabetes* 2014;**63**:A243. Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA, USA, 13–17 June 2014	Intervention
Nimri R, Muller I, Atlas E, Miller S, Fogel A, Bratina N, *et al.* MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. *Diabetes Care* 2014;**37**:3025–32	Intervention
Nixon R, Pickup JC. Fear of hypoglycemia in type 1 diabetes managed by continuous subcutaneous insulin infusion: is it associated with poor glycemic control? *Diabetes Technol Ther* 2011;**13**:93–8	Study design
Norgaard K, Sohlberg A, Goodall G. [Cost-effectiveness of continuous subcutaneous insulin infusion therapy for type 1 diabetes.] *Ugeskr Laeger* 2010;**172**:2020–5	Not found
Hermanides J. *Randomized, Controlled, Multinational, Multi-center, Clinical Trial to Examine Whether HbA1c Can Improve in Type 1 Diabetes Patients who Continuously Use the Paradigm® REAL-Time System with Alarm Function as Compared to Patients on Multiple Injection Therapy Receiving One Six-Day Period of Continuous Glucose Monitoring – Without Alarm Function (Guardian® REAL-Time Clinical)*. NTR863; 2007. URL: www.trialregister.nl/trialreg/admin/rctview.asp?TC=863 (accessed 11 January 2016)	Intervention
Nuboer R, Borsboom GJJM, Zoethout JA, Koot HM, Bruining J. Effects of insulin pump vs. injection treatment on quality of life and impact of disease in children with type 1 diabetes mellitus in a randomized, prospective comparison. *Pediatr Diabetes* 2008;**9**:291–6	Intervention
O'Connell R, Oroszlan G, Hamer G, Yusi J, Kaufman F, Welsh J, *et al.* Efficacy of low glucose suspend and low predictive alert: data analysis using the Medtronic carelink therapy management software database. *Diabetes Technol Ther* 2011;**13**:244. Conference: 4th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). London, UK, 16–19 February 2011	Study design
O'Grady MJ, Retterath AJ, Keenan DB, Kurtz N, Cantwell M, Spital G, *et al.* The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. *Diabetes Care* 2012;**35**:2182–7	Study design
Olivier P, Lawson ML, Huot C, Richardson C, Nakhla M, Romain J. Lessons learned from a pilot RCT of simultaneous versus delayed initiation of continuous glucose monitoring in children and adolescents with type 1 diabetes starting insulin pump therapy. *J Diabetes Sci Technol* 2014;**8**:523–8	Outcomes
Opipari-Arrigan L, Fredericks EM, Burkhart N, Dale L, Hodge M, Foster C. Continuous subcutaneous insulin infusion benefits quality of life in preschool-age children with type 1 diabetes mellitus. *Pediatr Diabetes* 2007;**8**:377–83	Intervention

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TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Pankowska E, Blazik M, Dziechciarz P, Szypowska A, Szajewska H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. *Pediatr Diabetes* 2009;**10**:52–8	Systematic review/ meta-analysis
Patrakeeva EM, Zalevskaya AG, Shlyakhto EV. Fear of hypoglycemia in relatives of young type 1 diabetes mellitus (T1DM) patients on MDI and CSII therapy. Paper presented at 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA, USA, 13–17 June 2014	Study design
Perkins BA, Halpern EM, Orszag A, Weisman A, Houlden RL, Bergenstal RM, *et al.* Sensor-augmented pump and multiple daily injection therapy in the USA and Canada: post-hoc analysis of a randomized controlled trial. *Can J Diabetes* 2015;**39**:50–4	Outcomes
Petkova E, Petkova V, Konstantinova M, Petrova G. Economic evaluation of continuous subcutaneous insulin infusion for children with diabetes – a pilot study: CSII application for children – economic evaluation. *BMC Pediatr* 2013;**13**:155	Outcomes
Petkova E, Petkova V, Konstantinova M, Petrova G. Economic evaluation of continuous subcutaneous insulin infusion for children with diabetes – part II. *Modern Economy* 2013;**4**:9–13	Outcomes
Petkova V, Petrova G, Petkova E. Comparative analysis of the cost and metabolic control in diabetic children using insulin pumps. *Value Health* 2013;**16**:A437. Conference: ISPOR 16th Annual European Congress. Dublin, Ireland, 2–6 November 2013	Outcomes
Petrovski G, Jovanovska B, Bitovska I, Ahmeti I. Constant or intermittent glucose monitoring: evaluation on pregnancy and glycemic outcome in type 1 diabetics on insulin pump. *Diabetes* 2013;**62**:A684. Conference: 73rd Scientific Sessions of the American Diabetes Association. Chicago, IL, USA, 21–25 June 2013	Intervention
Phillip M, Battelino T, Atlas E, Kordonouri O, Bratina N, Miller S, *et al.* Nocturnal glucose control with an artificial pancreas at a diabetes camp. *N Engl J Med* 2013;**368**:824–33	Study design
Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ* 2011;**343**:d3805	Systematic review/ meta-analysis
Pickup JC. The evidence base for diabetes technology: appropriate and inappropriate meta-analysis. *J Diabetes Sci Technol* 2013;**7**:1567–74	Background
Poolsup N, Suksomboon N, Kyaw AM. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetol Metab Syndr* 2013;**5**:39	Systematic review/ meta-analysis
Pozzilli P, Crino A, Schiaffini R, Manfrini S, Fioriti E, Coppolino G, *et al.* A 2-year pilot trial of continuous subcutaneous insulin infusion versus intensive insulin therapy in patients with newly diagnosed type 1 diabetes (IMDIAB 8). *Diabetes Technol Ther* 2003;**5**:965–74	Intervention
Price D, Nakamura K, Christiansen M, Bailey T, Watkins E, Liljenquist D, *et al.* Accuracy and reliability of a next generation continuous glucose monitoring system: the Dexcom G4 platinum pivotal trial results. *Diabetes Technol Ther* 2013;**15**:A70–1. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Paris, France, 27 February–2 March 2013	Study design
Price DA, Peyser T, Simpson P, Nakamura K, Mahalingam A. Impact of study design and analytic techniques on the reported accuracy of Continuous Glucose Monitoring (CGM) systems. *Diabetes* 2012;**61**:A1. Conference: 72nd Scientific Sessions of the American Diabetes Association. Philadelphia, PA, USA, 8–12 June 2012	Background
Price DA, Peyser TA, Graham C. Challenges with systematic reviews and meta-analyses of real-time continuous glucose monitoring (CGM). *Diabetes* 2013;**62**:A644. Conference: 73rd Scientific Sessions of the American Diabetes Association. Chicago, IL, USA, 21–25 June 2013	Background
Quiroz M, Machado F, Shafiroff J, Gill M, Molina M, Gonzalez P. Insulin pump cost–utility analysis compared to multiple daily injection in type 1 diabetic patients in the Mexican social security institute, 21st century hospital. *Value Health* 2012;**15**:A69. Conference: 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Washington, DC, USA, 2–6 June 2012	Outcomes

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Rabin Medical Center. *Treatment Satisfaction of Using OmniPod System Compared With Conventional Insulin Pump in Adults With Type 1 Diabetes*. 2012. URL: http://ClinicalTrials.gov/show/NCT00935129 (accessed 12 November 2015)	Intervention
Radermecker RP, Saint Remy A, Scheen AJ, Bringer J, Renard E. Continuous glucose monitoring reduces both hypoglycaemia and HbA_{1c} in hypoglycaemia-prone type 1 diabetic patients treated with a portable pump. *Diabetes Metab* 2010;**36**:409–13	Outcomes
Ranasinghe P, Maruthur N, Yeh HC, Brown T, Suh Y, Wilson L, *et al.* Comparative effectiveness of continuous subcutaneous insulin infusion with multiple daily injections among pregnant women with diabetes mellitus: a systematic review. *J Hos Med* 2012;**7**:S52. Conference: 2012 Annual Meeting of the Society of Hospital Medicine (SHM). San Diego, CA, USA, 1–4 April 2012	Systematic review/ meta-analysis
Reid SM, Lawson ML. Comparison of continuous subcutaneous insulin infusion versus conventional treatment of type 1 diabetes with respect to metabolic control, quality of life and treatment satisfaction. *Pediatr Res* 2002;**51**(Suppl. 4):122A–3A. Paper presented at Pediatric Academic Societies' annual meeting. Baltimore, MD, USA, 4–7 May 2002	Intervention
Riveline J-P, Schaepelynck P, Chaillous L, Renard E, Sola-Gazagnes A, Penfornis A, *et al.* Assessment of patient-led or physician-driven continuous glucose monitoring in patients with poorly controlled type 1 diabetes using basal-bolus insulin regimens: a 1-year multicenter study. *Diabetes Care* 2012;**35**:965–71	Intervention
Robinson-Vincent KA. Systematic review of the effects of continuous glucose monitoring on metabolic control in children and adolescents with type 1 diabetes. *Can J Diabetes* 2013;**37**:S21. Conference: 16th Annual Canadian Diabetes Association/Canadian Society of Endocrinology and Metabolism Professional Conference and Annual Meetings. Montreal, QC, Canada, 17–19 October 2013	Systematic review/ meta-analysis
Roy A, Kaufman FR, Spital G, Clark B, Grosman B, Parikh N, *et al.* An in-silico study of predictive low glucose management algorithm for minimizing hypoglycemia. *Diabetes Technol Ther* 2013;**15**:A81–2. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD). Paris, France, 27 February–2 March 2013	Study design
Roze S, Demessinov A, Zeityn M, Toktarova N, Abduakhassova G, Sissemaliev R, *et al.* Health-economic comparison of continuous subcutaneous insulin infusion versus multiple daily injections for the treatment of type 1 diabetes in Kazakhstan children. *Value Health* 2013;**16**:A439–40. Conference: ISPOR 16th Annual European Congress. Dublin, Ireland, 2–6 November 2013	Outcomes
Roze S, Lynch P, Cook M. Projection of long term health-economic benefits of Continuous Glucose Monitoring (CGM) versus self monitoring of blood glucose in type 1 diabetes, a UK perspective. *Diabetologia* 2012;**55**:S427. Conference: 48th Annual Meeting of the European Association for the Study of Diabetes (EASD). Berlin, Germany, 1–5 October 2012	Outcomes
Roze S, Valentine WJ, Zakrzewska KE, Palmer AJ. Health-economic comparison of continuous subcutaneous insulin infusion with multiple daily injection for the treatment of type 1 diabetes in the UK. *Diabet Med* 2005;**22**:1239–45	Outcomes
Rubin RR, Peyrot M. Patient-reported outcomes in the sensor-augmented pump therapy (SAPT) for A1c reduction (STAR) 3 trial. *Diabetes* 2011;**60**:A82. Conference: 71st Scientific Sessions of the American Diabetes Association. San Diego, CA, USA, 24–28 June 2011	Outcomes
Rys PM, Mucha A, Koprowski M, Nowicki M, Malecki MT. Efficacy and safety of continuous glucose monitoring systems vs. self-monitoring blood glucose in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. *Diabetes* 2011;**60**:A244. Conference: 71st Scientific Sessions of the American Diabetes Association. San Diego, CA, USA, 24–28 June 2011	Not found
Sadri H, Bereza BG, Longo CJ. Cost-consequence analysis of CSII vs. MDI: a Canadian perspective. *Value Health* 2010;**13**:A290. Conference: ISPOR 13th Annual European Congress. Prague, Czech Republic, 6–9 November 2011	Outcomes
Sahin SB, Cetinkalp S, Ozgen AG, Saygili F, Yilmaz C. The importance of anti-insulin antibody in patients with type 1 diabetes mellitus treated with continuous subcutaneous insulin infusion or multiple daily insulin injections therapy. *Acta Diabetol* 2010;**47**:325–30	Study design

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TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Saigí I, Chico A, Santos L, Aulinas A, Adelantado J, Ginovart G, *et al.* Glycaemic control and perinatal outcomes of pregnancies complicated by type 1 diabetes: multiple daily injections vs. continuous subcutaneous insulin infusion. Paper presented at 45th EASD Annual Meeting of the European Association for the Study of Diabetes. Vienna, Austria, 30 September–2 October 2009	Outcomes
Saigi I, Chico A, Santos L, Aulinas A, Adelantado J, Ginovart G, *et al.* Glycaemic control and perinatal outcomes of pregnancies complicated by type 1 diabetes: multiple daily injections vs. continuous subcutaneous insulin infusion. *Diabetologia* 2009;**52**(Suppl. 1):S46. Paper presented at 45th Annual Meeting of the European Association for the Study of Diabetes (EASD). Vienna, Austria, 29 September–2 October 2009	Study design
Saraiva J, Paiva S, Ruas L, Barros L, Baptista C, Melo M, *et al.* Type 1 diabetes and pregnancy: continuous subcutaneous insulin infusion systems versus multiple daily injection therapy. Paper presented at 49th Annual Meeting of the European Association for the Study of Diabetes (EASD). Barcelona, Spain, 23–27 September 2013	Study design
Saurbrey N, Arnold-Larsen S, Moller-Jensen B, Kuhl C. Comparison of continuous subcutaneous insulin infusion with multiple insulin injections using the NovoPen. *Diabet Med* 1988;**5**:150–3	Not found
Scaramuzza A, De Angelis L, Bosetti A, Gazzarri A, Platerote F, Redaelli F, *et al.* Evaluation of three bolus calculators in children with type 1 diabetes using insulin pump therapy. *Pediatr Diabetes* 2011;**12**:128. Conference: 37th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Miami Beach, FL, USA, 19–22 October 2011	Study design
Scaramuzza AE, De Angelis L, Gazzarri A, Bosetti A, Platerote F, Redaelli F, *et al.* Evaluation of 3 bolus calculators in children and adolescents with type 1 diabetes using insulin pump therapy. *Diabetologia* 2011;**54**:S352. Conference: 47th Annual Meeting of the European Association for the Study of Diabetes (EASD). Lisbon, Portugal, 12–16 September 2011	Study design
Schaepelynck P, Rocher L, Hanaire H, Chaillous L, Renard E, Sola A, *et al.* Patient- or physician-driven continuous glucose monitoring (CGM) improves control and quality of life (QoL) in poorly-controlled type 1 diabetic patients on intensified insulin therapy: a one-year multicenter study. *Diabetes* 2011;**60**:A65. Conference: 71st Scientific Sessions of the American Diabetes Association San Diego, CA, USA, 24–28 June 2011	Outcomes
Schaepelynck-Belicar P, Vague P, Simonin G, Lassmann-Vague V. Improved metabolic control in diabetic adolescents using the continuous glucose monitoring system (CGMS). *Diabetes Metab* 2003;**29**:608–12	Study design
Schiaffini R, Patera PI, Bizzarri C, Ciampalini P, Cappa M. Basal insulin supplementation in type 1 diabetic children: a long-term comparative observational study between continuous subcutaneous insulin infusion and glargine insulin. *J Endocrinol Invest* 2007;**30**:572–7	Intervention
Schiel R, Burgard D, Bambauer R, Perenthaler T, Kramer G. [Differences between intensified insulin therapy using multiple insulin injections (ICT) or continuous subcutaneous insulin infusion using pumps (CSII) in children and adolescents with type 1 diabetes mellitus.] *Diabetol Stoffwechs* 2013;**8**:380–6	Not found
Schiffrin A, Belmonte MM. Comparison between continuous subcutaneous insulin infusion and multiple injections of insulin. A one-year prospective study. *Diabetes* 1982;**31**:255–64	Study design
Schiffrin A, Desrosiers M, Moffatt M, Belmonte MM. Feasibility of strict diabetes control in insulin-dependent diabetic adolescents. *J Pediatr* 1983;**103**:522–7	Outcomes
Schiffrin AD, Desrosiers M, Aleyassine H, Belmonte MM. Intensified insulin therapy in the type 1 diabetic adolescent: a controlled trial. *Diabetes Care* 1984;**7**:107–13	Outcomes
Schmidt S, Norgaard K. Long-term effects of sensor-augmented pump therapy in type 1 diabetes: a 3-year follow-up study. *Diabetes* 2012;**61**:A3. Conference: 72nd Scientific Sessions of the American Diabetes Association. Philadelphia, PA, USA, 8–12 June 2012	Study design
Schmidt S, Norgaard K. Sensor-augmented pump therapy at 36 months. *Diabetes Technol Ther* 2012;**14**:1174–7	Study design
Schmitz A, Christiansen JS, Christensen CK, Hermansen K, Mogensen CE. Effect of pump versus pen treatment on glycaemic control and kidney function in long-term uncomplicated insulin-dependent diabetes mellitus (IDDM). *Dan Med Bull* 1989;**36**:176–8	Outcomes

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Schottenfeld-Naor Y, Galatzer A, Karp M. Comparison of metabolic and psychological parameters during continuous subcutaneous insulin infusion and intensified conventional insulin treatment in type I diabetic patients. *Isr J Med Sci* 1985;**21**:822–8	Not found
Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. *Diabetes Care* 2013;**36**:1877–83	Intervention
Selam JL, Haardt MJ, Slama G, Bethoux JP. A randomized cross-over cost–benefits comparison of intensive insulin therapy with intraperitoneal infusion via implantable pumps vs multiple subcutaneous injections in patients with type-I diabetes. *Diabetes* 1994;**43**(Suppl. 1):A167. Paper presented at 54th Annual Meeting of the American Diabetes Association. New Orleans, LA, USA, 11–14 June 1994	Outcomes
Selam JL, Raccah D, Jean-Didier N, Lozano JL, Waxman K, Charles MA. Randomized comparison of metabolic control achieved by intraperitoneal insulin infusion with implantable pumps versus intensive subcutaneous insulin therapy in type I diabetic patients. *Diabetes Care* 1992;**15**:53–8	Intervention
Self-monitoring of blood glucose. *Int J Clin Pract* 2012;**66**(Suppl. 175):2–93	Study design
Sequeira PA, Montoya L, Ruelas V, Xing D, Chen V, Beck R, *et al.* Continuous glucose monitoring pilot in low-income type 1 diabetes patients. *Diabetes Technol Ther* 2013;**15**:855–8	Outcomes
Shehadeh N, Battelino T, Galatzer A, Naveh T, Hadash A, de Vries L, *et al.* Insulin pump therapy for 1–6 year old children with type 1 diabetes. *Isr Med Assoc J* 2004;**6**:284–6	Study design
Sherr J, Carria LR, Weyman K, Zgorski M, Steffen AT, Tichy EM, *et al.* Effect of 2-hr suspensions of basal insulin on elevating nighttime sensor glucose concentrations. *Diabetes* 2013;**62**:A249. Conference: 73rd Scientific Sessions of the American Diabetes Association. Chicago, IL, USA, 21–25 June 2013	Study design
Sherr J, Collazo PM, Caria L, Steffen A, Weyman K, Zgorski M, *et al.* Safety of nighttime 2-hour suspension of basal insulin in pump-treated type 1 diabetes (T1D) even in absence of low glucose. *Diabetes Technol Ther* 2013;**15**:A22. Conference: 6th International Conference on Advanced Technologies and Treatments for Diabetes. Paris, France, 27 February–2 March 2013.	Study design
Sherr JL, Collazo MMP, Carria LR, Steffen AT, Zgorski M, Weyman K, *et al.* Safety of nighttime 2-hour suspensions of basal insulin in pump-treated type 1 diabetes (T1D) even in absence of low glucose. *Diabetes* 2012;**61**:A226–7. Conference: 72nd Scientific Sessions of the American Diabetes Association. Philadelphia, PA, USA, 8–12 June 2012	Study design
Sherr JL, Collazo PM, Cengiz E, Michaud C, Carria L, Steffen AT, *et al.* Safety of nighttime 2-hour suspension of basal insulin in pump-treated type 1 diabetes even in the absence of low glucose. *Diabetes Care* 2014;**37**:773–9	Study design
Skogsberg L, Fors H, Hanas R, Chaplin JE, Lindman E, Skogsberg J. Improved treatment satisfaction but no difference in metabolic control when using continuous subcutaneous insulin infusion vs. multiple daily injections in children at onset of type 1 diabetes mellitus. *Pediatr Diabetes* 2008;**9**:472–9	Intervention
Skogsberg L, Skogsberg J, Fors H. Improved treatment satisfaction using continuous subcutaneous insulin infusion compared to multiple daily injections in children at onset of type 1 diabetes mellitus – a five-year follow-up study. *Pediatr Diabetes* 2010;**11**:S14. Conference: 36th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes. Buenos Aires, Argentina, 27–30 October 2010	Outcomes
Slover R, Daniels MW, Foster CM, Wood MA, Kaufman FR, Welsh JB, *et al.* Insulin pump adjustments and glycemic outcomes in the pediatric cohort of the STAR 3 study. *Diabetes* 2011;**60**:A254. Conference: 71st Scientific Sessions of the American Diabetes Association. San Diego, CA, USA, 24–28 June 2011	Outcomes
Slover RH, Buckingham BA, Garg S, Brazg RL, Bailey TS, Klonoff DC, *et al.* Efficacy of automatic insulin pump suspension in youth with type 1 diabetes. *Pediatr Diabetes* 2012;**13**:40–1. Conference: 38th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes. Istanbul, Turkey, 10–13 October 2012	Study design

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TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Slover RH, Tamborlane WV, Battelino T, Criego A, Daniels M, Foster C, *et al.* Glucose excursions in children and adolescents in the STAR 3 study: a 1-year randomized controlled trial comparing sensor-augmented pump therapy to multiple daily injections. *Pediatr Diabetes* 2010;**11**(Suppl.14):33. Conference: 36th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes. Buenos Aires, Argentina, 27–30 October 2010	Outcomes
St Charles M, Lynch P, Graham C, Minshall ME. A cost-effectiveness analysis of continuous subcutaneous insulin injection versus multiple daily injections in type 1 diabetes patients: a third-party US payer perspective. *Value Health* 2009;**12**:674–86	Outcomes
St Charles ME, Sadri H, Minshall ME, Tunis SL. Health economic comparison between continuous subcutaneous insulin infusion and multiple daily injections of insulin for the treatment of adult type 1 diabetes in Canada. *Clin Ther* 2009;**31**:657–67	Outcomes
Szypowska A, Dżygało K, Ramotowska A, Lipka M, Procner-Czaplińska M, Trippenbach-Dulska H. The benefits of continuous subcutaneous insulin infusion in children with type 1 diabetes mellitus started at diabetes recognition. A 7 year follow-up. Paper presented at 46th Annual Meeting of the European Association for the Study of Diabetes, 20–24 September 2010, Stockholm, Sweden	Study design
Szypowska A, Ramotowska A, Dzygalo K, Golicki D. Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: systematic review and meta-analysis of randomized trials. *Eur J Endocrinol* 2012;**166**:567–74	Systematic review/ meta-analysis
Tamborlane W, Buse J, Slover R, Green J, Kaufman F, Shin J. Comparison of insulin pump settings and insulin usage patterns in adult and pediatric subjects in the star 3 study. *Diabetes Technol Ther* 2011;**13**:173–293. Conference: 4th International Conference on Advanced Technologies and Treatments for Diabetes. London, UK, 16–19 February 2011	Outcomes
Tamborlane WV, Batas SE, Rudolf MC. Comparison of continuous subcutaneous insulin infusion versus multiple daily injections in adolescents with insulin-dependent diabetes. *Adv Diabetol* 1989;**2**(Suppl. 1):24–7	Not found
Tamborlane WV, Ruedy KJ, Wysocki T, O'Grady M, Kollman C, Block J, *et al.* JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: research design and methods. *Diabetes Technol Ther* 2008;**10**:310–21	Intervention
Tanenberg R, Bode B, Lane W, Levetan C, Mestman J, Harmel AP, *et al.* Use of the continuous glucose monitoring system to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. *Mayo Clin Proc* 2004;**79**:1521–6	Intervention
Tanenberg RJ, Houlden RL, Tildesley HD, Kaufman FR, Welsh JB, Shin J. Insulin pump adjustments and glycemic outcomes in the adult cohort of the STAR 3 study. *Diabetes* 2011;**60**:A253–4. Conference: 71st Scientific Sessions of the American Diabetes Association. San Diego, CA, USA, 24–28 June 2011	Outcomes
Tanenberg RJ, Welsh JB. Patient behaviors associated with optimum glycemic outcomes with sensor-augmented pump therapy: insights from the STAR 3 study. *Endocr Pract* 2015;**21**:41–5	Outcomes
Thabit H, Lubina-Solomon A, Stadler M, Leelarathna L, Walkinshaw E, Pernet A, *et al.* Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study. *Lancet Diabetes Endocrinol* 2014;**2**:701–9	Study design
Thabit H, Lubina-Solomon A, Stadler M, Leelarathna LT, Walkinshaw E, Pernet A, *et al.* Four weeks' home use of overnight closed-loop insulin delivery in adults with type 1 diabetes: a multicentre, randomised, crossover study. *Diabetes* 2014;**63**:A61. Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA, USA, 13–17 June 2014	Intervention
Thomas LE, Kane MP, Bakst G, Busch RS, Hamilton RA, Abelseth JM. A glucose meter accuracy and precision comparison: the freestyle flash versus the Accu-Chek Advantage, Accu-Chek Compact Plus, Ascensia Contour, and the BD Logic. *Diabetes Technol Ther* 2008;**10**:102–10	Intervention
Trossarelli GF, Cavallo-Perin P, Meriggi E, Menato G, Dolfin G, Carta Q, *et al.* Metabolic and obstetrical results in type 1 (insulin-dependent) diabetic pregnancy: pump versus optimized conventional insulin therapy. *Diabetologia* 1984;**27**:340A	Not found
Tsioli C, Remus K, Blaesig S, Datz N, Schnell K, Marquardt E, *et al.* The predictive low glucose management system in youth with type 1 diabetes during exercise-data from the Pilgrim study. *Pediatr Diabetes* 2013;**14**:48. Conference: 39th Annual Conference of the International Society for Pediatric and Adolescent Diabetes. Gothenburg, Sweden, 16–19 October 2013	Study design

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Tumminia A, Crimi S, Sciacca L, Buscema M, Frittitta L, Squatrito S, *et al.* Efficacy of REAL-Time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomised controlled cross-over trial. *Diabetes Metab Res Rev* 2015;**31**:61–8	Outcomes
Uhrinak AN, Myers SJ, Kaufman FR, Lee SW, Yusi J, Huang S, *et al.* Retrospective analysis of events preceding low glucose suspend activation in adult subjects on the paradigm veo system. *J Diabetes Sci Technol* 2012;**6**;A182. Conference: 11th Annual Diabetes Technology Meeting. San Francisco, CA, USA 27–29 October 2011	Study design
Ulf S, Ragnar H, Arne WP, Johnny L. Do high blood glucose peaks contribute to higher HbA_{1c}? Results from repeated continuous glucose measurements in children. *World J Pediatr* 2008;**4**:215–21	Intervention
University of Ljubljana, Faculty of Medicine. *Prevention of Hypoglycaemia With Predictive Insulin Suspend Using Sensor Augmented Insulin Pump in Children*. NCT02179281; 2014. URL: https://clinicaltrials.gov/ct2/show/NCT02179281 (accessed 12 November 2015)	Study design
US Food and Drug Administration. *Dexcom G4 PLATINUM (Pediatric) Continuous Glucose Monitoring System – P120005/S002*. US Food and Drug Administration; 2014. URL: www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm386985.htm (accessed 5 September 2014)	Study design
US Food and Drug Administration. *Dexcom G4 PLATINUM (Pediatric) Continuous Glucose Monitoring System. FDA Summary of Safety and Effectiveness Data*. US Food and Drug Administration; 2014. URL: www.accessdata.fda.gov/cdrh_docs/pdf12/P120005S002b.pdf (accessed 5 September 2014)	Study design
US Food and Drug Administration. *MiniMed 530G System – P120010*. US Food and Drug Administration; 2014. URL: www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm372176.htm (accessed 5 September 2014)	Study design
Volpe L, Pancani F, Aragona M, Lencioni C, Battini L, Ghio A, *et al.* Continuous subcutaneous insulin infusion and multiple dose insulin injections in type 1 diabetic pregnant women: a case–control study. *Gynecol Endocrinol* 2010;**26**:193–6	Study design
von Hagen C, Bechtold S, Temme K, Tremml S, Wex S, Schwarz HP. [Metabolic control and quality of life in adolescents with type 1 diabetes: insulin pump therapy versus multiple daily injections.] *Diabetol Stoffwechs* 2007;**2**:238–47	Not found
Voormolen DN, DeVries JH, Evers IM, Mol BWJ, Franx A. The efficacy and effectiveness of continuous glucose monitoring during pregnancy: a systematic review. *Obstet Gynecol Surv* 2013;**68**:753–63	Systematic review/ meta-analysis
Weinstock RS, Bergenstal RM, Garg S, Bailey TS, Thrasher J, Mao M, *et al.* Reduction in hypoglycemia across a range of definitions in the aspire in-home study. *Diabetes* 2014;**51**(Suppl. 2):A240. Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA, USA, 13–17 June 2014	Outcomes
Weintrob N, Benzaquen H, Galatzer A, Shalitin S, Lazar L, Fayman G, *et al.* Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. Paper presented at 62nd Annual Meeting of the American Diabetes Association, 14–18 June 2002, San Francisco, USA. *Diabetes* 2002;**51**(Suppl. 2):A479	Outcomes
Weintrob N, Schechter A, Benzaquen H, Shalitin S, Lilos P, Galatzer A, *et al.* Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes mellitus treated by multiple daily injections vs continuous subcutaneous insulin infusion. *Arch Pediatr Adolesc Med* 2004;**158**:677–84	Study design
Weintrob N, Schechter A, Bezaquen H, Shalitin S, Lilos P, Galatzer A, *et al.* Glycemic patterns detected by continuous subcutaneous glucose sensing in children with type 1 diabetes treated by MDI or CSII. *Diabetes* 2003;**52**(Suppl. 1):A100	Outcomes

continued

TABLE 63 Studies excluded studies at full-paper screening stage with reason for exclusion (*continued*)

Excluded study	Reason for exclusion
Weinzimer SA, Ahern JH, Doyle EA, Vincent MR, Dziura J, Steffen AT, *et al.* Persistence of benefits of continuous subcutaneous insulin infusion in very young children with Type 1 diabetes: a follow-up report. *Pediatrics* 2004;**114**:1601–5	Study design
Weiss R, Bailey TS, Schwartz FL, Garg S, Ahmann AJ, Thrasher J, *et al.* Time spent (%) in hypoglycemia following automatic threshold suspend activation in the aspire in-home study. *Diabetes* 2014;**63**:A241. Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA, USA, 13–17 June 2014	Outcomes
Weiss R, Schwartz FL, Weinstock RS, Bode BW, Bailey TS, Ahmann AJ, *et al.* Bolus insulin dosing and nocturnal hypoglycemia in the aspire in-home study. *Diabetes* 2014;**63**:A601. Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA, USA, 13–17 June 2014	Outcomes
Wender-Ozegowska E, Zawiejska A, Ozegowska K, Wroblewska-Seniuk K, Iciek R, Mantaj U, *et al.* Multiple daily injections of insulin versus continuous subcutaneous insulin infusion for pregnant women with type 1 diabetes. *Aust N Z J Obstet Gynaecol* 2013;**53**:130–5	Study design
Wilson DC, Halliday HL, Reid M, McClure G, Dodge JA. Continuous insulin infusion in hyperglycaemic extremely low birthweight infants? A randomized trial. Proceedings of 14th European Congress of Perinatal Medicine, 14th European Congress. Helsinki, Finland, 5–8 June 1994	Not found
Wilson DM, Buckingham BA, Kunselman EL, Sullivan MM, Paguntalan HU, Gitelman SE. A two-center randomized controlled feasibility trial of insulin pump therapy in young children with diabetes. *Diabetes Care* 2005;**28**:15–19	Intervention
Wiseman MJ, Saunders AJ, Keen H, Viberti G. Effect of blood glucose control on increased glomerular filtration rate and kidney size in insulin-dependent diabetes. *N Engl J Med* 1985;**312**:617–21	Intervention
Wojciechowski P, Rys P, Lipowska A, Gaweska M, Malecki MT. Efficacy and safety comparison of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes: systematic review and meta-analysis. *Pol Arch Med Wewn* 2011;**121**:333–43	Systematic review/ meta-analysis
Yates K, Hasnat Milton A, Dear K, Ambler G. Continuous glucose monitoring-guided insulin adjustment in children and adolescents on near-physiological insulin regimens: a randomized controlled trial. *Diabetes Care* 2006;**29**:1512–17	Outcomes
Yeh HC, Brown TT, Maruthur N, Ranasinghe P, Berger Z, Suh YD, *et al.* Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med* 2012;**157**:336–47	Systematic review/ meta-analysis
Yogev Y, Chen R, Ben-Haroush A, Phillip M, Jovanovic L, Hod M. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. *Obstet Gynecol* 2003;**101**:633–8	Study design
Ziegler D, Dannehl K, Koschinsky T, Toeller M, Gries FA. Comparison of continuous subcutaneous insulin infusion and intensified conventional therapy in the treatment of type I diabetes: a two-year randomized study. *Diabetes Nutr Metab Clin Exp* 1990;**3**:203–13	Intervention
Zisser HC, Dassau E, Bevier W, Harvey RA, Jovanovic L, Doyle FJ III. Clinical evaluation of a fully-automated artificial pancreas using zone-model predictive control with health monitoring system. Paper presented at 72nd Scientific Sessions of the American Diabetes Association. Philadelphia, PA, USA, 8–12 June 2012	Study design
Zucchini S, Scipione M, Maltoni G, Rollo A, Balsamo C, Zanotti M, *et al.* Comparison between sensor-augmented insulin therapy with either insulin pump (CSII) or multiple daily injections (MDI) in everyday life: analysis of glucose variability and sensor reliability. *Horm Res Paediatr* 2011;**76**:157–8. Conference: 50th Annual Meeting of the European Society for Paediatric Endocrinology. Glasgow, UK, 25–28 September 2011	Study design

Appendix 3 Data extraction tables

TABLE 64 Study characteristics for included studies in adults

Follow-up, months	Study	Countries	Inclusion	Intervention	Number analysed for efficacy per arm
3	Bergenstal *et al.*, 2013[32]	USA	Age: 16–70 years; HbA_{1c}: 5.8–10%; CSII experience: 6 months prior CSII treatment; number of hypoglycaemic events: > 1; episode of severe hypoglycaemia in the previous 6 months: excluded; and ≥ 2 nocturnal hypoglycaemic events in the run-in period required	CSII + CGM + suspend: Paradigm Veo pump + Enlite sensor (Medtronic)	121
				CSII + CGM integrated: Paradigm Revel 2.0 pump + Enlite sensor	126
3.45	Lee *et al.*, 2007[38]	USA	Age: adults; HbA_{1c}: ≥ 7.5%; CSII experience: CSII naive; number of hypoglycaemic events: NR	Integrated CSII + CGM: MiniMed Paradigm REAL-Time 722 system as adjunct to SMBG (Paradigm Link™ glucose meter)[a]	8
				MDI + SMBG: SMBG (Paradigm Link glucose meter)	8
3.69	Peyrot and Rubin, 2009[39]	USA	Age: adults; HbA_{1c}: NR; CSII experience: CSII naive; number of hypoglycaemic events: NR	Integrated CSII + CGM: Paradigm 722 System (smart CSII pump with real-time CGM and CareLink™ data management software) as adjunct to SMBG [Becton Dickinson (Franklin Lakes, NJ) meters and strips]	14
				MDI + SMBG: SMBG (Becton Dickinson meters and strips) with CareLink™ data management software	13
3.69	DeVries *et al.*, 2002[42]	The Netherlands	Age: 18–70 years; HbA_{1c}: ≥ 8.5%; CSII experience: NR; number of hypoglycaemic events: NR	CSII + SMBG: Disetronic H-TRONplus insulin pump; Glucotouch or One Touch Profile memory glucose meter (LifeScan, Inc., Milpitas, CA)	32
				MDI + SMBG: Glucotouch or One Touch Profile memory glucose meter (LifeScan)	40
6	Bolli *et al.*, 2009[41]	Europe	Age: 18–70 years; HbA_{1c}: 6.5–9%; CSII experience: CSII naive; number of hypoglycaemic events: ≥ 2; episodes of severe hypoglycaemia in the previous 6 months: excluded	CSII + SMBG: MiniMed 508 with SMBG	24
				MDI + SMBG: NR	26

continued

TABLE 64 Study characteristics for included studies in adults (*continued*)

Follow-up, months	Study	Countries	Inclusion	Intervention	Number analysed for efficacy per arm
6	Hermanides *et al.*, 2011[37]	Denmark; Switzerland; Sweden; the Netherlands; France; UK; Belgium; Italy	Age: 18–65 years; HbA_{1c}: ≥ 8.2%; CSII experience: CSII in the previous 6 months excluded; number of hypoglycaemic events: NR	Integrated CSII + CGM: Paradigm REAL-Time system with SMBG (meter not described)	41
				MDI + SMBG: SMBG meter not described	36
6	Hirsch *et al.*, 2008[34]	USA	Age: 18–80 years; HbA_{1c}: ≥ 7.5%; CSII experience: ≥ 6 months prior CSII treatment; number of hypoglycaemic events: NR	Integrated CSII + CGM: Paradigm 722 System	17
				CSII + SMBG: SMBG and a Paradigm 715 Insulin Pump (Medtronic)	23
6	Thomas *et al.*, 2007[45]	UK	Age: adults; HbA_{1c}: NR; CSII experience: NR; number of hypoglycaemic events: ≥ 1 episode of severe hypoglyaemia in the previous 6 months	CSII + SMBG: Medtronic 508 with SMBG	7
				MDI + SMBG: NR	7
9	Tsui *et al.*, 2001[46]	Canada	Age: 18–60 years; HbA_{1c}: NR; CSII experience: CSII naive; number of hypoglycaemic events: ≥ 2; episodes of severe hypoglycaemia in the previous year excluded	CSII + SMBG: MiniMed 507 insulin infusion pump; Advantage meter (Roche Diagnostics, Bale, Switzerland)	12
				MDI + SMBG: Advantage meter (Roche Diagnostics)	14
12	Nosadini *et al.*, 1988[43]	Italy	Age: NR; HbA1c: NR; CSII experience: NR; number of hypoglycaemic events: NR	CSII + SMBG: Betatron II (Firenze, Italy) + SMBG (CSII-HOR)	10
				CSII + SMBG: Microjet Mc 20 (Miles-Ames, Cavenago, Italy) + SMBG (CSII-FBR)	19
				MDI + SMBG: NR (ICIT)	15
12	Bergenstal *et al.*, 2010[40]	USA; Canada	Age: 7–70 years; HbA_{1c}: 7.4–9.5%; CSII experience: CSII naive or no CSII in the last 3 years; number of hypoglycaemic events: ≥ 2 episodes of severe hypoglycaemia in the previous year excluded	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system	166
				MDI + SMBG: Guardian REAL-Time Clinical	163
84	Brinchmann-Hansen *et al.*, 1985[44]	Norway	Age: 18–45 years; HbA_{1c}: NR; CSII experience: NR; number of hypoglycaemic events: NR	CSII + SMBG: Nordisk Infuser ($n = 3$) or AutoSyringe AS6C ($n = 12$)	15
				MDI + SMBG: NR	15

FBR, fixed basal overnight insulin infusion rate; HOR, higher programmable overnight insulin infusion rate; ICIT, intensified conventional insulin therapy; NR, not reported.
a Paradigm Link™ glucose meter (Medtronic Inc., Northridge, CA, USA).

TABLE 65 Study characteristics for included studies in children

Follow-up, months	Study	Countries	Inclusion	Intervention	Number analysed for efficacy per arm
3.5	Weintrob *et al.*, 2003[47]	Israel	Age: 8–14 years; HbA_{1c}: NR; CSII experience: NR; number of hypoglycaemic events: NR	CSII + SMBG: programmable external pump (MiniMed 508) using insulin lispro	11
				MDI + SMBG: NR	12
3.69	Doyle *et al.*, 2004[49]	USA	Age: 8–21 years; HbA_{1c}: 6.5–11%; CSII experience: CSII naive; number of hypoglycaemic events: NR	CSII + SMBG: Medtronic MiniMed 508 or Paradigm 511; LifeScan InDuo™ glucose meter	16
				MDI + SMBG: MDI; LifeScan InDuo glucose meter	16
6	Hirsch *et al.*, 2008[34]	USA	Age: 12 to < 18 years; HbA_{1c}: ≥ 7.5%; CSII experience: ≥ 6 months prior CSII treatment; number of hypoglycaemic events: NR	Integrated CSII + CGM: Paradigm 722 System (Medtronic)	49
				CSII + SMBG: SMBG and a Paradigm 715 Insulin Pump (Medtronic)	49
12	Bergenstal *et al.*, 2010[40]	USA; Canada	Age: 7–70 years; HbA_{1c}: 7.4–9.5%; CSII experience: CSII naive or no CSII in the last 3 years; number of hypoglycaemic events: ≥ 2 episodes of severe hypoglycaemia in the previous year excluded	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System (Medtronic)	78
				MDI + SMBG: Medtronic Guardian REAL-Time Clinical	78
12	Thrailkill *et al.*, 2011[48]	USA	Age: 8–18 years; HbA_{1c}: NR; CSII experience: NR; number of hypoglycaemic events: NR	CSII + SMBG: Animas pump model IR 1250; OneTouch Ultra blood glucose meter (LifeScan)	NR
				MDI + SMBG: MDI; OneTouch Ultra blood glucose meter (LifeScan)	NR

NR, not reported.

TABLE 66 Study characteristics for included studies in mixed populations

Follow-up, months	Study	Countries	Inclusion	Intervention	Number analysed for efficacy per arm
3	O'Connell *et al.*, 2009[35]	Australia	Age: 13–40 years; HbA_{1c}: ≤ 8.5%; CSII experience: > 3 months experience with CSII; number of hypoglycaemic events: history of severe hypoglycaemia while using CSII excluded	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system	26
				CSII + SMBG: NR; continue their usual insulin pump therapy and SMBG regimen	29
6	Hirsch *et al.*, 2008[34]	USA	Age: 12–72 years; HbA_{1c}: ≥ 7.5%; CSII experience: ≥ 6 months prior CSII treatment; number of hypoglycaemic events: NR	Integrated CSII + CGM: Paradigm 722 System	66
				CSII + SMBG: SMBG and a Paradigm 715 insulin pump	72
6	Ly *et al.*, 2013[33]	Australia	Age: 4–50 years; HbA_{1c}: ≤ 8.5%; CSII experience: ≥ 6 months prior CSII treatment; number of hypoglycaemic events: NR	CSII + CGM + Suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	46
				CSII + SMBG: continue using their insulin pump	49
6	Raccah *et al.*, 2009[36]	France	Age: 2–65 years; HbA_{1c}: > 8%; CSII experience: NR; number of hypoglycaemic events: NR	Non-integrated CSII + CGM: insulin pump with Holter-type CGM device	55
				CSII + SMBG: Paradigm 512/712 with SMBG	60
12	Bergenstal *et al.*, 2010[40]	USA; Canada	Age: 7–70 years; HbA_{1c}: 7.4–9.5%; CSII experience: CSII naive or no CSII in the last 3 years; number of hypoglycaemic events: ≥ 2 episodes of severe hypoglycaemia in the previous year excluded	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System	244
				MDI + SMBG: Guardian REAL-Time Clinical	241

NR, not reported.

TABLE 67 Study characteristics for included studies in pregnant women

Follow-up, months	Study	Country	Inclusion	Intervention	Number analysed for efficacy per arm
NR (9 months)	Nosari *et al.*, 1993[50]	Italy	Age: adults; HbA_{1c}: NR; CSII experience: NR; number of hypoglycaemic events: NR	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps (Disetronic Medical Systems, Inc., FL, USA)	16
				MDI + SMBG: NR	16

NR, not reported.

TABLE 68 Baseline characteristics for included studies in adults

Follow-up, months	Study	Intervention	Total (*N*)	Age, years (SD)	Gender, *n* (%)	Duration of diabetes, years (SD)	BMI, kg/m^2 (SD)	Weight, kg (SD)	HbA_{1c}% (SD)
3	Bergenstal *et al.*, 2013[32]	CSII + CGM+ Suspend: Paradigm Veo pump with Enlite sensor	121	41.6 (12.8)	Male: 46 (38.0) Female: 75 (62.0)	27.1 (12.5)	27.6 (4.6)	79.6 (15.9)	7.26 (0.7)
		Integrated CSII + CGM: Paradigm Revel 2.0 pump with Enlite sensor	126	44.8 (13.8)	Male: 50 (39.7) Female: 76 (60.3)	26.7 (12.7)	27.1 (4.3)	79.1 (15.1)	7.21 (0.8)
3.45	Lee *et al.*, 2007[38]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time 722 System as adjunct to SMBG (Paradigm Link glucose meter)	8	NR (NR)	Male: NR (NR) Female: NR (NR)	NR (NR)	NR (NR)	NR (NR)	9.45 (0.6)
		MDI + SMBG: SMBG (Paradigm Link glucose meter)	8	NR (NR)	Male: NR (NR) Female: NR (NR)	NR (NR)	NR (NR)	NR (NR)	8.58 (1.3)
3.69	Peyrot and Rubin, 2009[39]	Integrated CSII + CGM: Paradigm 722 System (smart CSII pump with real-time CGM and CareLink data management software) as adjunct to SMBG (Becton Dickinson meters and strips)	14	NR (NR)	Male: NR (NR) Female: NR (NR)	NR (NR)	NR (NR)	77.69 (18.7)	8.87 (0.9)
		MDI + SMBG: SMBG (Becton Dickinson meters and strips) with CareLink data management software	13	NR (NR)	Male: NR (NR) Female: NR (NR)	NR (NR)	NR (NR)	82.61 (16.0)	8.32 (1.1)
3.69	DeVries *et al.*, 2002[42]	CSII + SMBG: Disetronic H-TRONplus insulin pump; Glucotouch or One Touch Profile memory glucose meter (LifeScan)	32	36.2 (10.3)	Male: 21 (54.0) Female: 18 (46.0)	17.6 (9.8)	NR (NR)	77.3 (13.6)	9.27 (1.4)
		MDI + SMBG: Glucotouch or One Touch Profile memory glucose meter (LifeScan)	40	37.3 (10.6)	Male: 21 (53.0) Female: 19 (47.0)	18 (9.4)	NR (NR)	79.8 (13.5)	9.25 (1.4)
6	Bolli *et al.*, 2009[41]	CSII + SMBG: MiniMed 508 with SMBG	24	37.6 (12.3)	Male: 13 (54.2) Female: 11 (45.8)	18.5 (8.4)	23.8 (2.7)	70.1 (11.6)	7.7 (0.7)
		MDI + SMBG: NR	26	42.4 (9.9)	Male: 14 (53.8) Female: 12 (46.2)	20.9 (10.6)	24.3 (1.9)	70.8 (10.5)	7.8 (0.6)
6	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic MiniMed Inc.) with SMBG (meter not described)	41	39.3 (11.9)	Male: 22 (50.0) Female: 22 (50.0)	16.9 (10.7)	NR (NR)	NR (NR)	8.47 (0.9)
		MDI + SMBG: SMBG (meter not described)	36	37.3 (10.7)	Male: 21 (53.8) Female: 18 (46.2)	21 (9.4)	NR (NR)	NR (NR)	8.64 (0.9)

continued

TABLE 68 Baseline characteristics for included studies in adults (*continued*)

Follow-up, months	Study	Intervention	Total (*N*)	Age, years (SD)	Gender, *n* (%)	Duration of diabetes, years (SD)	BMI, kg/m^2 (SD)	Weight, kg (SD)	HbA_{1c}% (SD)
6	Hirsch *et al.*, 2008[34]	Integrated CSII + CGM: Paradigm 722 System	17	NR (NR)	Male: NR (NR) Female: NR (NR)	NR (NR)	NR (NR)	NR (NR)	8.37 (0.6)
		CSII + SMBG: SMBG and a Paradigm 715 insulin pump	23	NR (NR)	Male: NR (NR) Female: NR (NR)	NR (NR)	NR (NR)	NR (NR)	8.3 (0.5)
6	Thomas *et al.*, 2007[45]	CSII + SMBG: Medtronic 508 with SMBG	7	NR (NR)	Male: NR (NR) Female: NR (NR)	NR (NR)	NR (NR)	72.5 (8.6)	8.5 (1.9)
		MDI + SMBG: NR	7	NR (NR)	Male: NR (NR) Female: NR (NR)	NR (NR)	NR (NR)	78 (15.2)	8.6 (1.1)
9	Tsui *et al.*, 2001[46]	CSII + SMBG: MiniMed 507 insulin infusion pump; Advantage meter (Roche Diagnostics)	12	36 (12.0)	Male: 8 (62.0) Female: 5 (38.0)	17 (10.0)	27 (4.0)	NR (NR)	7.7 (0.6)
		MDI + SMBG: Advantage meter (Roche Diagnostics)	14	36 (10.0)	Male: 10 (71.0) Female: 4 (29.0)	15 (9.0)	26 (3.0)	NR (NR)	8.2 (0.7)
12	Nosadini *et al.*, 1988[43]	CSII + SMBG: Betatron II + SMBG (CSII-HOR)	10	34 (3.0)	Male: 6 (60.0) Female: 4 (40.0)	7 (3.0)	NR (NR)	70 (7.0)	NR (NR)
		CSII + SMBG: Microjet Mc 20 + SMBG (CSII-FBR)	19	36 (6.0)	Male: 11 (57.9) Female: 8 (42.1)	8 (3.0)	NR (NR)	77 (7.0)	NR (NR)
		MDI + SMBG: NR (ICIT)	15	32 (9.0)	Male: 11 (73.3) Female: 4 (26.7)	7 (4.0)	NR (NR)	71 (6.0)	NR (NR)
12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System	166	41.9 (12.3)	Male: 94 (57.0) Female: 72 (43.0)	20.2 (12.2)	27.4 (4.4)	80.8 (15.9)	8.3 (0.5)
		MDI + SMBG: Guardian REAL-Time Clinical	163	40.6 (12.0)	Male: 93 (57.0) Female: 70 (43.0)	20.2 (11.7)	28.4 (5.7)	85.1 (18.5)	8.3 (0.5)
84	Brinchmann-Hansen *et al.*, 1985[44]	CSII + SMBG: Nordisk Infuser ($n = 3$) or AutoSyringe AS6C ($n = 12$)	15	26 (19.8)	Male: 7 (46.7) Female: 8 (53.3)	12.75 (NR)	NR (NR)	68.6 (NR)	8.7 (NR)
		MDI + SMBG: NR	15	26 (22.7)	Male: 7 (46.7) Female: 8 (53.3)	12.83 (NR)	NR (NR)	71.7 (NR)	8.3 (NR)

ICIT, intensified conventional insulin therapy; NR, not reported.

TABLE 69 Baseline characteristics for included studies in children

Follow-up, months	Study	Intervention	Total (*N*)	Age, years (SD)	Gender, *n* (%)	Duration of diabetes, years (SD)	BMI, kg/m^2 (SD)	Weight, kg (SD)	HbA_{1c}% (SD)
3.5	Weintrob *et al.*, 2003[47]	CSII + SMBG: programmable external pump (MiniMed 508) using insulin lispro	11	11.9 (1.4)	Male: 4 (36.4) Female: 7 (63.6)	5.3 (1.9)	NR (NR)	NR (NR)	7.9 (1.3)
		MDI + SMBG: NR	12	11.6 (1.5)	Male: 6 (50.0) Female: 6 (50.0)	6.3 (2.6)	NR (NR)	NR (NR)	8.6 (0.8)
3.69	Doyle *et al.*, 2004[49]	CSII + SMBG: Medtronic MiniMed 508 or Paradigm 511; LifeScan InDuo glucose meter	16	12.5 (3.2)	Male: 6 (37.5) Female: 10 (62.5)	6.8 (3.8)	NR (NR)	NR (NR)	8.1 (1.2)
		MDI + SMBG: MDI; LifeScan InDuo glucose meter	16	13 (2.8)	Male: 8 (50.0) Female: 8 (50.0)	5.6 (4.0)	NR (NR)	NR (NR)	8.2 (1.1)
6	Hirsch *et al.*, 2008[34]	Integrated CSII + CGM: Paradigm 722 System	49	NR (NR)	Male: NR (NR) Female: NR (NR)	NR (NR)	NR (NR)	NR (NR)	8.82 (1.1)
		CSII + SMBG: SMBG and a Paradigm 715 insulin pump	49	NR (NR)	Male: NR (NR) Female: NR (NR)	NR (NR)	NR (NR)	NR (NR)	8.59 (0.8)
12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System	78	11.7 (3.0)	Male: 46 (59.0) Female: 32 (41.0)	4.7 (3.1)	20.2 (3.8)	49 (17.9)	8.3 (0.6)
		MDI + SMBG: Guardian REAL-Time Clinical	78	12.7 (3.1)	Male: 41 (53.0) Female: 37 (47.0)	5.4 (3.7)	20.6 (4.5)	51.6 (19.3)	8.3 (0.5)
12	Thrailkill *et al.*, 2011[48]	CSII + SMBG: Animas pump model IR 1250; OneTouch Ultra blood glucose meter (LifeScan)	NR	12.1 (3.6)	Male: 5 (41.7) Female: 7 (58.3)	0 (NA)	19.56 (4.1)	40.56 (13.6)	11.2 (2.1)
		MDI + SMBG: MDI; OneTouch Ultra blood glucose meter (LifeScan)	NR	12.1 (2.5)	Male: 6 (50.0) Female: 6 (50.0)	0 (NA)	18.82 (3.4)	46.53 (12.6)	11.7 (2.6)

NA, not applicable; NR, not reported.

TABLE 70 Baseline characteristics for included studies in mixed populations

Follow-up, months	Study	Intervention	Total (*N*)	Age, years (SD)	Gender, *n* (%)	Duration of diabetes, years (SD)	BMI, kg/m^2 (SD)	Weight, kg (SD)	HbA_{1c}% (SD)
3	O'Connell *et al.*, 2009[35]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system	26	23.4 (8.6)	Male: 9 (29.0) Female: 22 (71.0)	11.1 (7.6)	NR (NR)	NR (NR)	7.3 (0.6)
		CSII + SMBG: NR; continue their usual insulin pump therapy and SMBG regimen	29	23 (8.1)	Male: 9 (29.0) Female: 22 (71.0)	9.2 (7.2)	NR (NR)	NR (NR)	7.5 (0.7)
6	Hirsch *et al.*, 2008[34]	Integrated CSII + CGM: Paradigm 722 System	66	33 (14.6)	Male: 32 (48.5) Female: 34 (51.5)	20.8 (12.4)	26.9 (5.5)	76.8 (19.3)	8.49 (0.8)
		CSII + SMBG: SMBG and a Paradigm 715 insulin pump	72	33.2 (16.4)	Male: 28 (39.9) Female: 44 (61.1)	16.7 (10.5)	26.3 (5.1)	75.4 (18.0)	8.39 (0.6)
6	Ly *et al.*, 2013[33]	CSII + CGM + Suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	46	17.4 (10.6)	Male: 26 (56.5) Female: 20 (43.5)	9.8 (7.4)	NR (NR)	NR (NR)	7.6 (0.9)
		CSII + SMBG: continue using their insulin pump	49	19.7 (12.9)	Male: 21 (42.9) Female: 28 (57.1)	12.1 (10.0)	NR (NR)	NR (NR)	7.4 (0.7)
6	Raccah *et al.*, 2009[36]	Non-integrated CSII + CGM: insulin pump with Holter-type CGM device	55	28.1 (15.1)	Male: 30 (54.5) Female: 25 (45.5)	11.2 (9.0)	23.5 (4.1)	65.7 (17.4)	9.11 (1.3)
		CSII + SMBG: Paradigm 512/712 with SMBG	60	28.8 (16.7)	Male: 34 (56.7) Female: 26 (43.3)	12.3 (8.8)	22.5 (4.4)	62.6 (18.6)	9.28 (1.2)
12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System	244	32.2 (17.5)	Male: 140 (57.0) Female: 104 (43.0)	15.2 (12.5)	25.3 (6.0)	71.9 (25.3)	8.3 (0.5)
		MDI + SMBG: Guardian REAL-Time Clinical	241	31.5 (16.5)	Male: 134 (56.0) Female: 107 (44.0)	15.4 (12.0)	25.6 (5.6)	73 (21.8)	8.3 (0.5)

NR, not reported.

TABLE 71 Baseline characteristics for included studies in pregnant women

Study	Intervention	Total (*N*)	Age, years (SD)	Gender, *n* (%)	Duration of diabetes, years (SD)	BMI, kg/m^2 (SD)	Weight, kg (SD)	HbA_{1c} % (SD)
Nosari *et al.*, 1993[50]	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	16	25.5 (1.8)	Male: 0 (0) Female: 16 (100.0)	NR (NR)	21.8 (0.4)	NR (NR)	NR (NR)
	MDI + SMBG: NR	16	27 (3.0)	Male: 0 (0) Female: 16 (100.0)	NR (NR)	21.6 (0.6)	NR (NR)	NR (NR)

NR, not reported.

TABLE 72 Results for change in HbA_{1c} levels from baseline in adults

Follow-up, months	Study	Intervention	Number analysed	Change in HbA_{1c} levels from baseline, % (SD)
2	Thomas *et al.*, 2007[45]	CSII + SMBG: Medtronic 508 with SMBG	7	Baseline: 8.5 (1.9); follow-up: 7.3 (0.67); change from baseline: NR (NR)
		MDI + SMBG: NR	7	Baseline: 8.6 (1.1); follow-up: 8.3 (1); change from baseline: NR (NR)
3	Bergenstal *et al.*, 2013[32]	CSII + CGM + suspend: Paradigm Veo pump with Enlite sensor	121	Baseline: 7.26 (0.71); follow-up: 7.24 (0.67); change from baseline: 0 (0.44)
		Integrated CSII + CGM: Paradigm Revel 2.0 pump with Enlite sensor	126	Baseline: 7.21 (0.77); follow-up: 7.14 (0.77); change from baseline: –0.04 (0.42)
3	Brinchmann-Hansen *et al.*, 1985[44]	CSII + SMBG: NR	15	Baseline: 10.1 (NR); follow-up: 8.9 (NR); change from baseline: NR (NR)
		MDI + SMBG: NR	15	Baseline: 9.4 (NR); follow-up: 8.7 (NR); change from baseline: NR (NR)
3.45	Lee *et al.*, 2007[38]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time 722 system as adjunct to SMBG (Paradigm Link glucose meter)	8	Baseline: 9.45 (0.55); follow-up: 7.4 (0.66); change from baseline: –2.05 (NR)
		MDI + SMBG: SMBG (Paradigm Link glucose meter)	8	Baseline: 8.58 (1.3); follow-up: 7.5 (1.01); change from baseline: –1.08 (NR)
3.68	Peyrot and Rubin, 2009[39]	Integrated CSII + CGM: Paradigm 722 system (smart CSII pump with real-time CGM and CareLink data management software) as adjunct to SMBG (Becton Dickinson meters and strips)	14	Baseline: 8.87 (0.89); follow-up: 7.16 (0.75); change from baseline: –1.71 (NR)
		MDI + SMBG: SMBG (Becton Dickinson meters and strips) with CareLink™ data management software	13	Baseline: 8.32 (1.05); follow-up: 7.3 (0.92); change from baseline: –1.02 (NR)

TABLE 72 Results for change in HbA_{1c} levels from baseline in adults (*continued*)

Follow-up, months	Study	Intervention	Number analysed	Change in HbA_{1c} levels from baseline, % (SD)
3.69	DeVries *et al.*, 2002[42]	CSII + SMBG: Disetronic H-TRONplus insulin pump; Glucotouch or One Touch Profile memory glucose meter (LifeScan)	32	Baseline: 9.27 (1.4); follow-up: NR (NR); change from baseline: –0.91 (1.28)
		MDI + SMBG: Glucotouch or One Touch Profile memory glucose meter (LifeScan)	40	Baseline: 9.25 (1.4); follow-up: NR (NR); change from baseline: –0.07 (0.7)
4	Thomas *et al.*, 2007[45]	CSII + SMBG: Medtronic 508 with SMBG	7	Baseline: 8.5 (1.9); follow-up: 7.4 (1.16); change from baseline: NR (NR)
		MDI + SMBG: NR	7	Baseline: 8.6 (1.1); follow-up: 8 (0.9); change from baseline: NR (NR)
6	Bolli *et al.*, 2009[41]	CSII + SMBG: MiniMed 508 + glucose monitor. Glucose monitor: NR	24	Baseline: 7.7 (0.7); follow-up: 7 (0.8); change from baseline: –0.7 (0.7)
		MDI + SMBG: insulin glargine (Lantus®, Sanofi-Aventis) plus mealtime insulin lispro. Glucose monitor: NR	26	Baseline: 7.8 (0.6); follow-up: 7.2 (0.7); change from baseline: –0.6 (0.8)
6	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic MiniMed Inc.) with SMBG (meter not described)	41	Baseline: 8.46 (0.95); follow-up: 7.23 (0.65); change from baseline: –1.23 (1.01)
		MDI + SMBG: SMBG (meter not described)	36	Baseline: 8.59 (0.82); follow-up: 8.46 (1.04); change from baseline: –0.13 (0.56)
6	Hirsch *et al.*, 2008[34]	Integrated CSII + CGM: Paradigm 722 System	49	Baseline: 8.37 (0.6); follow-up: 7.68 (0.84); change from baseline: –0.69 (0.73)
		CSII + SMBG: SMBG and a Paradigm 715 insulin pump	49	Baseline: 8.3 (0.54); follow-up: 7.66 (0.67); change from baseline: –0.64 (0.57)
6	Brinchmann-Hansen *et al.*, 1985[44]	CSII + SMBG: NR	15	Baseline: 10.1 (NR); follow-up: 9.1 (NR); change from baseline: NR (NR)
		MDI + SMBG: NR	15	Baseline: 9.4 (NR); follow-up: 8.8 (NR); change from baseline: NR (NR)
6	Thomas *et al.*, 2007[45]	CSII + SMBG: Medtronic 508 + SMBG	7	Baseline: 8.5 (1.9); follow-up: 7.4 (1); change from baseline: NR (NR)
		MDI + SMBG: NR	7	Baseline: 8.6 (1.1); follow-up: 7.6 (0.7); change from baseline: NR (NR)

TABLE 72 Results for change in HbA_{1c} levels from baseline in adults (*continued*)

Follow-up, months	Study	Intervention	Number analysed	Change in HbA_{1c} levels from baseline, % (SD)
9	Tsui *et al.*, 2001[46]	CSII + SMBG: MiniMed 507 insulin infusion pump; Advantage meter (Roche Diagnostics)	12	Baseline: 7.73 (0.6); follow-up: 7.38 (NR); change from baseline: NR (NR)
		MDI + SMBG: Advantage meter (Roche Diagnostics)	14	Baseline: 8.16 (0.7); follow-up: 7.56 (NR); change from baseline: NR (NR)
12	Nosadini *et al.*, 1988[43]	CSII + SMBG: Betatron II + SMBG (CSII-HOR)	10	Baseline: NR (NR); follow-up: 6.1 (0.9); change from baseline: NR (NR)
		CSII + SMBG: Microjet Mc 20 + SMBG (CSII-FBR)	19	Baseline: NR (NR); follow-up: 6.3 (0.7); change from baseline: NR (NR)
		MDI + SMBG: NR (ICIT)	15	Baseline: NR (NR); follow-up: 7.1 (0.9); change from baseline: NR (NR)
12	Brinchmann-Hansen *et al.*, 1985[44]	CSII + SMBG: NR	15	Baseline: 10.1 (NR); follow-up: 8.5 (NR); change from baseline: NR (NR)
		MDI + SMBG: NR	15	Baseline: 9.4 (NR); follow-up: 8.5 (NR); change from baseline: NR (NR)
12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System	166	Baseline: 8.3 (0.5); follow-up: NR (NR); change from baseline: –1 (0.7)
		MDI + SMBG: Guardian REAL-Time Clinical	163	Baseline: 8.3 (0.5); follow-up: NR (NR); change from baseline: –0.4 (0.8)
24	Brinchmann-Hansen *et al.*, 1985[44]	CSII + SMBG: NR	15	Baseline: 10.1 (NR); follow-up: 8.7 (NR); change from baseline: NR (NR)
		MDI + SMBG: NR	15	Baseline: 9.4 (NR); follow-up: 9.1 (NR); change from baseline: NR (NR)

FBR, fixed basal overnight insulin infusion rate; HOR, higher programmable overnight insulin infusion rate; ICIT, intensified conventional insulin therapy; NR, not reported.

TABLE 73 Results for change in HbA_{1c} levels from baseline in children

Follow-up, months	Study	Intervention	Number analysed	Change in HbA_{1c} levels from baseline, % (SD)
3.5	Weintrob *et al.*, 2003[47]	CSII + SMBG: programmable external pump (MiniMed 508) using insulin lispro	11	Baseline: 7.9 (1.3); follow-up: 7.9 (0.7); change from baseline: NR (NR)
		MDI + SMBG: NR	12	Baseline: 8.6 (0.8); follow-up: 8.2 (0.8); change from baseline: NR (NR)
3.69	Doyle *et al.*, 2004[49]	CSII + SMBG: Medtronic MiniMed 508 or Paradigm 511; LifeScan InDuo glucose meter	16	Baseline: 8.1 (1.2); follow-up: 7.2 (1); change from baseline: NR (NR)
		MDI + SMBG: MDIs and LifeScan InDuo glucose meter	16	Baseline: 8.2 (1.1); follow-up: 8.1 (1.2); change from baseline: NR (NR)
6	Hirsch *et al.*, 2008[34]	Integrated CSII + CGM: Paradigm 722 System (Medtronic)	17	Baseline: 8.82 (1.05); follow-up: 8.02 (1.11); change from baseline: –0.79 (0.65)
		CSII + SMBG: SMBG and a Paradigm 715 insulin pump (Medtronic)	23	Baseline: 8.59 (0.8); follow-up: 8.21 (0.97); change from baseline: –0.37 (0.95)
6	Thrailkill *et al.*, 2011[48]	CSII + SMBG: Animas pump model IR 1250; OneTouch Ultra blood glucose meter (LifeScan)	NR	Baseline: 11.2 (2.1); follow-up: 6.34 (0.7); change from baseline: NR (NR)
		MDI + SMBG: MDIs and OneTouch Ultra blood glucose meter (LifeScan)	NR	Baseline: 11.7 (2.6); follow-up: 7 (1.1); change from baseline: NR (NR)
12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System (Medtronic)	78	Baseline: 8.3 (0.6); follow-up: NR (NR); change from baseline: –0.4 (0.9)
		MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	78	Baseline: 8.3 (0.5); follow-up: NR (NR); change from baseline: 0.2 (1)
12	Thrailkill *et al.*, 2011[48]	CSII + SMBG: Animas pump model IR 1250; OneTouch Ultra blood glucose meter (LifeScan)	NR	Baseline: 11.2 (2.1); follow-up: 6.9 (0.7); change from baseline: NR (NR)
		MDI + SMBG: MDIs and OneTouch Ultra blood glucose meter (LifeScan)	NR	Baseline: 11.7 (2.6); follow-up: 6.9 (0.9); change from baseline: NR (NR)

NR, not reported.

TABLE 74 Results for change in HbA_{1c} levels from baseline in mixed populations

Follow-up, months	Study	Intervention	Number analysed	Change from baseline in HbA_{1c} (%)
3	O'Connell *et al.*, 2009[35]	CSII + CGM Integrated: MiniMed Paradigm REAL-Time system (Medtronic)	26	Baseline: 7.3 (0.6); follow-up: 7.1 (0.8); change from baseline: NR (NR)
		CSII + SMBG: continue their usual insulin pump therapy and SMBG regimen	29	Baseline: 7.5 (0.7); follow-up: 7.8 (0.9); change from baseline: NR (NR)
6	Hirsch *et al.*, 2008[34]	Integrated CSII + CGM: Paradigm 722 system (Medtronic)	66	Baseline: 8.39 (0.64); follow-up: 7.77 (0.92); change from baseline: –0.71 (0.71)
		CSII + SMBG: SMBG and a Paradigm 715 insulin pump (Medtronic)	72	Baseline: 8.49 (0.76); follow-up: 7.84 (0.81); change from baseline: –0.56 (0.72)
6	Ly *et al.*, 2013[33]	CSII + CGM + Suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	46	Baseline: 7.6 (NR); follow-up: 7.5 (NR); change from baseline: –0.1 (NR)
		CSII + SMBG: continue using their insulin pump	49	Baseline: 7.4 (NR); follow-up: 7.4 (NR); change from baseline: –0.06 (NR)
6	Raccah *et al.*, 2009[36]	Non-integrated CSII + CGM: insulin pump with Holter-type CGM device	55	Baseline: 9.11 (1.28); follow-up: NR (NR); change from baseline: –0.81 (1.09)
		CSII + SMBG: Paradigm 512/712 + SMBG	60	Baseline: 9.28 (1.19); follow-up: NR (NR); change from baseline: –0.57 (0.94)
12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System (Medtronic)	244	Baseline: 8.3 (0.5); follow-up: 7.5 (NR); change from baseline: –0.8 (0.84)
		MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	241	Baseline: 8.3 (0.5); follow-up: 8.1 (NR); change from baseline: –0.2 (0.89)

NR, not reported.

TABLE 75 Results for change in HbA_{1c} levels from baseline in pregnant women

Study	Follow-up, pregnancy trimester	Intervention	Number analysed	Change in HbA_{1c} levels from baseline, % (SD)
Nosari *et al.*, 1993[50]	First	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	16	Baseline: NR (NR); follow-up: 6 (NR); change from baseline: NR (NR)
		MDI + SMBG: NR	16	Baseline: NR (NR); follow-up: 6.2 (NR); change from baseline: NR (NR)
	Second	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	16	Baseline: NR (NR); follow-up: 6.8 (NR); change from baseline: NR (NR)
		MDI + SMBG: NR	16	Baseline: NR (NR); follow-up: 6.1 (NR); change from baseline: NR (NR)
	Third	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	16	Baseline: NR (NR); follow-up: 6.3 (NR); change from baseline: NR (NR)
		MDI + SMBG: NR	16	Baseline: NR (NR); follow-up: 6.2 (NR); change from baseline: NR (NR)

NR, not reported.

TABLE 76 Results for proportion achieving HbA_{1c} levels of $\leq 7\%$ in adult populations

Follow-up, months	Study	Intervention	Proportion achieving HbA_{1c} levels of $\leq 7\%$, *n* (%)	Total number analysed
6	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic) with SMBG (meter not described)	14 (34)	41
		MDI + SMBG: SMBG (meter not described)	0 (0)	36
12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System (Medtronic)	57 (34)	166
		MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	19 (12)	163

TABLE 77 Results for proportion achieving HbA_{1c} levels of ≤ 7% in child populations

Follow-up, months	Study	Intervention	Proportion achieving HbA_{1c} levels of ≤ 7%, *n* (%)	Total number analysed
3.69	Doyle *et al.*, 2004[49]	CSII + SMBG: Medtronic MiniMed 508 or Paradigm 511; LifeScan InDuo glucose meter	8 (50)	16
		MDI + SMBG: MDIs and LifeScan InDuo glucose meter	2 (12.5)	16
12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system (Medtronic)	10 (13)	78
		MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	4 (5)	78

TABLE 78 Results for proportion achieving HbA_{1c} levels of ≤ 7% in mixed populations

Follow-up, months	Study	Intervention	Proportion achieving HbA_{1c} levels of ≤ 7%, *n* (%)	Total number analysed
3	O'Connell *et al.*, 2009[35]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system (Medtronic)	14 (56)	26
		CSII + SMBG: continue their usual insulin pump therapy and SMBG regimen	5 (17)	29
6	Hirsch *et al.*, 2008[34]	Integrated CSII + CGM: Paradigm 722 System (Medtronic)	16 (24.2)	66
		CSII + SMBG: SMBG and a Paradigm 715 insulin pump (Medtronic)	12 (19.4)	72
12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system (Medtronic)	67 (27)	244
		MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	23 (10)	241

TABLE 79 Results: hypoglycaemia

Population	Severity	Follow-up, months	Study	Intervention	Number of people with hypoglycaemia/ number analysed (%)	Number of hypoglycaemic events/number of people analysed
Adults	Any	6	Bolli *et al.*, 2009[41]	CSII + SMBG: MiniMed 508 and glucose monitor (NR)	2/28 (7.14)	NR
				MDI + SMBG: insulin glargine plus mealtime insulin lispro; glucose monitor NR	2/29 (6.90)	NR
	Mild	6	Thomas *et al.*, 2007[45]	CSII + SMBG: Medtronic 508 with SMBG	NR	141/7
				MDI + SMBG: NR	NR	75/7
	NR	3.45	Lee *et al.*, 2007[38]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time 722 System as adjunct to SMBG (Paradigm Link glucose meter)	0/8 (0.00)	NR
				MDI + SMBG: SMBG (Paradigm Link glucose meter)	1/8 (12.50)	NR
	Severe	3.68	DeVries *et al.*, 2002[42]	CSII + SMBG: Disetronic H-TRONplus insulin pump; Glucotouch or One Touch Profile memory glucose meter (LifeScan)	3/32 (9.40)	NR
				MDI + SMBG: Glucotouch or One Touch Profile memory glucose meter (LifeScan)	6/40 (15.00)	NR
	Severe	3.68	Peyrot and Rubin, 2009[39]	Integrated CSII + CGM: Paradigm 722 System (smart CSII pump with real-time CGM and CareLink data management software) as adjunct to SMBG (Becton Dickinson meters and strips)	NR	0/14
				MDI + SMBG: SMBG (Becton Dickinson meters and strips) with CareLink data management software	NR	3/13
	Severe	6	Bolli *et al.*, 2009[41]	CSII + SMBG: MiniMed 508 with glucose monitor (NR)	23/28 (82.14)	NR
				MDI + SMBG: insulin glargine plus mealtime insulin lispro; glucose monitor NR	27/29 (93.10)	NR
			Thomas *et al.*, 2007[45]	CSII + SMBG: Medtronic 508 with SMBG	NR	3/7
				MDI + SMBG: NR	NR	2/7
	Severe	12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system (Medtronic)	17/169 (10.10)	NR
				MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	13/167 (7.80)	NR

Population	Severity	Follow-up, months	Study	Intervention	Number of people with hypoglycaemia/ number analysed (%)	Number of hypoglycaemic events/number of people analysed
Children	Severe	3.68	Doyle *et al.*, 2004[49]	CSII + SMBG: Medtronic MiniMed 508 or Paradigm 511; LifeScan InDuo glucose meter	2/16 (12.50)	2/16
				MDI + SMBG: MDIs with LifeScan InDuo glucose meter	4/16 (25.00)	5/16
	Severe	12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System (Medtronic)	4/78 (5.10)	NR
				MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	4/81 (4.90)	NR
	Severe	12	Thrailkill *et al.*, 2011[48]	CSII + SMBG: Animas pump model IR 1250; OneTouch Ultra blood glucose meter (LifeScan)	0/0 (0.00)	NR
				MDI + SMBG: MDIs with OneTouch Ultra blood glucose meter (LifeScan)	0/0 (0.00)	NR
Mixed	Moderate	6	Ly *et al.*, 2013[33]	CSII + CGM + suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	35/41 (85.37)	NR
				CSII + SMBG: continue using their insulin pump	13/45 (28.89)	NR
	Moderate and severe	6	Ly *et al.*, 2013[33]	CSII + CGM + suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	35/41 (85.37)	NR
				CSII + SMBG: continue using their insulin pump	13/45 (28.89)	NR
	Severe	6	Hirsch *et al.*, 2008[34]	Integrated CSII + CGM: Paradigm 722 System (Medtronic)	8/66 (NR)	11/66
				CSII + SMBG: SMBG and a Paradigm 715 insulin pump (Medtronic)	3/72 (NR)	3/72
	Severe	6	Ly *et al.*, 2013[33]	CSII + CGM + suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	0/41 (0.00)	NR
				CSII + SMBG: continue using their insulin pump	6/45 (13.33)	NR
	Severe	12	Bergenstal *et al.*,[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System (Medtronic)	21/247 (8.50)	NR
				MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	17/248 (6.90)	NR

continued

TABLE 79 Results: hypoglycaemia (*continued*)

Population	Severity	Follow-up, months	Study	Intervention	Number of people with hypoglycaemia/ number analysed (%)	Number of hypoglycaemic events/number of people analysed
Pregnant	Severe	NR	Nosari *et al.*, 1993[50]	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	NR	3/NR
				MDI + SMBG: NR	NR	1/NR

NR, not reported.

TABLE 80 Results for hypoglycaemic event rate

Population	Severity	Follow-up, months	Event rate definition	Study	Intervention	Hypoglycaemic event rate	Hyperglycaemic event rate	Total number analysed
Adults	Mild	3.69	Number of mild hypoglycaemic episodes per patient-week	DeVries *et al.*, 2002[42]	CSII + SMBG: Disetronic H-TRONplus insulin pump; Glucotouch or One Touch Profile memory glucose meter (LifeScan)	0.98 (2.0)	NR	32
					MDI + SMBG: Glucotouch or One Touch Profile memory glucose meter (LifeScan)	–0.02 (1.2)	NR	40
	Mild	6	Mild symptomatic hypoglycaemic events per patient-year	Thomas *et al.*, 2007[45]	CSII + SMBG: Medtronic 508 with SMBG	40 (NR)	NR	7
					MDI + SMBG: NR	21 (NR)	NR	7
	Mild	12	Hypoglycaemic events per patient per year	Nosadini *et al.*, 1988[43]	CSII + SMBG: Betatron II with SMBG (CSII-HOR)	30 (11.0)	NR	10
					CSII + SMBG: Microjet Mc 20 with SMBG (CSII-FBR)	36 (10.0)	NR	19
					MDI + SMBG: NR (ICIT)	59 (12.0)	NR	15
	NR	3	Day and night hypoglycaemia: events per patient-week	Bergenstal *et al.*, 2013[32]	CSII + CGM + suspend: Paradigm Veo pump with Enlite sensor	3.3 (2.0)	NR	121
					Integrated CSII + CGM: Paradigm Revel 2.0 pump with Enlite sensor	4.7 (2.7)	NR	126
	NR	3	Nocturnal hypoglycaemia: events per patient-week	Bergenstal *et al.*, 2013[32]	CSII + CGM + Suspend: Paradigm Veo pump with Enlite sensor	1.5 (1.0)	NR	121
					Integrated CSII + CGM: Paradigm Revel 2.0 pump with Enlite sensor	2.2 (1.3)	NR	126

continued

TABLE 80 Results for hypoglycaemic event rate (*continued*)

Population	Severity	Follow-up, months	Event rate definition	Study	Intervention	Hypoglycaemic event rate	Hyperglycaemic event rate	Total number analysed
	NR	6	Number of hyperglycaemic events standardised per day	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic) with SMBG (meter not described)	NR	2.1 (0.8)	40
					MDI + SMBG: SMBG (meter not described)	NR	2.2 (0.7)	31
	NR	6	Number of hypoglycaemic events standardised per day	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic) with SMBG (meter not described)	0.7 (0.7)	NR	40
					MDI + SMBG: SMBG (meter not described)	0.6 (0.7)	NR	31
	NR	12	Hyperglycaemic events per patient per year	Nosadini *et al.*, 1988[43]	CSII + SMBG: Betatron II with SMBG (CSII-HOR)	NR	17 (4.0)	10
					CSII + SMBG: Microjet Mc 20 with SMBG (CSII-FBR)	NR	18 (5.0)	19
					MDI + SMBG: NR (ICIT)	NR	20 (3.0)	15
	NR	24	Symptomatic hypoglycaemic episodes per patient per week	Brinchmann-Hansen *et al.*, 1985[44]	CSII + SMBG: NR	1.7 (NR)	NR	15
					MDI + SMBG: NR	1.2 (NR)	NR	15
	Severe	6	Severe hypoglycaemic events per patient-year	Thomas *et al.*, 2007[45]	CSII + SMBG: Medtronic 508 with SMBG	0.9 (NR)	NR	7
					MDI + SMBG: NR	0.6 (NR)	NR	7
	Severe	12	Hypoglycaemic events per patient per year	Nosadini *et al.*, 1988[43]	CSII + SMBG: Betatron II + SMBG (CSII-HOR)	0.16 (0.1)	NR	10
					CSII + SMBG: Microjet Mc 20 + SMBG (CSII-FBR)	0.14 (0.1)	NR	19
					MDI + SMBG: NR (ICIT)	0.42 (0.2)	NR	15
	Severe	12	Severe hypoglycaemic event rate per 100 person-years	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System (Medtronic)	15.31 (NR)	NR	169
					MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	17.62 (NR)	NR	167

Population	Severity	Follow-up, months	Event rate definition	Study	Intervention	Hypoglycaemic event rate	Hyperglycaemic event rate	Total number analysed
Children	Severe	12	Severe hypoglycaemic event rate per 100 person-years	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system (Medtronic)	8.98 (NR)	NR	78
					MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	4.95 (NR)	NR	81
Mixed	Moderate	6	Rate of hypoglycaemic events: 6-month rate per 100 patient-months	Ly *et al.*, 2013[33]	CSII + CGM + suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	28.5 (NR)	NR	46
					CSII + SMBG: continue using their insulin pump	9.6 (NR)	NR	49
	Moderate	6	Rate of hypoglycaemic events: incidence rate per 100 patient-months	Ly *et al.*, 2013[33]	CSII + CGM + suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	9.6 (NR)	NR	41
					CSII + SMBG: continue using their insulin pump	26.3 (NR)	NR	45
	Moderate + severe	6	Rate of hypoglycaemic events: 6-month rate per 100 patient-months	Ly *et al.*, 2013[33]	CSII + CGM + suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	28.4 (NR)	NR	46
					CSII + SMBG: continue using their insulin pump	11.9 (NR)	NR	49
	Moderate + severe	6	Rate of hypoglycaemic events: incidence rate per 100 patient-months	Ly *et al.*, 2013[33]	CSII + CGM + suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	9.5 (NR)	NR	41
					CSII + SMBG: continue using their insulin pump	34.2 (NR)	NR	45

continued

TABLE 80 Results for hypoglycaemic event rate (*continued*)

Population	Severity	Follow-up, months	Event rate definition	Study	Intervention	Hypoglycaemic event rate	Hyperglycaemic event rate	Total number analysed
	Severe	6	Rate of hypoglycaemic events: 6-month rate per 100 patient-months	Ly *et al.*, 2013[33]	CSII + CGM + suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	0 (NR)	NR	46
					CSII + SMBG: continue using their insulin pump	2.2 (NR)	NR	49
	Severe	6	Rate of hypoglycaemic events: incidence rate per 100 patient-months	Ly *et al.*, 2013[33]	CSII + CGM + suspend: sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic MiniMed) with automated insulin suspension	NR (NR)	NR	41
					CSII + SMBG: continue using their insulin pump	NR (NR)	NR	45
	Severe	12	Severe hypoglycaemia event rate per 100 person-years	Bergenstal *et al.*, 2010[40]	CSII + CGM integrated: MiniMed Paradigm REAL-Time System, Medtronic	13.31 (NR)	NR	247
					MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	13.48 (NR)	NR	248

FBR, fixed basal overnight insulin infusion rate; HOR, higher programmable overnight insulin infusion rate; ICIT, intensified conventional insulin therapy; NR, not reported.

TABLE 81 Results for HRQoL in adults (no data for children, mixed populations or pregnant women)

HRQoL scale	Follow-up, months	Study	Intervention	Number analysed	HRQoL score (SD)
Diabetes QOL	6	Thomas *et al.*, 2007[45]	CSII + SMBG: Medtronic 508 with SMBG	7	Baseline: 69 (19); follow-up: 74 (20); change from baseline: NR (NR)
			MDI + SMBG: NR	7	Baseline: 47 (20); follow-up: 70 (11); change from baseline: NR (NR)
Diabetes QOL; diabetic worry	9	Tsui *et al.*, 2001[46]	CSII + SMBG: MiniMed 507 insulin infusion pump; Advantage meter (Roche Diagnostics)	12	Baseline: NR (NR); follow-up: 85.2 (NR); change from baseline: NR (NR)
			MDI + SMBG: Advantage meter (Roche Diagnostics)	14	Baseline: NR (NR); follow-up: 79.8 (NR); change from baseline: NR (NR)
Diabetes QOL; global health	9	Tsui *et al.*, 2001[46]	CSII + SMBG: MiniMed 507 insulin infusion pump; Advantage meter (Roche Diagnostics)	12	Baseline: NR (NR); follow-up: 68.2 (NR); change from baseline: NR (NR)
			MDI + SMBG: Advantage meter (Roche Diagnostics)	14	Baseline: NR (NR); follow-up: 67.3 (NR); change from baseline: NR (NR)
Diabetes QOL; impact	9	Tsui *et al.*, 2001[46]	CSII + SMBG: MiniMed 507 insulin infusion pump; Advantage meter (Roche Diagnostics)	12	Baseline: NR (NR); follow-up: 69.9 (NR); change from baseline: NR (NR)
			MDI + SMBG: Advantage meter (Roche Diagnostics)	14	Baseline: NR (NR); follow-up: 68.4 (NR); change from baseline: NR (NR)
Diabetes QOL; satisfaction	9	Tsui *et al.*, 2001[46]	CSII + SMBG: MiniMed 507 insulin infusion pump; Advantage meter (Roche Diagnostics)	12	Baseline: NR (NR); follow-up: 75.6 (NR); change from baseline: NR (NR)
			MDI + SMBG: Advantage meter (Roche Diagnostics)	14	Baseline: NR (NR); follow-up: 68.3 (NR); change from baseline: NR (NR)
Diabetes QOL; social worry	9	Tsui *et al.*, 2001[46]	CSII + SMBG: MiniMed 507 insulin infusion pump; Advantage meter (Roche Diagnostics)	12	Baseline: NR (NR); follow-up: 89.6 (NR); change from baseline: NR (NR)
			MDI + SMBG: Advantage meter (Roche Diagnostics)	14	Baseline: NR (NR); follow-up: 94 (NR); change from baseline: NR (NR)
SF-36; bodily pain	6	Hermanides *et al.*,[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic) with SMBG (meter not described)	42	Baseline: 78.9 (25.4); follow-up: 79.9 (24.4); change from baseline: 1 (NR)
			MDI + SMBG: SMBG (meter not described)	33	Baseline: 78.7 (23); follow-up: 78.7 (22.6); change from baseline: 0 (NR)

continued

TABLE 81 Results for HRQoL in adults (no data for children, mixed populations or pregnant women) (*continued*)

HRQoL scale	Follow-up, months	Study	Intervention	Number analysed	HRQoL score (SD)
SF-36; general health	6	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic) with SMBG (meter not described)	42	Baseline: 55.5 (20.3); follow-up: 67.7 (21.6); change from baseline: 12.2 (NR)
			MDI + SMBG: SMBG (meter not described)	33	Baseline: 59.8 (22.3); follow-up: 63.1 (19.1); change from baseline: 3.3 (NR)
	12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system (Medtronic)	153	Baseline: NR (NR); follow-up: NR (NR); change from baseline: 2.7 (8.07)
			MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	151	Baseline: NR (NR); follow-up: NR (NR); change from baseline: –0.3 (7.13)
SF-36; general health	3.68	DeVries *et al.*, 2002[42]	CSII + SMBG: Disetronic H-TRONplus insulin pump; Glucotouch or One Touch Profile memory glucose meter (LifeScan)	NR	Baseline: 59.8 (37); follow-up: NR (NR); change from baseline: –1.2 (NR)
			MDI + SMBG: G Rucotouch or One Touch Profile memory glucose meter (Lifescan)		Baseline: 61.4 (20.5); follow-up: NR (NR); change from baseline: 5.9 (NR)
SF-36; mental composite score	12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System (Medtronic)	166	Baseline: 49.86 (9.64); follow-up: NR (NR); change from baseline: 0.05 (NR)
			MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	168	Baseline: 49.5 (9.09); follow-up: NR (NR); change from baseline: –1.26 (NR)
SF-36; mental health	6	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic) with SMBG (meter not described)	42	Baseline: 72.6 (14.8); follow-up: 79.2 (12.5); change from baseline: 6.6 (NR)
			MDI + SMBG: SMBG (meter not described)	33	Baseline: 77.9 (20.2); follow-up: 76.8 (16.5); change from baseline: –1.1 (NR)
SF-36; mental health	3.68	DeVries *et al.*, 2002[42]	CSII + SMBG: Disetronic H-TRONplus insulin pump; Glucotouch or One Touch Profile memory glucose meter (LifeScan)	NR	Baseline: 78 (NR); follow-up: NR (NR); change from baseline: –0.6 (NR)
					Baseline: 80 (NR); follow-up: NR (NR); change from baseline: 5.2 (NR)
SF-36; physical composite score	12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time System (Medtronic)	166	Baseline: 50.61 (7.12); follow-up: NR (NR); change from baseline: 1.22 (NR)
			MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	168	Baseline: 50.97 (7.86); follow-up: NR (NR); change from baseline: 0.26 (NR)

TABLE 81 Results for HRQoL in adults (no data for children, mixed populations or pregnant women) (*continued*)

HRQoL scale	Follow-up, months	Study	Intervention	Number analysed	HRQoL score (SD)
SF-36; physical functioning	6	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic) with SMBG (meter not described)	42	Baseline: 89.4 (14.5); follow-up: 92.7 (11.2); change from baseline: 3.3 (NR)
			MDI + SMBG: SMBG (meter not described)	33	Baseline: 90.5 (14.3); follow-up: 91.4 (12.7); change from baseline: 0.9 (NR)
SF-36; role – emotional	6	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic) with SMBG (meter not described)	42	Baseline: 84.9 (20.4); follow-up: 87.1 (19.6); change from baseline: 2.2 (NR)
			MDI + SMBG: SMBG (meter not described)	33	Baseline: 89.6 (16.7); follow-up: 88 (16); change from baseline: –1.6 (NR)
SF-36; role – physical	6	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic with SMBG (meter not described)	42	Baseline: 76.8 (23.8); follow-up: 85.7 (20.7); change from baseline: 8.9 (NR)
			MDI + SMBG: SMBG (meter not described)	33	Baseline: 84.4 (19.3); follow-up: 87.3 (20.4); change from baseline: 2.9 (NR)
SF-36; social functioning	6	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic) with SMBG (meter not described)	42	Baseline: 81.5 (20.3); follow-up: 89.3 (16); change from baseline: 7.8 (NR)
			MDI + SMBG: SMBG (meter not described)	33	Baseline: 86.4 (21); follow-up: 82.2 (25.2); change from baseline: –4.2 (NR)
SF-36; vitality	6	Hermanides *et al.*, 2011[37]	Integrated CSII + CGM: Paradigm REAL-Time System (Medtronic) with SMBG (meter not described)	42	Baseline: 53.9 (20); follow-up: 66.7 (20.2); change from baseline: 12.8 (NR)
			MDI + SMBG: SMBG (meter not described)	33	Baseline: 61 (23.7); follow-up: 65.2 (19.3); change from baseline: 4.2 (NR)

NR, not reported; QOL, quality of life; SF-36, Short Form questionnaire-36 items.

TABLE 82 Results for adverse events

Outcome definition	Population	Follow-up, months	Study	Intervention	Number with AE (%)	Total number analysed
All serious AEs	Adults	3.45	Lee *et al.*, 2007[38]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time 722 System as adjunct to SMBG (Paradigm Link glucose meter)	0 (0.0)	8
				MDI + SMBG: SMBG (Paradigm Link glucose meter)	1 (12.5)	8
	Mixed	6	Raccah *et al.*, 2009[36]	Non-integrated CSII + CGM: insulin pump + Holter-type CGM device	3 (NR)	NR
				CSII + SMBG: Paradigm 512/712 + SMBG	7 (NR)	NR
		12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system (Medtronic)	32 (13.0)	247
				MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	30 (12.1)	248
Death	Adults	3	Bergenstal *et al.*, 2013[32]	Integrated CSII + CGM: Paradigm Revel 2.0 pump with Enlite sensor	0 (0.0)	126
				CSII + CGM + suspend: Paradigm Veo pump with Enlite sensor	0 (0.0)	121
Device-related serious AEs	Adults	3	Bergenstal *et al.*, 2013[32]	Integrated CSII + CGM: Paradigm Revel 2.0 pump with Enlite sensor	0 (0.0)	126
				CSII + CGM + suspend: Paradigm Veo pump with Enlite sensor	0 (0.0)	121
Hypoglycaemic coma	Adults	24	Brinchmann-Hansen *et al.*, 1985[44]	MDI + SMBG: NR	6 (40.0)	15
				CSII + SMBG: NR	2 (13.3)	15
Subcutaneous abscess	Adults	24	Brinchmann-Hansen *et al.*, 1985[44]	MDI + SMBG: NR	0 (0.0)	15
				CSII + SMBG: NR	6 (40.0)	15
Total AEs, not including serious AEs	Mixed	12	Bergenstal *et al.*, 2010[40]	Integrated CSII + CGM: MiniMed Paradigm REAL-Time system (Medtronic)	96 (38.9)	247
				MDI + SMBG: Guardian REAL-Time Clinical (Medtronic)	49 (19.8)	248
Treatment emergent AE	Adults	6	Bolli *et al.*, 2009[41]	CSII + SMBG: MiniMed 508 with glucose monitor (NR)	18 (64.3)	28
				MDI + SMBG: insulin glargine plus mealtime insulin lispro glucose monitor (NR)	22 (75.9)	29

AE, adverse event; NR, not reported.

TABLE 83 Results for adverse events in pregnant women

Outcome definition	Follow-up, months	Study ID	Intervention	Number with AE (%)	Total number analysed
Fetal respiratory distress syndrome	NR	Nosari *et al.*, 1993[50]	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	1 (6.3)	16
			MDI + SMBG: NR	0 (0.0)	16
Intrauterine death	NR	Nosari *et al.*, 1993[50]	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	2 (12.5)	16
			MDI + SMBG: NR	1 (6.3)	16
Large for gestational age	NR	Nosari *et al.*, 1993[50]	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	1 (6.3)	16
			MDI + SMBG: NR	0 (0.0)	16
Neonatal hypoglycaemia (plasma glucose of < 30 mg/dl)	NR	Nosari *et al.*, 1993[50]	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	1 (6.3)	16
			MDI + SMBG: NR	1 (6.3)	16
Premature birth of a viable fetus	NR	Nosari *et al.*, 1993[50]	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	0 (0.0)	16
			MDI + SMBG: NR	1 (6.3)	16
Small for gestational age	NR	Nosari *et al.*, 1993[50]	CSII + SMBG: Microjet MC 20 and Dahedi B.V. portable battery-powered syringe infusion pumps	0 (0.0)	16
			MDI + SMBG: NR	2 (12.5)	16

AE, adverse event; NR, not reported.

Appendix 4 Risk-of-bias assessment results

TABLE 84 Risk-of-bias assessment for all included studies

Study ID	Random sequence generation	Allocation concealment	Participant blinding	Care staff blinding	Outcome assessor blinding	Selective outcome reporting	Incomplete data	Overall
Bergenstal *et al.*, 2013[32]	Unclear	Unclear	High	High	High	Low	High	High
Bolli *et al.*, 2009[41]	Low	Low	High	High	High	Low	High	High
DeVries *et al.*, 2002[42]	Low	Low	High	High	High	Low	High	High
Doyle *et al.*, 2004[49]	Low	Low	High	High	High	High	Low	Low
Hermanides *et al.*, 2011[37]	Low	Low	High	High	High	Low	Unclear	Low
Hirsch *et al.*, 2008[34]	Unclear	Unclear	High	High	High	Low	High	High
Lee *et al.*, 2007[38]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Ly *et al.*, 2013[33]	Low	Unclear	High	High	High	Low	High	High
Nosadini *et al.*, 1988[43]	Unclear	Low	High	High	High	High	High	High
Nosari *et al.*, 1993[50]	Unclear	Unclear	High	High	High	Low	High	High
O'Connell *et al.*, 2009[35]	Low	Unclear	High	High	High	Low	High	High
Brinchmann-Hansen *et al.*, 1985[44]	Low	Unclear	High	High	High	Low	Low	Low
Peyrot and Rubin, 2009[39]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Raccah *et al.*, 2009[36]	Unclear	Unclear	High	High	High	High	High	High
Bergenstal *et al.*, 2010[40]	Unclear	Low	High	High	High	Low	High	High
Thomas *et al.*, 2007[45]	Unclear	Unclear	High	High	High	Low	Unclear	Unclear
Thrailkill *et al.*, 2011[48]	Low	Unclear	High	High	High	Low	High	High
Tsui *et al.*, 2001[46]	Low	Low	Unclear	Unclear	Unclear	Low	High	Unclear
Weintrob *et al.*, 2003[47]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low

Appendix 5 Conversion tables for glycated haemoglobin and glucose values

TABLE 85 Glycated haemoglobin conversion table: older DCCT-aligned (%) and newer IFCC-standardised (mmol/mol) concentrations (IFCC-standardised values are rounded to the nearest whole number)

HbA_{1c} 'old'	HbA_{1c} 'new'	HbA_{1c} 'old'	HbA_{1c} 'new'
4.0	20	9.1	76
4.1	21	9.2	77
4.2	22	9.3	78
4.3	23	9.4	79
4.4	25	9.5	80
4.5	26	9.6	81
4.6	27	9.7	83
4.7	28	9.8	84
4.8	29	9.9	85
4.9	30	10.0	86
5.0	31	10.1	87
5.1	32	10.2	88
5.2	33	10.3	89
5.3	34	10.4	90
5.4	36	10.5	91
5.5	37	10.6	92
5.6	38	10.7	93
5.7	39	10.8	95
5.8	40	10.9	96
5.9	41	11.0	97
6.0	42	11.1	98
6.1	43	11.2	99
6.2	44	11.3	100
6.3	45	11.4	101
6.4	46	11.5	102
6.5	48	11.6	103
6.6	49	11.7	104
6.7	50	11.8	105
6.8	51	11.9	107

continued

TABLE 85 Glycated haemoglobin conversion table: older DCCT-aligned (%) and newer IFCC-standardised (mmol/mol) concentrations (IFCC-standardised values are rounded to the nearest whole number) (*continued*)

HbA_{1c} 'old'	HbA_{1c} 'new'	HbA_{1c} 'old'	HbA_{1c} 'new'
6.9	52	12.0	108
7.0	53	13.0	119
7.1	54	13.1	120
7.2	55	13.2	121
7.3	56	13.3	122
7.4	57	13.4	123
7.5	58	13.5	124
7.6	60	13.6	125
7.7	61	13.7	126
7.8	62	13.8	127
7.9	63	13.9	128
8.0	64	14.0	130
8.1	65	14.1	131
8.2	66	14.2	132
8.3	67	14.3	133
8.4	68	14.4	134
8.5	69	14.5	135
8.6	70	14.6	136
8.7	72	14.7	137
8.8	73	14.8	138
8.9	74	14.9	139
9.0	75		

IFCC, International Federation of Clinical Chemistry.
Definitions: 'old' unit = DCCT unit (%); 'new' unit = IFCC unit (mmol/mol).
Conversion formulas: 'old' = (0.0915 × 'new') + 2.15%; 'new' = (10.93 × 'old') − 23.5 mmol/mol.

TABLE 86 Glucose values conversion table (mg/dl to mmol/l)

mg/dl to mmol/l		mmol/l to mg/dl	
mg/dl	mmol/l	mmol/l	mg/dl
40	2.2	2.0	36
45	2.5	2.5	45
50	2.8	3.0	54
55	3.1	3.5	63
60	3.3	4.0	72
65	3.6	4.5	81
70	3.9	5.0	90
75	4.2	5.5	99
80	4.4	6.0	108
85	4.7	6.5	117
90	5.0	7.0	126
95	5.3	7.5	135
100	5.6	8.0	144
110	6.2	8.5	153
120	6.7	9.0	162
130	7.2	9.5	171
140	7.8	10.0	180
150	8.3	10.5	189
160	8.9	11.0	198
170	9.4	11.5	207
180	10.0	12.0	216
190	10.6	12.5	225
200	11.1	13.0	234
220	12.2	13.5	243
240	13.3	14.0	252
260	14.4	14.5	261
280	15.5	15.0	270
300	16.7	16.0	288
320	17.8	17.0	306
340	18.9	18.0	324
360	20.0	19.0	342
380	21.1	20.0	360
400	22.2	21.0	378
420	23.3	22.0	396
440	24.4	23.0	414
460	25.5	24.0	432

Conversion formulas: mg/dl × 0.0555 = mmol/l; mmol/l × 18.018 = mg/dl.

Appendix 6 Detailed description of the IMS core diabetes model

The IMS CDM is a multilayer internet application linked to a mathematical calculation model and structured query language (SQL) database sited on a central server. Online access to the IMS CDM software is available under license from IMS, the developers of the model. The structure is based on four separate elements: the user interface, the input databases, the data processor and the output databases. *Figure 24* outlines the overview of the IMS CDM software structure.

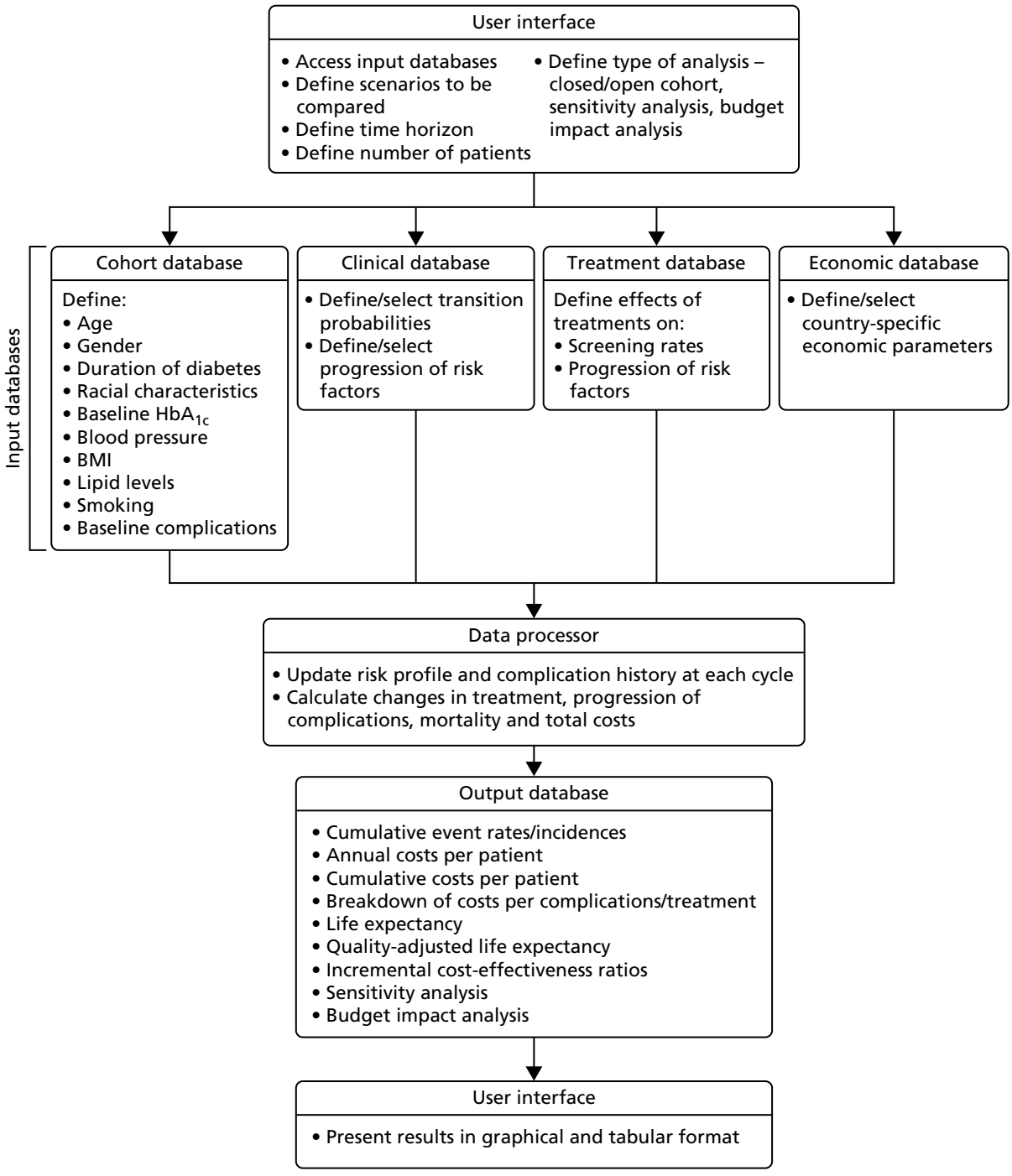

FIGURE 24 IMS CDM software model structure.

Complication submodels

The myocardial infarction submodel

The MI submodel is made up of three states: no history of MI, history of MI and death following MI. Transition probabilities between the states can be taken from the UK Prospective Diabetes Study (UKPDS) risk engine,[98] Framingham[93] or the UKPDS outcomes model.[91] In our calculations, Framingham[92] was chosen as it is the only one that is based on T1DM only.

Unstable angina submodel

The unstable angina submodel is made up of two states: no history of angina and history of angina. Transition probabilities between the states are derived from Framingham.[93] They are adjusted according to HbA_{1c} levels and renal function.

Congestive heart failure submodel

The CHF submodel is composed of three states: no CHF, history of CHF and death following CHF. A logistic regression based on Framingham[95] generates the risk profile and includes the following risk factors: age, sex, left ventricular hypertrophy, heart rate, SBP, congenital heart disease, valve disease, presence of diabetes, BMI, presence of diabetes and valve disease jointly.

Stroke submodel

The stroke submodel is composed of three states: no stroke, history of stroke and death following stroke. Transition probabilities between the states can be taken from the UKPDS risk engine,[96] Framingham[153] or the UKPDS outcomes model.[91] In our calculations, Framingham was chosen as it is the only one that is based on T1DM only.

Peripheral vascular disease submodel

The PVD submodel is made up of two states: no PVD and PVD. Transition probabilities are the same as T1DM and T2DM. A logistic regression based on Framingham[97] is used to generate the risk for PVD, including the following risk factors: age, sex, blood pressure (normal–high), stage 1 hypertension (yes/no), stage 2 hypertension (yes/no), presence of diabetes, number of cigarettes per day, cholesterol level and heart failure history.

Neuropathy submodel

The neuropathy submodel is made up of two states: no neuropathy and neuropathy. Transition probabilities for T1DM are derived from DCCT.[92] Transition probabilities are indexed by diabetes duration and are adjusted for HbA_{1c} levels, SBP and angiotensin-converting enzyme inhibitor (ACEI) use.

Foot ulcer/amputation submodel

This submodel consists of nine states: (1) no foot ulcer; (2) uninfected ulcer; (3) infected ulcer; (4) healed ulcer; (5) uninfected recurrent ulcer; (6) infected recurrent ulcer; (7) gangrene; (8) history of amputation; and (9) death resulting from foot ulcer. Transition probabilities are the same for T1DM and T2DM. Unlike other submodels, this submodel runs in monthly cycles. Therefore, patients may have multiple foot ulcers in a single year.

Diabetic retinopathy submodel

This submodel is composed of 10 states: (1) no retinopathy and not screened; (2) no retinopathy and screened; (3) background diabetic retinopathy (BDR) and not screened; (4) BDR and screened; (5) BDR and wrongly diagnosed as proliferative; (6) diabetic retinopathy and laser (retinal photocoagulation) treated; (7) proliferative diabetic retinopathy (PDR), not screened and no laser treatment; (8) PDR, screened, detected and laser treated; (9) PDR, screened and not detected; and (10) severe vision loss.

Severe vision loss is a terminal state. Transition probabilities for T1DM are derived from DCCT,[92] and are adjusted for HbA_{1c} levels, SBP and ACEI use.

Macular oedema submodel

The macular oedema submodel consists of six states: (1) no macular oedema and not screened; (2) no macular oedema and screened; (3) macular oedema, not screened and no laser treatment; (4) macular oedema, screened and not detected; (5) macular oedema, screened, detected and laser treated; and (6) severe vision loss.

Severe vision loss is a terminal state. Transition probabilities for T1DM are derived from DCCT,[92] and are adjusted for HbA_{1c} levels, SBP and ACEI use.

Cataract submodel

The cataract submodel is composed of three states: no cataract, first cataract with operation and second cataract with operation. Transition probabilities are the same for T1DM and T2DM and are taken from a study in diabetes outpatients in the UK published by Janghorbani *et al.*[154]

Nephropathy submodel

This submodel is composed of 13 states: (1) no renal complications and no treatment with ACEI; (2) no renal complications and treated with ACEI; (3) no renal complications after ACEI side effects; (4) microalbuminuira and no treatment with ACEI; (5) microalbuminuira, screened, detected and treated with ACEI; (6) microalbuminuira after ACEI side effects; (7) gross proteinuria and no treatment with ACEI; (8) gross proteinuria, screened, detected and treated with ACEI; (9) gross proteinuria after ACEI side effects; (10) end-stage renal disease, treated with haemodialysis; (11) end-stage renal disease, treated with peritoneal dialysis; (12) end-stage renal disease, treated with renal transplant; and (13) end-stage renal disease death.

Data on the cumulative incidence of progression of microalbuminuria and gross proteinuria were taken from the DCCT,[92] probabilities for the progression from gross proteinuria to end-stage renal disease are based on cumulative incidence data for T2DM patients in the Rochester population.[155] It is assumed that the probability of progression from gross proteinuria to end-stage renal disease is the same for T1DM and T2DM. The probability of progression from end-stage renal disease states to death is dependent on treatment and ethnic group (Wolfe *et al.*[156]). Transition probabilities are adjusted according to patient HbA_{1c} levels, SBP and concomitant ACEI treatment

Hypoglycaemia submodel

The hypoglycaemia submodel is a state in which the minor and severe hypoglycaemic episodes are counted. Minor hypoglycaemic events are calculated on a daily basis (cycle length = 1 day). For the simulation of severe hypoglycaemic events, the submodel runs four times for each year of simulation. All rates (defined as number of events per 100 patient-years) are adjusted to the 1-day or 3-month cycle length. Therefore, patients can have multiple hypoglycaemic episodes in a single year. The patients may die after a severe hypoglycaemic episode. The definition of severe and minor hypoglycaemia can be refined by the user according to the available data. In our analysis, hypoglycaemic episode rates are treatment specific and any hypoglycaemic episode that required assistance from a third party is considered as severe. It should be noted that in our base-case analysis the probability of death as a result of a severe hypoglycaemic episode was assumed to be zero.

Ketoacidosis submodel

The ketoacidosis submodel has two states: alive and dead (as a result of ketoacidosis). There are no probability adjustments in the ketoacidosis submodel.

Depression submodel

The depression submodel has three states: no depression, depression receiving antidepression programme and depression not receiving antidepression programme. The onset probability of depression is the same for T1DM and T2DM, and is dependent on gender.

Lactic acidosis submodel

This submodel is relevant for T2DM only.

Peripheral oedema submodel

This submodel is relevant for T2DM only.

Non-specific mortality submodel

This submodel consists of two states: alive or dead. The transition probabilities are indexed by age, sex and ethnicity, and reflect the UK life tables.[94]

Appendix 7 Results (full incremental and intervention vs. comparator) of base-case and scenario analyses

TABLE 87 Base-case model results (all technologies) for probabilistic simulation

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.4146	61,050	–	–	–
CSII + SMBG	11.9756	90,436	0.561	29,386	52,381
MiniMed Veo system	12.0412	138,357	Extendedly dominated[a] by stand-alone CSII + CGM		
Stand-alone CSII + CGM	12.0604	146,476	0.0849	56,039	660,376
Integrated CSII + CGM (Vibe)	12.0604	147,150	Dominated by stand-alone CSII + CGM		

a An extendedly dominated strategy has an ICER higher than that of the next most effective strategy.

TABLE 88 Base-case model results (intervention vs. comparator only) for probabilistic simulation

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.6266	77,307	123,375
MiniMed Veo system	CSII + SMBG	0.0656	47,921	730,501
MiniMed Veo system	Stand-alone CSII + CGM	–0.0192	–8119	422,849
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.6458	86,100	133,323
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.0849	56,713	668,789
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	674	Undefined

TABLE 89 Base-case model results (all technologies) for deterministic simulation

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	12.1450	62,927	–	–	–
CSII + SMBG	12.7258	93,433	0.5808	30,506	52,524
MiniMed Veo system	12.8087	143,309	0.0829	49,876	601,641
Stand-alone CSII + CGM	12.8223	151,671	0.0136	8363	614,910
Integrated CSII + CGM (Vibe)	12.8223	152,372	Dominated by stand-alone CSII+ CGM		

TABLE 90 Base-case model results (intervention vs. comparator only) for deterministic simulation

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.6637	80,382	121,112
MiniMed Veo system	CSII + SMBG	0.0829	49,876	601,639
MiniMed Veo system	Stand-alone CSII + CGM	–0.0136	–8363	614,910
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.6773	89,445	132,061
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.0965	58,939	610,772
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	701	Undefined

TABLE 91 Model results (all technologies) for scenario with different baseline population characteristics

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	9.6117	65,070	–	–	–
CSII + SMBG	10.0991	91,189	0.4874	26,119	53,588
MiniMed Veo system	10.1474	132,149	Extendedly dominated by stand-alone CSII + CGM		
Stand-alone CSII + CGM	10.164	139,157	0.0649	47,967	738,593
Integrated CSII + CGM (Vibe)	10.164	139,733	Dominated by stand-alone CSII + CGM		

TABLE 92 Model results (intervention vs. comparator only) for scenario with different baseline population characteristics

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.5357	67,079	125,217
MiniMed Veo system	CSII + SMBG	0.0483	40,960	848,028
MiniMed Veo system	Stand-alone CSII + CGM	–0.0166	–7008	422,148
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.5523	74,663	135,186
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.0649	48,543	747,971
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	576	Undefined

TABLE 93 Model results (all technologies) for scenario with two (CGM) vs. eight (SMBG) BG tests per day

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.4146	68,460	–	–	–
CSII + SMBG	11.9756	98,034	0.561	29,574	52,717
MiniMed Veo system	12.0412	138,357	Extendedly dominated by stand-alone CSII + CGM		
Stand-alone CSII + CGM	12.0604	146,476	0.0849	48,441	570,844
Integrated CSII + CGM (Vibe)	12.0604	147,150	Dominated by stand-alone CSII + CGM		

TABLE 94 Model results (intervention vs. comparator only) for scenario with two (CGM) vs. eight (SMBG) BG tests per day

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.6266	69,897	111,550
MiniMed Veo system	CSII + SMBG	0.0656	40,323	614,683
MiniMed Veo system	Stand-alone CSII + CGM	–0.0192	–8119	422,849
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.6458	78,690	121,849
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.0849	49,116	579,194
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	674	Undefined

TABLE 95 Model results (all technologies) for scenario with increased amount of daily insulin for MDIs

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.4146	62,114	–	–	–
CSII + SMBG	11.9756	90,437	0.5610	28,323	50,487
MiniMed Veo system	12.0412	138,358	Extendedly dominated by stand-alone CSII + CGM		
Stand-alone CSII + CGM	12.0604	146,476	0.0849	56,040	660,376
Integrated CSII + CGM (Vibe)	12.0604	147,150	Dominated by stand-alone CSII + CGM		

TABLE 96 Model results (intervention vs. comparator only) for scenario with increased amount of daily insulin for MDIs

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.6266	76,244	121,679
MiniMed Veo system	CSII + SMBG	0.0656	47,921	730,501
MiniMed Veo system	Stand-alone CSII + CGM	–0.0192	–8119	422,849
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.6458	85,036	131,675
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.0848	56,713	668,789
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	674	Undefined

TABLE 97 Model results (all technologies) for scenario with no HbA_{1c} progression

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.8715	58,520	–	–	–
CSII + SMBG	12.4558	88,663	0.5843	30,143	51,615
MiniMed Veo system	12.5228	137,739	Extendedly dominated by stand-alone CSII + CGM		
Stand-alone CSII + CGM	12.5398	146,076	0.0840	57,414	683,889
Integrated CSII + CGM (Vibe)	12.5398	146,767	Dominated by stand-alone CSII + CGM		

TABLE 98 Model results (intervention vs. comparator only) for scenario with no HbA_{1c} progression

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.6513	79,219	121,632
MiniMed Veo system	CSII + SMBG	0.067	49,076	732,483
MiniMed Veo system	Stand-alone CSII + CGM	–0.017	–8337	490,424
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.6683	88,247	132,047
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.084	58,104	691,715
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	690	Undefined

TABLE 99 Cost-effectiveness results when no treatment effect (in terms of change in HbA_{1c} levels) is assumed in the first year (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
Stand-alone CSII + CGM	12.0006	146,632	Dominated by MDI + SMBG		
Integrated CSII + CGM (Vibe)	12.0006	147,304	Dominated by MDI + SMBG		
MDI + SMBG	12.0016	56,928	–	–	–
CSII + SMBG	12.016	90,178	0.0144	33,250	2,309,028
MiniMed Veo system	12.026	138,538	0.0099	48,360	4,871,356

TABLE 100 Cost-effectiveness results when no treatment effect (in terms of change in HbA_{1c} levels) is assumed in the first year (intervention vs. comparator only)

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.0244	81,610	3,344,672
MiniMed Veo system	CSII + SMBG	0.0099	48,360	4,871,356
MiniMed Veo system	Stand-alone CSII + CGM	0.0254	–8093	–318,634
Integrated CSII + CGM (Vibe)	MDI + SMBG	–0.0009	90,376	–100,417,778
Integrated CSII + CGM (Vibe)	CSII + SMBG	–0.0154	57,126	–3,709,460
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	672	Undefined

TABLE 101 Cost-effectiveness results if a RR of 0.125 is used for the MiniMed Veo system severe hypoglycaemic rate (all technologies)

Hypo MiniMed Veo system RR	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.412	60,812	–	–	–
CSII + SMBG	11.9597	91,195	0.5477	30,383	55,474
MiniMed Veo system	12.0453	138,333	Extendedly dominated by stand-alone CSII + CGM		
Stand-alone CSII + CGM	12.0604	146,476	0.1007	55,281	549,080
Integrated CSII + CGM (Vibe)	12.0604	147,150	Dominated by stand-alone CSII + CGM		

TABLE 102 Cost-effectiveness results if a RR of 0.125 is used for the MiniMed Veo system severe hypoglycaemic rate (intervention vs. comparator only)

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.6333	77,521	122,408
MiniMed Veo system	CSII + SMBG	0.0856	47,138	550,675
MiniMed Veo system	Stand-alone CSII + CGM	–0.0151	–8143	539,295
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.6484	86,338	133,155
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.1007	55,955	555,659
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	674	Undefined

TABLE 103 Cost-effectiveness results for mortality due to severe hypoglycaemia scenario (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.1041	58,510	–	–	–
Stand-alone CSII + CGM	11.7701	142,215	Dominated by CSII + SMBG		
Integrated CSII + CGM (Vibe)	11.7701	142,872	Dominated by CSII + SMBG		
CSII + SMBG	11.8781	89,475	0.774	30,965	40,006
MiniMed Veo system	12.0071	137,801	0.129	8326	374,531

TABLE 104 Cost-effectiveness results for mortality due to severe hypoglycaemia scenario (intervention vs. comparator only)

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.9029	79,291	87,818
MiniMed Veo system	CSII + SMBG	0.1290	48,327	374,626
MiniMed Veo system	Stand-alone CSII + CGM	0.2369	–4413	–18,622
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.6659	84,362	126,689
Integrated CSII + CGM (Vibe)	CSII + SMBG	–0.1079	53,397	–494,418
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	657	Undefined

TABLE 105 Cost-effectiveness results for minimum QALY estimation method scenario (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	12.1327	61,050			
CSII + SMBG	12.5861	90,436	0.4534	29,386	64,813
MiniMed Veo system	12.6408	138,357	0.0546	47,920	876,987
Stand-alone CSII + CGM	12.6462	146,476	0.0601	56,039	932,305
Integrated CSII + CGM (Vibe)	12.6462	147,150	Dominated by stand-alone CSII + CGM		

TABLE 106 Cost-effectiveness results for minimum QALY estimation method scenario (intervention vs. comparator only)

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.5081	77,307	152,149
MiniMed Veo system	CSII + SMBG	0.0547	47,921	876,067
MiniMed Veo system	Stand-alone CSII + CGM	–0.0054	–8119	1,503,465
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.5135	86,100	167,673
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.0601	56,713	943,649
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	674	Undefined

TABLE 107 Four-year time horizon scenario (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	2.7718	6706	–	–	–
Stand-alone CSII + CGM	2.7882	24,803	Dominated by CSII + SMBG		
Integrated CSII + CGM (Vibe)	2.7886	24,939	Dominated by CSII + SMBG		
CSII + SMBG	2.7906	13,365	0.0188	6659	354,202
MiniMed Veo system	2.7928	23,144	0.0022	9778	4,461,063

TABLE 108 Four-year time horizon scenario (intervention vs. comparator only)

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.0210	16,438	782,762
MiniMed Veo system	CSII + SMBG	0.0022	9779	4,445,000
MiniMed Veo system	Stand-alone CSII + CGM	0.0046	–1659	–360,652
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.0168	18,233	1,085,298
Integrated CSII + CGM (Vibe)	CSII + SMBG	–0.0020	11,574	–5,787,000
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0.0004	136	340,000

TABLE 109 Cost-effectiveness results for fear of hypoglycaemia scenario (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.4146	61,050	–	–	–
CSII + SMBG	11.9756	90,436	0.5610	29,386	52,381
Stand-alone CSII + CGM	12.0604	146,476	Extendedly dominated by MiniMed Veo system		
MiniMed Veo system	12.6224	138,357	0.6468	47,920	74,088
Integrated CSII + CGM (Vibe)	12.6429	147,150	0.0205	8792	428,595

TABLE 110 Cost-effectiveness results for fear of hypoglycaemia scenario (intervention vs. comparator only)

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	1.2077	77,307	64,012
MiniMed Veo system	CSII + SMBG	0.6468	47,921	74,088
MiniMed Veo system	Stand-alone CSII + CGM	0.5619	–8119	–14,448
Integrated CSII + CGM (Vibe)	MDI + SMBG	1.2282	86,100	70,103
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.6468	47,921	74,089
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0.5824	674	1157

TABLE 111 Cost-effectiveness results for cost of stand-alone CSII + CGM without market share scenario (all technologies)

Intervention	QALYs	Cost (£)	Incremental QALY	Incremental cost (£)	ICER (£)
MDI + SMBG	11.4146	61,050	–	–	–
CSII + SMBG	11.9756	92,272	0.561	31,222	55,654
MiniMed Veo system	12.0412	138,357	Extendedly dominated by Integrated CSII + CGM		
Integrated CSII + CGM (Vibe)	12.0604	147,150	0.0849	54,878	646,692
Stand-alone CSII + CGM	12.0604	150,063	Dominated by integrated CSII + CGM		

TABLE 112 Cost-effectiveness results for cost of stand-alone CSII + CGM without market share scenario (intervention vs. comparator only)

Intervention	Comparator	Incremental QALY	Incremental cost (£)	ICER (£)
MiniMed Veo system	MDI + SMBG	0.6266	77,307	123,375
MiniMed Veo system	CSII + SMBG	0.0656	46,086	702,530
MiniMed Veo system	Stand-alone CSII + CGM	–0.0192	–11,705	609,635
Integrated CSII + CGM (Vibe)	MDI + SMBG	0.6458	86,100	133,323
Integrated CSII + CGM (Vibe)	CSII + SMBG	0.0848	54,878	647,146
Integrated CSII + CGM (Vibe)	Stand-alone CSII + CGM	0	–2913	Undefined

Appendix 8 Disease natural history parameters and transition probabilities

The parameters that will determine the natural course of the disease and their corresponding sources can be seen in *Table 113*. We considered the same values as in NICE Guideline NG17.[81]

Transition probabilities values were provided by the IMS CDM developers and were not changed in our analyses given the high degree of validation of the model. These were UK specific if possible and based on relevant sources (e.g. DCCT trial).[92] In *Table 114* we report these sources. We do not report the complete set of probabilities as we believe this would be too extensive and not very informative because of the complexity of the model.

TABLE 113 Disease natural history parameters

Parameter	Mean value	Source
HbA_{1c} adjustments		
Risk reduction of BDR with 10% lower HbA_{1c}	39%	DCCT[92]
Risk reduction of proliferative diabetic retinopathy with 10% lower HbA_{1c}	43%	DCCT[92]
Risk reduction of sever vision loss with 10% lower HbA_{1c}	0%	No data
Risk reduction of macular oedema with 10% lower HbA_{1c}	13%	Klein *et al.*, 2009[157]
Risk reduction of microalbuminuria with 10% lower HbA_{1c}	28%	DCCT[92]
Risk reduction of gross proteinuria with 10% lower HbA_{1c}	37%	DCCT[92]
Risk reduction of end-stage renal disease with 10% lower HbA_{1c}	21%	Rosolowsky *et al.*, 2011[158]
Risk reduction of neuropathy with 10% lower HbA_{1c}	32%	DCCT[92]
Risk reduction of MI with 1% lower HbA_{1c}	20%	DCCT[92]
Risk reduction of cataract with 1% lower HbA_{1c}	0%	Grauslund *et al.*, 2011[159]
Risk reduction of heart failure with 1% lower HbA_{1c}	23%	Lind *et al.*, 2011[160]
Risk reduction of stroke with 1% lower HbA_{1c}	20%	DCCT[92]
Risk reduction of angina with 1% lower HbA_{1c}	20%	DCCT[92]
Risk reduction of haemodialysis mortality with 1% lower HbA_{1c}	12%	Morioka *et al.*, 2001[161]
Risk reduction of peritoneal dialysis mortality with 1% lower HbA_{1c}	12%	Morioka *et al.*, 2001[161]
Risk reduction of renal transplant mortality with 1% lower HbA_{1c}	0%	Wiesbauer *et al.*, 2010[162]
Risk reduction of first ulcer with 1% lower HbA_{1c}	17%	Monami *et al.*, 2009[163]
SBP adjustments		
Risk reduction of microalbuminuria with 10 mmHg lower SBP	13%	Adler *et al.*, 2000[164]
Risk reduction of severe vision loss with 10 mmHg lower SBP	0%	No data

continued

TABLE 113 Disease natural history parameters (*continued*)

Parameter	Mean value	Source
MI adjustments		
Proportion with MI having an initial CHD event, female	0.361	D'Agostino *et al.*, 2000[93]
Proportion with MI having an initial CHD event, male	0.522	D'Agostino *et al.*, 2000[93]
Proportion with MI having a subsequent CHD event MI, female	0.474	D'Agostino *et al.*, 2000[93]
Proportion with MI having a subsequent CHD event MI, male	0.451	D'Agostino *et al.*, 2000[93]
RR of MI if microalbuminuria is present	1	No data
RR of MI if gross proteinuria is present	1	No data
RR of MI if end-stage renal disease is present	1	No data
RR of recurrent MI if DIGAMI[165] intensive control is used	1	No data
RR of MI mortality if DIGAMI[165] intensive control is used	1	No data
RR of MI if aspirin used for primary prevention	0.82	Baigent *et al.*, 2009[166]
RR of MI if aspirin used for secondary prevention	0.80	Baigent *et al.*, 2009[166]
RR of MI if statins used for primary prevention	0.70	Brugts *et al.*, 2009[167]
RR of MI if statins used for secondary prevention	0.81	Shepherd *et al.*, 2002[168]
RR of MI if ACEIs used for primary prevention	0.78	HOPE Study Investigators, 2000[169]
RR of MI if ACEIs used for secondary prevention	0.78	D'Agostino *et al.*, 2000[93]
MI mortality		
Probability of sudden death after first MI, male	0.393	Sonke *et al.*, 1996[170]
Probability of sudden death after first MI, female	0.364	Sonke *et al.*, 1996[170]
Probability of sudden death after recurrent MI, male	0.393	Sonke *et al.*, 1996[170]
Probability of sudden death after recurrent MI, female	0.364	Sonke *et al.*, 1996[170]
RR of 12-month mortality after MI conventional treatment	1.45	Malmberg *et al.*, 1995[165]
RR of mortality first year after MI aspirin treatment	0.88	Antiplatelet Triallists' Collaboration, 1994[171]
RR of mortality each subsequent year after MI aspirin treatment	0.88	
RR of mortality first year after MI statin treatment	0.75	Stenestrand *et al.*, 2001[172]
RR of mortality each subsequent year after MI statin treatment	1.00	No data
RR of sudden death after MI aspirin treatment	1.00	No data
RR of sudden death after MI statin treatment	1.00	Briel *et al.*, 2006[173]
RR of sudden death after MI ACEI treatment	1.00	No data
RR of long-term mortality after MI using ACEIs	0.64	Gustafsson *et al.*, 1999[174]
RR 12-month mortality after MI using ACEIs	0.64	Sonke *et al.*, 1996[170]

TABLE 113 Disease natural history parameters (*continued*)

Parameter	Mean value	Source
Stroke		
RR of stroke with microalbuminuria	1.00	No data
RR of stroke with gross proteinuria	1.00	No data
RR of stroke with end-stage renal disease	1.00	No data
RR of first stroke if aspirin used	0.86	Baigent *et al.*, 2009[166]
RR of second stroke if aspirin used	0.78	Baigent *et al.*, 2009[166]
RR of first stroke if statins used	0.81	Brugts *et al.*, 2009[167]
RR of second stroke if statins used	0.84	Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators, 2006[175]
RR of first stroke if ACEIs used	0.67	HOPE Study investigators, 2000[169]
RR of recurrent stroke if ACEIs used	0.72	PROGRESS Collaborative Group, 2001[176]
Stroke mortality		
Probability of 30-day death after first stroke	0.124	Eriksson and Olsson, 2001[177]
Probability of 30-day death after recurrent stroke	0.422	
RR of mortality after stroke if aspirin used	0.84	Antiplatelet Triallists' Collaboration, 1994[171]
RR of mortality if statins used	1.00	Manktelow and Potter, 2009[178]
RR of sudden death after stroke if aspirin used	0.95	Sandercock *et al.*, 2008[179]
RR of sudden death after stroke if statins used	1.00	Briel *et al.*, 2006[173]
RR of sudden death after stroke if ACEIs used	0.49	Chitravas *et al.*, 2007[180]
RR of long-term mortality after stroke using ACEIs	1.000	Asberg *et al.*, 2010[181]
RR of 12-month mortality after stroke using ACEIs	1.000	Eriksson and Olsson, 2001[177]
Angina adjustments		
Proportion with angina having first CHD event, female	0.621	D'Agostino *et al.*, 2000[93]
Proportion with angina having first CHD event, male	0.420	D'Agostino *et al.*, 2000[93]
Proportion with angina having subsequent CHD event, female	0.359	D'Agostino *et al.*, 2000[93]
Proportion with angina having subsequent CHD event, male	0.301	D'Agostino *et al.*, 2000[93]
RR of angina with microalbuminuria	1.00	No data
RR of angina with gross proteinuria	1.00	No data
RR of angina with end-stage renal disease	1.00	No data

continued

TABLE 113 Disease natural history parameters (*continued*)

Parameter	Mean value	Source
CHF adjustments		
RR of heart failure with microalbuminuria	1.00	No data
RR of heart failure with gross proteinuria	1.00	No data
RR of heart failure with end-stage renal disease	1.00	No data
RR of heart failure if aspirin used	1.00	No data
RR of heart failure if statins used	1.00	No data
RR of heart failure if ACEIs used	0.80	HOPE Study Investigators, 2000[169]
RR of heart failure death if ACEIs used	0.80	Ascenção *et al.*, 2008[182]
RR of heart failure death diabetic, male	1.00	Ho *et al.*, 1993[183]
RR of heart failure death diabetic, female	1.70	Ho *et al.*, 1993[183]
ACEI adjustments for micro-vascular complications		
RR of BDR if ACEIs used	0.75	Chaturvedi *et al.*, 1998[184]
RR of proliferative diabetic retinopathy if ACEIs used	0.19	Chaturvedi *et al.*, 1998[184]
RR of macular oedema if ACEIs used	1.00	No data
RR of severe vision loss if ACEIs used	1.00	No data
RR of worsening microalbuminuria if ACEIs used, no complications	0.79	Penno *et al.*, 1998[185]
RR of worsening gross proteinuria if ACEIs used, with microalbuminuria	0.41	Penno *et al.*, 1998[185]
RR of worsening end stage renal disease if ACEIs used, with gross proteinuria	0.63	Lewis *et al.*, 1993[186]
RR of neuropathy if ACEIs used	1.00	No data
Side effects of ACEIs		
Probability stopping ACEIs because of side effects first year	0	Assumption
Probability stopping ACEIs because of side effects each subsequent year	0	Assumption
Adverse events		
Probability death from severe hypoglycaemic event	0	Assumption
Probability death from severe ketoacidosis event	0.027	MacIsaac *et al.*, 2002[187]
RR of hypoglycaemic events with ACEIs	1.00	No data

TABLE 113 Disease natural history parameters (*continued*)

Parameter	Mean value	Source
Foot ulcer and amputation		
Probability gangrene to amputation	0.181800	Persson *et al.*, 2000[188]
Probability gangrene to healed amputation	0.308200	Persson *et al.*, 2000[188]
Probability death following onset gangrene	0.009800	Persson *et al.*, 2000[188]
Probability death with history amputation	0.004000	Persson *et al.*, 2000[188]
Probability death following healed ulcer	0.004000	Persson *et al.*, 2000[188]
Probability developing recurrent uninfected ulcer	0.039300	Persson *et al.*, 2000[188]
Probability amputation following infected ulcer	0.003700	Persson *et al.*, 2000[188]
Probability infected ulcer after amputation healed	0.044500	Persson *et al.*, 2000[188]
Probability of death from infected ulcer	0.009800	Persson *et al.*, 2000[188]
Probability of gangrene from infected ulcer	0.007500	Persson *et al.*, 2000[188]
Probability of infected ulcer from uninfected ulcer	0.139700	Persson *et al.*, 2000[188]
Probability of recurrent amputation	0.008451	Borkosky *et al.*, 2012[189]
Probability of death from uninfected ulcer	0.004000	Persson *et al.*, 2000[188]
Probability of uninfected ulcer from infected ulcer	0.047300	Persson *et al.*, 2000[188]
Probability of healed ulcer from uninfected ulcer	0.078700	Persson *et al.*, 2000[188]
Probability developing ulcer with neither neuropathy or PVD	0.000250	Ragnarson *et al.*, 2001[190]
Probability developing ulcer with either neuropathy or PVD	0.006092	Ragnarson *et al.*, 2001[190]
Probability developing ulcer with both neuropathy or PVD	0.006092	Persson *et al.*, 2000[188]
Depression		
RR for all-cause death if depression	1.33	Egede *et al.*, 2005[191]
RR for CHF if depression	1.00	No data
RR for MI if depression	1.00	No data
RR for depression if neuropathy	3.10	Yoshida *et al.*, 2009[192]
RR for depression if stroke	6.30	Whyte *et al.*, 2004[193]
RR for depression if amputation	1.00	No data
Other		
Probability of severe vision loss from BDR	0.015	CORE default, 2004[81]
Probability of reversal of neuropathy	0.000	No data

CHD, coronary heart disease; CORE, Centre for Outcomes Research and Effectiveness; DIGAMI, Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction.

TABLE 114 Transition probabilities dependencies and sources

Parameter	Dependent on	Source
Renal disease		
Probability of onset of microalbuminuria	Duration of diabetes	DCCT[92]
Probability of worsening from microalbuminuria to gross proteinuria	Duration of diabetes	DCCT[92]
Probability of worsening from gross proteinuria to end-stage renal disease	Duration of gross proteinuria	Rosolowsky *et al.*, 2011[158]
Proportion of end-stage renal disease with haemodialysis, peritoneal dialysis or renal transplant	Current age	US Renal Data System (USRDS), 2010[194]
Probability of death end-stage renal disease under haemodialysis, peritoneal dialysis or renal transplant	Current age	US Renal Data System (USRDS), 2010[194]
Eye disease		
Probability of onset BDR, proliferative diabetic retinopathy, macular oedema or severe vision loss	Duration of diabetes	DCCT[92]
Probability of onset of cataract extraction; male, female	Current age	Janghorbani *et al.*, 2000[154]
Probability of recurrent cataract extraction; male, female	Current age	Janghorbani *et al.*, 2000[154]
Neuropathy		
Probability of onset of neuropathy	Duration of diabetes	DCCT[92]
Heart failure		
Probability of heart failure long-term mortality, per gender and age range	Time since onset of heart failure	Ho *et al.*, 1993[183]
MI		
Probability of death within 12 months of first/recurrent MI; male, female	Current age	Malmberg *et al.*, 1995[165]
Probability of post-MI long-term mortality; male, female	Time since first MI	Malmberg *et al.*, 1995[165]
Stroke		
Probability of death within 12 months of first/recurrent stroke; male, female	Current age	Eriksson and Olsson, 2001[177]
Probability of post-stroke long-term mortality; male, female	Time since first stroke	Eriksson and Olsson, 2001[177]
Probability of recurrent stroke; male, female	Time since first stroke	Eriksson and Olsson, 2001[177]
Depression		
Probability of onset of depression; male, female	Time of simulation	Golden *et al.*, 2008[195]
Probability of depression reversal for patients receiving/not receiving anti-depression programme	Time of simulation	Valenstein *et al.*, 2001[196]
Non-specific mortality		
Probability of non-specific mortality per ethnicity and gender	Current age	UK life tables[94]
Physiological parameter progression tables		
HbA_{1c} progression	Time of simulation	DCCT[92]
BMI, haemodialysis, LDL, SBP, T-CHOL, triglyceride progression	Time of simulation	CORE default, 2004[81]
Other adjustment factors		
Quality of life adjustment based on current BMI	BMI	Bagust and Beale, 2005[197]
Age adjustment for MI mortality	Current age	Herlitz *et al.*, 1996[198]

CORE, Centre for Outcomes Research and Effectiveness; LOL, low-density lipoprotein; T-CHOL, total cholesterol.

Appendix 9 Guidance relevant to the treatment of type 1 diabetes

Published National Institute for Health and Care Excellence guidance

NICE Pathway. *Diabetes Overview*. 2013. URL: http://pathways.nice.org.uk/pathways/diabetes (accessed 15 February 2016).

NICE Pathway. *Preventing Type 2 Diabetes*. June 2013. URL: http://pathways.nice.org.uk/pathways/preventing-type-2-diabetes (accessed 15 February 2016).

NICE Clinical Guideline CG15. *Diagnosis and Management of Type 1 Diabetes in Children, Young People and Adults*. 2004. URL: www.nice.org.uk/CG15 (accessed 15 February 2016). Date for review: reviewed in August 2011 and decision was made to update the guideline. Update scheduled to be published in 2015.

NICE Clinical Guideline CG119. *Diabetic Foot: Inpatient Management of People with Diabetic Foot Ulcers and Infection*. 2011. URL: http://guidance.nice.org.uk/CG119 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Clinical Guideline CG66. *Type 2 Diabetes: The Management of Type 2 Diabetes (update)*. 2008. URL: http://guidance.nice.org.uk/CG66 (accessed 15 February 2016). Date for review: following a review in 2011 an update of this guideline is currently in the process of being scheduled into the work programme.

NICE Clinical Guideline CG10. *Type 2 Diabetes: Prevention and Management of Foot Problems*. 2004. URL: http://guidance.nice.org.uk/CG10 (accessed 15 February 2016). Date for review: an update of this guideline is under way to coincide with publication of the four diabetes guidelines currently being updated.

NICE Clinical Guideline CG87. *Type 2 Diabetes: Newer Agents (Partial Update of CG66) (CG87)*. 2009. URL: http://guidance.nice.org.uk/CG87 (accessed 15 February 2016). Date for review: following the recent review recommendation, an update of this guideline is in progress.

NICE Clinical Guideline. *Diabetes in Pregnancy: Management of Diabetes and its Complications from Pre-conception to the Postnatal Period*. 2008. URL: http://guidance.nice.org.uk/CG63 (accessed 15 February 2016). Date for review: this guideline is currently being updated. Further information can be found on the *Diabetes in Pregnancy* guideline in development page.

NICE Clinical Guideline CG173. *Neuropathic Pain – Pharmacological Management: the Pharmacological Management of Neuropathic Pain in Adults in Non-specialist Settings*. 2013. URL: http://guidance.nice.org.uk/CG173 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Clinical Guideline CG130. *Hyperglycaemia in Acute Coronary Syndrome*. 2011. URL: www.nice.org.uk/guidance/CG130 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Technology Appraisal Guidance TA53. *The Clinical Effectiveness and Cost-effectiveness of Long Acting Insulin Analogues for Diabetes*. 2002. URL: www.nice.org.uk/guidance/TA53 (accessed 15 February 2016). Date for review: the recommendations in this technology appraisal relating to type 2 diabetes have been replaced by recommendations in the *Diabetes: Type 2* (update) clinical guideline published in May 2008. Please note that the recommendations in this technology appraisal relating to type 1 diabetes have not changed.

NICE Technology Appraisal Guidance TA151. *Continuous Subcutaneous Insulin Infusion for the Treatment of Diabetes Mellitus (Review)*. 2008. URL: http://guidance.nice.org.uk/TA151 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Technology Appraisal Guidance TA301. *Fluocinolone Acetonide Intravitreal Implant for Treating Chronic Diabetic Macular Oedema After an Inadequate Response to Prior Therapy (Rapid Review of Technology Appraisal Guidance 271)*. 2013. URL: http://guidance.nice.org.uk/TA301 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Technology Appraisal Guidance TA288. *Dapagliflozin in Combination Therapy for Treating Type 2 Diabetes*. 2013. URL: http://guidance.nice.org.uk/TA288 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Technology Appraisal Guidance TA274. *Ranibizumab for the Treatment of Diabetic Macular Oedema (Rapid Review of TA237)*. 2013. URL: http://guidance.nice.org.uk/TA274 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Technology Appraisal Guidance TA248. *Exenatide Prolonged-release Suspension for Injection in Combination with Oral Antidiabetic Therapy for the Treatment of Type 2 Diabetes*: 2012. URL: http://guidance.nice.org.uk/TA248 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Technology Appraisal Guidance TA203. *Liraglutide for the Treatment of Type 2 Diabetes Mellitus*. 2010. URL: http://guidance.nice.org.uk/TA203 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Technology Appraisal Guidance TA60. *The Clinical Effectiveness and Cost-effectiveness of Patient Education Models for Diabetes.* 2003. URL: http://guidance.nice.org.uk/TA60 (accessed 15 February 2016). Date for review: in December 2005, following consultation, the Institute proposed that the guidance be updated as part of the reviews of the guidelines on type 1 and type 2 diabetes. The recommendations in this technology appraisal relating to type 2 diabetes have been replaced by recommendations in the *Diabetes: Type 2* (update) clinical guideline published in May 2008. Please note that the recommendations in this technology appraisal relating to type 1diabetes have not changed.

NICE Technology Appraisal TA288. *Dapagliflozin in Combination Therapy for Treating Type 2 Diabetes*. 2013. URL: http://guidance.nice.org.uk/TA288 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Technology Appraisal TA271. *Fluocinolone Acetonide Intravitreal Implant for the Treatment of Chronic Diabetic Macular Oedema After an Inadequate Response to Prior Therapy*. 2013. URL: http://guidance.nice.org.uk/TA271 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Interventional Procedure IPG257. *Allogenic Pancreatic Islet Cell Transplantation for Type 1 Diabetes Mellitus*. 2008. URL: http://guidance.nice.org.uk/IPG257 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Interventional Procedure IPG274. *Autologous Pancreatic Islet Cell Transplantation for Improved Glycaemic Control After Pancreatectomy*. 2008. URL: http://guidance.nice.org.uk/IPG274 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Interventional Procedure IPG316. *Extracorporeal Albumin Dialysis for Acute Liver Failure*. 2009. URL: http://guidance.nice.org.uk/IPG316 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Public Health Guidance PH38. *Preventing Type 2 Diabetes: Risk Identification and Interventions for Individuals at High Risk*. 2012. URL: http://guidance.nice.org.uk/PH38 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Public Health Guidance PH35. *Preventing Type 2 Diabetes: Population and Community-level Interventions in High-risk Groups and the General Population*. 2011. URL: www.nice.org.uk/guidance/PH35 (accessed 15 February 2016). Date for review: May 2014.

NICE Evidence Summaries: New Medicines ESNM20. *Type 2 Diabetes: Alogliptin*. 2013. URL: http://publications.nice.org.uk/esnm20-type-2-diabetes-alogliptin-esnm20 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Evidence Summaries: New Medicines ESNM26. *Type 2 Diabetes: Lixisenatide*. 2013 URL: http://publications.nice.org.uk/esnm26type-2-diabetes-lixisenatide-esnm26 (accessed 15 February 2016). Date for review: to be confirmed.

NICE Evidence Summaries: New Medicines ESNM5. *Type 1 Diabetes: Insulin Degludec*. 2012. URL: www.nice.org.uk/mpc/evidencesummariesnewmedicines/ESNM5.jsp (accessed 15 February 2016). Date for review: to be confirmed.

NICE Evidence Summaries: New Medicines ESNM4. *Type 2 Diabetes: Insulin Degludec*. 2012. URL: www.nice.org.uk/mpc/evidencesummariesnewmedicines/ESNM4.jsp (accessed 15 February 2016). Date for review: to be confirmed.

NICE Quality Standard QS6. *Diabetes in Adults*. 2011. URL: http://guidance.nice.org.uk/QS6. In a statement dated August 2015, NICE explains that this quality standard was updated to make sure it was aligned with new NICE guidance (NG17 and NG19) for diabetes and diabetic foot problems, which superseded some previous development sources for the quality standard.

National Institute for Health and Care Excellence guidance under development

Diabetes in children and young people (update); NICE clinical guideline (publication expected August 2015).

Type 1 Diabetes (update); NICE clinical guideline (publication expected August 2015).

Type 2 Diabetes (update); NICE clinical guideline (publication expected August 2015).

Diabetes in Pregnancy (update); NICE clinical guideline (publication expected February 2015).

Diabetic Foot Problems (update); NICE clinical guideline (publication expected June 2015).

National Institute for Health and Care Excellence pathways

The guidance *Type 1 Diabetes: Integrated Sensor-augmented Pump Therapy Systems for Managing Blood Glucose Levels (the MiniMed Paradigm Veo System and the Vibe and G4 PLATINUM CGM system)* will be included in the NICE diabetes pathway.

Relevant guidance from other organisations

Scottish Intercollegiate Guidelines Network guideline 116. *Management of Diabetes*. 2010. URL: www.sign.ac.uk/guidelines/fulltext/116/ (accessed 15 February 2016).

Diabetes UK. *The Hospital Management of Hypoglycaemia in Adults with Diabetes Mellitus*. 2010. URL: www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_Hypo_Adults.pdf (accessed 15 February 2016).

Diabetes UK. *State of the Nation: England 2013*. 2013. URL: www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/0160b-state-nation-2013-england-1213.pdf (accessed 15 February 2016).

Diabetes UK. *Use of Analogue Insulins*. 2012. URL: www.diabetes.org.uk/Documents/Position%20statements/Analogue-insulin-pos-statement.2012.pdf (accessed 15 February 2016).

Diabetes UK. *End of Life Diabetes Care*. 2013. URL: www.diabetes.org.uk/upload/Position%20statements/End-of-life-care-Clinical-recs111113.pdf (accessed 15 February 2016).

Diabetes UK. *Recommendations for the Provision of Services in Primary Care for People with Diabetes*. 2005. URL: www.diabetes.org.uk/documents/professionals/primary_recs.pdf (accessed 15 February 2016).

Joint Royal Colleges Ambulance Liaison Committee. *Glycaemic Emergencies in Children*. 2006. URL: www.swast.nhs.uk/Downloads/SWASFT%20campaigns/clinical_guidelines_2006.pdf (accessed 15 February 2016). (See Part 3 – Paediatric Guidelines; Section 1: Emergencies in Children – Glycaemic emergencies in children.)

National Metabolic Biochemistry Network. *Guidelines for the Investigation of Hypoglycaemia in Infants and Children*. 2012. URL: www.metbio.net/docs/MetBio-Guideline-GARU968012-23-01-2012.pdf (accessed 15 February 2016).

British Inherited Metabolic Diseases Group. *Recurrent Hypoglycaemia*. 2013. URL: www.bimdg.org.uk/store/guidelines/Hypoglycaemiav1-2-461185-22-05-2013.pdf (accessed 15 February 2016).

British Inherited Metabolic Diseases Group. *Ketotic Hypoglycaemia*. 2008. URL: www.bimdg.org.uk/store/guidelines/ER-KH-v3_616477_18032015.pdf (accessed 15 February 2016).

British Inherited Metabolic Diseases Group. *Management of Surgery in Children at Risk of Hypoglycaemia*. 2013. URL: www.bimdg.org.uk/store/guidelines/Management-of-surgery-in-those-at-risk-of-hypoglycaemiav4-755756-22-05-2013.pdf (accessed 15 February 2016).

Joint Royal Colleges Ambulance Liaison Committee. *Glycaemic Emergencies in Adults*. 2006. URL: www.swast.nhs.uk/Downloads/SWASFT%20campaigns/clinical_guidelines_2006.pdf (accessed 15 February 2016). (See Part 2 – Adult Guidelines, Section 3: Specific Treatment Options, Glycaemic emergencies in adults.)

Driver and Vehicle Licensing Agency. *DVLA's Current Medical Guidelines for Professionals – Conditions D to F*. 2013. URL: www.gov.uk/guidance/current-medical-guidelines-dvla-guidance-for-professionals-conditions-d-to-f (accessed 15 February 2016).

Driver and Vehicle Licensing Agency. *DVLA's Current Medical Guidelines for Professionals – Conditions G to I*. 2013. URL: www.gov.uk/guidance/current-medical-guidelines-dvla-guidance-for-professionals-conditions-g-to-i (accessed 15 February 2016).

Royal College of Nursing. *Children and Young People with Diabetes: RCN Guidance for Newly-appointed Nurse Specialists*. 2013. URL: www2.rcn.org.uk/__data/assets/pdf_file/0009/78633/002474.pdf (accessed 15 February 2016).

Royal College of Nursing. *Supporting Children and Young People with Diabetes*. 2013. URL: www2.rcn.org.uk/__data/assets/pdf_file/0008/267389/003_318.pdf (accessed 15 February 2016).

Royal College of Nursing. *Specialist Nursing Services for Children and Young People with Diabetes*. 2006. URL: www2.rcn.org.uk/__data/assets/pdf_file/0009/78687/003015.pdf (accessed 15 February 2016).

Royal College of Nursing. *Starting Injectable Treatment in Adults with Type 2 Diabetes*. 2012. URL: www2.rcn.org.uk/__data/assets/pdf_file/0009/78606/002254.pdf (accessed 15 February 2016).

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