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The research reported in this issue of the journal was commissioned by the HTA programme as project number 01/13/03. The contractual start date was in December 2002. The draft report began editorial review in April 2007 and was accepted for publication in October 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE)

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Objectives: To evaluate whether the additional information provided by minimally invasive glucose monitors results in improved glycaemic control in people with poorly controlled insulin-requiring diabetes, and to assess the acceptability and health economic impact of the devices.
Design: A four-arm randomised controlled trial was undertaken.
Setting: Participants were recruited from secondary care diabetes clinics in four hospitals in England.
Participants: 404 people aged over 18 years with insulin-treated diabetes mellitus (types 1 or 2) for at least 6 months who were receiving two or more injections of insulin daily were eligible. Participants had to have had two glycosylated haemoglobin (HbA1c) values ≥ 7.5% in the last 15 months.
Interventions: Participants were randomised to one of four groups. Two groups received minimally invasive glucose monitoring devices [GlucoWatch Biographer or MiniMed Continuous Glucose Monitoring System (CGMS)]. These groups were compared with an attention control group (standard treatment with nurse feedback sessions at the same frequency as those in the device groups) and a standard control group (reflecting common practice in the clinical management of diabetes in the UK).
Main outcome measures: Change in HbA1c from baseline to 3, 6, 12 and 18 months was the primary indicator of short- to long-term efficacy in this study. Perceived acceptability of the devices was assessed by use and a self-report questionnaire. A health economic analysis was also performed.
Results: At 18 months all groups demonstrated a decline in HbA1c levels from baseline. Mean percentage changes in HbA1c were –1.4 for the GlucoWatch group, –4.2 for the CGMS group, –5.1 for the attention control group and –4.9 for the standard care control group. At 18 months the relative percentage reduction in HbA1c in each of the intervention arms was less than that in the standard care control group. In the intention to treat analysis no significant differences were found between any of the groups at any of the assessment times. There was no evidence that the additional information provided by the devices resulted in any change in the number or nature of treatment recommendations offered by the nurses. The health economics analysis indicated no advantage in the groups who received the devices; a lower cost and higher benefit were found for the attention control arm. Assessment of device use and acceptability indicated a decline in use of both devices, which was most marked in the GlucoWatch group by 18 months (20% still using GlucoWatch versus 57%

still using the CGMS). The GlucoWatch group reported more side effects, greater interference with daily activities and more difficulty in using the device than the CGMS group.
Conclusions: Continuous glucose monitors do not lead to improved clinical outcomes and are not cost-effective for improving HbA1c in unselected individuals with poorly controlled insulin-requiring diabetes. On acceptability grounds the data suggest that the GlucoWatch will not be frequently used by individuals with diabetes because of the large number of side effects.
Trial registration: Current Controlled Trials ISRCTN33678610.

Contents

List of abbreviations

ADDLoC	Audit of Diabetes-Dependent Locus of Control
ADDQoL	Audit of Diabetes-Dependent Quality of Life
ANOVA	analysis of variance
BMI	body mass index
CGMS	continuous glucose monitoring system
CRF	case report form
CSII	continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
DRN	diabetes research nurse
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EQ-5D	European Quality of Life – 5 dimensions
FDA	Food and Drug Administration
GLM	general linear model
HbA1c	glycosylated haemoglobin
HRQoL	health-related quality of life
ICE	imputation by chained equations
ICER	incremental cost-effectiveness ratio
LREC	local research ethics committee
MREC	multicentre research ethics committee
NICE	National Institute for Health and Clinical Excellence
PCA	principal components analysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SAE	serious adverse event
SDSCA	Summary of Diabetes Self-Care Activities
SMBG	self-monitoring of blood glucose
UCLH	University College London Hospitals
UKPDS	UK Prospective Diabetes Study
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Diabetes is associated with significant morbidity, which has been shown to be reduced by improved glycaemic control. Although subject to much debate, self-monitoring of blood glucose is seen as a key element in implementing intensive therapy as it provides real-time feedback on the effects of diet, exercise and stress on the actual blood glucose, thus allowing patients to determine blood glucose values and identify hypo- or hyperglycaemia. Patients are, however, reluctant to test their blood glucose because of the pain, inconvenience and discomfort experienced, as well as any perceived stigma associated with the procedure. Even if performed more frequently, this form of blood glucose monitoring only provides a snapshot and may miss debilitating episodes of hypo- and hyperglycaemia. To address these limitations, minimally invasive continuous glucose monitoring devices have been developed to provide more detailed information along with analyses of trends of blood glucose. It has been assumed that this additional information will lead to more appropriately targeted advice and improved glycaemic control.

Objectives

The objective of this study was to evaluate whether the additional information provided by two minimally invasive glucose monitors resulted in improved glycaemic control in people with poorly controlled insulin-requiring diabetes in both the long and medium term. In addition, the acceptability and health economic impact of the devices was assessed.

Methods

Design

This was a four-arm randomised controlled trial. Two groups (groups 1 and 2) received minimally invasive glucose monitoring devices. Group 1 received the GlucoWatch Biographer device and group 2 the MiniMed Continuous Glucose Monitoring System (CGMS). These groups were compared with group 3, an attention control group that received standard treatment but with nurse feedback sessions at the same frequency as those in the groups receiving the devices, and group 4, a standard control group that reflected common practice in the clinical management of diabetes in the UK.

Setting

Participants were recruited from secondary care diabetes clinics in four hospitals. Two sites were inner-city locations, the third was an urban, relatively affluent area with a high proportion of retired people and the fourth was a socioeconomically deprived area. Assessment visits took place in diabetes outpatient clinics.

Participants

Participants were eligible if they were aged over 18 years, had insulin-treated diabetes mellitus (type 1 or type 2) and were receiving two or more injections of insulin daily. They also had to have been diagnosed with diabetes for at least 6 months and to have had two glycosylated haemoglobin (HbA1c) values greater than or equal to 7.5% in the last 15 months.

In total, 100 participants were recruited and randomised to receive the GlucoWatch (group 1), 102 were recruited to receive the CGMS (group 2), 100 were recruited to the attention control group and 102 were recruited to the standard care control group. At baseline HbA1c ranged from 7.0% to 15.5% with group means ranging from 8.9% to 9.4%.

Intervention

The intervention was divided into two phases.

- Phase 1 (0–3 months for participants in groups 1–3). Participants in the device groups were provided with the GlucoWatch Biographer or CGMS monitors. Those in the GlucoWatch group were trained and asked to use the device a minimum of four times per month and a maximum attempted use of four times per week. The information provided by the

GlucoWatch was downloaded at the nurse feedback sessions. Participants in the CGMS group were requested to be fitted with the device at baseline and at 6 and 12 weeks and received nurse feedback sessions 72 hours later. Participants in groups 1–3 also attended three nurse feedback sessions in this phase.

- Phase 2 (3–18 months for each participant). During this phase participants in group 1 used the GlucoWatch Biographer as desired and participants in group 2 were fitted with the CGMS at 6, 12 and 18 months. Participants in groups 1–3 also attended nurse feedback sessions at 6, 12 and 18 months.

All participants were provided with the same self-monitoring glucose meter and trained in its use at the baseline clinic visit.

Main outcomes

Change in HbA1c from baseline to 18 months was the primary indicator of long-term efficacy in this study. Change in HbA1c from baseline to 3 and 6 months evaluated short-term efficacy, and change from baseline to 12 months assessed efficacy in the medium term. Perceived acceptability of the GlucoWatch and CGMS was assessed by use and a self-report questionnaire, developed for the purpose of this study, at 3, 6, 12 and 18 months. A health economic analysis of the trial was also performed.

Results

At 18 months all groups demonstrated a decline in their HbA1c levels from baseline. Mean percentage changes in HbA1c were –1.4 for the GlucoWatch group, –4.2 for the CGMS group, –5.1 for the attention control group and –4.9 for the standard care control group. At 18 months the relative percentage reduction in HbA1c in each of the intervention arms was less than that in the standard care control group. In the intention to treat analysis the difference in the relative percentage reduction between the GlucoWatch and standard care control groups was 3.7% [95% confidence interval (CI) –1.1 to 8.5], for the CGMS 0.9% (95% CI –3.8 to 5.7) and for the attention control group 0.1% (–4.3 to 5.4). No significant differences were found between any of the groups at any of the assessment times. The findings indicated no advantage of having the additional information provided by a continuous glucose monitoring device on change in HbA1c in unselected individuals with poorly controlled insulin-requiring diabetes.

There was also no evidence that the additional information provided by the minimally invasive glucose devices resulted in any change in the number or nature of treatment recommendations offered by the nurses.

The health economics analysis indicated no advantage in the groups who received the continuous blood glucose monitoring devices. Using the health economic tools a lower cost and higher benefit was found for the attention control arm in the trial period.

A comparison between the devices in terms of use and acceptability indicated a decline in use of both devices but this was most marked in the GlucoWatch group, as opposed to the CGMS group, by 18 months (20% still using the GlucoWatch device versus 57% still using the CGMS). The participants using the GlucoWatch device reported more side effects, greater interference with daily activities and more difficulty in using the device than those using the CGMS.

Conclusions

The outcomes indicate that continuous glucose monitors as assessed in this study do not lead to improved clinical outcomes in unselected individuals with poorly controlled insulin-requiring diabetes.

In addition, the data suggest that the additional information provided by the two continuous glucose monitoring devices in this study (CGMS and GlucoWatch) is not cost-effective for improving HbA1c in an unselected population with poorly controlled type 1 or type 2 diabetes.

The findings also indicate that the two devices were accepted differently by participants. The GlucoWatch device was associated with a large number of side effects and its acceptability to participants was particularly low with only 20% of participants continuing to use the device at 18 months. On acceptability grounds alone the data suggest that the GlucoWatch technology assessed in this study will not be frequently used by individuals with diabetes. The findings emphasise the importance of examining acceptability, as devices may demonstrate clinical value, but if potential users find them unacceptable or choose

not to use them then it is unlikely that they could be introduced into routine care.

Future studies of continuous glucose monitoring devices should target specific subgroups for study such as poorly controlled type 1 patients with hypoglycaemia unawareness. The acceptability of these devices to participants and health-care professionals is an area that needs further research and should be included in studies of their potential clinical benefit.

Trial registration

This trial is registered as ISRCTN33678610.

Chapter 1
Introduction

Epidemiology and burden of diabetes

In 2000, the World Health Organization (WHO) estimated that the prevalence of diabetes mellitus for all age groups was 2.8%.[1] Because of increasing risk factors (ageing populations and increasing rates of urbanisation, obesity and physical inactivity) it is predicted that the number of people with diabetes will more than double by 2030 from 171 million to 366 million.[2] Using the Netherlands as a proxy the WHO estimates the UK prevalence rate to be 2.7%; however, this is likely to underestimate the prevalence of diabetes in the UK because of the lower rates of obesity and higher rates of physical activity in the Netherlands' population.[3]

By far the greatest proportion (over 90%) of this 'rising epidemic' is due to an increase in type 2 diabetes.[4] Type 2 diabetes is characterised by both insulin resistance and insulin secretory defects. Treatment is based initially on dietary measures, with the subsequent addition of oral hypoglycaemic medication. In the later stages insulin therapy may be required to achieve adequate glycaemic control. Type 1 diabetes is caused by autoimmune-mediated destruction of the pancreatic β-cell islets, resulting in insulin deficiency and a prerequisite for insulin therapy.

The proportion of patients treated with insulin has increased markedly in recent years in the UK.[5] This is likely to be due to increasing disease prevalence but also more aggressive treatment of type 2 diabetes through use of insulin to improve glycaemic control, following publication of the UK Prospective Diabetes Study (UKPDS).[6–8]

The management of diabetes has enormous implications for society and the provision of health care.[9] The total annual cost of diabetes to the NHS has been estimated at £1.3 billion.[10] A significant proportion of this cost is spent on dealing with the microvascular and macrovascular complications associated with poorly controlled diabetes. One in 20 people with type 2 diabetes incurs social services costs and the presence of complications increases these costs fourfold.[11]

The cost of diabetes to the individual and their family/carers may also be considerable. Estimates of the indirect costs of diabetes, for example the cost of loss of work and a reduction in working hours, may be as high as the direct costs.[12] In terms of mortality the available evidence clearly shows a reduced life expectancy for people with both types of diabetes.[13] This literature may underestimate mortality rates because of the under-reporting of diabetes as a cause of death.[14] The complex management regimen that individuals with diabetes are required to follow requires lifelong self-regulation of behaviour.[15] There are consistent reports in the literature that quality of life is reduced and the risk of clinical depression is increased in people with diabetes compared with the general population.[16,17] Several studies indicate that good glycaemic control is associated with better quality of life, although the causal direction of this relationship is unclear.[18–21]

Role of glycaemic control

Diabetes is associated with significant morbidity in the form of both microvascular and macrovascular complications. Improved glycaemic control has been shown to significantly reduce the incidence of microvascular complications such as retinopathy, nephropathy and neuropathy in both type 1 and type 2 diabetes.[8,22] In addition, both studies demonstrated a reduction in macrovascular disease such as heart disease although this did not reach statistical significance. Long-term follow-up of the Diabetes Control and Complications Trial (DCCT) has subsequently demonstrated the beneficial effects of improved glycaemic control on the risk of cardiovascular disease in type 1 diabetes.[23] To optimise glycaemic control in the DCCT, patients with type 1 diabetes received significant support and intensive therapy with four insulin injections daily.[22] In the UKPDS, patients with type 2 diabetes received intensive therapy with both oral agents and insulin.[8]

Self-monitoring of blood glucose (SMBG) is a key element in implementing intensive therapy. This provides real-time feedback on the effects of diet, exercise and stress on the actual blood glucose,

allowing patients to determine blood glucose values and identify hypo- or hyperglycaemia. There has been much debate over the value of such monitoring,[24–27] fuelled in large part by the failure to perform high-quality efficacy trials.[28] It is, however, widely acknowledged that patients should have access to SMBG at different stages of their disease and that the degree of monitoring should reflect the medications that they are administering. Particularly for insulin-requiring patients, blood glucose readings are an important tool for recognising patterns in blood glucose levels that can guide adjustment of therapy.[29] Hence, patients may be advised to test their blood glucose before meals, at bedtime and on waking in the morning so that these readings may be used to identify the effect of exercise, diet and insulin on blood glucose. Within both the DCCT and the UKPDS, intensive therapy was associated with a greater risk of hypoglycaemia. The introduction and widespread use of rapid and long-acting insulin analogues since the publication of these studies have reduced this risk, but hypoglycaemia is still a common side effect of intensive therapy. Self-monitoring can identify hypoglycaemia and therefore testing may be desirable before driving, undertaking any dangerous sport or activity, or at night for those patients who are prone to frequent hypoglycaemia.

Intermittent capillary blood glucose monitoring only provides a snapshot and not the trends in fluctuations of blood glucose levels over time.[30] It has been shown that even testing seven times daily may miss debilitating episodes of hypo- and hyperglycaemia.[31] The average number of finger prick blood glucose measurements performed by a patient with type 1 diabetes is estimated to be only two per day. Despite encouragement to perform more tests, many patients are reluctant because of the pain, inconvenience and discomfort experienced, as well as the perceived stigma associated with the procedure.[32,33] In addition, not all patients perform blood glucose testing accurately or make appropriate use of the information. Ideally, patients should use the information obtained to adjust their therapy and should record the information for review with health-care professionals to provide the basis for further changes to their therapy. Unfortunately, this is not always done as frequently or accurately as would be desirable and it is difficult to envisage how such limited data can be used to modify insulin regimes to optimise glycaemic control.[33] Consequently it has been argued that there is a need to obtain detailed information on individual glucose excursions in a more patient-friendly manner.

Non- and minimally invasive continuous glucose monitoring devices

Non- and minimally invasive continuous glucose monitoring techniques have been developed in response to the limitations of home blood glucose monitoring. The race to use continuous glucose monitoring technology in the development of an automated pancreas or closed-loop system also underlies this highly competitive industry. Several non- and minimally invasive continuous glucose monitoring techniques have been developed involving local radiation or body fluid sampling.[34]

Despite intensive interest in this area developments have been slow because of the complexity of the measurement of glucose across a dynamic multilayer consisting of lipids, protein, water and other biomolecules. There are a variety of non-invasive devices under development including a skin patch designed to monitor glucose levels in interstitial fluid; contact lens sensors of tears that change colour depending on the amount of glucose present; infrared devices that measure blood glucose levels either through the skin, without penetrating it, or as an implantable device; and implantable sensors.[35] The Pendra® (Pendragon Medical) was a truly non-invasive device based on impedance spectroscopy, that is, the tissue fluid compartment of interest (microcirculation) was not violated and nothing was extracted from it.[36,37] This is in contrast to the minimally invasive devices described below. CE certification for the Pendra was obtained in Europe but the device was subsequently withdrawn by the manufacturer because of concerns over accuracy and alert features and operational failure of the device in approximately one-third of users.[37,38]

As of May 2008, 36 minimally invasive continuous glucose monitoring devices had obtained Food and Drug Administration (FDA) approval and are available for clinical use. The majority of these are newer models of the same core group of monitors. Several evaluations of these and other continuous glucose monitoring devices have been published in recent years, although there are limitations in the evidence that is currently available. A description of the main devices that have obtained FDA/CE approval is provided, followed by a summary

and critique of the available evidence base on continuous glucose monitoring devices.

The GlucoWatch® G2™ Biographer (Animas Corporation, West Chester, PA, USA)

The GlucoWatch (*Figure 1*) is slightly larger than a watch and can be worn on any part of the body, although the forearm is favoured. The device consists of two parts: (1) a reusable portion, which contains the microprocessor, electronics and output display, and (2) the disposable portion or autosensor that comes into contact with and adheres to skin. The sensor consists of two electrodes and two hydrogel discs that contain glucose oxidase. The sensor extracts fluid electro-osmotically through the skin.

The GlucoWatch requires a 2-hour warm-up period followed by a single capillary glucose estimation for calibration. Following the warm-up period the device may be worn for up to 13 hours, providing the patient with up to 78 estimates over that period. A measurement is made every 10 minutes and the device takes the average of the last two recordings to provide real-time glucose values to the patient every 10 minutes. The usable accurate range is reported to be between 2.2 and 22.0 mmol/l . Over 8500 recordings can be stored in the memory. This information can be downloaded to a personal computer to provide information for the patient and health-care professional on profiles and trends in glucose. Thus, patients can obtain feedback on their glucose profiles without attendance at a clinic.

The device can be programmed to provide audible warnings should the glucose level rise above or fall below preset values; however, the device does not work properly if the skin has excess perspiration or has rapidly changed in temperature, as these will confound the recording. The optimum frequency of use has yet to be determined.

FIGURE 1 *GlucoWatch G2 Biographer (Animas Corporation).*

Most studies on the GlucoWatch have focused on the correlation between the GlucoWatch and capillary blood glucose values. Two early studies have shown this to be acceptable with an *r*-value of 0.85–0.90.[39,40] GlucoWatch readings lag behind blood glucose concentrations by approximately 20 minutes. It is important to note that the GlucoWatch manufacturers stopped selling this device from the end of July 2007.

The Continuous Glucose Monitoring System® (MiniMed, Northridge, CA, USA)

The MiniMed Continuous Glucose Monitoring System (CGMS) (*Figures 2* and *3*) is a halter-style device similar in size to a radio pager. The device is worn on the waist and connected via a wire to a subcutaneous sensor. The sensor is a small flexible device containing glucose oxidase that harvests interstitial fluid. This is inserted into the abdominal wall using a rigid introducer and then secured to skin. The patient then wears the device for up to 72 hours. The CGMS does not provide real-time blood glucose readings. Calibration requires the patient to record at least four capillary blood glucose values daily and enter the values into the device. The device samples every 10 seconds and records an average glucose estimation every 5 minutes, i.e. 288 recordings are made in a 24-hour period. The usable accurate range is reported to be between 2.2 and 22.0 mmol/l . A total of 2 weeks of results can be stored in the device.

The patient is asked to perform frequent capillary glucose testing, if possible, in addition to the recordings required for basic calibration, and to record this information on the device. At the end of the 72-hour period the patient then attends the diabetes unit for downloading of the results to form a glucose profile. This can then be reviewed with a health-care professional and adjustments to treatment made as appropriate. The device may be refitted at intervals to review the change in trends. The optimal frequency of use of the device has not yet been established, although it is suggested that it should be used 4–6 weekly during initial treatment changes and 4–6 monthly during review.

Studies have confirmed that the measurements of interstitial fluid glucose by the device reflect plasma glucose levels across a broad range.[41,42]

FIGURE 2 *MiniMed CGMS.*

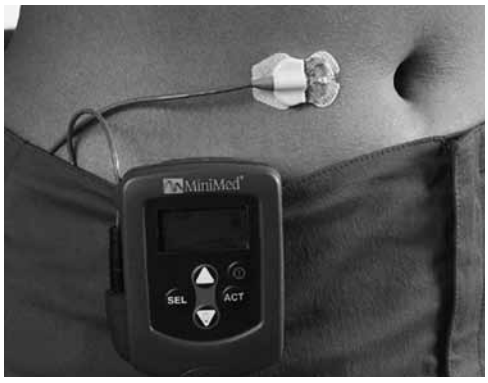

FIGURE 3 *MiniMed CGMS.*

GlucoDay® (A. Menarini, Florence, Italy)

The GlucoDay measures glucose through a microdialysis probe, which is inserted into the abdominal wall. A portable unit is wrapped around the wearer's abdomen. Glucose levels are measured every 3 minutes for 48 hours and only one calibration is required at 48 hours. The device can provide real-time or retrospective readings, depending on how the monitor is set up. Results can be read continuously through an infrared communicating port and downloaded to a personal computer; thus, individual glucose profiles can be observed over a 24-hour continuous monitoring period. A series of alarms are built into the system and can alert the wearer to take appropriate action.[43]

Guardian® Real-Time Continuous Glucose Monitoring System (MiniMed)

The Guardian is the successor to the CGMS and is based on exactly the same technology; however, unlike the CGMS it provides real-time data and hypo- and hyperglycaemic alarms that will sound outside a preset range.

FreeStyle Navigator® (Abbott Diabetes Care, Alameda, CA, USA)

This uses an enzyme-tipped subcutaneous sensor attached to a transmitter, which sends data to a receiver that can be located up to 10 feet away. The device records glucose readings every minute and presents real-time data. The receiver presents data in various formats including a trend function in which arrows indicate the immediate glucose trend (horizontal: no change; slightly up: increase; strongly up: rapid increase; slightly down: decrease; strongly down: rapid decrease). These data can be downloaded to a computer for analysis.[44]

STS™ System (DexCom, San Diego, CA, USA)

The DexCom STS System (3 day and 7 day) uses a disposable sensor placed just below the skin in the abdomen to measure the level of glucose in the fluid found in the body's tissues (interstitial fluid). Sensor placement causes minimal discomfort and can easily be carried out by the patient. The sensor must be replaced weekly. An alarm can be programmed to sound if a patient's glucose level reaches preset lows or highs.

It is important to note that none of these devices are intended to provide an alternative to traditional SMBG. FDA labelling states that they should serve as an adjunct to SMBG, supplying additional information on glucose trends that is not available from traditional monitoring.

Summary and critique of available literature evaluating the clinical effectiveness and acceptability of continuous glucose monitoring devices

A descriptive review of the available literature was conducted to assess the evidence of clinical effectiveness, user acceptability and psychological impact of continuous glucose monitoring devices. A summary of this review is presented here.

Meta-analysis was not considered as an appropriate method for summarising the studies identified through the literature searches because of variation in the measurement of the outcomes and in the delivery and content of the interventions.

The MEDLINE (1966–5/2008), EMBASE (1980–5/2008), CINAHL (Cumulative Index to Nursing and Allied Health Literature; 1982–5/2008) and PsycINFO (1972–5/2008) databases were searched using the following search terms: continuous glucose monitoring.

Articles were also identified from the reference lists of studies identified through database searches.

Inclusion criteria

- Evaluation of any continuous glucose monitoring device in which statistical analysis of one or more of the following outcomes was reported:
  - glycosylated haemoglobin (HbA1c)
  - acceptability (including side effects and device-related adverse events, discontinuation rates, reasons for stopping use, treatment satisfaction, ease of use, interference with normal daily activities and withdrawals related to device use)
  - frequency or duration of hypo- or hyperglycaemic episodes or euglycaemia
  - psychosocial measures (including quality of life, depression, anxiety).
- With regard to measures of acceptability of continuous glucose monitoring devices, articles were also included if the population studied did not have diabetes.
- Paediatric or adult populations.

Exclusion criteria

- Case studies.
- Studies that did not report any statistical analysis of outcomes (HbA1c, psychosocial, hypo- or hyperglycaemic episodes or euglycaemia).
- Studies in which the focus was primarily on establishing the accuracy of continuous glucose monitoring devices unless there was also an evaluation of acceptability.
- Studies in which the primary focus was on the use of continuous glucose monitoring devices to establish efficacy of another device/drug, for example as a control group, unless there was also an evaluation of acceptability.
- Non-English language articles.

Outcomes

Glycaemic control (HbA1c) as a surrogate indicator of morbidity and mortality in diabetes mellitus

A total of 22 studies examining the impact on a surrogate indicator of morbidity and mortality in diabetes mellitus of wearing a continuous glucose monitoring device on glycaemic control, as measured by HbA1c, were identified using the search strategy described.[45–66] The majority of these studies ($n = 15$) evaluated the MiniMed CGMS. Five of the studies were carried out in adult populations, three in combined adult and paediatric populations and the remaining seven in children and/or adolescents. Three studies evaluated the impact of wearing the GlucoWatch in children. One assessed the Guardian, one assessed the DexCom STS meter and two the FreeStyle Navigator. A distinction is warranted here between paediatric and adult populations. Stable glycaemic control is harder to achieve in paediatric/adolescent patients and has important implications for growth and development. It is possible that continuous glucose monitoring may have a clearer beneficial effect in this age group in which large fluctuations in glucose levels are more common. Studies on adults may miss this benefit.

Six of these studies[49,52,53,60,64,66] were randomised controlled trials (RCTs) with between-group analysis. Three[53,64,66] of these reported no significant differences in HbA1c between the intervention and control groups. The DirecNet group study[53] is the highest quality study to date in this area. This study employed an RCT design, had 90% power to detect a 0.5% difference in HbA1c between the groups, used an intention to treat analysis and independently evaluated the GlucoWatch. The study found no significant differences in HbA1c between the GlucoWatch group and the control group at 6 months' follow-up amongst their population of children and adolescents. Declining use of the GlucoWatch over this 6-month period may explain the lack of effect.

Tanenberg *et al.*[64] found no significant differences in HbA1c levels between groups at weeks 8 or 12 following use of the CGMS in weeks 1 and 3. The authors found significant improvement in HbA1c over time but these changes were very similar in the two groups, suggesting that improvement may have been due to therapy adjustments based on increased frequency of SMBG, which averaged seven tests per day in both groups, rather than from additional information obtained from the

CGMS. This study was the second largest in terms of sample size ($n = 128$) after the DirecNet group study but, after accounting for missing data and losses to follow-up, it is unlikely that the study was sufficiently powered. Yates *et al*.[66] also found no significant differences in HbA1c or fructosamine levels between groups at 6 weeks', 12 weeks' and 6 months' follow-up in a relatively small sample size (CGMS: $n = 19$; control: $n = 17$). This study followed CGMS use at weekly intervals over a period of 3 months.

Amongst the studies reporting improved outcomes in relation to HbA1c, Chase *et al*.[49] reported a lower median HbA1c in their intervention group at 3 months' follow-up. The intervention group had worn the GlucoWatch an average of 3.5 times per week during these 3 months, although use was greater in the initial weeks of the intervention. Sabbah *et al*.[60] reported lower HbA1c levels in the CGMS group than in the control group, which was approaching statistical significance at week 8 and was significant by week 12, although it is unclear whether adjustments were made for multiple testing. Their intervention consisted of two CGMS uses at weeks 1 and 3. The sample size in both of these studies was small ($n = 40$ and $n = 20$ respectively). An RCT[52] evaluating the Guardian system reported significant reductions in HbA1c from baseline at 1 and 3 months' follow-up amongst a combined adult/paediatric population whose baseline HbA1c was ≥ 8.0%. The possibility of conflict of interest must be highlighted here as, in two of these studies, one or more of the authors was employed by the company that manufactured the device under evaluation and, in the other, several of the authors declared conflicts of interest in the form of receipt of consulting fees or honoraria from Medtronic, manufacturer of the Guardian device.

Two studies[51,58] reported reductions in HbA1c by study completion in intervention groups that wore the CGMS three times over a 4- and 6-month period respectively. The first of these was a single-blind RCT in which the control group's CGMS data were not utilised. The other was a randomised controlled cross-over trial in which, again, one arm was not given feedback on the CGMS results. Both of these studies suffer from having sample sizes of only 30 or less.

Ten of the fourteen studies[45–48,50,54,57,59,61,62,65] conducting within-group analysis reported significant improvements over time in HbA1c results. Seven of these were evaluations of the CGMS, one of the DexCom STS System and two of the FreeStyle Navigator. Four studies[47,55,56,63] conducting within-group analysis reported non-significant improvements in HbA1c results. Three of these were evaluating the CGMS and one the GlucoWatch.

Taken together, the studies carried out to date on the efficacy of continuous glucose monitors do not provide sufficient evidence to recommend their widespread use in clinical practice. This was also the conclusion reached by the Technology Evaluation Centre in its review of continuous glucose monitoring devices for the Blue Cross and Blue Shield Association in the USA.[67] One of its key criticisms was that, when statistically significant changes in HbA1c are reported, these are too small to be considered clinically significant. Two papers[68,69] have subsequently argued that even a 0.3% absolute decrease in HbA1c as a result of using the CGMS device could result in substantially reduced diabetes-related mortality and morbidity. These conclusions are also supported by recent reviews in the area[70,71] and a meta-analysis[72] of trials comparing the effects of CGMS with SMBG on glycaemic control in children with type 1 diabetes.

Acceptability

Acceptability has been defined as an individual's willingness to use a device, which in turn depends on several interrelated factors: the needs of the individual, perceptions of safety and utility of the device and whether the person feels that use of the device either supports or undermines their sense of personal identity and control over their condition.[73]

Side effects and device-related adverse events

CGMS studies

In total, 10[56–58,66,74–79] of the 15 CGMS studies that reported on adverse events found no evidence of either skin irritation or inflammation and no adverse device-related events. Of the remaining five studies, one[41] reported seven device-related adverse events, all involving minor irritation of the sensor insertion site, and another[64] reported five adverse device-related events. In one study,[51] eight (11%) participants said that they experienced discomfort whilst wearing the CGMS, and mild local side effects were reported in 21 (23%) cases in another study.[80] One study[81] reported 29 adverse device-related events in half of their sample ($n = 11$) who wore the CGMS for 9 days. All of these were rated mild and none resulted in sensor removal.

All of these studies were then examined in terms of monitor usage, i.e. the length of time and number of times that the monitor was worn. Five[57,74,75,77,79] of the ten studies that reported no adverse device-related events, skin irritation or inflammation required the CGMS to be worn once. Amongst the other five studies the CGMS was worn once or more,[41] twice,[56] three times[58] or four times.[66,78] In the studies reporting device-related adverse events, the CGMS was worn once,[50] twice,[51,64] for an average of 18 days using seven sensors consecutively[76] or continuously for 9 days.[81]

These findings need to be interpreted with caution as not all of these studies describe how, or at what time points, skin irritation, adverse events or tolerance of the device were assessed. This means that one cannot necessarily be certain of the validity of the findings. It appears that, in relation to the CGMS, there is no relationship between the number of times the device was worn and the reporting of adverse device-related events, skin irritation or inflammation.

GlucoWatch studies

All of the eight GlucoWatch studies[39,40,53,82–86] that reported device-related adverse events noted some degree of skin irritation or instances of adverse events related to use of the watch. All of these studies provided descriptions of their assessment methods.

In three of the studies[39,40,84] the severity of the skin irritation was rated as mild and it resolved within a few days following either three uses over 3 days[39] or one use;[40] the other study[84] did not report the number of times that the GlucoWatch was worn. One study[86] reported no or mild irritation in 'virtually all' of the participants, intense erythema in one (0.09%), and strong oedema in 13 (1.2%). Irritation resolved without treatment within several days amongst most of these participants, all of whom either wore two GlucoWatches over a 24-hour period or wore one watch per day over 5 days.

In another study,[85] no or mild irritation was reported for the majority of participants and moderate irritation in 9% and 13% of two treatment groups after one use of the GlucoWatch. The same study reported one device-related adverse event that involved bruising at the GlucoWatch application sites and at other skin locations on the forearm. In another study,[82] 77% of the sample reported skin reactions that all resolved rapidly; however, no information is provided on the number of times that the watch was worn. In one of the DirecNet studies,[83] participants wore two GlucoWatches simultaneously for 24 hours and 3/97 people reported a score of 5 on the modified Draize scale (range 0–8). A score of 6 represents a reportable adverse event.

The other DirecNet study[53] is the most informative in this area as it has the longest follow-up period (6 months). GlucoWatch use averaged 2.1 times per week by the end of the first month and 1.5 times per week during the last month of the study. Skin irritation was reported at least once during the study by all of the participants, whether by weekly contact questionnaires or follow-up phone calls or at the 6-month visit. One participant experienced a severe skin reaction and 48% had moderate skin reactions. At 6 months, 55% showed acute changes corresponding to watch use that were rated as mild (36%) or moderate (19%). A total of 50% of the sample was considered to have non-acute changes (scabbing, dry skin, hypo- and hyperpigmentation or scarring).

Several of these studies[39,40,86] describe how irritation resolves within a few days; however, if participants are only ever followed up for a few days then it is not possible to make this conclusion. It would appear that prolonged use of the GlucoWatch may cause non-acute changes at the application sites based on the DirecNet study's findings.[53]

Other continuous glucose monitoring devices

In the studies that looked at other continuous glucose monitoring devices there were either no local complications at the site of implantation or complications that were rated as mild. This was the case for all of the studies assessing one use of the GlucoDay device,[87,88] the CGMS Datalogger, which was worn for 7 days,[89] the ExacTech, worn once for 75 hours,[31] and the Roche SCGM System, worn once for 72 hours.[90] There were no serious or unanticipated device-related events in two of the studies evaluating the DexCom STS System,[91,92] although one[91] of these reported 45 sensor insertion site effects and 75 sensor adhesive effects. In the other studies evaluating this system, 21 adverse events were reported in 16 patients, which were all mild and resolved within 7 days,[93] and four adverse events were considered 'probably related' to monitor use.[45] In a study[94] of an experimental real-time glucose sensing system, three participants (3%) had a skin reaction to the adhesive that resolved spontaneously. In the DirecNet study[54] of the FreeStyle Navigator most of the participants tolerated the sensor well, although two had severe skin reactions related to the adhesive. At

the 13-week visit in that study, eight (29%) of 28 participants had acute skin changes reflective of Navigator use (moderate in 14% and mild in 14%); 11 (39%) were considered to have non-acute changes such as scabbing (32%), dry skin (21%) and changes in pigmentation (7%).

The user perspective

A total of 21 studies[31,41,43,49,50,53,55,56,59,74,79,81,82,84,87,89,90,95–98] report on some aspect of the user's perspective on the various continuous glucose monitoring devices. The majority of these studies limited their assessment of the user perspective to either anecdotal or subjective reports on the part of the investigator.[41,49,50,55,56,59,74,79,90,96,97] For example, one study[90] stated that daily activities were not limited but the authors do not say how this was assessed. Similarly, another study described how use of the CGMS did not interfere with the care of the child and was well accepted by the children and their families.[56] Again, no information is provided on how this was assessed. Another stated that 'patients felt confident and satisfied with the CGMS' but there is no information on how confidence and satisfaction were measured.

Seven studies[54,81,82,84,89,98,99] developed questionnaires specifically to assess various aspects of the user's perspective. It is assumed that the three studies[43,87,95] assessing the GlucoDay used the same patient-reported questionnaire to measure levels of pain and discomfort. These findings are reported in the previous section on adverse device-related events.

In the study by McLachlan and colleagues,[98] the majority of respondents reported that the CGMS was either 'very easy to use' or 'easy to use' ($n = 44$, 92%), the level of inconvenience was 'minimal' or 'minor' ($n = 39$, 81%), their understanding of how they could control blood glucose was either 'clearly better' or 'better' ($n = 43$, 90%) and they felt that the benefits of the CGMS outweighed the inconvenience ($n = 37$, 77%). In a study of 9 days of continuous CGMS[81] use in 22 patients, 9% reported sleep disturbances, 5% attention deficits, 18% discomfort related to the sensor, 27% discomfort related to the adhesive tape and 23% technical monitor-related problems. In a study of the CGMS DataLogger worn by 20 patients,[89] 75% felt that wearing the sensors did not change their daily activities, 95% believed that the device was not obvious to others, 90% would have liked to see a daily display of their results, 80% thought that the sensor was comfortable to wear for 3 days, 50% thought that it comfortable to wear for 5–6 days and only 30% felt that it was comfortable to wear for 7 days.

The study by Gandrud and colleagues[84] is of particular interest because, having described how minor pruritis was evident in their sample when the GlucoWatch was initially placed on the forearm, they then went on to ask participants ($n = 57$) how much of a problem this skin irritation was. It is possible that the higher the perceived value of the CGMS device and the perceived benefit of using it, the more likely participants are to accept side effects. That is, are the side effects a worthwhile trade-off? In total, 43% of the children in this study did not rate skin irritation as a problem, 43% rated it as a minor problem and 14% rated it as a major problem; 74% found it helpful overnight but 32% said that their sleep had been disrupted by alarms at night. In another GlucoWatch study involving 44 participants,[82] 84% of the sample said that they would use the watch again, 48% said that it was too large to be worn every day and 25% described it as difficult to use; only 51% were able to retrieve any data from the watch.

The DirecNet group published a measure of satisfaction and perceived therapeutic impact of continuous glucose monitoring devices.[99] In their GlucoWatch study they reported higher scores on this scale amongst people who had averaged two or more uses of the GlucoWatch G2 Biographer per week, although this only approached significance. For most of the items (81% for parents, 73% for youths), the mean satisfaction rating was less than 3.0, indicating low levels of satisfaction with the GlucoWatch. In their pilot trial[54] of the FreeStyle Navigator they reported high levels of satisfaction from participants and their parents with this monitor.

Discontinuation rates and reasons for stopping use

Decisions to stop using a continuous glucose monitoring device provide an indicator of acceptability of these technologies to users. In this review this can be examined in the studies evaluating the GlucoWatch in paediatric samples. One of these required participants to use the watch four times per week for 12 weeks, then as desired for 6 months.[49] The watch was used an average of 3.5 times per week during the first 12 weeks. Usage was greater during the initial weeks than during the final weeks, although no other information is provided. In another study it is unclear how often children were meant to be wearing the watch, but it is apparent from the study results that reported

use was low, for example only 28% of successfully calibrated watches were worn for the entire night and only 15 (33%) children wore the watch on all of the nights that it was available for them to wear. The other studies provide a similar picture to this one with regard to declining use. In one,[53] participants were encouraged to wear the watch as often as desired for 6 months. By the end of the first month, use averaged 2.1 times per week. During the last month, amongst those still using the watch, use averaged 1.5 times per week. The number of uses with more than 8 hours of data averaged 0.7 per week. By the third month of the study, seven (7%) participants had stopped using the watch. This had risen to 27 (27%) participants by 6 months. Reasons for stopping use or not using the watch more often (more than one reason possible) were skin irritation (76%), skips too frequently (56%), alarms too frequently (47%) and does not provide accurate readings (33%). In the remaining study[55] just over half of the participants met the required protocol usage (four times per week) by 3 months' follow-up.

There seems to be a pattern of declining use of the GlucoWatch in children with type 1 diabetes followed for 3 months or longer. The studies in adults have not been carried out for a sufficient duration to establish whether similar patterns would be observed. With regard to the CGMS, in the studies that require it to be worn more than once, similar patterns of declining use are not evident.[56,59,64,66,76,78,97]

In the studies evaluating other continuous glucose monitoring devices, the devices tend to be worn either continuously or once for a short period of time, so these are considered in the next section on attrition rates.

Attrition

Rates of attrition varied quite considerably from 0% to 52% amongst those studies reporting this information. The majority of studies ($n = 16$) reported some degree of attrition.[46,48,49,52–56,59,61,63–66,91,100] Five studies[50,57,58,62,92] reported no loss to follow-up. When reasons for withdrawal were reported, the demands of the protocol and difficulties relating to the device appeared to be the most common causes.

Hypoglycaemia, hyperglycaemia and euglycaemia

Sixteen studies[47,49,51,53,55,56,59,62–64,66,91–93,100,101] that assessed the effect of continuous glucose monitoring devices on hypo- or hyperglycaemic episodes or periods of euglycaemia were identified in the literature.

Randomised controlled trials conducting analysis between groups

Seven studies[51,53,59,64,66,93,100] used an RCT design and carried out between-group analysis. Four[64,66,93,100] of these measured the duration of hypoglycaemic episodes and three[64,93,100] found reductions in the duration of time spent in the hypoglycaemic range. These same three studies also assessed the duration of time spent in hyperglycaemia and two[93,100] found significant reductions compared with the control group. One[93] of these also found that those wearing the DexCom STS 3-day sensor spent more time in the target euglycaemic range than did control subjects.

Four studies[51,53,59,64] compared the frequency of hypoglycaemic episodes between intervention and control groups and two of these also assessed the frequency of hyperglycaemic episodes. None of these studies found any significant differences between the groups on these measures.

Randomised controlled trials conducting analysis over time and single group prospective studies

Twelve studies[45,47,49,55,56,62,63,66,91–93,100] conducted within-group analysis on the duration/frequency of hypo- and/or hyperglycaemic episodes. Six studies assessed the duration of time spent in the hypoglycaemic range. Four studies[91–93,100] found a statistically significant reduction in the time spent in the hypoglycaemic range. Three of these studies[91–93] also found a corresponding decrease in the amount of time spent in the hyperglycaemic range. In addition, one study reported a significantly increased time spent within the target glycaemic range.[91] Two studies[45,56] found no difference over time in the duration of hypoglycaemic episodes.

Nine studies examined the frequency of hypoglycaemic episodes over time after use of a continuous glucose monitoring device. Three reported reductions in the frequency of hypoglycaemic episodes.[47,55,63] One reported a reduction in the frequency of nocturnal hypoglycaemia.[101] Two reported increases in the frequency of hypoglycaemia[49,66] and two reported no significant differences over time.[56,100] One study[62] reported no change in the low blood glucose index, a measure of the risk of severe hypoglycaemia, but did find a reduction in the frequency of glycaemic excursions (episodes of

high and low blood glucose). Two of these studies also evaluated the impact of wearing the devices on the frequency of hyperglycaemic episodes; one reported a marginally significant increase[100] and one reported a decrease.[49] It must be noted that all nine of these studies had sample sizes of less than 50.

Psychosocial outcomes

Much less work has examined the psychosocial impact of wearing a continuous glucose monitoring device. Five studies[48,49,54,65,99] were identified using the search strategy outlined. All were RCTs conducted in paediatric samples, although three of these are likely to be underpowered as they have very small sample sizes. In the two studies examining the GlucoWatch,[49,99] use of this device was less than that stated in the two respective protocols and declined over time. The CGMS study[48] found no significant differences between groups or over time in fear of hypoglycaemia or on the DCCT quality of life scale but they used a very small sample. The two GlucoWatch studies[49,99] found no significant differences between groups on any of the psychosocial measures used including fear of hypoglycaemia, quality of life, the Diabetes Self-Management Profile or the Diabetes Worry Scale. The two studies[54,65] using the FreeStyle Navigator found no significant differences over time in fear of hypoglycaemia or quality of life or on the Diabetes Self-Management Profile. It seems that continuous glucose monitoring devices, in these studies at least, did not result in an impaired quality of life. It remains to be seen whether studies in adult samples would produce similar results.

Taken together the studies carried out to date do not provide sufficient evidence to recommend the wider use of continuous glucose monitoring devices in clinical practice; however, there are a number of methodological and design issues that must be addressed to determine the efficacy and acceptability of these devices.

Study design and sample size

Approximately half of the studies assessing HbA1c or hypo- and hyperglycaemic episodes were RCTs. Not all of these studies carried out between-group analyses. The sample sizes in many of the studies were very small, for example 17 of the 22 studies assessing HbA1c as an outcome had total sample sizes of less than 50. Of all of the studies reviewed only two reported performing power calculations.[53,64] These two studies were also the only ones to report the randomisation process. Several factors are important here: how the allocation sequence was generated, allocation concealment up to the point of treatment, blinding to type of treatment following randomisation and whether randomisation was stratified or restricted in any way. The reduction of selection bias in trials depends upon all of these factors.

Another important consideration is that of the Hawthorne effect.[102] In terms of evaluation of continuous glucose monitoring devices, when significant effects have been reported in the literature, is this due to the devices or can the effects be attributed to the increased levels of attention and care from the health-care team? The importance of including attention control arms within clinical trials of continuous glucose monitoring devices as a way of controlling for this effect has been highlighted.[103] Only one study reviewed here acknowledges the Hawthorne effect.[46] A person with diabetes who used the CGMS has also described the impact of increased attention when participating in a trial:

> I am also a bit sceptical about the relevance of short trials of any device for assisting in blood glucose control, since in my personal experience, I find that the relatively intense care and attention from physicians and paramedical personnel associated with any new or special trial or regime often has a remarkable short-term effect on my blood glucose, regardless of what the new regime is – I have attributed it to some combination of enhanced self-control in food choices and timing of eating, positive attitude and state of mind, and the increased physical activity which, for me at least, generally accompanies such optimism and interest.
>
> Freedman[104]

Optimal levels of usage

The clinical efficacy of continuous glucose monitoring devices has not yet been established, nor has the optimal level of usage to achieve improvements in glycaemic control.[105] An examination of the literature to date reveals no clear pattern as to how many times continuous glucose monitoring devices may need to be worn to improve glycaemic control or reduce the duration or frequency of hypo- and hyperglycaemia episodes.

Once a continuous glucose monitoring device has been worn and therapy adjustments have been made based on the results it may still take time for these adjustments to have an effect on

glycaemic control, if at all. It is unclear at what time point these adjustments will have an effect of glycaemic control. If they do have an effect, is this improvement in control maintained and for how long are repeated uses of the continuous glucose monitoring device required? The studies reviewed do not permit any of these questions to be answered. The majority of the studies had follow-up periods of less than 16 weeks. It is arguable whether this is long enough to observe a change in HbA1c as this is a measure of glycaemic control over the preceding 12 weeks.

Inclusion criteria

Most of the studies were limited to participants with type 1 diabetes. From examining the studies reviewed here, it is clear that there is a need for a more systematic evaluation of the potential role of continuous glucose monitoring devices in managing people with type 2 diabetes treated with insulin. Approximately 27% of people with type 2 diabetes require insulin injections and therefore an increased level of SMBG to modify insulin therapy. This highlights the size of the population that may benefit from the use of continuous glucose monitoring devices if they are shown to be efficacious.

Independent evaluations of the technologies

The need for independent evaluations of continuous glucose monitoring technologies has been highlighted.

Type of feedback/therapy adjustments and person delivering care

Very few studies described the type of therapy adjustments made to the diabetes management plan based on the continuous glucose monitoring data and SMBG results. This information is necessary both to replicate studies and for decision-making about how continuous glucose monitoring devices should be used in clinical practice and by whom.

Formal systematic assessments of acceptability

An assessment of the user's perspective has been recommended for further research on continuous glucose monitoring devices.[71,106] In the studies that have been carried out to date, more often than not when the investigators claim to have assessed acceptability this is based on anecdotal or subjective reports on the part of the researchers. More recent studies have begun to address these shortcomings. Evaluation of user acceptability is an essential component in the assessment of any new technology.

Study rationale

At the time that this study commenced in 2002 the GlucoWatch G2 Biographer and the MiniMed CGMS were the only continuous glucose monitoring devices that had obtained FDA/CE approval and were available for use in clinical practice.

By providing access to a large amount of data in a very short period both devices have the potential to illustrate trends in glucose concentration and aid adjustment in medication to optimise or at least improve glycaemic control. By virtue of the differences between the devices, however, the impact on the individual may be very different. The GlucoWatch gives a rapid read-out of glucose readings and trends in glucose levels over a 13-hour period. It provides real-time information and alarm features that can be set by the wearer. The CGMS records more information over a longer period (72 hours) but does not display this information to the patient whilst it is being worn. It provides retrospective data and requires a visit to the diabetes clinic to download the results. Hence, whereas the GlucoWatch provides patients with an opportunity for regulation of their own glycaemic control and may promote empowerment, the CGMS relies on feedback from the diabetes team.

To date it is not clear what impact the devices have on diabetes control (HbA1c and reduction of hypo- and hyperglycaemic episodes) and whether the costs incurred are justified. These devices may also be differentially acceptable to patients and may have different effects on patient health outcomes, patient perceptions of their diabetes and psychological factors such as fear of hypoglycaemia. It is important, therefore, to assess the physical, biochemical, behavioural and psychological impacts of these devices before they become more widely available.

Further, it is possible that these devices may be most useful for patients with poorly controlled diabetes, those prone to hypoglycaemia or diabetic ketoacidosis or those with a high or low sense of control over their diabetes. It is important to understand whether such devices are more suitable for subgroups of patients with certain characteristics, although to do so adequately would require a very large study.

The most appropriate way to address these aims was by conducting a sufficiently powered well-designed RCT. It was decided to include both types of continuous glucose meter within a trial to compare the respective acceptability of both for patients. An attention control group was included to account for the additional input from the diabetes research nurse (DRN) received by patients in the monitor groups.

It is important to note that this trial was not intended to assess the accuracy of the devices as this would require a very different design incorporating many more planned data points while the devices were active.

Primary objectives

- To compare the benefits of the additional information provided by using two continuous glucose monitoring devices (the GlucoWatch and CGMS) on glycaemic control in terms of glycosylated haemoglobin levels relative to an attention control and standard treatment.
- To assess patient acceptability and ease of use of the two minimally invasive glucose monitors.
- To model the long-term health benefits, costs and cost-effectiveness of these technologies.

Secondary objectives

- To assess the impact of the devices on health-care utilisation for diabetes-related illnesses and number of diabetes-related patient sick days/absenteeism.
- To assess the impact of the devices on patient satisfaction, attitudes towards their diabetes and quality of life.
- To assess the extent to which demographic factors and individual differences in health-related cognitions influence outcome.

Chapter 2
Design and methods

Ethical approval

The protocol received multicentre research ethics committee (MREC) approval (reference number 02/2083) and local research ethics committee (LREC) approval at each participating centre.

Trial design

All participants were provided with a OneTouch® Ultra® self-monitoring glucose meter (Lifescan, UK) and trained in its use at the baseline clinic visit. Participants were asked to use this meter instead of their usual glucose meter. Data (i.e. the last 150 recorded values) were downloaded and saved at each research visit. All participants received normal clinical treatment, typically taking the form of 6-monthly clinic visits with access to diabetes advice when required. This treatment took place alongside any specific treatment/advice given as part of the trial.

This was a four-arm randomised controlled trial:

- Group 1 (GlucoWatch) was allocated to wear the GlucoWatch G2 Biographer (further details given in the following sections).
- Group 2 (CGMS) was allocated to wear the MiniMed CGMS (further details given in the following sections).
- Group 3 (attention control) received standard treatment but with nurse feedback sessions at the same frequency as those in groups 1 and 2.
- Group 4 (standard care control) received standard treatment without extra nurse feedback at intervals reflecting common practice in the UK, i.e. every 6 months.

Description of intervention

Following randomisation, the treatment and follow-up period consisted of two phases:

- Phase 1 (0–3 months for participants in groups 1–3). This was the intensive part of the trial, addressing short-term clinical efficacy, acceptability and impact on psychosocial outcomes. All participants attended clinic for baseline assessment. Participants in groups 1 and 2 were trained in how to use the GlucoWatch or CGMS monitors. Participants in groups 1–3 also attended three nurse feedback sessions in this phase.
- Phase 2 (3–18 months for each participant). This was designed to assess the medium-term (6 and 12 months) and long-term (18 months) clinical efficacy, quality of life and psychosocial and economic impacts of the devices. During this phase, participants in group 1 used the GlucoWatch as desired and participants in group 2 were fitted with the CGMS at 6, 12 and 18 months. Participants in groups 1–3 also attended nurse feedback sessions at 6, 12 and 18 months. Participants in all groups completed assessments at 6, 12 and 18 months.

Figure 4 shows the follow-up periods for each of the study arms.

The specific procedures for each group are detailed in the following sections.

Group 1: GlucoWatch

Phase 1

At the baseline clinic visit the research nurse trained and provided participants with the OneTouch Ultra monitor and the GlucoWatch. Participants were asked to use the GlucoWatch at times of their choice but with a minimum attempted use of four times per month and a maximum attempted use of four times per week. In addition, they were told to continue to perform capillary blood glucose monitoring as desired. One calibration finger prick test was required each time they used the GlucoWatch. They were also advised to check capillary glucose if the GlucoWatch sounded a high or low alarm. It was explained to participants that the GlucoWatch must not be relied upon for estimating insulin requirements. During this period, participants were reviewed by the research nurse at 4, 8 and 12 weeks from baseline, at which point the results from both the GlucoWatch and the OneTouch Ultra meter were downloaded, saved and printed. These results were used as the basis for adjustment of treatment regimes when delivering feedback.

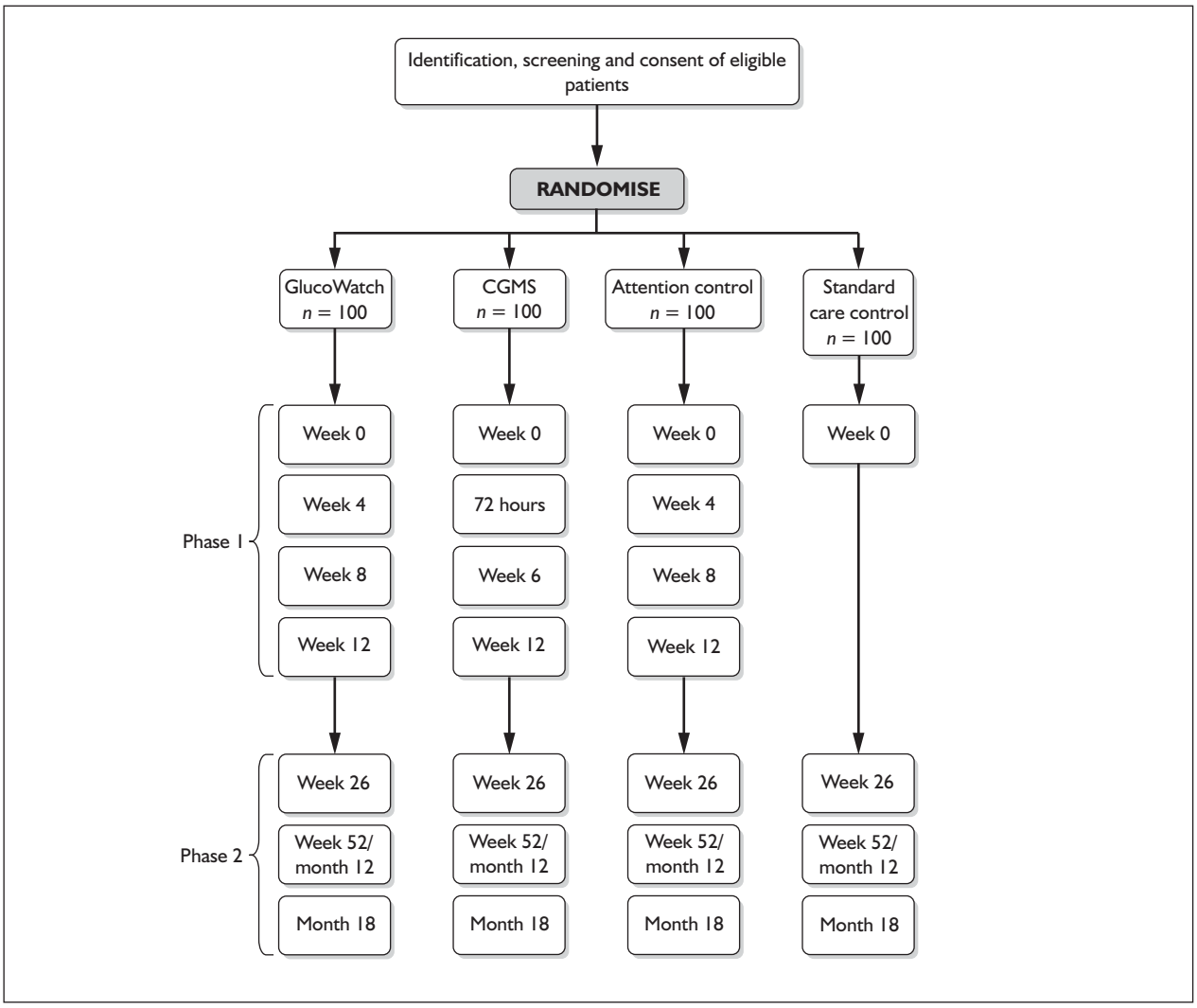

FIGURE 4 *Study assessment points.*

Phase 2

Participants were asked to continue using the GlucoWatch as often as they wished but were recommended to use the device at least twice per week. They were reviewed by the research nurse at 6, 12 and 18 months from baseline.

Group 2: CGMS

Phase 1

At the baseline clinic visit, the research nurse trained and provided participants with the OneTouch Ultra monitor and the CGMS. The CGMS was fitted by the research nurse and participants were requested to wear it for 72 hours. In addition to wearing the CGMS, participants were asked to continue to perform capillary blood glucose monitoring as desired. They returned to the clinic 72 hours later for the device to be removed or in some cases they removed the device themselves and returned to the clinic as soon as possible but no more than 1 week after device removal. On the return visits, glucose readings from both the CGMS and the OneTouch Ultra were downloaded, saved and printed. These results were reviewed by the research nurse and used to provide feedback for and adjustment to therapy. Participants were also fitted with the device at 6 and 12 weeks from baseline and received nurse feedback sessions 72 hours later.

Phase 2

Participants were fitted with the CGMS and received nurse feedback sessions at 6, 12 and 18 months. During the 'fitting' visits, discussion concerning diabetes control was avoided and participants were told that this would be discussed in detail at the visit when the results were

downloaded. At each fitting, participants were requested to wear the CGMS for 72 hours. If the device failed within 24 hours of fitting then participants were encouraged to return to the clinic for a refitting. If the device failed more than 24 hours after fitting then the available data were reviewed in the nurse feedback session.

Group 3: attention control

Phase 1

At the baseline clinic visit, the research nurse trained and provided participants with the OneTouch Ultra monitor. Participants were asked to monitor capillary blood glucose at their normal frequency for 3 months and to attend nurse feedback sessions at 4, 8 and 12 weeks. At these feedback sessions the results from the OneTouch Ultra meter were downloaded and used to give feedback.

Phase 2

Participants were asked to continue using the OneTouch Ultra meter at their normal frequency. They were reviewed by the research nurse and provided with feedback on their test results at 6, 12 and 18 months. Throughout phase two, the research nurse was available via the telephone/email to discuss any problems.

Group 4: standard care control

Phases 1 and 2

At the baseline clinic visit, the research nurse trained and provided participants with a OneTouch Ultra meter. They were asked to monitor capillary blood glucose at their normal frequency. Participants received standard treatment, which typically consisted of 6-monthly clinic visits and access to diabetes advice when required. At subsequent research visits at 6, 12 and 18 months, no feedback was given by the research nurse.

Nurse feedback sessions

The research nurses underwent a 2-day training course in use of each of the devices, interpretation of blood glucose results and delivery of appropriate clinical feedback before the trial started. At each feedback session the research nurse downloaded and reviewed glucose results from both the standard and the minimally invasive glucose monitors, and in groups 1–3 appropriate lifestyle advice and adjustments to medication were also made according to the study protocol (see Appendix 1). To ensure consistency in approach across the different centres and between study staff, all of the research nurses were requested to adhere to this guidance. Furthermore, the research nurses met on a regular basis to discuss individual cases and to ensure a common approach.

Two weeks before each follow-up appointment participants were sent an approved reminder letter to prompt them to come in for their visit and asking them to bring their meters, diaries and completed questionnaires. Throughout both phases of the trial the research nurse was available via the telephone/email to discuss any problems with groups 1–3.

Inclusion and exclusion criteria

Inclusion criteria

1. Individuals with insulin-treated diabetes mellitus receiving two or more injections daily [including continuous subcutaneous insulin infusion (CSII) pump users].
2. Age over 18 years.
3. Duration of diabetes over 6 months.
4. Fluent in English, Bengali, Cantonese or Turkish.
5. HbA1c results:
   i. Two HbA1c levels greater than or equal to 7.5%, one in the last 3 months and another within the previous 15 months. Research nurses followed the normal consent procedure for participants fulfilling this criterion.
   ii. Individuals with one HbA1c level greater than or equal to 7.5% in the last 3 months and either a second HbA1c level greater than or equal to 7.5% over 15 months previously or no other HbA1c levels greater than or equal to 7.5% were invited to have a screening blood test carried out 3 months later. If that was greater than or equal to 7.5% and the participant consented to the study then this was used as the baseline HbA1c. Research nurses then followed the consent procedure for individuals requiring a screening blood test.
   iii. If a participant had an HbA1c level greater than or equal to 7.5% but this had been measured more than 3 months previously

then they were invited to have a screening blood test carried out as soon as possible. If that was greater than or equal to 7.5% and the participant consented to the study then this was used as the baseline HbA1c. Research nurses then followed the consent procedure for individuals requiring a screening blood test.

iv. In all cases, the two HbA1c results had to be a minimum of 12 weeks apart. At the outset of the study the inclusion criterion for HbA1c was two consecutive HbA1cs greater than 8.0% (one obtained at screening and one at the last assessment but within 12 months). In light of advances in diabetes management, changes in clinical targets and difficulties experienced in recruitment, the HbA1c inclusion criterion was subsequently changed and the protocol amended (as described above).

5. Willingness to comply with the consent and trial procedure.

Exclusion criteria

1. Previous inability to use a capillary glucose meter.
2. Previous use of the GlucoWatch or CGMS sensor.
3. Presence of abnormal haemoglobin (presence of elevated levels of HbF or HbS).
4. Pregnancy, or planned pregnancy in the next 18 months.
5. Skin conditions, e.g. eczema, psoriasis or other skin irritation, at the sites of monitor use.
6. Receiving dialysis.
7. Visual or physical impairment limiting ability to use monitors.
8. Planned major surgery (e.g. coronary artery bypass graft, hip replacement) within 3 months of consent.
9. Participation in any other ongoing trial.

Participants who spoke English, Bengali, Cantonese or Turkish were included to ensure that individuals from different ethnic backgrounds were evaluated. When participants were non-English speakers, the nurse feedback sessions were held with the assistance of an appropriately trained translator. All of the questionnaires were translated.

Recruitment procedure

Trial site location

Participants were enrolled from four sites:

- Royal Bournemouth Hospital
- Queen Elizabeth Hospital/Bensham Hospital, Gateshead
- University College London Hospitals (UCLH)
- Whittington Hospital, London.

The sites selected were chosen to improve the diversity of the sample population. The two London sites represent inner-city locations, Gateshead an urban and socioeconomically deprived area and Bournemouth a relatively affluent area with a high proportion of retired people.

Identification of participants

People with diabetes were identified from three sources:

- local diabetes databases
- posters advertising the trial in the waiting rooms of the different sites
- review of clinic notes.

Potential participants were identified primarily by the research nurses at each site assisted by the local investigators. Those identified as potentially eligible were given an information sheet and invited to discuss the trial in more detail with the research nurse or the local investigator. Invitations to participate were issued in person, by telephone contact or through the approved invitation letter.

Consent procedure (see Appendices 3–5)

Eligible participants were provided with a full explanation of each arm of the trial including the potential problems with use of the devices (see Appendix 2). It was clearly explained that participants would have a one in four chance of being in any arm of the trial. Participants were asked to provide verbal agreement that they would not use a non-invasive or minimally invasive blood glucose monitor independently of the trial, regardless of which arm of the trial they were randomised to. Participants were informed that if they were allocated to the attention control or standard treatment arms and if the final results indicated either of the monitors to be beneficial then they would be given priority for use of the GlucoWatch or CGMS on trial completion. Following explanation of the trial, a period of at least 24 hours but no more than 4 weeks had to elapse before written consent was obtained and subsequent randomisation carried out. The

exception to this consent procedure was individuals fulfilling inclusion criterion 5(b). In this case participants completed a screening consent form and returned for an HbA1c test 3 months later.

Randomisation

Once written consent had been obtained, the research nurse phoned the Medical Research Council's Clinical Trials Unit randomisation line. Randomisation was site specific and ensured balanced allocation in terms of centre, age and type of diabetes by use of the minimisation method. Randomisation occurred immediately before the baseline visit and assessment. A facility for randomisation of participants before 9 AM was also made available.

Recruitment logs

A record of all individuals approached to take part in the trial was maintained by the research nurses. This recorded demographics, data on lack of suitability for trial and reasons for refusal.

Primary end points

Glycaemic control

Percentage change in HbA1c from baseline to 18 months was the primary outcome in this study. Three blood samples were taken at each assessment by the research nurse. One was analysed locally, one was sent to the Department of Diabetes and Endocrinology at UCLH for analysis and standardisation, and the third sample was retained and stored locally in case of damage or loss to the standardised sample.

Perceived acceptability of the devices

At the outset of the study no suitable measure had been developed that would have been able to adequately assess the acceptability of the minimally invasive blood glucose monitors under evaluation. Hence, a questionnaire was developed for this purpose (see Appendix 7). Details about the process of developing this questionnaire measure are provided in Appendix 8. The number of times that people chose to wear the devices also provided an indicator of acceptability.

Secondary end points

Clinical assessments

1. Change in HbA1c (baseline to 3, 6 and 12 months). Percentage change in HbA1c at the end of the intensive phase of the trial (3 months' follow-up) was measured to assess short-term efficacy. Percentage change in HbA1c was also measured from baseline to 6 and 12 months to assess efficacy in the medium term.
2. Hypoglycaemic episodes (defined as blood sugar ≤ 3.5 mmol/l). Hypoglycaemic episodes, the time and date that they occurred and how they were detected were recorded by the DRN. To collect these data, participants were asked to keep diaries. When possible the incidence of hypoglycaemia was confirmed by the OneTouch Ultra meter and recorded as such in the case report form (CRF). In the case of groups 1 and 2, downloaded data from the GlucoWatch and CGMS were also used. A hypoglycaemic episode was recorded if (a) blood glucose was ≤ 3.5 mmol/l for > 20 minutes (i.e. two or more readings for the GlucoWatch, four or more readings for the CGMS), (b) blood glucose of ≤ 3.5 mmol/l was followed by one or more skipped readings followed by a reading of ≤ 3.5 mmol/l for the GlucoWatch or (c) blood glucose of ≤ 3.5 mmol/l was followed by two or more skipped readings coded PRSP (perspiration) on the GlucoWatch. Awareness of hypoglycaemia was assessed through completion of the Edinburgh Hypoglycaemia Symptoms Scale and the Hypoglycaemia Symptoms Awareness Questionnaire.[107]
3. Hyperglycaemic episodes (defined as blood sugar ≥ 10.0 mmol/l). The percentage of finger prick blood glucose values ≥ 10.0 mmol/l were recorded in the CRF by the DRN. These data were drawn from participant diaries and the OneTouch Ultra meters. In the case of groups 1 and 2, downloaded data from the GlucoWatch and CGMS were also used and recorded as the number of glucose readings ≥ 10 mmol/l for > 20 minutes (two or more readings for the GlucoWatch, four or more readings for the CGMS).
4. Skin reactions (GlucoWatch and CGMS groups). During nurse feedback sessions the DRN recorded the extent of any skin irritation for each application of the monitor. These data were drawn from participants' ratings

and recordings in their diaries using the MITRE Skin Scale (see Appendix 6). Data were recorded in the CRF by the DRN at baseline and at each feedback session. Adverse device-related event forms were completed if reactions were rated as severe (i.e. ≥ 6 on the MITRE Skin Scale). If a participant reported a score on the MITRE Skin Scale of ≥ 6 between research visits then they were instructed to attend the diabetes clinic for review by the DRN. The DRN reviewed and photographed the site and when appropriate considered the individual for withdrawal from treatment.

5. Side effects. Any side effects reported by participants from either the minimally invasive glucose monitors or the standard monitors were recorded in the CRF by the DRN. Participants were also asked about side effects on the self-reported acceptability questionnaire that was developed for the purpose of this study (see Appendix 7). This questionnaire included asking participants to rate the acceptability of any side effects experienced.

Selection and development of psychological measures

Psychological assessments

The following assessments were carried out at 3, 6, 12 and 18 months in all of the groups with the exception of participants in the standard treatment arm who were not assessed at 3 months:

1. Quality of life. Diabetes-specific quality of life was assessed at each follow-up time using the Audit of Diabetes-Dependent Quality of Life (ADDQoL) scale[108] to allow comparisons to be made across the different arms of the trial. The original 13-item version of the ADDQoL was used. Respondents were asked to rate the impact of their diabetes on different aspects of their lives, for example their social lives. They were then asked to rate how important that aspect of their life was to them. For each applicable item the score is multiplied by its importance rating and averaged to determine the final score. Scores range from –9 (maximum negative impact of diabetes on quality of life) to +9 (maximum positive impact of diabetes on quality of life).
2. Self-management behaviours. The self-reported Summary of Diabetes Self-Care Activities (SDSCA) scale is a 10-item scale used to assess the frequency with which participants carried out diet, exercise, blood glucose monitoring and foot-care behaviours during the past week.[109] Each self-care activity is rated according to how many days it was performed (0–7 days).
3. Fear of hypoglycaemia. This was assessed using the self-reported 13-item worry subscale of the Fear of Hypoglycaemia questionnaire.[110] Each item is scored from 0 to 4 with higher scores indicating more worry about hypoglycaemia. Scores range from 0 to 52.
4. Satisfaction with treatment. This was assessed using the self-reported eight-item Diabetes Treatment Satisfaction Questionnaire (status version) (DTSQs) at baseline and the Diabetes Treatment Satisfaction Questionnaire (change version) (DTSQc) at follow-up.[111,112] Each item on the DTSQs is scored from 0 to 6, with higher scores indicating greater satisfaction. Three subscales are formed: diabetes treatment satisfaction consisting of six items (score range 0–36) and satisfaction with perceived frequency of hypo- and hyperglycaemia (these are both scored from single items). The DTSQc was developed to overcome ceiling effects in the status version. It has the same eight items as the status version but is reworded slightly to measure the change in satisfaction rather than absolute satisfaction. Respondents are asked to rate how their experience of treatment has changed over the last 3 months. Each item is scored on a scale of –3 to +3. Negative scores indicate less satisfaction and positive scores indicate improvements in satisfaction. A score of zero indicates no change in satisfaction.
5. Diabetes beliefs. This was assessed by two self-report questionnaires: the Audit of Diabetes-Dependent Locus of Control (ADDLoC)[113] and the Personal Models Of Diabetes Questionnaire.[114] Social learning theory introduced the concept of locus of control. This refers to our expectations about control over future events. It has been hypothesised that diabetes-specific measures of locus of control may be useful in understanding and predicting self-management behaviours. The ADDLoC is made up of 24 items that form four locus of control subscales: internality, chance, significant others and medical others. Each scale is scored from 6 to 36, with higher scores indicating greater locus of control. Personal models are patients' representations of their illness and include illness-related beliefs, emotions, experiences and knowledge.[115] Beliefs about treatment effectiveness and how serious the illness is have been shown to predict certain self-management behaviours in diabetes.[116] The Personal Models Of

Diabetes Questionnaire assesses these two aspects of illness representation. It consists of a 10-item questionnaire from which two subscales are formed: treatment effectiveness and seriousness of illness. Each item is scored on a five-point Likert scale, with higher scores indicating greater beliefs in treatment effectiveness and the seriousness of diabetes. An additional item was also incorporated into this study to assess respondents' control over their blood glucose levels: 'How much control do you feel you have over your blood sugar levels?'

Serious adverse events

A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in death, was life-threatening, required unplanned inpatient hospitalisation or prolongation of existing hospitalisation, or resulted in persistent or significant disability. DRNs recorded all SAEs in the CRF.

Sample size calculations

Primary end point: glycaemic control at 18 months' follow-up

Percentage change in HbA1c from baseline was measured, looking for a clinically important difference of 12.5%. This proportional change took into account the baseline HbA1c of the participants and equates to an absolute drop of 1% in participants entering the study with an HbA1c of 8%, or an absolute drop of 1.1% in participants entering the study with an HbA1c of 9%. Based on clinical data, a 5% mean change from baseline was expected in the standard care control group, with a standard deviation of 15.5%. Allowing for a 10% attrition rate, 100 participants per arm were calculated to provide 90% power to detect a 12.5% reduction in HbA1c from baseline at the 5% significance level. A total of 400 participants were therefore required from the four participating centres.

In the original protocol the sample size target was 600 based upon the proportion of patients allocated achieving an absolute reduction of 1% in HbA1c from baseline to 18 months' follow-up. However, in light of advances in diabetes management and changes in clinical targets combined with difficulties in recruitment, the protocol was amended so that the power calculations were based upon identifying a 12.5% reduction from baseline instead.

Analysis

The baseline characteristics of all four arms were compared to assess the similarity of the groups.

Primary end point: glycaemic control

All analyses were conducted on an intention to treat basis, comparing each of the device groups with the standard care and attention control groups. The trial was not powered to make a direct comparison between the GlucoWatch and CGMS groups. The primary outcome, the percentage change in HbA1c from baseline, was calculated looking for a mean relative reduction in HbA1c of 12.5% from baseline to 18 months, for example a baseline HbA1c of 10% decreasing to 8.75% at 18 months' follow-up.

When available, HbA1c results from routine clinic/GP appointments were recorded if participants missed study visits or if participants who had withdrawn from all other aspects of the study gave their consent. All of the HbA1c results analysed in the study were those obtained from the local laboratories at each of the four centres. All four laboratories used standardised (DCCT-aligned) methods for measurement of HbA1c. Each individual's HbA1c results across the duration of the study period were analysed at the same local laboratory. HbA1c results were included in the analysis if they fell within a prespecified period of time around the research visit:

- 3 months: up to 4 weeks before and 4 weeks after the date of the scheduled visit
- 6 months: up to 8 weeks before and 8 weeks after the date of the scheduled visit
- 12 and 18 months: up to 12 weeks before and 12 weeks after the date of the scheduled visit.

Primary end point: acceptability

Comparison of the GlucoWatch and CGMS groups to assess whether the two non-invasive devices differed in levels of acceptability was by parametric/non-parametric tests depending on the distribution of the data.

Secondary end point: glycaemic control

The same analyses of percentage change in HbA1c from baseline to 18 months were carried out as on

the data for 3, 6 and 12 months described above. Analyses of variance (ANOVA) were performed to examine the relative reduction in HbA1c from baseline at each of the follow-up periods (follow-up HbA1c−baseline HbA1c/baseline HbA1c×100).

Secondary end point: psychosocial outcomes

Groups were compared on the psychosocial data (quality of life, diabetes self-care activities, treatment satisfaction, etc.) using repeated measures, ANOVA, when the data were normally distributed and using non-parametric analyses when distributions were skewed.

Health economic evaluation

Cost-effectiveness analysis methods

Economic evaluation of health-care treatments combines measures of outcome with measures of opportunity cost, to answer the question of whether reallocating resources to a programme would result in a more efficient allocation of resources. The most commonly followed practice in economic evaluation is cost-effectiveness analysis in which the aim is to maximise outcomes given the constrained resources in the NHS. In cost-effectiveness analysis both the costs and consequences of an intervention are considered simultaneously against other relevant comparators (e.g. best alternative care). The comparative nature of these evaluations is key as it is not possible to establish cost-effectiveness without formal comparison with other ways of using these resources.[117]

Quality-adjusted life-years

Quality-adjusted life-years (QALYs) are a generic (non-disease-specific) measure of health outcome that simultaneously captures morbidity [health-related quality of life (HRQoL) gains] and mortality (survival duration gains) and combines the two into a single measure. QALYs are generated by the summation across all health states of the length of time in a particular health state multiplied by a weight representing the HRQoL (utility value) attached to that health state. The utility values are based on a scale in which 1 represents full health and 0 represents death. The utility values of the participants in the MITRE trial were measured using the EQ-5D (European Quality of Life – 5 dimensions) questionnaire.[118] The EQ-5D is a standardised instrument for the measurement of health outcome and will be discussed further later in this report.

Decision rules

Let A and B represent two alternative treatments. If intervention A is less costly and more effective, it is said to 'dominate' B. Similarly, if A is more costly and less effective, it would be dominated by B. Under either of these conditions it is easy to conclude that the dominant option is the more cost-effective. In practice it is rare that the cost and outcomes lend themselves to the dominance rule, and it is usually the case that an intervention is more effective but also more costly. The critical issue here is whether the additional (incremental) cost is worth paying for the incremental benefits. The decision rules developed to address this issue focus on the incremental cost-effectiveness ratio (ICER), which is defined as:

$$ICER_{AB} = \frac{Costs_A - Costs_B}{QALYS_A - QALYS_B}$$

At this point the decision about whether an intervention is considered cost-effective hinges on the cost-effectiveness threshold, which is considered to represent a reasonable 'willingness to pay' for an additional QALY. The threshold considered to be appropriate by the National Institute for Health and Clinical Excellence (NICE) is between £20,000 and £30,000.[80] If the ICER of the intervention is lower than this threshold then the intervention can be viewed as a cost-effective use of NHS resources.

The decision rules of cost-effectiveness analysis can be extended to deal with multiple treatment comparisons. Further discussions of such extensions and the related net benefit framework can be found in Drummond *et al*.[117]

Overview of economic analysis

The aim of the economic analysis is to compare the costs and consequences (in terms of utilities) of the four trial arms of the MITRE trial. These include the GlucoWatch, CGMS, attention control and standard care control arms. The costs to be considered are those faced by the NHS in terms of health service resource use. The unit costs/prices used are for 2005–6. The consequences to be considered are those to the treated patients, which will be measured in terms of utilities using the EQ-5D questionnaire. Costs and consequences should

be measured or extrapolated over the time that they could be expected to differ between treatment arms.

Data collection methods and frequency

Patient numbers

The economic analysis was undertaken on the 404 participants in the four arms of the trial.

Components and data collection

Resource use data were collected on all patients in the trial using a mixture of patient questionnaires and CRFs completed in clinic. *Table 1* details the resource use data collected in the trial and the points at which it was collected.

Health service resource use (excluding medication)

Using detailed CRFs, information on resource utilisation of hospitalisation, diabetes clinic visits, GP clinic visits and A&E visits was collected by the nurse during visits by patients to the clinic for nurse feedback sessions (or during a brief patient interview for the standard care control arm). Data were collected at baseline and at 3, 6, 12 and 18 months (with the exception of those in the standard care control arm who did not visit the clinic at 3 months and will hence not have a CRF completed on their behalf). For those participants for whom a CRF was completed following an appointment, it was assumed that they had attended their training session, nurse feedback session or brief patient interview.

Patients were asked about their use of health service resources over the 3 months preceding the nurse feedback sessions. Therefore, during the trial period no data were collected for the 3 months following the 6- and 12-month visits.

The number of device sensors used by participants in the GlucoWatch and CGMS arms of the trial was also collected on the CRFs.

Medication

Using detailed CRFs data on current diabetic treatment (including insulin) were collected by the nurse during visits by patients to the clinic for nurse feedback sessions at baseline and at 3, 6, 12 and 18 months (with the exception of those in the standard care arm who did not visit the clinic at 3 months). This meant that data were collected on the medications that individuals were taking at the time of each visit. The nurses also collected information on any other medications that the patients had been taking in the week preceding each of the nurse feedback sessions.

As these data were not based on a 3-month period but instead on what participants were taking either at the time of the visit or in the week preceding the visit, it has been assumed that patients were on the same medications for the 3 months preceding each nurse feedback session.

Unit costs

Unit costs at 2005–6 prices were used to value the resource use measured in the trial when available. These were average costs. It was assumed that

TABLE 1 *Details of health service resource use data collected in the trial*

Resource use variable	When collected?[a]
Hospital admissions (by type and speciality) and length of stay	Baseline and 3, 6, 12 and 18 months
Diabetes clinic visits (by type of contact and duration): doctor, nurse, dietician/ podiatrist	Baseline and 3, 6, 12 and 18 months
Outpatient visits	Baseline and 3, 6, 12 and 18 months
GP clinic visits: GP, nurse	Baseline and 3, 6, 12 and 18 months
A&E: visits to A&E, paramedic assistance outside A&E	Baseline and 3, 6, 12 and 18 months
Medications: insulin, antidiabetic, other	Baseline and 3, 6, 12 and 18 months
Days off work	Baseline and 3, 6, 12 and 18 months
Device-related consumables	Baseline and 3, 6, 12 and 18 months
Trial appointments (including training sessions, nurse feedback sessions and brief patient interviews)	Baseline and 3, 6, 12 and 18 months

a In the standard care control arm of the trial no data were collected at 3 months.

the cost of a nurse's time for a patient interview or feedback session is the same as that for an appointment with a nurse. As only the type of medication and not the brand was specified in the CRFs, it was assumed that the participants were prescribed the most commonly prescribed brand (as given by *Prescription cost analysis: England 2004*[119]). Although there may have been some change in the most commonly prescribed drug brands, the earliest date of randomisation in the trial was 20 May 2003 and so the use of *Prescription cost analysis: England 2004* provides a reasonably accurate indication of the medications that patients were taking.

Resource costs

Multiplication of resource use by the unit costs gives the resource costs. The costs presented represent the costs over the 3 months preceding each nurse feedback session (or patient interview for the standard care arm). As the data collected for medication were not based on a 3-month period but instead on what patients were taking either at the time of the visit or in the previous week, it has been assumed that the patients were on the same medications recorded for the 3 months preceding each nurse feedback session (or patient interview for those in the standard care arm).

As a consequence of problems with missing data (which are discussed further in the section on statistical methods), the resource costs are presented at a higher level of aggregation than the resource use data (e.g. the total diabetic clinic cost per period is presented, not by type of visit). The resource cost components that are presented are shown in *Table 2*.

The device costs for the GlucoWatch arm were based on the total number of sensor boxes (a box contains 16 sensors) that would be required given the number of sensors used, for example an individual using 17 sensors would be charged for two boxes of sensors. As an individual might use one box of sensors over several trial periods, the analysis has taken the total number of sensors used during the trial, converted it to the number of boxes needed and then split the costs of the boxes equally over the trial period.

As the interventions investigated in the MITRE trial were primarily community based, it is unsurprising that the number of hospitalisations observed in the trial is very low and mostly uncorrelated with the disease condition. For these reasons, the health economists in the study felt that the inclusion of hospitalisation costs in the main analysis might confound the economic results. Therefore, it was decided to perform analyses with and without hospitalisation costs to assess whether their inclusion was likely to have affected the main conclusions.

TABLE 2 *Categories of resource costs to be presented*

Resource cost groups
Insulin
Other antidiabetic medicine
Other medication
Hospitalisation
Diabetes clinic
GP clinic
Other resources
Device cost
Trial clinic appointments
Total cost

European Quality of Life – 5 dimensions

The EQ-5D questionnaire was completed by trial participants to provide preference data for the estimation of utilities.[118,120] The EQ-5D is a standardised instrument for the measurement of health outcome. It is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for a patient's health status. Its descriptive system consists of five dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) with each dimension having three levels (no problem, some problem or extreme problem). The five dimensions with three levels each yield 243 possible health states. These health states have been valued on the 0 (equivalent to dead) to 1 (equivalent to full health) utility scale, using a community sample of people from the UK who valued the health states using the time trade-off technique.[121]

Within the trial the EQ-5D questionnaire was completed at baseline and at 3, 6, 12 and 18 months (with the exception of the standard care arm whose participants did not complete the questionnaire at 3 months). At baseline the questionnaire was completed by participants during the baseline assessment period. They were expected to complete it in privacy although

they could ask for instruction if they were unclear how to complete an assessment. At 3, 6, 12 and 18 months the participants were requested to complete the questionnaire before the assessment session.

Within-trial analysis

The within-trial analysis involved quantification of the mean resource use and costs at 18 months, as well as estimation of the mean EQ-5D scores at baseline and at different follow-up points. Estimates are reported together with an appropriate measure of sampling uncertainty (e.g. standard deviation) at different follow-up times in the four arms of the trial. QALYs were not calculated because, in chronic health conditions, costs and health benefits manifest themselves over the entire lifetime of the patient. Any intervention that aims to affect future costs and/or health benefits in this patient population needs to be evaluated within the relevant time horizon. It follows that estimation of within-trial QALYs is often inappropriate if not misleading, as benefits extend beyond the trial follow-up period. In this case a long-term extrapolation of the results of the trial is needed. In light of this, the within-trial analyses are reported as summary statistics for resource use, costs and EQ-5D scores in each arm of the trial at baseline and at different follow-up points.

To estimate the cost-effectiveness of alternative minimally invasive continuous glucose monitoring devices against conventional monitoring, a beyond follow-up analysis is required to estimate long-term resource use, costs and QALYs over an appropriate time horizon. However, this would only be necessary if the difference in clinical outcome between the trial arms was found to be potentially clinically and economically significant, as in this case a difference in costs and benefits in the long run would be expected.

Statistical methods

Missing data

As a consequence of participants missing appointments or missing responses in questionnaires there is a large proportion of data missing. The extent of the missing data is such that if the analysis was confined to complete cases we would be ignoring a large proportion of the patients and breaking from an intention to treat analysis. Therefore, techniques have been used to tackle the missing data problem and these are explained below. However, a complete case analysis for each time period was also undertaken for comparison.

Multiple imputation using imputation by chained equations

To tackle the missing data problem described above, the method of multiple imputation using imputation by chained equations (ICE) was undertaken on the resource costs and EQ-5D scores. This involved imputing the values that were missing, using the available data.

The ICE approach to multiple imputation is based on each conditional density of a variable given all other variables. Unlike other approaches to multiple imputation, it does not require the assumption of a multivariate normal distribution. This is the key benefit of the approach for the MITRE trial as cost data are likely to be positively skewed and therefore it would have been inappropriate to assume normality of the resource cost components. When using ICE we have to assume that the data are missing at random or missing completely at random; however, there is clearly the possibility that this might not be the case.

ICE has two major conceptual steps: first, the imputation of a single variable given a set of predictor variables and, second, 'regression switching', which is a scheme for cycling through all of the variables to be imputed. ICE is discussed further in Royston.[122]

The imputation involved the imputation of the resource cost variables and the EQ-5D scores at baseline and at 3, 6, 12 and 18 months. The sets of predictor variables for each variable were chosen based on what were thought to be important explanatory variables. These included the dependent variable at all other time points as well as a group of important covariates including age, smoking status, type of diabetes, trial centre and body mass index (BMI). The data set was imputed five times and the ICE software uses all five data sets simultaneously for statistical analysis, taking account of both the within-data set and the between-data set variability.

Regression analysis

Following the imputation of the data sets, regression analysis was undertaken using both the resource costs and the EQ-5D scores. This was conducted with the aim of controlling for other covariates to help distinguish any treatment-specific effects on costs or utility. As the regression

analysis was based on imputed data sets, methods were needed to take account of the between-data set variability as well as the within-data set variability. These methods are part of the ICE software package in Stata and are discussed further in Royston 2004.[122]

It is also worth briefly discussing the nature of the data being analysed. For example, cost data tend to be right skewed as costs are naturally bounded at zero. Within a trial it is quite common to have a small proportion of patients with very high costs and these patients have a much larger effect on mean cost than on median cost, resulting in the right skewed distribution.[117] The standard method of dealing with this is to provide summary measures of the distribution such as medians and lower and upper quartiles; however, the nature of the distributions can lead to problems with standard regression techniques.

A basic ordinary least squares regression equation is as follows:

$$C_i = \alpha + \beta_1 T_{1i} + \beta_2 T_{2i} + \beta_3 T_{3i} + \varepsilon_i$$

where C_i is the cost of the trial to individual i, α is the intercept term, T_{1i} is the dummy variable equalling 1 if the individual is in the attention control trial arm and 0 otherwise, T_{2i} is the dummy variable equalling 1 if the individual is in the GlucoWatch trial arm and 0 otherwise, T_{3i} is the dummy variable equalling 1 if the individual is in the CGMS trial arm and 0 otherwise and ε_i is the individual error term.

In the above regression, α can be interpreted as the mean cost of an individual in the standard care control trial arm; β_1 can be interpreted as the change in mean cost of an individual in the attention control trial arm when compared with the standard care control trial arm; β_2 can be interpreted as the change in mean cost of an individual in the GlucoWatch trial arm when compared with the standard care control trial arm; and β_3 can be interpreted as the change in mean cost of an individual in the CGMS trial arm when compared with the standard care control trial arm. The ordinary least squares technique can also be used on the EQ-5D scores data with C_i being replaced by the EQ-5D. The intercept term can be interpreted as the mean EQ-5D score for the standard care control arm and the β coefficients can be interpreted as the changes in mean EQ-5D scores of participants in each trial arm compared with the standard care control arm. Regression analyses were also undertaken to look at any differences in trial arm effects between particular subgroups of participants. This was achieved through the use of interaction terms.

However, as cost data are unlikely to be normally distributed, estimating the regression using ordinary least squares is unlikely to result in the best unbiased estimates of the coefficients. Instead, because of cost data being skewed it is more appropriate to use a general linear model (GLM) with an identity link and a gamma distribution function. The identity link means that the explanatory variables still act additively on the dependent variable and thus the interpretation of the coefficients is the same as with the ordinary least squares model.[123]

Chapter 3
Sample characteristics

Information on the number of people screened for participation in the trial, the refusal rates and the number successfully recruited into the study is provided in *Table 3*. In total, 2335 people were screened for participation in the trial across the four different centres. Of these, 710 (30%) were ineligible. The exclusion criteria for the trial changed part-way through the trial, hence the two different types of exclusion criteria listed for time since most recent HbA1c (> 6 weeks changed to > 3 months) and for HbA1c levels (HbA1c ≤ 8.0% changed to HbA1c < 7.5%). The focus of this trial was on people with poorly controlled insulin-requiring diabetes. The most common reason for someone being classified as ineligible for the trial was an HbA1c level below the defined threshold ($n = 342$, 48%). Of the remaining 1625 eligible prospective participants, 1221 (75%) refused trial entry and 404 were admitted into the study and randomised (25%). Almost half of those who refused trial entry did not give a reason for declining the invitation to take part ($n = 601$, 49%). Excluding those who did not give a reason for refusal, the most common reasons for refusing trial entry were being too busy/work commitments ($n = 137$, 22%) and travelling difficulties (emigrating/moving away, travel issues, being away from home a lot and too many hospital visits; $n = 135$, 22%). The next most common reason for refusal was device-related issues, for example not wishing to be randomised to the CGMS ($n = 113$, 18%).

The screening data were analysed to establish whether those who refused participation were different from those who were recruited in terms of age, sex, type of diabetes, most recent HbA1c result or duration of diabetes. In *Table 4* the descriptive statistics for age, most recent HbA1c result and duration of diabetes are presented. These data were not normally distributed, hence non-parametric Mann–Whitney U-tests were performed to examine whether there were differences between the groups. Chi-squared tests were used to see if there were differences between the groups in the type of diabetes and the proportions of men and women (*Table 5*). Data on type of diabetes were only collected at the two London centres, hence separate analyses are presented for these two hospitals. There were no significant differences between those who were recruited into the study and those who refused participation in terms of age, most recent HbA1c result, duration of diabetes or proportions of men and women. Amongst the UCLH population, it appeared that there may have been a tendency for greater numbers of people with type 2 diabetes to refuse trial participation.

In *Table 6* the demographic characteristics of participants in the four different trial arms are presented. These factors were not subjected to statistical analysis as it was assumed that randomisation controlled for differences between the groups. It can be seen that the groups were broadly very similar on the different characteristics presented. Across the four arms of the trial there was a slightly higher proportion of participants with type 1 than with type 2 diabetes (53–60% versus 38–44%). A similar picture was found with the occupational class/social class groupings. The groups were very similar regarding the numbers of participants within each category but overall the managerial/professional category had more participants (35–47%). In terms of ethnicity the study was originally designed in a way that facilitated recruitment of three prominent ethnic minority groups in the population that the two London hospitals serve: Turkish, Bengali and Cantonese. All study documentation was translated into these three languages, and interpreters were available for participants from these particular groups. As the study progressed it became clear that if a participant was randomised to one of the device arms, he or she was more likely to need additional support and input outside of the research visits either in person with the research nurse or over the telephone. It was difficult for the research nurses to provide this support on an ad hoc basis, hence very few non-English speaking participants were randomised to the study.

In *Table 7* the baseline clinical characteristics of the study population are presented. These characteristics were broadly similar across the different study groups.

Figure 5 shows the number of people screened for trial participation and the number of people participating at each assessment point with regard to the main outcome (HbA1c).

TABLE 3 *Screening and randomisation*

	Bournemouth	Gateshead	UCLH	Whittington	Total
Number screened	606	520	715	494	2335
Total number ineligible	275	90	221	124	710
Last HbA1c > 6 weeks	0	0	35	26	61
Last HbA1c > 3 months	12	0	5	5	22
HbA1c ≤ 8.0%	50	37	77	19	183
HbA1c < 7.5%	82	19	27	31	159
Planned pregnancy	2	0	4	1	7
Used monitor before	21	0	18	0	39
Poor vision/health	28	22	9	10	69
Poor English	0	1	29	21	51
One daily injection	47	1	4	1	53
In another trial	8	0	2	2	12
On dialysis	0	1	0	1	2
Newly diagnosed	5	0	0	0	5
Skin conditions	1	2	1	0	4
One or no HbA1c results	3	0	1	4	8
No injections	8	2	0	0	10
Other	8	5	9	3	25
Number eligible	331	430	494	370	1625
Total refusals	244	318	367	292	1221
Busy/work commitments	4	41	57	35	137
Device related	1	22	53	37	113
Travel issues	14	5	34	10	63
Health problems	4	15	25	8	52
Not interested	1	11	20	19	51
Too many hospital visits	1	7	12	7	27
Emigrating/moving away	1	3	11	8	23
Away from home a lot	1	3	6	12	22
Too old	6	7	4	2	19
Too much trouble	0	0	6	9	15
Carer	2	3	5	5	15
Does not monitor glucose	1	1	4	3	9
Could not manage	4	2	1	1	8
Has done other research	1	0	3	4	8
Other	5	18	18	17	58
Not stated/no reason given	198	180	108	115	601
Total recruited	87	112	127	78	404
GlucoWatch	21	28	32	19	100
CGMS	23	29	31	19	102
Attention control	21	27	32	20	100
Standard care control	22	28	32	20	102

TABLE 4 *Demographic characteristics of those refusing trial entry and those randomised into the trial*

	Recruited	Valid, *n*	Mean rank	Refused	Valid, *n*	Mean rank	Mann–Whitney U-test	*p*-value
Age (years), median (IQR)	51.9 (40.9–63.4)	404	780	53.3 (40.6–66.0)	1208	815	233,448	0.19
Last HbA1c (%), median (IQR)	9.1 (8.3–9.9)	370	796	8.9 (8.3–9.9)	1185	772	212,384	0.36
Duration of diabetes (years), median (IQR)	15.0 (9.0–25.0)	404	720	16.0 (10.0–25.0)	1085	754	209,073	0.17

IQR, interquartile range.

TABLE 5 *Comparison of gender and type of diabetes between those refusing trial entry and those randomised into the trial*

	Recruited, *n* (%)	Refused, *n* (%)	Total	χ^2	df	*p*-value
Gender						
Female	185 (46)	535 (44)	720	0.48	1	0.49
Male	219 (54)	686 (56)	905			
Total	404	1221	1025			
Type of diabetes						
UCLH						
Type 1	90 (75)	231 (65)	321	4.0	1	0.05
Type 2	30 (25)	124 (35)	154			
Total	120	355	475			
Whittington						
Type 1	51 (66)	161 (56)	212	2.6	1	0.11
Type 2	26 (34)	126 (44)	152			
Total	77	287	364			

In *Figure 6* the percentage of participants with valid HbA1c data at each time point are presented. As a total group this ranged from 75% at 3 months' follow-up to 84% at 6 months' follow-up, 85% at 12 months' follow-up and 82% at 18 months' follow-up. The study was powered on the basis of a 10% attrition rate. Implications of this for the power of the study are considered in the discussion section of the report.

In total, 41 participants (10%) withdrew from the trial (*Table 8*), of whom 25 consented to HbA1c data (primary end point) being collected from routine clinic visits.

In total, across the 18-month duration of the trial, 158 SAEs were reported, of which 30 were considered related to the trial (*Table 9*); 27 of these were adverse device-related reactions (MITRE Skin Scale score ≥ 6) to the GlucoWatch reported amongst 19 different participants and three were other events related to the devices (see final three entries in *Table 9*).

There were 34 diabetes-related SAEs reported throughout the course of the trial (*Table 10*). These SAEs occurred among 23 trial participants but were not considered related to trial participation. There were 11 episodes of diabetic ketoacidosis resulting

TABLE 6 *Demographic characteristics of the trial participants*

	GlucoWatch	CGMS	Attention control	Standard care control	Total
n	100	102	100	102	404
Age (years), median (IQR)	55 (37–66)	53 (42–63)	53 (42–63)	51 (42–59)	52 (41–63)
Sex, *n* (%)					
Male	56 (56)	57 (56)	54 (54)	54 (53)	221 (55)
Female	44 (44)	45 (44)	46 (46)	48 (47)	183 (45)
Type of diabetes, *n* (%)					
Type 1	53 (53)	61 (60)	57 (57)	61 (60)	232 (57)
Type 2	44 (44)	41 (40)	41 (41)	39 (38)	165 (41)
Other	3 (3)	0 (0)	2 (2)	2 (2)	7 (2)
Ethnicity, *n* (%)					
White	87 (87)	93 (91)	90 (90)	87 (85)	328 (92)
Asian	7 (7)	2 (2)	5 (5)	6 (6)	20 (5)
Black	5 (5)	4 (4)	3 (3)	7 (7)	19 (5)
Mixed	1 (1)	1 (1)	0 (0)	0 (0)	2 (0.5)
Other	0 (0)	2 (2)	2 (2)	2 (2)	6 (1.5)
Employment, *n* (%)					
Full-time	33 (33)	45 (44)	40 (40)	36 (35)	154 (38)
Part-time	11 (11)	8 (8)	12 (12)	14 (14)	45 (11)
Looking after house/family	2 (2)	3 (3)	6 (6)	4 (4)	15 (4)
Permanently sick/disabled	16 (16)	8 (8)	10 (10)	16 (16)	50 (12)
Retired	31 (31)	29 (28)	25 (25)	24 (24)	109 (27)
Student	4 (4)	2 (2)	0 (0)	3 (3)	9 (2)
Unemployed	3 (3)	7 (7)	7 (7)	5 (5)	22 (5)
Education, *n* (%)					
Degree	17 (17)	18 (18)	26 (26)	28 (27)	89 (22)
Other higher education	15 (15)	13 (13)	9 (9)	9 (9)	46 (11)
A-levels	16 (16)	15 (15)	9 (9)	13 (13)	53 (13)
Trade apprenticeships	26 (26)	27 (26)	20 (20)	20 (20)	93(23)
Qualifications at level 1	4 (4)	7 (7)	9 (9)	4 (4)	24 (6)
Other qualifications	2 (2)	2 (2)	4 (4)	4 (4)	12 (3)
No qualifications	20 (20)	20 (20)	23 (23)	24 (24)	21 (22)
Social class, *n* (%)					
Managerial and professional	41 (41)	36 (35)	47 (47)	41 (40)	165 (41)
Intermediate occupations	14 (14)	9 (9)	10 (10)	13 (13)	46 (11)
Small employers and own account workers	11 (11)	13 (13)	11 (11)	13 (14)	48 (12)
Lower supervisory and technical	16 (16)	24 (24)	13 (13)	15 (15)	68 (17)
Semiroutine and routine	17 (17)	17 (17)	18 (18)	17 (17)	69 (17)
Not known	1 (1)	3 (3)	1 (2)	3 (2)	8 (2)

TABLE 7 *Baseline clinical characteristics of the study population*

	GlucoWatch	CGMS	Attention control	Standard care control	Total
Number randomised	100	102	100	102	404
Duration of diabetes (years), median (IQR)	16 (10.2–23.5)	15 (9–26)	18 (9–27)	14 (9–24)	16 (10–25)
Years on insulin, median (IQR)	12 (6–21)	11 (5–25)	12.5 (5.5–22.0)	11 (6–24)	11 (6–22)
Number of injections per day, *n* (%)					
Pump	2 (2)	3 (3)	1 (1)	3 (3)	9 (2)
Two	45 (45)	41 (40)	33 (33)	40 (39)	159 (39)
Three or four	50 (50)	55 (54)	64 (64)	55 (54)	224 (55)
Five or six	3 (3)	3 (3)	2 (2)	4 (4)	12 (3)
Number of units of insulin per day, median (IQR)	59 (41–78)	55 (40–74)	55 (42–76)	57 (40–72)	56 (40–76)
Other diabetes medication, *n* (%)					
Metformin	26 (26)	27 (26)	34 (34)	27 (26)	114 (28)
Sulphonylureas	8 (8)	11 (11)	5 (5)	7 (7)	31 (8)
Other antidiabetic	3 (3)	1 (1)	5 (5)	1 (1)	10 (2)
Systolic blood pressure (mmHg), median (IQR)	134 (120–145)	134 (120–143)	132 (123–140)	130 (117–141)	132 (120–142)
Diastolic blood pressure (mmHg), median (IQR)	75 (69–84)	77 (71–84)	78 (74–83)	80 (71–84)	78 (71–84)
Body mass index (kg/m^2), median (IQR)	29 (24–31)	29 (26–32)	29 (25–31)	28 (24–32)	28 (25–31)
Waist circumference (cm), median (IQR)	96 (86–107)	98 (88–110)	95 (85–104)	94 (82–103)	96 (86–105)
Number diagnosed with (number affected moderately or a great deal)					
Respiratory disease	22 (9)	13 (8)	16 (9)	16 (8)	67 (34)
Stroke	8 (2)	6 (2)	3 (1)	4 (3)	21 (8)
Neurological disease	5 (2)	0 (0)	3 (1)	3 (3)	11 (6)
Heart disease	18 (6)	15 (6)	15 (7)	28 (16)	76 (34)
Arthritis	24 (15)	34 (16)	29 (13)	28 (20)	115 (64)
Cancer	3 (1)	8 (2)	4 (1)	4 (1)	19 (5)
High blood pressure	42 (9)	47 (7)	49 (8)	54 (10)	192 (34)
Kidney disease	5 (2)	9 (0)	5 (3)	9 (2)	28 (7)
Number with hospital admissions in previous 3 months for					
Diabetic ketoacidosis/ hyperosmolar non-ketotic acidosis	1	0	0	1	2
Hypoglycaemia	2	0	0	0	2
Hyperglycaemia	0	0	1	0	1

IQR, interquartile range.

in hospital admissions totalling 77 days. None of these occurred in the CGMS group. There were 10 hospital admissions for hyperglycaemia that resulted in a total of 48 days in hospital. There were six episodes of hypoglycaemia requiring A&E attendance or treatment from a paramedic amongst five individuals, and seven episodes of hypoglycaemia amongst four people, resulting in hospital admissions that lasted 94 days.

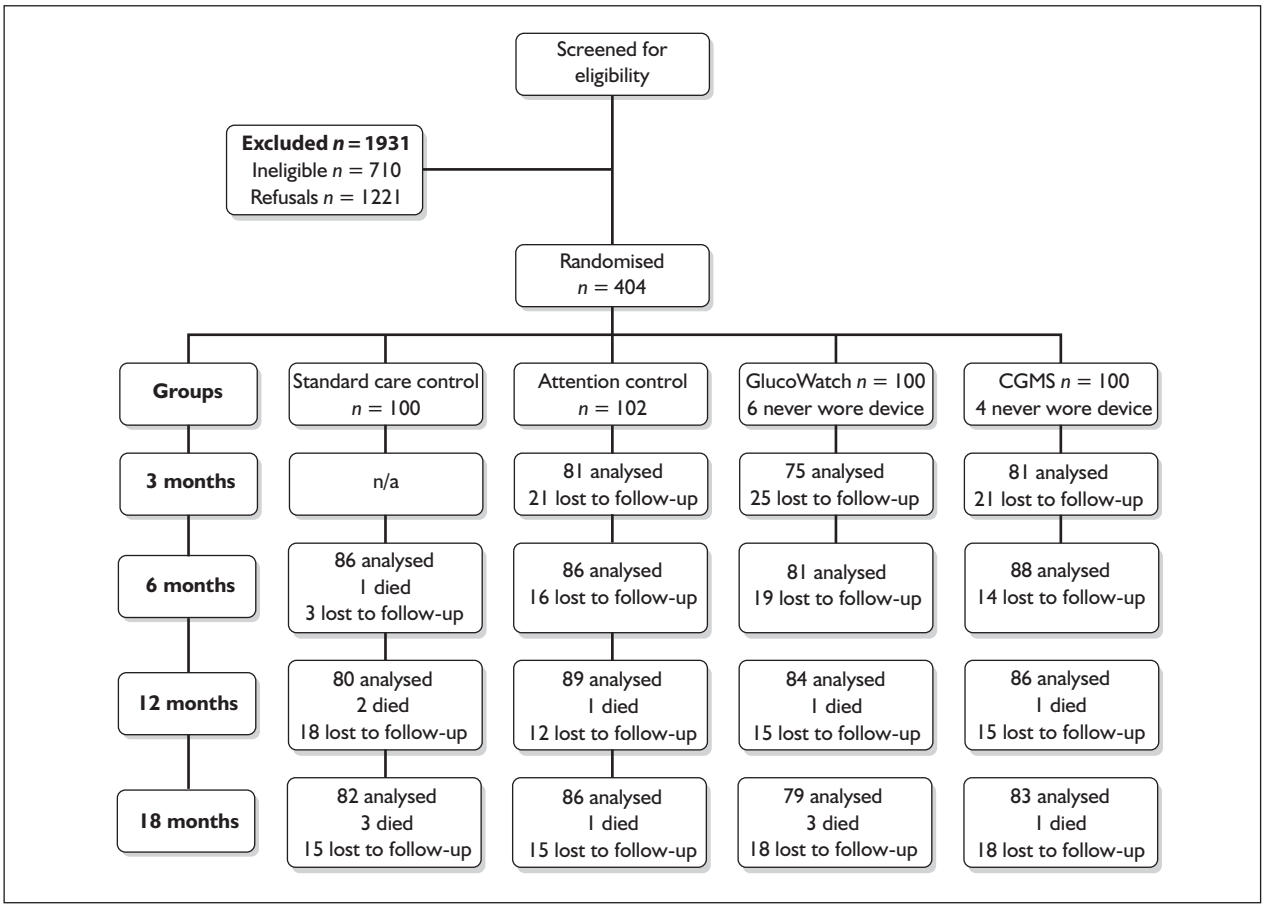

FIGURE 5 *Screening and participation in relation to collection of primary outcome data (HbA1c).*

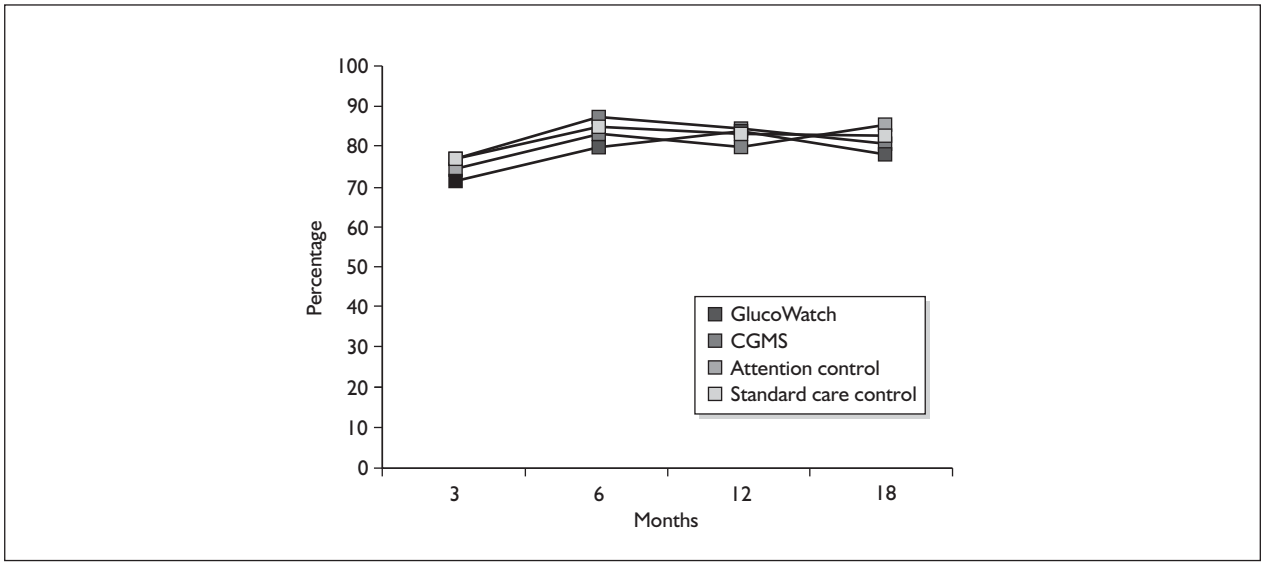

FIGURE 6 *Percentage of participants with valid HbA1c data (intention to treat) across study visits.*

TABLE 8 *Trial withdrawals*

Reason for trial withdrawal	Number
Self-withdrawal	25
Death	8
Pregnancy	5
Adverse device-related reactions	3 (skin reactions to GlucoWatch which meant that participants did not want to continue)
Total number of withdrawals	41 (25 consented to HbA1c data being accessed from routine clinic appointments)

TABLE 9 *Serious adverse events (device related)*

Study, *n*	Duration (days)	Narrative
2005	7	Skin reaction score = 8
2005	7	Skin score: redness = 4, swelling = 4, total = 8
2012	97	Skin redness and swelling = 6 in area that GlucoWatch device was worn
2054	42	Skin score > 6
2059	60	Skin score: redness = 3, swelling = 4, total = 7. However, patient has scored GlucoWatch reaction 6 on previous days. Patient score = 7 on telephone
2059	9	Skin score: redness = 3, swelling = 4, total = 7
2062	26	Photograph shows scabs formed after blisters had burst
2062	19	Skin score = 6
2070	48	Skin score related to GlucoWatch use
2072	13	Skin score = 6. Patient has decided to withdraw from the study
2078	24	Skin score = 6
3028	14	Skin reaction right arm
3028	14	Skin reaction left arm
3054	0	Adverse skin reaction left arm. MITRE score = 6
3054	21	Adverse skin reaction left arm. MITRE score = 8
3054	21	Adverse skin reaction to device on left arm. MITRE score = 8. Patient reports that a few days ago MITRE score was 11
3080	7	Skin reaction = 6 right arm
3080	31	Skin reaction = 6 left arm
3104	Not known	Adverse skin reaction scoring 6 on MITRE scale
4045	8	GlucoWatch instilled on left inner forearm; 2 hours afterwards patient noticed extreme itchiness and took watch off; two red lumps, intense redness, size of a five pence. 'Blisters noticed – not broken' – swelling observed today
4060	90	Adverse device-related reaction left arm
4060	26	Adverse device-related reaction right arm
4060	57	Adverse device-related reaction left arm
4060	Not known	Adverse device-related reaction right arm
4066	16	Adverse skin reaction left arm – MITRE score = 6. No photograph – camera not available – unable to come back for photograph
4078	20	Adverse device-related reaction right arm – MITRE score = 6. Watch taken off after 15 hours of use. Skin reaction noticed but not reported to research nurse. Not willing to wear watch again. Advised to use hand cream, e.g. E45, on dry skin areas
4078	19	Adverse device-related reaction left arm – MITRE score = 6. Watch taken off after 15 hours of use. Skin reaction noticed but did not contact research nurse. Not willing to wear watch again. Advised to use hand cream, e.g. E45, on dry skin areas
2023	0	Patient panicked whilst using the CGMS device and attended A&E for its removal. Sensor removed by casualty staff. No local reaction – wound clean, dry and intact
2024	Not known	Patient presented with six areas of scarring on arms relating to episodes of wearing the GlucoWatch at the beginning of the study, which have subsequently healed – three scars on each arm, brown in colour
4072	0	CGMS sensor inserted and explanation given of how to turn off and remove the monitor. Monitor started to bleep and read 'disconnected'. Patient was concerned and tried to contact research nurse but was unable to as it was a Sunday. Patient attended A&E for removal

TABLE 10 *Diabetes-related serious adverse events*

	GlucoWatch	CGMS	Attention control	Standard care control
Diabetic ketoacidosis				
Number reporting	3	0	1	3
Number admissions	5	0	1	5
Total length of hospital stay (days)	52	0	8	17
Hyperglycaemia				
Number reporting	2	2	4	2
Number admissions	2	2	4	2
Total length of hospital stay (days)	11	6	11	20
Hypoglycaemia (treated by paramedic/A&E attendance)				
Number reporting	2	2	1	0
Number episodes	2	3	1	0
Hypoglycaemia resulting in hospital admission				
Number reporting	1	2	0	1
Number admissions	1	2	0	4
Total length of hospital stay (days)	4	6	0	84

Chapter 4

Clinical outcome data – HbA1c results

The clinical findings are presented below with the primary end points presented first followed by the secondary end points. These findings are reported on an intention to treat basis. In the third section of this chapter a sensitivity analysis is presented using baseline HbA1c values carried forward when missing data are present. The fourth section presents a per protocol analysis in which minimum use of the devices was prespecified. The fifth section presents the findings of an analysis of subgroups in the study. Finally, in the sixth section, data on the nature and frequency of treatment recommendations given to participants at each research visit are described, together with data on the extent to which clinical feedback was altered by the additional information from the two continuous glucose monitors.

Primary clinical outcomes

One of the primary outcomes of this trial was the effect of the devices on changes in glycaemic control (HbA1c) in the long term (18-month end point). These data are presented first.

The distribution of HbA1c results by treatment arm is shown in *Table 11*. At baseline, HbA1c ranged from 7.0% to 15.5% with group means ranging from 8.9% to 9.4%. The baseline HbA1c approximates to a normal distribution, although the amendment to the inclusion criterion of HbA1c ≥ 7.5% means that the lower end has been censored.

Long-term impact on HbA1c (18 months)

The primary analysis of the study was intention to treat to determine the long-term impact on HbA1c of wearing minimally invasive continuous glucose monitors. These findings are displayed in *Table 12* and *Figure 7*.

These data indicate that all arms showed a reduction in HbA1c by 18 months' follow-up. There was, however, no statistically significant advantage to the continuous glucose monitoring devices at 18 months.

Secondary clinical outcomes

Secondary end points: short- and medium-term impact on HbA1c

Short-term impact on HbA1c (3 months)

As it is possible that the use of continuous glucose monitors may have led to improved glycaemic control in the short term, changes in HbA1c from baseline to 3 months' follow-up were analysed. The 3-month time point followed the end of the intensive intervention period and included only three of the groups as the standard care control arm was not assessed at this point.

Each trial arm showed improvements in HbA1c at 3 months' follow-up (*Table 13*), although this was not significantly different between the groups. The GlucoWatch arm showed the least improvement

TABLE 11 *Baseline HbA1c results by group*

		HbA1c (%)			
Trial arm	**Number**	**Mean (SD)**	**Median**	**IQR**	**Range**
GlucoWatch	100	9.2 (1.5)	8.8	8.2–9.8	7.3–15.4
CGMS	102	9.0 (1.1)	9.0	8.3–9.6	7.0–15.5
Attention control	100	8.9 (1.1)	8.6	8.2–9.5	7.2–11.6
Standard care control	102	9.4 (1.3)	9.3	8.5–10.2	7.3–14.1
Total	404	9.1 (1.3)	8.9	8.3–9.7	7.0–15.5

IQR, interquartile range.

TABLE 12 *Relative percentage change in HbA1c from baseline to 18 months' follow-up*

				Relative percentage change in HbA1c		
	n	Baseline HbA1c (%), mean (SD)	18-month HbA1c (%), mean (SD)	Mean difference within group (SD)	Mean difference compared with standard care control	95% CI
GlucoWatch	79	9.3 (1.6)	9.1 (1.4)	–1.4 (14.4)	3.5	–1.3 to 8.3
CGMS	83	8.9 (1.0)	8.5 (1.2)	–4.2 (14.8)	0.7	–4.0 to 5.5
Attention control	86	8.9 (1.1)	8.4 (1.2)	–5.1 (13.0)	–0.1	–4.6 to 4.3
Standard care control	82	9.4 (1.3)	8.9 (1.6)	–4.9 (16.2)		
Total	330	9.1 (1.3)	8.7 (1.4)	–4.0 (14.6)		

CI, confidence interval.
ANOVA: F = 1.1 (3, 326), $p = 0.36$.

in HbA1c compared with the CGMS and attention control arms.

Medium-term impact on HbA1c (6 and 12 months)

The medium-term impact on HbA1c was also examined by assessing the change in HbA1c from baseline to 6 and 12 months' follow-up. These findings are displayed in *Tables 14* and *15*, respectively, and in *Figure 8*.

As at the 18-month follow-up time point, at both 6 and 12 months' follow-up all of the groups showed a reduction in HbA1c from baseline. Although the GlucoWatch group seemed to do less well at the 6-month follow-up point than the other

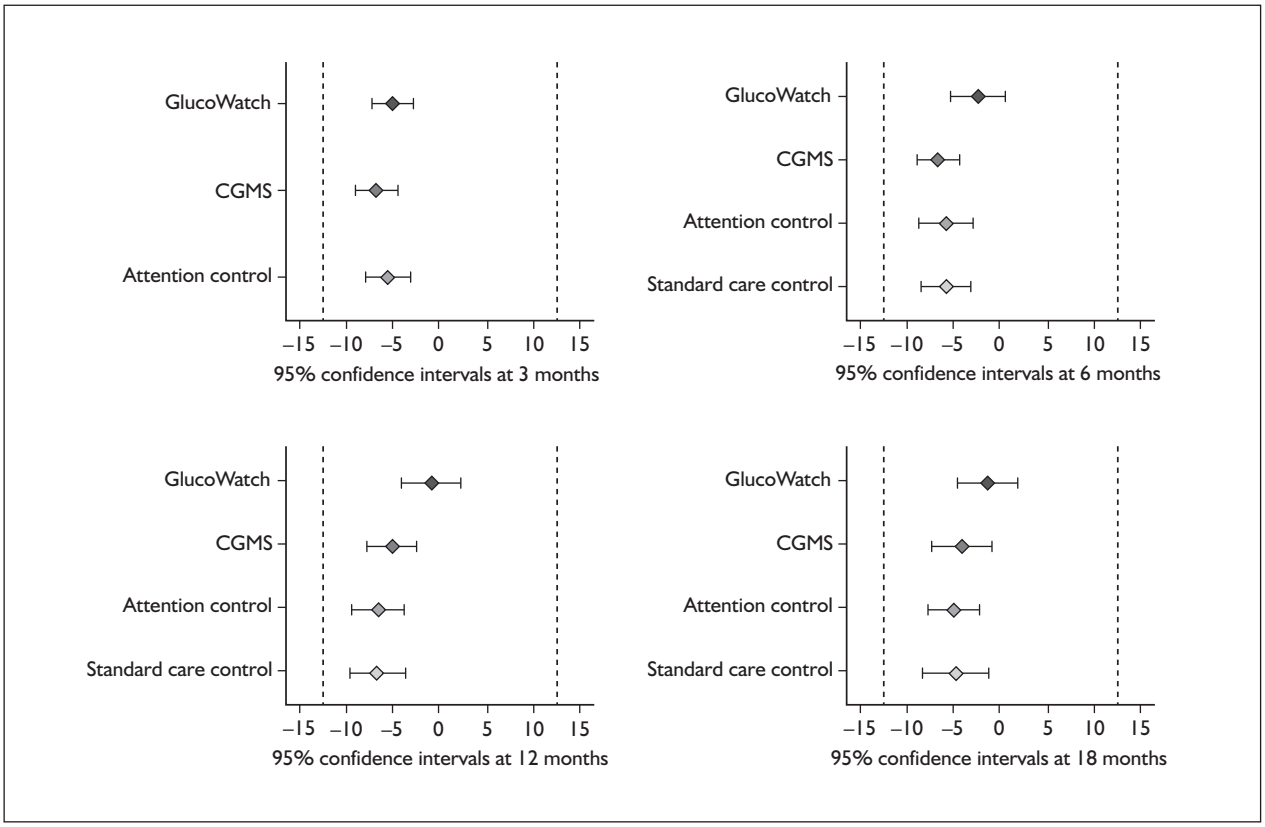

FIGURE 7 *Mean percentage change in HbA1c from baseline to 3, 6, 12 and 18 months; follow-up with confidence intervals.*

TABLE 13 *Relative percentage change in HbA1c from baseline to 3 months' follow-up*

	n	Baseline HbA1c (%), mean (SD)	3-month HbA1c (%), mean (SD)	Relative percentage change in HbA1c, mean (SD)
GlucoWatch	75	9.2 (1.6)	8.7 (1.3)	–5.0 (9.7)
CGMS	81	8.9 (1.0)	8.3 (0.9)	–6.7 (10.1)
Attention control	81	8.9 (1.1)	8.4 (1.1)	–5.5 (10.8)
Total	237	9.0 (1.2)	8.4 (1.1)	–5.8 (10.2)

Note: Standard care was not assessed at 3 months.
ANOVA: F = 0.61 (2, 234), $p = 0.54$.

TABLE 14 *Relative percentage change in HbA1c from baseline to 6 months' follow-up*

				Relative percentage change in HbA1c		
	n	Baseline HbA1c (%), mean (SD)	6-month HbA1c (%), mean (SD)	Mean difference within group (SD)	Mean difference compared with standard care control	95% CI compared with standard care control
GlucoWatch	81	9.0 (1.2)	8.7 (1.3)	–2.5 (12.9)	3.4	–0.4 to 7.3
CGMS	88	9.1 (1.2)	8.4 (1.4)	–6.7 (10.6)	–0.8	–4.2 to 2.6
Attention control	86	8.9 (1.1)	8.3 (1.1)	–6.0 (13.5)	–0.1	–3.9 to 3.8
Standard care control	86	9.5 (1.4)	8.8 (1.4)	–5.9 (12.1)		
Total	341	9.1 (1.2)	8.6 (1.3)	–5.3 (12.4)		

CI, confidence interval.
ANOVA: F = 1.97 (3, 337), $p = 0.12$.

TABLE 15 *Relative percentage change in HbA1c from baseline to 12 months' follow-up*

				Relative percentage change in HbA1c		
	n	Baseline HbA1c (%), mean (SD)	12-month HbA1c (%), mean (SD)	Mean difference within group (SD)	Mean difference compared with standard care control	95% CI compared with standard care control
GlucoWatch	84	9.1 (1.4)	9.0 (1.6)	–0.9 (14.5)	5.7	1.4–10.0
CGMS	86	8.9 (1.0)	8.4 (1.1)	–5.1 (12.4)	1.5	–2.4 to 5.5
Attention Control	89	8.9 (1.1)	8.3 (1.2)	–6.6 (13.4)	0.0	–4.0 to 4.1
Standard care control	80	9.4 (1.3)	8.7 (1.4)	–6.6 (13.4)		
Total	339	9.1 (1.2)	8.6 (1.3)	–4.8 (13.6)		

CI, confidence interval.
ANOVA: F = 3.39, (3, 335), $p = 0.02$.

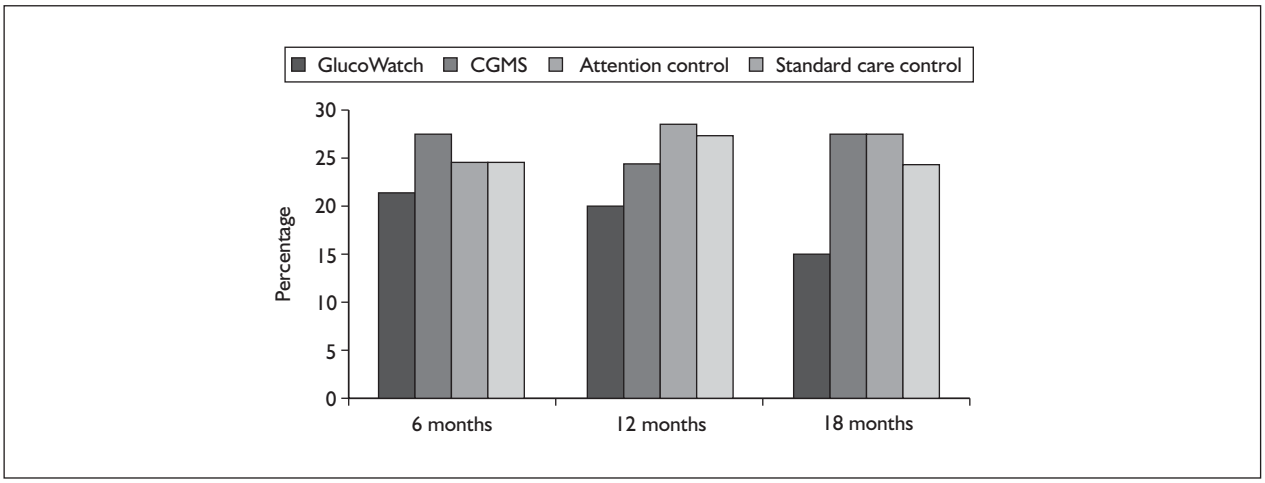

FIGURE 8 *Percentage of participants maintaining a clinically significant reduction in HbA1c (12.5%) at 6, 12 and 18 months by trial arm.*

groups, there was no significant group effect at this assessment point. There was a statistically significant difference in HbA1c levels between the groups at 12 months ($p = 0.02$), indicating slightly less improvement in the GlucoWatch group than in the other groups. The mean relative reduction in HbA1c ranged from 0.8% (GlucoWatch) to 5% (CGMS) and 7% (attention and standard care control groups). This translates to absolute mean differences in HbA1c from baseline of 0.1% in the GlucoWatch group, 0.5% in the CGMS group and 0.6% in the other groups. This reflected the relatively poorer performance of the GlucoWatch group at the other time points but, given the number of comparisons performed, may have occurred by chance.

Proportion of individuals achieving a clinically meaningful reduction in HbA1c

As part of the secondary analysis the proportion of participants achieving a 12.5% reduction in HbA1c from baseline at each follow-up period was examined and tested using the chi-squared test. This analysis is presented in *Table 16*. There were no significant differences between the groups in the proportion of people achieving a 12.5% reduction in HbA1c. Overall, almost 25% of the total group achieved this reduction at each follow-up period.

Percentage maintaining a clinically meaningful reduction in HbA1c

Further descriptive analysis, was undertaken to examine how many participants maintained a reduction of 12.5% in their HbAlc levels. Maintenance was defined as demonstrating a 12.5% reduction in HbA1c at two consecutive visits. Only patients with consecutive visits were included in this comparison, which is shown in *Figure 8*.

Although the proportion attaining and maintaining benefit in the GlucoWatch arm was consistently lower than the proportions in the other three arms, the difference did not achieve statistical significance.

Hypoglycaemic episodes

The following data were derived from the Lifescan meters used by all participants in all arms of the trial. At each research visit the number of hypoglycaemic readings reported over the past 28 days was recorded. A hypoglycaemic reading was defined as a glucose reading of ≤ 3.5 mmol/l or self-reported hypoglycaemia even if a glucose reading (taken at the time) was > 3.5 mmol/l . Lifescan data were downloaded at each research visit and information on hypoglycaemic episodes was gathered from the downloaded data. In the few instances in which participants did not remember to bring their meters in but data were available from their diaries, the data were used instead. The data on hypoglycaemic episodes are displayed in *Table 17*. The baseline data has not been reported here as this was based on retrospective reporting of hypoglycaemic episodes in the past 28 days (with or without diaries/meters). These data showed some differences in the percentage of participants reporting hypoglycaemic episodes, as well as in the proportion of total glucose readings that were classified as hypoglycaemic. No consistent pattern emerged between groups or over time.

TABLE 16 *Number (%) of individuals achieving a 12.5% reduction in HbA1c from baseline*

	3 months		6 months		12 months		18 months	
	Assessed, *n*	**Achieved reduction, *n* (%)**	**Assessed, *n***	**Achieved reduction, *n* (%)**	**Assessed, *n***	**Achieved reduction, *n* (%)**	**Assessed, *n***	**Achieved reduction, *n* (%)**
GlucoWatch	75	13 (17)	81	17 (21)	84	17 (20)	79	12 (15)
CGMS	81	24 (30)	88	24 (27)	86	21 (24)	83	22 (27)
Attention control	81	18 (22)	86	20 (23)	89	25 (28)	86	23 (27)
Standard care control	–	–	86	21 (24)	80	22 (28)	82	19 (23)
Total	237	55 (23)	341	82 (24)	339	85 (25)	330	76 (23)
Pearson chi-squared test	$\chi^2 = 3.37$, $p = 0.19$		$\chi^2 = 0.95$, $p = 0.81$		$\chi^2 = 1.75$, $p = 0.63$		$\chi^2 = 3.98$, $p = 0.26$	

TABLE 17 *Proportion of hypoglycaemic episodes at each time point by group*

Week	Arm	*n*	Any hypoglycaemic episodes, *n*	Any hypoglycaemic episodes, %	Total hypoglycaemic episodes	Total readings	%	Relative risk (95% CI)[a]
0	GlucoWatch	100	56	56	Unreliable data			
	CGMS	102	61	60				
	Attention	100	65	65				
	Standard care	102	66	65				
4	GlucoWatch	85	56	66	316	4536	7.0	0.99 (0.85–1.13)
	Attention	84	62	74	394	5683	6.9	
8	GlucoWatch	71	48	68	330	4210	7.8	1.02 (0.88–1.15)
6	CGMS	93	71	76	426	6606	6.4	1.23 (1.11–1.36)
8	Attention	82	59	72	451	5666	8.0	
12	GlucoWatch	74	54	73	332	4259	7.8	1.16 (1.03–1.29)
	CGMS	82	58	71	414	5749	7.2	1.07 (0.94–1.21)
	Attention	81	62	77	441	5268	8.4	
26	GlucoWatch	70	42	60	344	3664	9.4	0.70 (0.55–0.85)
	CGMS	79	53	67	354	5844	6.1	1.08 (0.94–1.23)
	Attention	83	64	77	434	5629	7.7	0.85 (0.71–0.99)
	Standard care	77	42	55	306	4662	6.6	
52	GlucoWatch	69	54	78	296	3517	8.4	0.83 (0.67–0.99)
	CGMS	75	54	72	342	4753	7.2	0.97 (0.82–1.12)
	Attention	85	62	73	453	5439	8.3	0.84 (0.69–0.98)
	Standard care	70	46	66	285	4086	7.0	
78	GlucoWatch	74	50	68	331	3527	9.4	0.83 (0.68–0.98)
	CGMS	77	50	65	337	3984	8.5	0.92 (0.77–1.07)
	Attention	81	58	72	343	5103	6.7	1.16 (1.01–1.31)
	Standard care	77	49	64	296	3788	7.8	

CI, confidence interval.
a Relative risks and 95% CIs are presented for each group compared with the standard care control group except at weeks 4–12 when they are given compared with the attention control group.

Severe hypoglycaemia, when the person with diabetes is unable to recognise the symptoms of low blood glucose and requires assistance from another person to administer treatment, was also assessed. Throughout the trial, the number of respondents reporting severe episodes of hypoglycaemia was very low – five or less people in any one trial arm (*Table 18*). These episodes of severe hypoglycaemia accounted for less than 0.02% of the total hypoglycaemic episodes throughout the course of the trial.

At each assessment period, participants were asked whether they knew when hypoglycaemia was commencing. They rated this on a visual analogue scale from 1 (never) to 5 (always). *Table 19* documents the number and percentage of respondents within each trial arm who scored 1–5 on that scale. *Table 20* shows the median scores by trial arm at each assessment point. From these tables it can be seen that the trial population included few people suffering from problems with hypoglycaemia awareness. At each assessment point the majority of people scored 4 or 5 on this scale.

Hyperglycaemic episodes

Data on hyperglycaemic episodes were collected as described for hypoglycaemic episodes. A hyperglycaemic reading was defined as ≥10.0 mmol/l . These data are presented in *Table 21*.

As with the data on hypoglycaemic episodes, there did not appear to be any consistent differences between the study groups in either the number of people reporting hyperglycaemic episodes or the proportion of total readings that were hyperglycaemic.

Secondary sensitivity analysis – HbA1c data

A sensitivity analysis using baseline HbA1c values carried forward to account for missing data was conducted for the primary 18-month end point as part of the secondary data analysis (*Table 22*). There was no evidence for any differences between the trial arms on the global ANOVA test. The GlucoWatch group showed the least improvement from baseline. As in earlier sections, the mean difference within each group and the mean difference in comparison with the standard care control group with 95% confidence intervals are presented.

Secondary per protocol analysis – clinical outcomes

A per protocol analysis was performed to determine the effectiveness of the devices in those participants who had used them for a prespecified minimum number of times in phase 1 of the trial. The per protocol analysis was defined as follows:

- CGMS: worn at least once
- GlucoWatch: worn at least three times
- attention control: attended one research visit in addition to baseline.

As with the intention to treat analysis, HbA1c results were included in the analysis if they fell within a prespecified period of time, scheduled around the research visit.

Four ANOVAs were performed to examine the relative reduction in HbA1c from baseline at each of the follow-up periods [follow-up HbA1c – baseline HbA1c/baseline HbA1c × 100].

Long-term impact on HbA1c – per protocol analysis

There was no group effect in terms of relative change in HbA1c from baseline to 18 months in the per protocol analysis (*Table 23*).

Short- and medium-term impact on HbA1c – per protocol analysis

Tables 24–26 display the results for the short- and medium-term impact of the devices on HbA1c for the per protocol analysis (3, 6 and 12 months' follow-up respectively).

The per protocol analysis examining the impact of the monitors when worn a minimum number of occasions on HbA1c in the short and medium term mirrored the results of the intention to treat analysis. As in the intention to treat analysis, at the 3-, 6- and 12-month follow-up, all of the groups showed some reduction in HbA1c from baseline. The GlucoWatch group appeared to show the least improvement in comparison with the other groups, although this was not statistically significant.

Proportion of individuals achieving a clinically meaningful reduction in HbA1c – per protocol analysis

The per protocol analysis of the proportion of individuals achieving a clinically meaningful

TABLE 18 *Proportion of people reporting severe hypoglycaemia*

Week	Arm	*n*	Any hypoglycaemic episodes, *n*	Any hypoglycaemic episodes, %	Severe hypoglycaemic episodes, *n*	Total hypoglycaemic episodes	Total severe hypoglycaemic episodes	%
0	GlucoWatch	100	56	56	3	Unreliable data	13	
	CGMS	102	61	60	1		1	
	Attention	100	65	65	5		6	
	Standard care	102	66	65	0		0	
4	GlucoWatch	85	56	66	0	316	0	0
	Attention	84	62	74	0	394	0	0
8	GlucoWatch	71	48	68	1	330	1	0.003
6	CGMS	93	71	76	1	426	3	0.007
8	Attention	82	59	72	2	451	2	0.004
12	GlucoWatch	74	54	73	0	332	0	0
	CGMS	82	58	71	1	414	1	0.002
	Attention	81	62	77	2	441	4	0.009
26	GlucoWatch	70	42	60	0	344	0	0
	CGMS	79	53	67	1	354	7	0.020
	Attention	83	64	77	1	434	12	0.028
	Standard care	77	42	55	1	306	1	0.003
52	GlucoWatch	69	54	78	1	296	4	0.014
	CGMS	75	54	72	1	342	2	0.006
	Attention	85	62	73	0	453	0	0
	Standard care	70	46	66	1	285	1	0.004
78	GlucoWatch	74	50	68	1	331	6	0.018
	CGMS	77	50	65	0	337	0	0
	Attention	81	58	72	2	343	4	0.012
	Standard care	77	49	64	2	296	3	0.010

TABLE 19 *Hypoglycaemia awareness symptoms, n (%)*

	Hypoglycaemia awareness	GlucoWatch	CGMS	Attention control	Standard care control	Total
Baseline	1	0	1 (1)	0	0	1 (0.3)
	2	8 (9)	8 (8)	11 (12)	16 (17)	43 (11)
	3	18 (20)	18 (19)	14 (15)	13 (14)	63 (17)
	4	24 (26)	19 (20)	21 (22)	20 (22)	84 (22)
	5	42 (46)	52 (54)	47 (50)	43 (47)	184 (49)
	Total, *n*	92	94	97	92	375
3 months	1	1 (2)	3 (4)	3 (4)		7 (3)
	2	5 (8)	4 (5)	7 (9)		16 (7)
	3	18 (27)	16 (21)	8 (11)		42 (19)
	4	9 (14)	13 (17)	18 (24)		40 (19)
	5	33 (50)	39 (52)	39 (52)		111 (51)
	Total, *n*	66	75	75		216
6 months	1	2 (3)	2 (3)	2 (3)	2 (3)	8 (3)
	2	2 (3)	6 (8)	5 (7)	2 (3)	15 (5)
	3	6 (10)	9 (12)	12 (16)	12 (17)	39 (14)
	4	16 (26)	21 (28)	15 (20)	16 (23)	68 (24)
	5	36 (58)	37 (49)	41 (55)	38 (54)	152 (54)
	Total, *n*	62	75	75	70	282
12 months	1	1 (2)	2 (3)	0	2 (3)	5 (2)
	2	5 (8)	2 (3)	11 (14)	3 (5)	21 (8)
	3	17 (27)	15 (22)	10 (13)	7 (11)	49 (18)
	4	13 (21)	16 (23)	18 (23)	13 (21)	60 (22)
	5	27 (43)	34 (49)	39 (50)	37 (60)	137 (50)
	Total, *n*	63	69	78	62	272
18 months	1	4 (6)	4 (6)	3 (4)	1 (1)	12 (4)
	2	5 (7)	0	10 (13)	2 (3)	17 (6)
	3	9 (13)	11 (16)	10 (13)	8 (12)	38 (13)
	4	20 (29)	20 (28)	13 (17)	17 (25)	70 (25)
	5	30 (44)	36 (51)	40 (53)	41 (59)	147 (52)
	Total, *n*	68	71	76	69	284

TABLE 20 *Median scores (interquartile range) on the hypoglycaemia awareness scale*

	Baseline	3 months	6 months	12 months	18 months
GlucoWatch	4.0 (3.0–5.0)	4.5 (3.0–5.0)	5.0 (4.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)
CGMS	5.0 (3.0–5.0)	5.0 (3.0–5.0)	4.0 (4.0–5.0)	4.0 (3.0–5.0)	5.0 (4.0–5.0)
Attention control	4.5 (3.0–5.0)	5.0 (4.0–5.0)	5.0 (3.0–5.0)	4.5 (3.0–5.0)	5.0 (3.0–5.0)
Standard care control	4.0 (3.0–5.0)		5.0 (4.0–5.0)	5.0 (4.0–5.0)	5.0 (4.0–5.0)

TABLE 21 *Hyperglycaemia at each time point by trial arm*

Week	Arm	*n*	Any hyperglycaemic episodes, *n*	Any hyperglycaemic episodes, %	Total hyperglycaemic episodes	Total readings	%	Relative risk (95% CI)
0	GlucoWatch	100	72	72	Unreliable data			
	CGMS	102	76	75				
	Attention	100	70	70				
	Standard care	102	79	77				
4	GlucoWatch	85	78	92	1994	4536	44.0	1.02 (0.98–1.06)
	Attention	84	82	98	2546	5683	44.8	
8	GlucoWatch	71	69	97	1821	4210	43.3	0.94 (0.89–0.98)
6	CGMS	93	87	94	2960	6606	44.8	0.90 (0.86–0.94)
8	Attention	82	78	95	2293	5666	40.5	
12	GlucoWatch	74	72	97	1809	4259	42.5	0.94 (0.89–0.98)
	CGMS	82	79	96	2524	5749	43.9	0.91 (0.86–0.95)
	Attention	81	78	96	2095	5268	39.8	
26	GlucoWatch	70	63	90	1521	3664	41.5	1.14 (1.09–1.19)
	CGMS	79	76	96	2570	5844	44.0	1.07 (1.03–1.12)
	Attention	83	76	92	2181	5629	38.7	1.22 (1.17–1.26)
	Standard care	77	67	87	2200	4662	47.2	
52	GlucoWatch	69	62	90	1677	3517	47.7	1.00 (0.96–1.05)
	CGMS	75	67	89	2028	4753	42.7	1.12 (1.08–1.17)
	Attention	85	73	86	2138	5439	39.3	1.22 (1.17–1.26)
	Standard care	70	65	93	1957	4086	47.9	
78	GlucoWatch	74	61	82	1632	3527	46.3	1.05 (1.0–1.10)
	CGMS	77	61	79	1545	3984	38.8	1.25 (1.20–1.30)
	Attention	81	71	88	1984	5103	38.9	1.25 (1.20–1.30)
	Standard care	77	61	79	1836	3788	48.5	

CI, confidence interval.

TABLE 22 *Relative percentage change in HbA1c from baseline to 18 months' follow-up: sensitivity analysis*

	n	Baseline HbA1c, mean (SD)	18-month HbA1c, mean (SD)	Mean difference within group (SD)	Mean difference compared with standard care control	95% CI
GlucoWatch	100			–0.9 (12.9)	3.3	–0.6 to 7.2
CGMS	102			–3.5 (13.7)	0.7	–3.3 to 4.6
Attention control	100			–4.1 (12.4)	0.1	–3.7 to 3.9
Standard care control	102			–4.2 (15.0)		
Total	404			–3.2 (13.6)		

CI, confidence interval.
ANOVA: F = 1.3 (3, 400), $p = 0.28$.

TABLE 23 *Per protocol analysis: relative percentage change in HbA1c from baseline to 18 months' follow-up*

				Relative percentage change in HbA1c		
	n	Baseline HbA1c (%), mean (SD)	18-month HbA1c (%), mean (SD)	Mean difference within group (SD)	Mean difference compared with standard care control	95% CI
GlucoWatch	57	9.2 (1.3)	8.9 (1.3)	–1.9 (13.1)	3.0	–2.1 to 8.2
CGMS	74	8.9 (1.0)	8.4 (1.2)	–4.9 (14.9)	0.1	–4.9 to 5.0
Attention control	77	8.9 (1.1)	8.3 (1.2)	–5.8 (12.8)	–0.8	–5.4 to 3.8
Standard care control	82	9.4 (1.3)	8.9 (1.6)	–4.9 (16.2)		
Total	290	9.1 (1.2)	8.6 (1.4)	–4.6 (14.4)		

CI, confidence interval.
ANOVA: F = 0.86 (3, 286), $p = 0.46$.

reduction in HbA1c is displayed in *Table 27*. No significant difference was found between the groups.

Clinical outcomes – subgroup analyses

Although the study was not powered to examine subgroups, an exploratory analysis of prespecified subgroups was performed to determine whether particular subgroups derived any benefits from the devices. This was only carried out on the long-term HbA1c outcome (18 months).

The subgroups were specified a priori based upon either the distributions of the baseline sample characteristics or established knowledge and previous literature regarding the characteristics. For example, it is accepted that daily SMBG is important for insulin-treated people with diabetes (DCCT, UKPDS). At baseline, 46% of the sample were testing blood glucose at least daily, hence it was considered reasonable to split the sample into those who were testing daily and those who were testing less than daily. For duration of diabetes, 50% of the sample had been diagnosed with diabetes for between 6 months and 15 years, whereas the other 50% had been diagnosed for 16 years or more, and so the group was split into two based on these distributions.

The subgroups were specified as follows:

- type of diabetes: type 1 and type 2
- number of injections: two or three and more than 4 or CSII
- age: ≤ 44 years, 45–59 years and 60–84 years

TABLE 24 *Per protocol analysis: relative percentage change in HbA1c from baseline to 3 months*

		Mean (SD) HbA1c (%)		
	n	**Baseline**	**3 months**	**Mean difference within group (SD)**
GlucoWatch	58	9.1 (1.3)	8.6 (1.1)	–5.4 (9.4)
CGMS	78	8.9 (1.0)	8.2 (0.9)	–7.0 (10.0)
Attention control	76	8.9 (1.1)	8.4 (1.1)	–5.6 (10.7)
Total	212	9.0 (1.1)	8.4 (1.1)	–6.1 (10.0)
ANOVA: F = 0.54 (2, 209), $p = 0.58$.				

TABLE 25 *Per protocol analysis: relative percentage change in HbA1c from baseline to 6 months*

				Relative percentage change in HbA1c		
	n	**Baseline HbA1c (%), mean (SD)**	**6-month HbA1c (%), mean (SD)**	**Mean difference within group (SD)**	**Mean difference compared with standard care control**	**95% CI**
GlucoWatch	55	9.0 (1.1)	8.6 (1.3)	–3.8 (12.5)	2.1	–2.1 to 6.3
CGMS	78	8.9 (1.0)	8.2 (1.0)	–7.3 (10.3)	–1.4	–4.9 to 2.1
Attention control	75	8.9 (1.0)	8.2 (1.1)	–7.1 (13.5)	–1.2	–5.2 to 2.8
Standard care control	86	9.5 (1.4)	8.8 (1.4)	–5.9 (12.1)		
Total	294	9.1 (1.1)	8.5 (1.2)	–6.2 (12.1)		
CI, confidence interval. ANOVA: F = 1.1 (3, 290), $p = 0.36$.						

TABLE 26 *Per protocol analysis: relative percentage change from baseline to 12 months*

				Relative percentage change in HbA1c		
	n	**Baseline HbA1c (%), mean (SD)**	**12-month HbA1c (%), mean (SD)**	**Mean difference within group (SD)**	**Mean difference compared with standard care control**	**95% CI**
GlucoWatch	56	9.1 (1.2)	8.8 (1.4)	–2.2 (13.8)	4.4	–0.3 to 9.1
CGMS	76	8.9 (1.0)	8.3 (1.1)	–5.7 (12.0)	0.9	–3.1 to 5.0
Attention control	78	8.9 (1.0)	8.2 (1.1)	–7.6 (13.1)	–1.0	–5.1 to 3.2
Standard care control	80	9.4 (1.3)	8.7 (1.4)	–6.6 (13.4)		
Total	290	9.1 (1.1)	8.5 (1.3)	–5.8 (13.1)		
CI, confidence interval. ANOVA: F = 2.0 (3, 286), $p = 0.11$.						

TABLE 27 *Per protocol analysis: number (%) of individuals achieving a 12.5% reduction in HbA1c from baseline*

	3 months		6 months		12 months		18 months	
	Assessed, *n*	**Achieved reduction, *n* (%)**	**Assessed, *n***	**Achieved reduction, *n* (%)**	**Assessed, *n***	**Achieved reduction, *n* (%)**	**Assessed, *n***	**Achieved reduction, *n* (%)**
GlucoWatch	58	11 (19)	55	13 (24)	56	13 (23)	57	10 (18)
CGMS	78	23 (29)	78	23 (29)	76	20 (26)	74	21 (28)
Attention control	76	17 (22)	75	19 (25)	78	24 (31)	77	21 (27)
Standard care control			86	21 (24)	80	22 (28)	82	19 (23)
Total	212	51 (24)	294	80 (27)	290	79 (27)	290	71 (24)
Pearson chi-squared test	$\chi^2 = 2.20$, $p = 0.33$		$\chi^2 = 0.78$, $p = 0.85$		$\chi^2 = 0.98$, $p = 0.81$		$\chi^2 = 2.49$, $p = 0.48$	

- duration of diabetes: from 6 months to 15 years and 16+ years
- years using insulin: 0–9 years and 10+ years
- diabetes complications: absence or presence
- HbA1c: ≤ 8.9% and ≥ 9.0%
- BMI: normal, overweight and obese
- SMBG: daily and less than daily
- exercise: ≤ 2.5 days over the last week and ≥ 3 days over the last week
- healthy eating: ≤ 4.0 days over the last week and ≥ 4.5 days over the last week.

The data and analysis for each of the subgroup comparisons are displayed in *Table 28*. None of these comparisons indicated any differences between the different arms of the study.

Treatment recommendations and the extent to which clinical feedback was altered by information from the monitors

The additional information provided by the continuous blood glucose monitors may have altered the nature and frequency of treatment recommendations relating to the diabetes regimen from the nurses. *Table 29* shows the numbers and percentages of people receiving different treatment recommendations at each visit in the two device groups and the attention control group. The standard care control group did not receive any recommendations regarding therapy adjustments as these were carried out at their routine clinic visits. *Figure 9* displays the percentages of participants by group at each visit who received the most commonly recommended changes to the treatment regimen.

These data indicate little difference in the percentages of patients receiving advice from the nurses in the two continuous glucose monitoring device groups compared with the percentage in the attention control group. The extent to which the nurses felt that their clinical advice to the participants was altered by the additional information received from the devices was also assessed. The nurses completed a five-point single-item visual analogue scale (1 = no alteration through to 5 = complete alteration) at each visit. These data are displayed in *Table 30*.

The extent to which the nurses' clinical advice was altered by the additional information from the monitors varied, but overall the information provided by the CGMS tended to alter clinical feedback more than the data from the GlucoWatch.

Summary

The results of the intention to treat analysis indicated no group differences in the primary or secondary outcomes. The findings of the per protocol analysis were similar. These findings therefore suggest that the continuous glucose monitoring devices have no impact, both in the short and long term, on clinical outcomes over and above standard or more intensive care without the monitors. Furthermore, when the participants were categorised on demographic, clinical and behavioural dimensions there was no suggestion that the continuous glucose monitoring devices resulted in clinically better outcomes for any subgroup. Participants in the device groups did not appear to receive more treatment recommendations in relation to management of their diabetes than participants in the attention control group. Clinical feedback to the participants seemed to be influenced more by the data from the CGMS than by the GlucoWatch data.

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TABLE 28 *Subgroup analyses: relative percentage change in HbA1c from baseline to 18 months' follow-up*

Subgroup	*n*	Gluco	*n*	CGMS	*n*	Attention	*n*	Standard	F-statistic	df	*p*-value
Type of diabetes											
Type 1	43	–3.8 (7.4)	53	–5.7 (9.4)	52	–3.1 (14.8)	53	–3.8 (9.9)	0.5	3	0.66
Type 2	40	–0.1 (17.1)	39	–7.7 (11.8)	36	–7.6 (14.3)	35	–8.3 (14.4)	2.8	3	0.04
Number of injections											
Two or three	43	–2.6 (15.9)	43	–4.3 (18.3)	31	–7.5 (13.2)	40	–7.2 (18.7)	0.7	3	0.53
>Four	42	0.2 (11.8)	46	–3.5 (10.7)	60	–3.6 (13.3)	47	–3.1 (13.5)	0.9	3	0.43
Age (years)											
≤ 44	30	–0.7 (11.1)	22	-4.6 (10.4)	26	–2.2 (15.4)	29	–4.5 (14.2)	0.6	3	0.63
45–59	29	–3.8 (14.2)	36	–5.9 (13.9)	33	–3.8 (13.5)	37	–8.0 (14.7)	0.7	3	0.56
60–84	26	1.0 (16.7)	31	–1.1 (18.0)	32	–8.3 (10.9)	21	–0.3 (20.1)	1.9	3	0.13
Duration of diabetes											
6 months to 15 years	40	–0.6 (16.1)	48	–2.1 (17.9)	40	–3.1 (13.9)	48	–4.1 (17.9)	0.4	3	0.79
16+ years	45	–1.8 (12.0)	41	–5.9 (9.9)	51	–6.3 (12.8)	39	–6.0 (13.8)	1.4	3	0.26
Years using insulin											
0–9	37	1.8 (14.1)	39	–3.0 (18.9)	35	–3.5 (15.7)	39	–4.0 (19.4)	0.9	3	0.44
10+	48	–3.6 (13.7)	50	–4.6 (10.8)	56	–5.8 (11.7)	48	–5.7 (13.0)	0.4	3	0.78
Diabetes complications											
Absence	21	1.7 (11.8)	24	–4.8 (12.4)	27	–1.8 (13.7)	23	–4.3 (11.7)	1.2	3	0.30
Presence	64	–2.2 (14.6)	65	–3.6 (15.6)	64	–6.2 (13.1)	64	–5.2 (17.5)	0.9	3	0.46
Level of HbA1c											
≤ 8.9%	38	3.3 (14.3)	43	0.4 (14.9)	51	–0.6 (10.9)	31	–0.6 (11.2)	0.8	3	0.51
≥ 9.0%	40	–6.0 (13.2)	40	–9.2 (13.1)	35	–11.6 (13.2)	53	–7.9 (17.9)	1.0	3	0.41

continued

TABLE 28 *Subgroup analyses: relative percentage change in HbA1c from baseline to 18 months' follow-up (continued)*

Subgroup	*n*	Gluco	*n*	CGMS	*n*	Attention	*n*	Standard	F-statistic	df	*p*-value
BMI											
Normal	24	–3.0 (10.6)	18	–2.3 (12.7)	24	–3.3 (12.5)	25	–8.6 (13.7)	1.3	3	0.28
Overweight	34	–0.8 (13.1)	37	–5.6 (10.4)	33	–7.3 (10.9)	30	0.5 (15.7)	2.9	3	0.04
Obese	27	–0.2 (17.7)	34	–2.9 (19.4)	33	–3.3 (15.9)	32	–7.2 (17.3)	0.8	3	0.50
SMBG											
Less than daily	48	1.1 (15.5)	46	–5.4 (13.8)	49	–6.3 (13.3)	47	–6.7 (16.7)	2.9	3	0.04
Daily	31	–4.1 (12.3)	42	–2.6 (15.8)	40	–3.7 (12.6)	38	–4.3 (12.1)	0.1	3	0.95
Exercise (days)											
0–2.5	36	–0.5 (17.3)	44	–2.4 (16.5)	39	–6.8 (13.6)	37	–5.4 (16.1)	1.2	3	0.31
3–7	43	–1.4 (11.8)	44	–5.8 (12.7)	50	–3.8 (12.5)	48	–5.7 (13.8)	1.2	3	0.32
Healthy eating (days)											
0–4	36	–2.0 (12.8)	33	–4.1 (11.6)	35	–5.9 (11.4)	39	–5.4 (15.5)	0.7	3	0.59
4.5–7.0	42	0.1 (15.9)	55	–4.1 (16.4)	54	–4.6 (14.0)	46	–5.8 (14.3)	1.3	3	0.29

Attention, Attention control; Gluco, GlucoWatch; SMBG, self-monitoring of blood glucose; Standard, standard care control.

TABLE 29 *Recommended changes to treatment regimen at each research visit*

	GlucoWatch						CGMS	Attention control										
Week number	4	8	12	26	52	78	72 hours	6	12	26	52	78	4	8	12	26	52	78
Valid, *n*	85	71	74	70	69	74	97	92	82	79	75	77	84	82	81	83	85	81
Change in insulin dose, *n* (%)	47 (55)	46 (65)	56 (76)	41 (59)	44 (64)	35 (47)	67 (69)	71 (77)	58 (71)	49 (62)	46 (61)	44 (57)	54 (64)	56 (68)	58 (72)	55 (66)	58 (68)	44 (54)
Change in insulin type, *n* (%)	9 (11)	7 (10)	0	2 (3)	6 (9)	0	17 (18)	4 (4)	6 (7)	3 (4)	2 (3)	3 (4)	13 (16)	10 (12)	9 (11)	11 (13)	4 (5)	3 (4)
Change in insulin timing, *n* (%)	9 (11)	6 (8)	7 (9)	6 (9)	8 (12)	3 (4)	18 (19)	13 (14)	9 (11)	10 (13)	8 (11)	7 (9)	10 (12)	9 (11)	7 (9)	12 (15)	10 (12)	9 (11)
Change in injection site, *n* (%)	5 (6)	2 (3)	2 (3)	2 (3)	3 (4)	2 (3)	9 (9)	7 (8)	5 (6)	3 (4)	2 (3)	1 (1)	8 (10)	3 (4)	5 (6)	2 (2)	3 (4)	1 (1)
Change in diabetic tablets, *n* (%)	5 (6)	5 (7)	5 (7)	4 (6)	5 (7)	3 (4)	3 (3)	4 (4)	7 (9)	3 (4)	13 (17)	8 (10)	6 (7)	4 (5)	2 (3)	6 (7)	8 (9)	6 (7)
Change in exercise, *n* (%)	29 (34)	21 (30)	24 (32)	26 (37)	24 (35)	24 (32)	31 (32)	24 (26)	26 (32)	29 (37)	24 (32)	21 (27)	35 (42)	34 (42)	28 (35)	43 (52)	28 (33)	28 (35)
Change in diet, *n* (%)	44 (52)	38 (54)	40 (54)	32 (46)	26 (38)	28 (38)	57 (59)	54 (59)	37 (45)	45 (57)	39 (52)	29 (38)	45 (54)	42 (51)	35 (43)	38 (46)	33 (39)	28 (35)

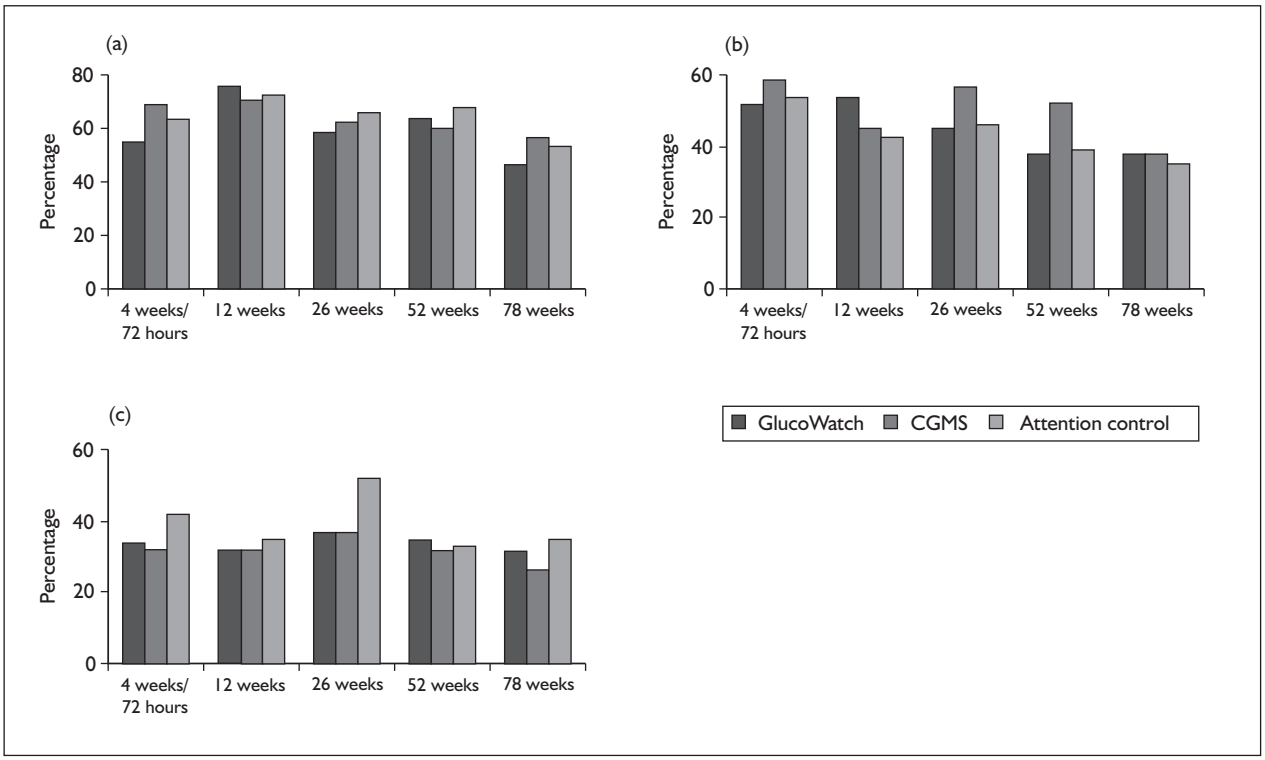

FIGURE 9 *Percentage of patients receiving most commonly recommended treatment changes. (a) Insulin dose; (b) diet; (c) exercise.*

TABLE 30 *Extent to which clinical advice was altered by information from monitors – nurse self-report [n, (%)]*

	Week 4/72 hours		Week 12		Week 26		Week 52		Week 78	
	GlucoWatch	**CGMS**	**GlucoWatch**	**CGMS**	**GlucoWatch**	**CGMS**	**GlucoWatch**	**CGMS**	**GlucoWatch**	**CGMS**
1 (no alteration)	41 (62)	13 (14)	23 (59)	11 (16)	14 (64)	10 (16)	12 (75)	11 (92)	11 (92)	5 (10)
2	12 (18)	25 (27)	11 (28)	14 (20)	4 (18)	16 (25)	0	0	0	11 (23)
3	7 (11)	25 (27)	2 (5)	22 (31)	3 (14)	20 (31)	4 (25)	1 (8)	1 (8)	17 (35)
4	4 (6)	27 (29)	2 (5)	20 (29)	1 (5)	14 (22)	0	0	0	13 (27)
5 (complete alteration)	2 (3)	4 (4)	1 (3)	3 (4)	0	4 (6)	0	0	0	2 (4)

Chapter 5

Participant-reported outcomes

Trial acceptability

Recruitment into the trial reflects the overall acceptability of taking part in an RCT in which the probability of receiving a continuous glucose monitoring device is 50%. Reasons for non-participation at this level can be diverse and may include aspects of the devices. The overall refusal rate for this trial was 75%. Some information can be gleaned on the acceptability of the study protocol and the devices by examining screened participants' reasons for refusal, although this is incomplete as approximately half of those who refused trial entry did not provide a reason. Amongst those who did give a reason for declining to take part, being busy and/or work commitments (22%, $n = 137$) and problems with travelling to and from the hospital for frequent appointments (22%, $n = 135$) were the most common reasons. In some cases these general reasons may mask other reasons for not wanting to participate. Importantly, the third most common reason for declining to participate was related to the devices (18%, $n = 113$), in particular, not wanting to be randomised to the CGMS arm of the trial ($n = 64$).

Monitor use and acceptability

To assess acceptability of the devices, a specific questionnaire was developed as no other suitable questionnaire existed at the time. The development of the questionnaire involved conducting a qualitative study to generate questions, which were then piloted with a small sample of patients who had experience of wearing the devices. Further details of the process of developing the questionnaire can be found in Appendix 8.

Monitor use and acceptability of the devices were assessed at 3, 6, 12 and 18 months.

Monitor use

Table 31 displays the number of times that the devices were worn for each participant at each time point, as well as the cumulative number (%) of people who had stopped using the devices and their reasons for stopping. The overall percentages continuing to use the devices are shown in *Figure 10*.

In phase 1 of the trial GlucoWatch patients were asked to use the watch at times of their choice but with a minimum attempted use of four times per month (12 times in phase 1, the first 3-month period) and a maximum attempted use of four times per week (52 times in phase 1). It was planned that the CGMS group would have the device fitted at baseline and at 6 and 12 weeks, that is, three times in phase 1 of the trial.

The per protocol analysis for phase 1 (0–3 months) was defined as:

- CGMS: worn at least once
- GlucoWatch: worn at least three times.

During this period the majority of the CGMS group wore the device at least once ($n = 98$, 96%). In the GlucoWatch group, 68 (68%) individuals wore the device at least three times during phase 1; median use of the devices was five times by 4 weeks' follow-up, three times between 4 and 8 weeks' follow-up and once between the 8- and 12-week visits. Six participants allocated to the GlucoWatch and four CGMS participants chose not to wear the devices at all throughout the course of the study.

During phase 2 (3–18 months) of the study, use of both devices declined, although the decline was considerably greater in the GlucoWatch group. Skin reactions were the most common reason given for stopping use in this group.

As can be seen in *Table 31* and *Figure 10*, a greater number of CGMS participants than GlucoWatch participants used the device throughout the course of the study. In both arms of the trial it was unusual to see participants interrupt using the device and then start using it again ($n = 9$ GlucoWatch versus $n = 3$ CGMS).

Skin reactions over the course of the study (0–18 months)

Skin reactions are known to be commonly associated with use of the GlucoWatch. In *Table 32*

TABLE 31 *Use of the monitors*

Trial arm	Week number	Assessed, *n*	Number of times worn					Stopped, *n* (%)	Reason for stopping use					
			0	1	2	3	≥ 4		Skin reaction	Difficulty	Not working	Not useful	Other[a]	Miss
GlucoWatch	4	85	4	14	5	9	53	4 (5)	0	2	0	0	2	0
	8	71	25	6	2	3	35	25 (35)	15	5	1	0	4	0
	12	74	32	8	2	3	29	32 (43)	19	8	2	0	3	0
	26	70	46	4	2	1	17	46 (66)	25	10	0	0	10	1
	52	69	50	1	4	2	12	50 (73)	27	8	1	5	6	3
	78	74	59	3	2	2	8	59 (80)	29	10	0	8	11	1
CGMS	72 hours	97	1	96				1 (1)	0	0	0	0	1	0
	6	92	9	83				9 (10)	0	1	0	0	6	2
	12	82	10	72				10 (12)	0	2	0	0	7	1
	26	79	12	67				12 (15)	1	2	0	0	9	0
	52	75	15	60				15 (20)	1	4	0	0	10	0
	78	77	25	52				25 (33)	1	3	0	0	21	0

a Other reasons included: GlucoWatch – inconvenient, time-consuming, did not fit in with lifestyle, too busy, uncomfortable to wear; CGMS – inconvenient, unable to sleep as too uncomfortable, cannot go swimming with monitor on, did not want to wear whilst taking part in sporting activities.

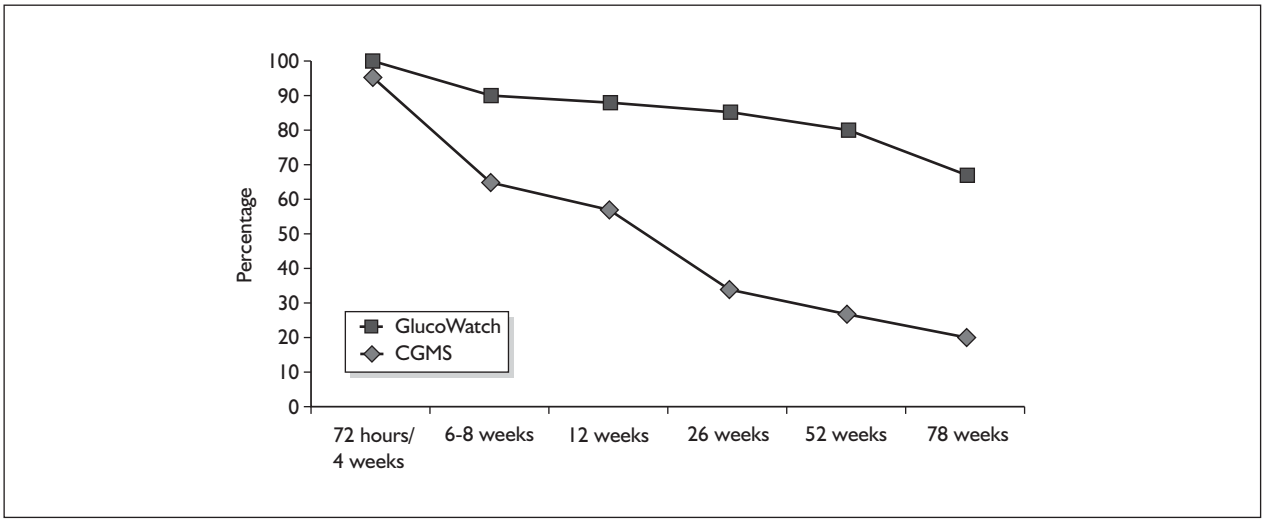

FIGURE 10 *Percentage of participants continuing to use the devices over the course of the study (data relate to those people who attended research visits).*

the number of people reporting skin reactions, the duration of skin problems, the number of people who removed the monitor because of skin problems, the typical MITRE Skin Scale score for those reactions and the number of people reporting severe skin reactions are presented. The majority of the GlucoWatch group reported skin reactions. The median duration of skin problems ranged from 3 to 60 days in this group. A higher MITRE Skin Scale score indicates a greater severity of skin reaction. The median MITRE Skin Scale scores reported in the GlucoWatch group tended to

be higher than those in the CGMS group. No-one in the CGMS group reported a severe skin reaction (MITRE Skin Scale score ≥ 6). The proportion of people reporting severe skin reactions in the GlucoWatch group ranged from 14% to 48%. The number of people removing the device because of skin reactions provides an indicator of how willing participants were to tolerate skin reactions. In the GlucoWatch group the proportion of people removing the device at each time point because of skin problems ranged from 9% to 23%.

Secondary data analysis: factors associated with use of the devices

As part of an exploratory secondary data analysis, four factors assessed at baseline and agreed a priori (age, sex, type of diabetes and fear of hypoglycaemia) were examined to see if there were differences in the level of use of the two devices during the intensive phase of the study (0–3 months) according to these factors. For these analyses, the distributions for the frequency of use data were examined to determine appropriate categories of use. The following categories were applied: CGMS worn one or two times versus three times; GlucoWatch worn one or two times, three to six times, 7–15 times or ≥ 16 times. Chi-squared tests, ANOVAs and *t*-tests were used to perform these analyses. There were no significant differences in frequency of use according to any of these factors. In the GlucoWatch group, those in the highest use group (worn 16 times or more during phase 1) reported the highest scores on the fear of hypoglycaemia scale, indicating greater fear, but this was not statistically significant (data not presented here).

Side effects, interference with lifestyle and impact of wearing the monitors during phase 1 (0–3 months)

This section presents the results of the analysis of the acceptability data collected at 3 months' follow-up, that is, after completion of phase 1, the intensive part of the study. A total of 10 participants (six GlucoWatch, four CGMS) did not wear the devices at any point during the study, and so it was not appropriate for them to complete the acceptability questionnaire as the questions are based on use of the devices. In addition, 43 participants (23 GlucoWatch, 20 CGMS) did not complete the acceptability questionnaire at 3 months' follow-up. For these reasons the valid numbers in the following analyses do not correspond to those for the analyses on HbA1c and monitor use, as detailed previously.

Side effects

Participants were asked whether they had experienced any of nine specific side effects. If they answered 'yes' to any of these questions, they were then asked to rate how acceptable these side effects were to them. *Tables 33* and *34* show the numbers of people reporting each of the nine side effects and their acceptability ratings for both devices respectively.

In total, 63% (48/76) of the CGMS group and 97% (69/71) of the GlucoWatch group reported at least one side effect. In the CGMS group 17% (8/48) of those who reported one or more side effect rated at least one of these as 'not at all acceptable'. The figure for the GlucoWatch group was 63% (44/71).

The relationships between the percentage of each device group experiencing side effects and the number of times that each device was worn are shown in *Figures 11* and *12* respectively; there would appear to be no relationship for the GlucoWatch but a suggestion of an increase in the percentage of the device group experiencing side effects with an increase in the number of times that the device was worn in the case of the CGMS.

Interference with lifestyle

Participants were asked to rate on a five-point Likert scale the extent to which wearing the device interfered with their normal activities. If they reported interference, they were asked to rate how acceptable this was to them.

For example: 'When wearing the monitor it interfered with my normal washing (e.g. bath/showering) routine not at all, a little, moderately, a lot, completely'. 'I found this not at all acceptable, slightly acceptable, moderately acceptable, very acceptable, completely acceptable'.

Participants were asked about nine different activities in total. Participants' responses to each of these questions, in terms of interference, are presented in *Table 35*. Over 45% of the participants in both the CGMS and the GlucoWatch groups stated that wearing the monitor interfered with five of these daily activities (washing, exercise, sleep, work and choice of clothes); washing was the commonest problem reported. Those asked about work are a small subgroup to whom this question was applicable.

TABLE 32 *Skin reactions*

Trial arm	Week number	Wearing device, *n*	Reported skin reaction, *n* (%)	Reported *n*ew reaction, *n*	Duration of skin problems (days), median (IQR)	Removed monitor because of skin problem, *n* (%)	Score of typical skin reaction, median (IQR)[a]	Severe reaction scale ≥ 6, *n* (%)
GlucoWatch	4	81	74 (91)	–	12 (3–28)	17 (23)	2 (1–4)	21 (28)
	8	46	43 (93)	3	18 (7–28)	6 (14)	4 (2–5)	7 (16)
	12	42	41 (98)	2	13 (5–28)	8 (20)	4 (2–5)	11 (27)
	26	24	23 (96)	1	15 (6–60)	2 (9)	4 (2–5)	11 (48)
	52	19	16 (84)	1	14 (5–40)	2 (13)	3 (2–4)	4 (25)
	78	15	14 (93)	0	17 (5–37)	2 (14)	2 (2–4)	2 (14)
CGMS	72 hours	96	13 (14)	–	2 (1–3)	0	1 (1–2)	0
	6	83	6 (7)	6	3 (1–4)	0	1 (1–3)	0
	12	72	5 (7)	3	3 (2–4)	0	0 (0–3)	0
	26	67	5 (7)	5	3 (2–6)	0	1 (0–1)	0
	52	60	2 (3)	1	5 (3–6)	0	4 (2–5)	0
	78	52	3 (6)	3	3 (1–3)	0	1 (1–2)	0

IQR, interquartile range.
a Redness and lumpiness.

TABLE 33 *Number of CGMS participants reporting side effects and their acceptability ratings in phase 1 (0–3 months)*

			Acceptability of side effect				
	Not reporting side effect, *n* (%)	**Reporting side effect, *n* (%)**	**Not at all acceptable, *n* (%)**	**Slightly acceptable, *n* (%)**	**Moderately acceptable, *n* (%)**	**Very acceptable, *n* (%)**	**Completely acceptable, *n* (%)**
Itching	50 (66)	26 (34)	1 (1)	9 (12)	7 (9)	3 (4)	6 (8)
Tingling	73 (96)	3 (4)	0	3 (4)	0	0	0
Soreness	58 (76)	18 (24)	3 (4)	6 (8)	7 (9)	0	2 (3)
Dry skin	71 (93)	5 (7)	1 (1)	0	4 (5)	0	0
Red marks	50 (66)	26 (34)	2 (3)	4 (5)	8 (11)	4 (5)	8 (11)
Discomfort	50 (66)	26 (34)	2 (3)	10 (13)	9 (12)	2 (3)	3 (4)
Bruising	68 (90)	8 (11)	3 (4)	2 (3)	1 (1)	1 (1)	1 (1)
Pain	65 (86)	11 (14)	2 (3)	5 (7)	2 (3)	2 (3)	0
Blisters	71 (93)	5 (7)	1 (1)	2 (3)	2 (3)	0	0

TABLE 34 *Number of GlucoWatch participants reporting side effects and their acceptability ratings in phase 1 (0–3 months)*

			Acceptability of side effect				
	Not reporting side effect, *n* (%)	**Reporting side effect, *n* (%)**	**Not at all acceptable, *n* (%)**	**Slightly acceptable, *n* (%)**	**Moderately acceptable, *n* (%)**	**Very acceptable, *n* (%)**	**Completely acceptable, *n* (%)**
Itching	5 (7)	66 (93)	22 (31)	27 (38)	15 (21)	0	2 (3)
Tingling	24 (34)	47 (66)	9 (13)	25 (35)	8 (11)	1 (1)	4 (6)
Soreness	19 (27)	52 (73)	25 (35)	19 (27)	7 (10)	0	1 (1)
Dry skin	29 (42)	40 (58)	11 (16)	18 (26)	7 (10)	2 (3)	2 (3)
Red marks	5 (7)	66 (93)	28 (39)	22 (31)	12 (17)	0	4 (6)
Discomfort	18 (25)	53 (75)	20 (28)	22 (31)	10 (14)	0	1 (1)
Bruising	54 (76)	17 (24)	6 (8)	3 (4)	5 (7)	1 (1)	2 (3)
Pain	35 (49)	36 (51)	13 (18)	12 (17)	10 (14)	0	1 (1)
Blisters	25 (35)	46 (65)	26 (37)	12 (17)	6 (8)	1 (1)	1 (1)

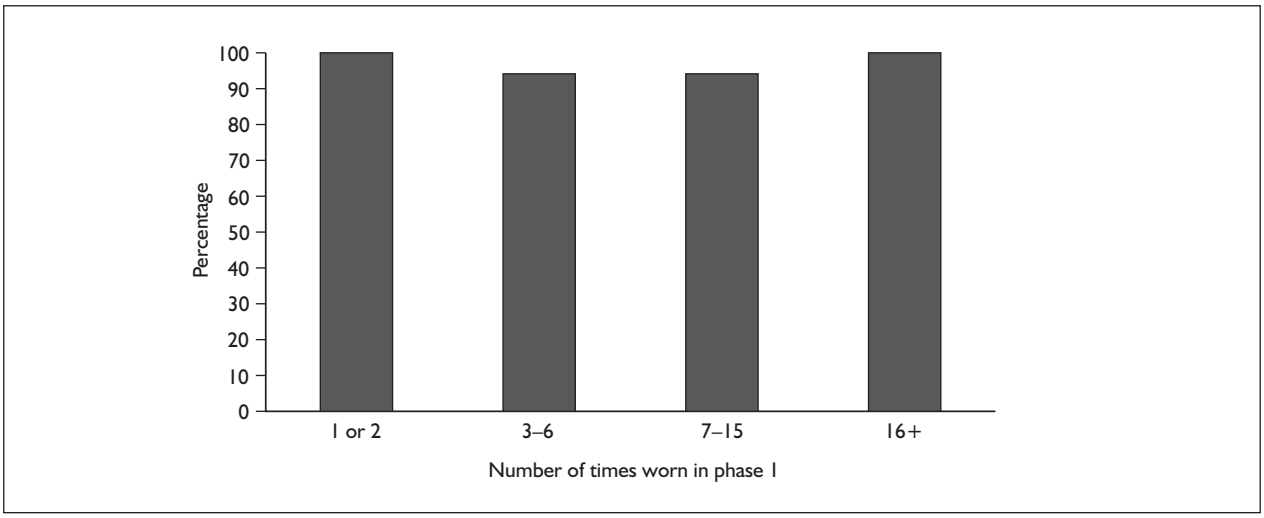

FIGURE 11 *Percentage of GlucoWatch group experiencing side effects by number of times worn.*

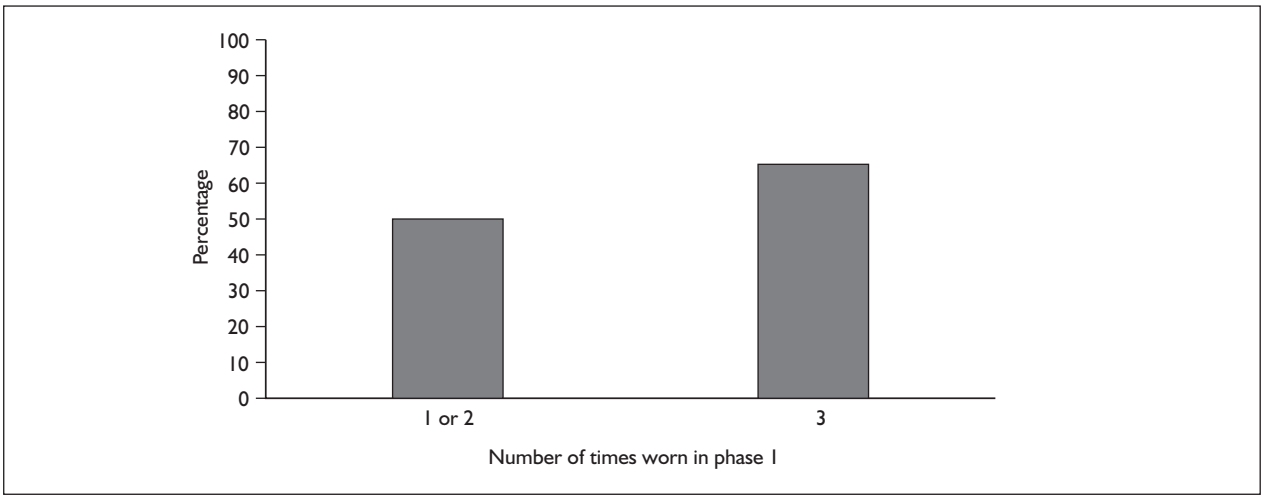

FIGURE 12 *Percentage of CGMS group experiencing side effects by number of times worn.*

As the data were not normally distributed, non-parametric Mann–Whitney U-tests were performed to examine whether the CGMS and GlucoWatch groups differed in their interference ratings (*Table 36*).

The GlucoWatch group participants had significantly greater interference with their skin care routine and work than the CGMS group participants. The CGMS group had significantly more problems regarding mobility.

Participants' responses to each of the nine questions, in terms of acceptability of interference, are presented in *Table 37*.

The percentage of people in the GlucoWatch group who rated the device's interference with lifestyle as 'not at all acceptable' ranged from 6% to 22%, with the highest proportion (22%) giving that rating for exercise. In the CGMS group those rating the device's interference with lifestyle as 'not at all acceptable' ranged from 0% to 11%. Once again, exercise was the aspect of lifestyle for which the highest proportion of people gave that rating. As the data were not normally distributed, non-parametric Mann–Whitney U-tests were performed to examine whether the CGMS and GlucoWatch groups differed in their ratings of acceptability (*Table 38*).

The GlucoWatch group reported significantly poorer acceptability ratings for the interference they experienced with their washing routines than did the CGMS group. That is, they were less willing to tolerate this interference than the CGMS group.

TABLE 35 *Ratings of degree of interference with normal activities*

	Not at all, *n* (%)	A little, *n* (%)	Moderately, *n* (%)	A lot, *n* (%)	Completely, *n* (%)	Total, *n*
Washing routine						
GlucoWatch	15 (22)	16 (24)	13 (19)	17 (25)	7 (10)	68
CGMS	11 (14)	24 (31)	23 (30)	17 (22)	3 (4)	78
Skin care routine						
GlucoWatch	30 (45)	12 (18)	11 (16)	13 (19)	1 (2)	67
CGMS	53 (68)	13 (17)	8 (10)	4 (5)	0	78
Exercise routine						
GlucoWatch	8 (25)	8 (25)	4 (13)	5 (16)	7 (22)	32
CGMS	13 (34)	10 (26)	4 (11)	7 (18)	4 (11)	38
Daily travel						
GlucoWatch	51 (75)	9 (13)	3 (4)	4 (6)	1 (2)	68
CGMS	65 (83)	9 (12)	2 (3)	2 (3)	0	78
Sleep						
GlucoWatch	21 (33)	22 (35)	6 (10)	10 (16)	4 (6)	63
CGMS	28 (36)	30 (39)	13 (17)	7 (9)	0	78
Mobility						
GlucoWatch	49 (71)	12 (17)	3 (4)	2 (3)	3 (4)	69
CGMS	25 (32)	34 (44)	14 (18)	5 (6)	0	78
Social life						
GlucoWatch	42 (64)	14 (21)	5 (8)	4 (6)	1 (2)	66
CGMS	53 (68)	15 (19)	6 (8)	3 (4)	1 (1)	78
Work						
GlucoWatch	14 (40)	10 (29)	4 (11)	6 (17)	1 (3)	35
CGMS	21 (51)	18 (44)	2 (5)	0	0	41
Choice of clothes						
GlucoWatch	29 (42)	26 (38)	9 (13)	3 (4)	2 (3)	69
CGMS	40 (51)	26 (33)	5 (6)	6 (8)	1 (1)	78

Change in normal activities

Participants were asked whether they changed any of their normal activities when wearing the monitor.

For example: 'When I was wearing the monitor I changed my normal exercise routine not at all, sometimes, always'.

Chi-squared tests were carried out to see if participants in the two device arms of the study responded differently to the questions about changes in normal routine. *Table 39* compares those who felt that they made no changes to their normal routine ('not at all') with those who made some changes ('sometimes' and 'always' categories).

Compared with the GlucoWatch group, more people in the CGMS group answered that they did not change their normal travel routine when wearing the device. There were no other differences between the groups.

Because the fitting and wearing of the GlucoWatch is under the control of the participant, some of the questionnaire items on the acceptability measure

TABLE 36 *Mann–Whitney U-test: group comparison of interference with normal activities*

	Valid, *n*	Mean rank	Mann–Whitney U-test	*p*-value
Washing routine				
GlucoWatch	68	74.5	2583	0.78
CGMS	78	72.6		
Skin care routine				
GlucoWatch	67	83.9	1881	0.01
CGMS	78	63.6		
Exercise routine				
GlucoWatch	32	38.4	515	0.26
CGMS	38	33.1		
Daily travel				
GlucoWatch	68	77.1	2410	0.18
CGMS	78	70.4		
Sleep				
GlucoWatch	63	74.6	2230	0.32
CGMS	78	68.1		
Mobility				
GlucoWatch	69	59.6	1700	0.00
CGMS	78	86.7		
Social life				
GlucoWatch	66	74.3	2453	0.57
CGMS	78	71.0		
Work				
GlucoWatch	35	43.5	541	0.05
CGMS	41	34.2		
Choice of clothes				
GlucoWatch	69	77.8	2430	0.27
CGMS	78	70.7		

were specific to this group. The GlucoWatch group was asked how often they avoided wearing the device in particular situations (*Table 40*). Over 50% were found to avoid wearing the GlucoWatch to some extent while exercising and between 40% and 50% avoided wearing it, at least to some extent, while sleeping, going out socially, at work and travelling. For the remaining items ('going out for long periods of time', 'eating out' and 'meeting people I didn't know') between 30% and 40% of participants avoided wearing the GlucoWatch to some extent in these situations.

In *Table 41* participant responses to the questionnaire items about the alarm feature, which was only available on the GlucoWatch, are presented.

Slightly higher proportions of participants responded positively rather than negatively to the five questionnaire items on the GlucoWatch alarms. For example, 54% of the group agreed to some extent with the statement 'I found the alarms for hypoglcyaemia were useful' whereas 32% disagreed to some extent. Overall, the data indicate a mixed response to the alarm feature on this device. It

TABLE 37 *Acceptability ratings of interference with lifestyle*

	Total, *n*	Completely, *n* (%)	Very, *n* (%)	Moderately, *n* (%)	Slightly, *n* (%)	Not at all, *n* (%)
Washing routine						
GlucoWatch	68	19 (28)	3 (4)	14 (21)	10 (15)	7 (10)
CGMS	78	34 (44)	4 (5)	19 (24)	8 (10)	2 (3)
Skin care routine						
GlucoWatch	67	1 (1)	2 (3)	15 (22)	15 (22)	5 (7)
CGMS	78	1 (1)	2 (3)	13 (17)	8 (10)	1 (1)
Exercise routine						
GlucoWatch	32	0	0	13 (41)	5 (16)	7 (22)
CGMS	38	2 (5)	0	7 (18)	12 (32)	4 (11)
Daily travel						
GlucoWatch	68	0	2 (3)	7 (10)	5 (7)	4 (6)
CGMS	78	0	2 (3)	7 (9)	3 (4)	1 (1)
Sleep						
GlucoWatch	63	2 (3)	4 (6)	17 (27)	13 (21)	7 (11)
CGMS	78	1 (1)	7 (9)	25 (32)	15 (19)	2 (3)
Mobility						
GlucoWatch	69	2 (3)	3 (4)	10 (14)	2 (3)	4 (6)
CGMS	78	3 (4)	11 (14)	23 (29)	15 (19)	1 (1)
Social life						
GlucoWatch	66	2 (3)	3 (5)	12 (18)	4 (6)	4 (6)
CGMS	78	0	6 (8)	12 (15)	6 (8)	1 (1)
Work						
GlucoWatch	35	0	5 (14)	8 (23)	5 (14)	4 (11)
CGMS	41	1 (2)	8 (20)	6 (15)	5 (12)	0
Choice of clothes						
GlucoWatch	69	3 (4)	7 (10)	15 (22)	12 (17)	4 (6)
CGMS	78	2 (3)	10 (13)	13 (17)	11 (14)	2 (3)

Note: Percentages are reported for the total group wearing the device and so they do not add up to 100%.

is possible that the alarm may never have been triggered for some participants and therefore they had no first-hand experience of the alarm feature. This may, in part, explain the fairly high proportion of respondents who marked 'neither agree nor disagree' for these questions.

Impact of wearing the monitor

Participants were asked to complete a 33-item questionnaire that related more generally to the impact of wearing the monitor. For each of the 33 statements they were asked to indicate the extent to which they agreed or disagreed on a five-point Likert scale. The positively worded items were reverse scored so that a higher score meant a more negative impact from wearing the device.

Principal components analysis

A principal components analysis (PCA) was conducted to examine the factor structure of this questionnaire. PCA is a factor analytic technique that assists in detecting structure in the relationships between variables (questionnaire items) and thereby allows a reduction of the

TABLE 38 *Mann–Whitney U-test: between-group comparison of acceptability ratings of interference during phase 1 (applies to subgroup who answered that they had experienced some degree of interference)*

	Valid, *n*	Mean rank	Mann–Whitney U-test	*p*-value
Washing routine				
GlucoWatch	53	53.1	1383	0.03
CGMS	67	66.4		
Skin care routine				
GlucoWatch	38	29.5	381	0.15
CGMS	25	35.8		
Exercise routine				
GlucoWatch	25	25.7	308	0.92
CGMS	25	25.3		
Daily travel				
GlucoWatch	18	14.6	91	0.27
CGMS	13	18.0		
Sleep				
GlucoWatch	43	43.2	913	0.18
CGMS	50	50.2		
Mobility				
GlucoWatch	21	36.3	531	0.74
CGMS	53	38.0		
Social life				
GlucoWatch	25	24.6	290	0.64
CGMS	25	26.4		
Work				
GlucoWatch	22	18.4	152	0.07
CGMS	20	24.9		
Choice of clothes				
GlucoWatch	41	38.4	715	0.51
CGMS	38	41.7		

number of variables. A PCA of this section of the questionnaire indicated a three-factor solution that included 24 items and accounted for 42% of the variance. The components were:

- Factor 1: Ease of use, practicality (10 items, scored 0–50). Example items:
  - I could not always enter information into the machine as instructed to
  - I found the use of the monitor required careful planning.
- Factor 2: Value of the device, improvement in glycaemic control (eight items, scored 0–40). Example items:
  - Wearing the monitor has helped me reduce the number of hypoglycaemic episodes I experience
  - I would be interested in using the machine in the future.
- Factor 3: Appearance, self-consciousness, disclosure (six items, scored 0–30). Example items:

TABLE 39 *Changes in normal routine*

	Number answering 'not at all' (%)	Pearson chi-squared test	df	*p*-value
Exercise				
GlucoWatch	24 (64.9)	1.04	1	0.307
CGMS	18 (52.9)			
Travel				
GlucoWatch	73 (97.3)	Fisher's exact test, $p < 0.001$		
CGMS	45 (71.4)			
Sleep				
GlucoWatch	58 (78.4)	2.37	1	0.124
CGMS	42 (66.7)			
Social life				
GlucoWatch	61 (83.6)	3.62	1	0.057
CGMS	44 (69.8)			
Work				
GlucoWatch	35 (85.4)	1.31	1	0.252
CGMS	27 (75.0)			

TABLE 40 *Number of participants who avoided wearing the monitor in particular situations (GlucoWatch group)*

	Not at all, *n* (%)	Sometimes, *n* (%)	Always, *n* (%)	Total, *n*
Exercising	14 (41.2)	9 (26.5)	11 (32.4)	34
Travelling	37 (59.7)	17 (27.4)	8 (12.9)	62
Sleeping	31 (50.0)	17 (27.4)	14 (22.6)	62
Going out socially	32 (53.3)	13 (21.7)	15 (25.0)	60
At work	19 (52.8)	10 (27.8)	7 (19.4)	36
Meeting people I didn't know	43 (69.4)	8 (12.9)	11 (17.7)	62
Going out for long periods of time	38 (61.3)	9 (14.5)	15 (24.2)	62
Eating out	35 (61.4)	11 (19.3)	11 (19.3)	57

- I felt more self-conscious of my appearance when I was wearing the monitor
- I was happy to explain what the monitor was to anyone who asked.

There were nine redundant items in total. The authors would recommend omitting these nine items in future work with this questionnaire. The complete list of questionnaire items and their factor loadings is provided in Appendix 9.

The two devices were compared on each of these three factors using *t*-tests (*Table 42*). The mean scores for each device on each subscale of the questionnaire are also displayed in *Figure 13*.

Summary

Overall, the CGMS was more acceptable to participants than the GlucoWatch in terms of both discontinuation rates and interference with lifestyle. It is notable that many participants continued to use both of these devices despite reporting significant interference with daily living. The use of these devices in the face of significant

TABLE 41 *Alarms (GlucoWatch group)*

	Strongly disagree, *n* (%)	Slightly disagree, *n* (%)	Neither agree nor disagree, *n* (%)	Slightly agree, *n* (%)	Strongly agree, *n* (%)
Item 34: I found the alarms for hypoglycaemia were useful	9 (13.2)	13 (19.1)	9 (13.2)	16 (23.5)	21 (30.9)
Item 35: I thought the alarm for hypoglycaemia was accurate	12 (17.6)	11 (16.2)	13 (19.1)	16 (23.5)	16 (23.5)
Item 36: I found it embarrassing when the alarm sounded at work	13 (35.1)	4 (10.8)	8 (21.6)	12 (32.4)	0
Item 37: I did not find the alarms for high blood sugar useful	16 (23.2)	14 (20.3)	19 (27.5)	10 (14.5)	10 (14.5)
Item 38: I did not think the alarms for high blood sugar were accurate	15 (21.7)	10 (14.5)	30 (43.5)	8 (11.6)	6 (8.7)

TABLE 42 *Comparison of mean scores on the subscales of the impact questionnaire*

Subscales	Valid, *n*	Mean score (SD)	*t*-value	df	*p*-value
Ease of use					
GlucoWatch	69	33.4 (8.2)	–9.3	145	0.000
CGMS	78	21.8 (6.9)			
Value of device					
GlucoWatch	69	23.1 (8.3)	–2.6	130	0.010
CGMS	78	19.9 (6.7)			
Appearance, self-consciousness, disclosure					
GlucoWatch	69	13.0 (4.8)	–9.6	145	0.339
CGMS	78	12.2 (4.8)			

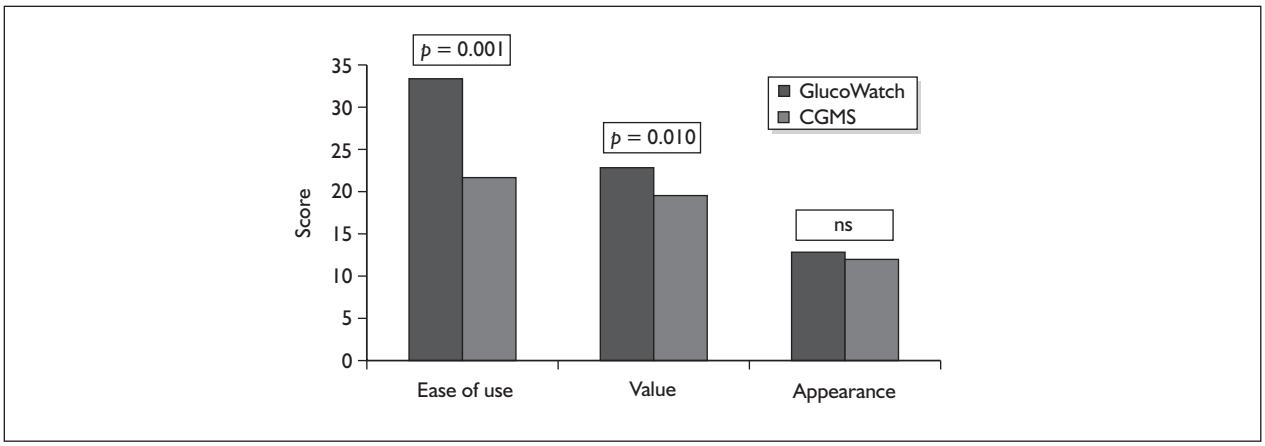

FIGURE 13 *Mean scores on the subscales of the impact questionnaire (higher scores indicate a more negative impact from wearing the device). ns, not significant.*

interference suggests that this is balanced by patients' perceptions of the potential value or importance of the devices in their care. This study demonstrates that it is possible to assess the relative acceptability of devices in diabetes. This is a crucial aspect in determining whether a device can be routinely incorporated into diabetes management.

Chapter 6
Psychological self-report data

At the outset of the study it was planned to assess differences over time between the trial arms on a number of psychological measures. Thus, a decision was made to focus on the 203 participants who had completed self-report questionnaires at all time points. An initial comparison, however, was made of the demographic, clinical and psychological variables between those participants who completed questionnaires at all time points ($n = 203$) and those who did not ($n = 201$) (*Tables 43* and *44*). When categories of particular variables have been collapsed to perform the analysis, these are numbered in *Table 43*.

Treatment of missing data

Very few participants had missing data on any of the measures, and there was no discernible pattern to the items that were missed. For example, on the Personal Models of Diabetes Questionnaire,[114] at baseline three participants had missed one item. At 3 months' follow-up four participants had missed one item. At the 6-month assessment point five participants had missed one item and one had missed nine items on the questionnaire. At 12 months' follow-up three participants had missed one item and one participant had missed two items. Finally, at 18 months' follow-up four participants had missed one item. In the case of the self-reported questionnaire measures, when participants had missing data for 50% or less of the items on a particular scale or subscale, the mean was imputed for that individual from the items that they had completed. The diabetes-specific locus of control scale (ADDLoC) provided by Bradley *et al.*[108] included all 24 items, but questionnaires were retyped by the present study team; and item 15 (an item from the internality subscale) was omitted in error from all of the questionnaire packs. Item 15 is one of six items on the internality subscale. The mean of the other five items on that subscale was used to impute missing data for item 15.

Statistically significant differences between the completers and non-completers are in bold text in *Table 43*. The group who completed questionnaires at all time points was significantly older, and had a significantly lower baseline HbA1c value and a higher proportion of people with macrovascular complications than the group who missed one or more questionnaire assessments. The number of daily injections was recoded into two injections per day, three plus or pump. There were less people on three or more injections per day in the group completing questionnaires at all time points, although this is likely to be related to the difference in age between the two groups. The Gateshead centre appeared to have a higher proportion of people who completed questionnaires at all time points than the other centres. There were no other statistically significant differences between the groups.

A small number of outliers, i.e. people with extreme scores on particular questionnaire measures, was identified. The number of outliers was small, with the highest on the ADDQoL ($n = 6$). This small group of participants scored the maximum negative impact (–9.0) on this diabetes-specific quality of life scale. The statistical comparison of participants who completed questionnaires at all time points and participants who did not was performed with and without outliers. No differences were found between these analyses, hence a decision was made to include outliers in further analyses.

Non-completers were significantly less satisfied with their diabetes treatment, reported slightly poorer diabetes-specific quality of life and exercised on significantly less days at baseline. The possible range of treatment satisfaction scores is from 0 to 36 and both groups scored towards the upper end of this range. Similarly, the mean number of days that participants reported exercising at baseline, although statistically significant, was arguably not meaningfully different between the groups (2.7 versus 3.3 days). The groups were not significantly different at baseline on any of the other psychological measures (*Table 44*). The specific diet subscale of the SDSCA measure comprises two items although, in accordance with the scale authors' recommendation, these were analysed separately here because of low correlations between them, both amongst the total group ($r = –0.02$) and amongst the group who completed questionnaires at all time points ($r = –0.06$).

TABLE 43 *Baseline demographic and clinical characteristics of participants who did and did not complete self-report questionnaire measures at all time points*

	Completers	Non-completers	*t*-value or χ^2	df	*p*-value
n	203	201			
Age (years)	54 (14)	49 (15)	–3.6	402	0.000
Duration of diabetes (years)	18 (12)	18 (11)	0.1	402	0.887
Years on insulin	15 (13)	16 (12)	0.7	402	0.461
Body mass index (kg/m^2)	29 (6)	29 (6)	–0.7	401	0.500
Systolic blood pressure (mmHg)	134 (17)	132 (19)	–0.8	402	0.410
Diastolic blood pressure (mmHg)	77 (10)	78 (10)	0.6	402	0.519
Waist circumference (cm)	98 (16)	95 (17)	–1.9	399	0.060
HbA1c (%)	9.0 (1.1)	9.3 (1.4)	2.5	399	0.013
Female, *n* (%)	87 (43)	96 (48)	1.0	1	0.322
Type of diabetes, *n* (%)					
Type 1	109 (54)	123 (61)	2.6	1	0.109
Type 2	91 (45)	74 (37)			
Other	3 (2)	4 (2)			
Ethnicity, *n* (%)					
White	189 (93)	168 (84)			
Asian	6 (3)	14 (7)			
Black	6 (3)	13 (7)			
Other	2 (1)	6 (3)			
Employment status, *n* (%)					
Full-time	71 (35)	83 (41)	1.4	1	0.233
Part-time	23 (11)	22 (11)			
Looking after house/family	3 (2)	12 (6)			
Permanently sick/disabled	29 (14)	21 (10)			
Retired	65 (32)	44 (22)			
Student	4 (2)	5 (3)			
Unemployed	8 (4)	14 (7)			
Education, *n* (%)					
Degree, equivalent or higher	40 (20)	49 (24)	0.5	1	0.489
Other higher education	24 (12)	22 (11)			
A-levels or equivalent	27 (13)	26 (13)			
Trade apprenticeship	45 (22)	48 (24)			
Level 1 qualifications and below	12 (6)	12 (6)			
Other qualifications: level unknown	9 (4)	3 (2)			
No qualifications	46 (23)	41 (20)			

TABLE 43 *Baseline demographic and clinical characteristics of participants who did and did not complete self-report questionnaire measures at all time points (continued)*

	Completers	Non-completers	*t*-value or χ^2	df	*p*-value
Social class, *n* (%)					
Managerial and professional	75 (38)	90 (46)	3.3	1	0.069
Intermediate	22 (11)	24 (12)			
Small employers and own account	27 (14)	21 (11)			
Lower supervisory and technical	38 (19)	30 (15)			
Semiroutine and routine	37 (19)	32 (16)			
Centre, *n* (%)					
Bournemouth	34 (17)	53 (26)	23.4	3	0.000
Gateshead	77 (38)	35 (17)			
UCLH	61 (30)	66 (33)			
Whittington	31(15)	47 (23)			
Trial arm, *n* (%)					
Standard care control	51 (25)	51 (25)			
Attention control	56 (28)	44 (22)			
CGMS	55 (27)	47 (23)			
GlucoWatch	41 (20)	59 (29)			
Number of injections per day, *n* (%)					
Two	90 (44)	69 (34)	4.2	1	0.040
Three or more	111 (55)	125 (63)			
Pump	2 (1)	7 (4)			
Presence of macrovascular complications, *n* (%)	125 (62)	98 (49)	6.7	1	0.010
Presence of microvascular complications, *n* (%)	114 (56)	116 (58)	1.0	1	0.752
Number diagnosed with (number affected moderately or a great deal)					
Respiratory disease	36 (21)	31 (13)			
Stroke	8 (2)	13 (6)			
Neurological disease	4 (3)	7 (3)			
Heart disease	46 (23)	30 (12)			
Arthritis	67 (38)	48 (26)			
Cancer	9 (2)	10 (3)			
High blood pressure	105 (19)	87 (15)			
Kidney disease	12 (2)	16 (5)			
Number of admissions with DKA/HONK	0	2			
Number of admissions with hypoglycaemia	0	2			
Number of admissions with hyperglycaemia	1	0			

DKA/HONK, diabetic ketoacidosis/hyperosmolar non-ketotic acidosis.

TABLE 44 *Baseline psychological characteristics of participants who did and did not complete self-report questionnaire measures at all time points*

Questionnaire measure (score range)	*n*	Completers	Non-completers	*t*-value	df	*p*-value
Diabetes-specific quality of life (–9 to +9)	391	–2.4 (1.9)	–2.8 (2.1)	–2.0	389	0.047
Diabetes treatment satisfaction (0–36)	389	28.5 (5.9)	26.7 (7.0)	–2.8	362	0.006
Hypoglycaemia Fear Survey (0–52)	389	19.5 (12.9)	18.9 (12.3)	–0.5	387	0.653
Diabetes–specific locus of control						
Internality (6–36)	390	28.3 (5.2)	28.0 (6.0)	–0.7	388	0.491
Medical others (6–36)	390	21.7 (4.9)	21.5 (4.9)	–0.4	388	0.715
Significant others (6–36)	390	19.9 (5.7)	19.2 (5.6)	–1.2	388	0.229
Chance (6–36)	390	14.5 (7.2)	14.1 (7.2)	–0.6	388	0.548
Personal Models of Diabetes						
Seriousness of diabetes (4–20)	391	12.5 (3.3)	13.2 (3.3)	1.8	389	0.067
Treatment effectiveness (6–30)	391	23.2 (3.9)	23.2 (3.4)	0	389	0.998
Summary of Diabetes Self-Care Activities (mean number of days over last week)						
General diet	390	4.7 (2.0)	4.8 (1.8)	0.8	388	0.423
Specific diet (eating five or more portions of fruit and vegetables per day)	389	4.7 (2.1)	4.4 (2.3)	–1.3	387	0.199
Specific diet (eating high-fat foods every day)	389	2.7 (1.8)	2.8 (2.0)	–0.4	387	0.673
Exercise	390	3.3 (2.3)	2.7 (2.0)	–2.5	387	0.012
Testing blood glucose daily, *n* (%)	391	102 (50)	110 (59)	$\chi^2 = 2.7$	1	0.101

Group who completed questionnaires at all time points: comparison of baseline demographic, clinical and psychological data between the four trial arms

In the group who completed questionnaires at every assessment point, the four trial arms were very similar in terms of their baseline demographic, clinical and psychological characteristics (*Tables 45* and *46*). There were no statistically significant differences at baseline between the trial arms on any of the factors that were assessed.

Repeated measures ANOVAs were conducted to assess the impact of the continuous glucose monitoring devices on each of the psychological variables throughout the study period. Descriptive statistics for each of these variables are displayed in *Table 47*. The repeated measures ANOVA results are displayed in *Table 48*. The standard care control group was not assessed at the end of phase 1 (3 months' follow-up), hence two sets of analyses were conducted for each psychological variable: one including data from the attention control, CGMS and GlucoWatch groups at baseline and 3 months' follow-up; and one using data from all of the groups at baseline and at 6, 12 and 18 months' follow-up. The exception to this were the analyses carried out on the diabetes-specific locus of control (ADDLoC) subscales for which data were only collected at baseline and at 3 months. In this case, one repeated measures ANOVA was conducted for each of the four ADDLoC subscales.

There was a main effect for time on the Hypoglycaemia Fear Survey, with post hoc tests showing that the attention control and the two device groups reported significantly less fear of hypoglycaemia at 3 months than at baseline, and all of the groups reporting less fear of hypoglycaemia at 12 months than at baseline (mean difference 2.0, $p = 0.021$). There was a main effect for time on the internality subscale of the diabetes-specific locus of control measure. Scores on this subscale reduced from baseline to 3 months for the attention control group and the two device

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TABLE 45 *Group who completed questionnaires at all time points (n = 203): comparison of baseline demographic and clinical characteristics between the four trial arms*

	Standard care control	Attention control	CGMS	GlucoWatch	F-statistic or χ^2	df	*p*-value
n	51	56	55	41			
Age (years)	53 (14)	56 (13)	55 (14)	53 (15)	0.7	3	0.563
Duration of diabetes (years)	18 (11)	20 (13)	17 (11)	17 (12)	0.9	3	0.460
Years on insulin	14 (12)	17 (14)	15 (12)	13 (12)	0.7	3	0.558
Body mass index (kg/m^2)	29 (5)	29 (6)	30 (6)	29 (5)	1.0	3	0.411
Systolic blood pressure (mmHg)	136 (18)	132 (16)	134 (14)	132 (19)	0.5	3	0.670
Diastolic blood pressure (mmHg)	79 (10)	77 (9)	78 (10)	74 (10)	2.0	3	0.119
Waist circumference (cm)	96 (17)	96 (16)	102 (15)	99 (18)	1.4	3	0.234
HbA1c (%)	9.3 (1.3)	8.8 (0.9)	8.9 (1.0)	9.0 (8.6)	1.9	3	0.131
Female, *n* (%)	21 (41)	25 (45)	22 (40)	19 (46)	0.5	3	0.915
Type of diabetes, *n* (%)							
Type 1	28 (55)	30 (54)	31 (56)	20 (49)	0.4	3	0.930
Type 2	22 (43)	25 (45)	24 (44)	20 (49)			
Other	1 (2)	1 (2)	0	1 (2)			
Ethnicity, *n* (%)							
White	46 (90)	54 (96)	51 (93)	38 (93)			
Asian	2 (4)	1 (2)	0	3 (7)			
Black	2 (4)	1 (2)	3 (6)	0			
Other	1 (2)	0	1 (2)	0			
Employment status, *n* (%)							
Full-time	15 (29)	19 (34)	26 (47)	11 (27)	1.8	3	0.611
Part-time	8 (16)	7 (13)	3 (6)	5 (12)			
Looking after house/family	1 (2)	1 (2)	1 (2)	0			
Permanently sick/disabled	8 (16)	8 (14)	4 (7)	9 (22)			
Retired	15 (29)	19 (34)	18 (33)	13 (32)			

continued

TABLE 45 *Group who completed questionnaires at all time points (n = 203): comparison of baseline demographic and clinical characteristics between the four trial arms (continued)*

	Standard care control	Attention control	CGMS	GlucoWatch	F-statistic or χ^2	df	*p*-value
Student	2 (4)	0	0	2 (5)			
Unemployed	2 (4)	2 (4)	3 (6)	1 (2)			
Education, *n* (%)							
Degree, equivalent or higher	11 (22)	14 (25)	9 (16)	6 (15)	3.0	3	0.393
Other higher education	6 (12)	4 (7)	6 (11)	8 (20)			
A-levels or equivalent	4 (8)	3 (5)	13 (24)	7 (17)			
Trade apprenticeships	12 (24)	11 (20)	13 (24)	9 (22)			
Level 1 qualifications and below	3 (6)	5 (9)	3 (6)	1 (2)			
Other: level (unknown)	3 (6)	2 (4)	2 (4)	2 (5)			
No qualifications	12 (24)	17 (30)	9 (16)	8 (20)			
Social class, *n* (%)							
Managerial and professional	18 (37)	24 (44)	19 (35)	14 (35)	3.2	3	0.356
Intermediate	6 (12)	8 (15)	4 (7)	4 (10)			
Small employers and own account	8 (16)	7 (13)	8 (15)	4 (10)			
Lower supervisory and technical	10 (20)	8 (15)	13 (24)	7 (18)			
Semiroutine and routine	7 (14)	8 (15)	11 (20)	11 (28)			
Centre, *n* (%)							
Bournemouth	7 (14)	11 (20)	9 (16)	7 (17)	2.6	9	0.977
Gateshead	20 (39)	20 (36)	20 (36)	17 (42)			
UCLH	14 (28)	16 (29)	18 (33)	13 (32)			
Whittington	10 (20)	9 (16)	8 (15)	4 (10)			

	Standard care control	Attention control	CGMS	GlucoWatch	F-statistic or χ^2	df	*p*-value
Number of injections per day, *n* (%)							
Two	25 (49)	21 (38)	25 (46)	19 (46)	1.7	3	0.629
Three or more	26 (51)	35 (63)	28 (51)	22 (53)			
Pump	0	0	2 (4)	0			
Macrovascular complications, *n* (%)	33 (65)	35 (63)	31 (56)	26 (63)	0.9	3	0.820
Microvascular complications, *n* (%)	30 (59)	29 (52)	32 (58)	23 (56)	0.674	3	0.879
Number diagnosed with (number affected moderately or a great deal)							
Respiratory disease	9 (6)	13 (7)	6 (3)	8 (5)			
Stroke	1 (0)	2 (1)	2 (0)	3 (1)			
Neurological disease	2 (2)	2 (1)	0	0			
Heart disease	18 (12)	12 (6)	11 (4)	5 (1)			
Arthritis	17 (14)	21 (9)	17 (8)	12 (7)			
Cancer	2 (0)	4 (1)	2 (1)	1 (0)			
High blood pressure	28 (6)	33 (4)	24 (4)	20 (5)			
Kidney disease	6 (1)	3 (1)	3 (0)	0			
Number of admissions for DKA/HONK	0	0	0	0			
Number of admissions for hypoglycaemia	0	0	0	0			
Number of admissions for hyperglycaemia	0	1	0	0			

DKA/HONK, diabetic ketoacidosis/hyperosmolar non-ketotic acidosis.

TABLE 46 *Group who completed questionnaires at all time points (n = 203): comparison of baseline psychological characteristics between the four trial arms*

Questionnaire measure (score range)	Standard care control	Attention control	CGMS	GlucoWatch	F-statistic or χ^2	df	*p*-value
Diabetes-specific quality of life (–9 to +9)	–2.5 (2.2)	–2.2 (1.7)	–2.5 (2.0)	–2.5 (1.7)	0.4	3	0.768
Diabetes treatment satisfaction (0–36)	27.8 (6.1)	28.8 (5.7)	28.8 (6.2)	28.4 (5.4)	0.3	3	0.819
Hypoglycaemia Fear Survey (0–52)	18.4 (13.0)	18.4 (12.4)	18.8 (12.0)	23.2 (14.2)	1.5	3	0.226
Diabetes-specific locus of control (ADDLoC)							
Internality (6–36)	27.7 (5.6)	28.1 (5.2)	30.0 (4.7)	27.8 (5.2)	1.5	3	0.208
Medical others (6–36)	22.1 (5.2)	21.0 (4.3)	21.7 (4.5)	22.0 (5.6)	0.6	3	0.613
Significant others (6–36)	19.1 (6.3)	19.8 (5.0)	21.0 (6.3)	20.1 (5.1)	0.6	3	0.600
Chance (6–36)	14.9 (7.6)	14.1 (6.9)	14.1 (7.1)	15.3 (7.6)	0.3	3	0.832
Personal Models of Diabetes							
Treatment effectiveness (6–30)	23.3 (3.5)	22.3 (4.2)	23.4 (4.1)	24.0 (3.4)	1.6	3	0.197
Seriousness of diabetes (4–20)	12.9 (3.7)	12.1 (3.3)	12.6 (3.4)	12.5 (3.1)	0.6	3	0.640
Summary of Diabetes Self-Care Activities (mean number of days over last week)							
General diet	4.6 (2.2)	4.8 (2.0)	4.4 (2.3)	5.1 (1.5)	0.9	3	0.424
Specific diet (eating five or more portions of fruit and vegetables per day)	4.2 (2.3)	5.0 (1.9)	4.7 (2.3)	4.9 (1.8)	1.4	3	0.253
Specific diet (eating high-fat foods every day)	2.5 (1.6)	2.8 (2.0)	2.5 (1.8)	2.9 (2.0)	0.6	3	0.592
Exercise	3.5 (2.4)	3.3 (2.4)	3.0 (2.4)	3.3 (2.1)	0.3	3	0.830
Testing blood glucose daily, *n* (%)	26 (51)	30 (54)	27 (49)	19 (46)	0.5	3	0.910

TABLE 47 *Descriptive statistics (mean and standard deviation unless stated) for the psychological variables for each trial arm at each time point*

		Standard care control	Attention control	CGMS	GlucoWatch
Diabetes-specific quality of life	*n*	50	56	55	41
	Baseline	–2.5 (2.2)	–2.2 (1.8)	–2.5 (2.0)	–2.5 (1.7)
	3 months		–2.1 (1.8)	–2.6 (1.9)	–2.5 (1.8)
	6 months	–3.0 (1.9)	–2.1 (1.8)	–2.7 (2.2)	–2.2 (1.8)
	12 months	–3.1 (2.1)	–2.0 (1.6)	–2.8 (2.1)	–2.3 (1.9)
	18 months	–3.0 (2.1)	–2.0 (1.8)	–2.6 (2.1)	–2.6 (2.2)
Hypoglycaemia Fear Survey	*n*	50	56	55	41
	Baseline	18.4 (13.0)	18.4 (12.4)	18.8 (12.0)	23.2 (14.2)
	3 months		16.2 (11.5)	17.4 (12.5)	21.6 (14.8)
	6 months	18.0 (13.3)	17.6 (13.5)	18.4 (13.3)	22.3 (13.5)
	12 months	17.3 (10.6)	16.4 (11.5)	16.7 (12.5)	20.4 (14.6)
	18 months	17.6 (11.7)	16.3 (10.7)	16.2 (12.3)	21.9 (15.6)
Diabetes-specific locus of control					
Internality	*n*		53	54	40
	Baseline		28.3 (5.2)	29.5 (4.8)	27.7 (5.2)
	3 months		26.6 (5.7)	27.7 (5.7)	25.9 (5.8)
Medical others	*n*		53	54	39
	Baseline		20.9 (4.4)	21.9 (4.4)	22.1 (5.8)
	3 months		20.2 (4.3)	21.7 (4.4)	21.4 (4.5)
Significant others	*n*		53	54	39
	Baseline		19.7 (5.1)	20.1 (6.4)	20.2 (5.2)
	3 months		18.8 (5.0)	20.4 (5.6)	20.0 (4.9)
Chance	*n*		53	54	40
	Baseline		13.9 (6.8)	14.0 (7.2)	15.5 (7.5)
	3 months		13.5 (6.3)	14.1 (6.1)	15.0 (7.0)
Personal Models of Diabetes					
Treatment effectiveness	*n*	50	56	55	41
	Baseline	23.3 (3.5)	22.3 (4.2)	23.4 (4.1)	24.0 (3.4)
	3 months		22.9 (3.6)	23.4 (3.5)	23.8 (3.4)
	6 months	24.0 (4.1)	23.1 (3.7)	23.3 (3.4)	24.0 (3.5)
	12 months	23.5 (3.4)	22.8 (3.9)	22.9 (3.9)	23.2 (3.7)
	18 months	23.7 (4.2)	23.1 (4.0)	23.7 (3.8)	23.5 (3.8)
Treatment seriousness	*n*	50	56	55	41
	Baseline	13.0 (3.7)	12.1 (3.3)	12.6 (3.4)	12.5 (3.1)
	3 months		12.1 (3.0)	13.2 (3.1)	12.8 (3.5)
	6 months	13.0 (3.5)	11.9 (3.2)	12.8 (3.3)	12.5 (3.0)
	12 months	13.2 (3.5)	11.9 (3.2)	13.3 (3.3)	13.3 (3.6)
	18 months	13.1 (3.5)	12.0 (2.8)	13.1 (3.4)	13.4 (3.2)

continued

TABLE 47 *Descriptive statistics (mean and standard deviation unless stated) for the psychological variables for each trial arm at each time point (continued)*

		Standard care control	Attention control	CGMS	GlucoWatch
Self-care activities:					
General diet	*n*	51	55	54	40
	Baseline	4.6 (2.2)	4.9 (1.9)	4.4 (2.3)	5.1 (1.5)
	3 months		5.0 (1.9)	4.9 (1.6)	4.5 (1.8)
	6 months	4.9 (1.9)	4.8 (1.8)	4.7 (1.8)	5.2 (1.4)
	12 months	5.0 (1.8)	5.1 (1.6)	4.9 (1.7)	4.6 (1.7)
	18 months	4.6 (1.7)	5.0 (1.8)	5.0 (1.6)	4.8 (1.6)
On how many of the last 7 days did you eat five or more servings of fruit and vegetables?	*n*	51	55	55	40
	Baseline	4.2 (2.3)	5.0 (1.9)	4.7 (2.3)	4.9 (1.8)
	3 months		4.8 (2.0)	4.3 (2.3)	5.2 (2.2)
	6 months	4.3 (2.2)	4.5 (2.0)	4.6 (2.1)	5.2 (1.8)
	12 months	4.3 (2.1)	5.0 (1.9)	4.5 (2.2)	5.2 (2.0)
	18 months	4.5 (2.2)	5.0 (2.3)	4.8 (2.0)	5.1 (1.8)
On how many of the last 7 days did you eat high-fat foods?	*n*	51	55	55	40
	Baseline	2.5 (1.6)	2.8 (2.0)	2.5 (1.8)	2.9 (2.0)
	3 months		3.0 (2.0)	2.3 (1.6)	2.8 (1.9)
	6 months	2.6 (1.5)	3.0 (1.8)	2.6 (1.7)	2.6 (1.6)
	12 months	2.3 (1.4)	2.7 (1.9)	2.4 (1.5)	2.5 (1.6)
	18 months	2.3 (1.4)	2.5 (1.7)	2.4 (1.7)	2.9 (1.8)
On how many of the last 7 days did you exercise?	*n*	50	54	55	41
	Baseline	3.5 (2.4)	3.4 (2.4)	3.0 (2.4)	3.3 (2.1)
	3 months		3.2 (2.4)	2.7 (2.1)	2.6 (2.1)
	6 months	3.4 (2.4)	3.1 (2.2)	2.7 (2.2)	2.9 (1.9)
	12 months	3.1 (2.3)	3.3 (2.4)	2.5 (2.3)	3.0 (1.9)
	18 months	3.2 (2.3)	3.3 (2.4)	3.1 (2.3)	2.9 (1.9)
Testing blood glucose daily, *n* (%)	*n*	49–51	54–56	54–56	40–41
	Baseline	26 (51)	30 (54)	27 (49)	19 (46)
	3 months		40 (71)	33 (60)	29 (73)
	6 months	26 (53)	35 (63)	33 (61)	25 (61)
	12 months	27 (54)	38 (70)	35 (65)	26 (63)
	18 months	26 (51)	39 (71)	32 (58)	22 (54)

groups, indicating less internal locus of control. There were, however, no other effects on the other three locus of control dimensions.

In terms of diabetes self-care behaviours, there was a main effect for time on the exercise subscale with a deterioration in the mean number of days exercised in the attention and two device groups from baseline to 3 months' follow-up. There was an interaction effect for the general diet subscale from baseline to 3 months' follow-up. The GlucoWatch group showed a deterioration in the level of general diet self-care behaviours compared with the CGMS and attention control groups. There was also an interaction effect for general diet from baseline to 12 months' follow-up. Once again, the GlucoWatch group showed a deterioration in the level of general diet self-care behaviours compared with the CGMS, attention control and standard care control groups, who all demonstrated improvements on this measure. There were no other interactions or main effects. A series of chi-

TABLE 48 *Results of repeated measures ANOVAs on psychosocial data*

		df	Sum of squares	Mean square	F-statistic	*p*-value
Diabetes-specific quality of life						
Baseline to 3 months	Time	1, 149	0.047	0.047	0.038	0.845
	Arm	2, 149	9.160	4.580	0.829	0.439
	Time×arm	2, 149	0.275	0.138	0.111	0.895
Baseline to 6, 12 and 18 months	Time	3, 196	2.544	0.845	0.622	0.602
	Arm	3, 198	78.436	26.145	2.205	0.089
	Time×arm	9, 477	8.664	2.074	1.670	0.093
Fear of Hypoglycaemia Survey						
Baseline to 3 months	Time	1, 149	225.242	225.242	5.889	0.016
	Arm	2, 149	1377.924	688.962	2.387	0.095
	Time×arm	2, 149	10.430	5.215	0.136	0.873
Baseline to 6, 12 and 18 months	Time	3, 196	514.464	171.488	3.522	0.016
	Arm	3, 198	2633.933	877.978	1.685	0.171
	Time×arm	9, 477	108.070	12.008	0.343	0.960
Diabetes-specific locus of control						
Internality	Time	1, 144	220.888	220.888	23.451	0.000
	Arm	2, 144	166.114	83.057	1.711	0.184
	Time×arm	2, 144	0.512	0.256	0.027	0.973
Medical others	Time	1, 143	20.286	20.286	2.316	0.130
	Arm	2, 143	92.757	46.378	1.398	0.250
	Time×arm	2, 143	3.914	1.957	0.223	0.800
Significant others	Time	1, 143	14.844	14.844	1.282	0.259
	Arm	2, 143	93.340	46.670	0.992	0.373
	Time×arm	2, 143	9.012	4.506	0.389	0.678
Chance	Time	1, 144	5.088	5.088	0.404	0.526
	Arm	2, 144	115.763	57.881	0.730	0.484
	Time×arm	2, 144	3.961	1.981	0.157	0.855
Personal Models of Diabetes						
Treatment effectiveness						
Baseline to 3 months	Time	1, 149	0.798	0.798	0.224	0.637
	Arm	2, 149	77.143	38.572	1.572	0.211
	Time×arm	2, 149	9.327	4.664	1.307	0.274
Baseline to 6, 12 and 18 months	Time	3, 196	27.809	9.270	2.243	0.085
	Arm	3, 196	92.531	30.844	0.691	0.559
	Time×arm	9, 477	38.206	4.245	0.924	0.504

continued

squared tests were carried out in relation to the SMBG scale. There were no differences in the proportions of people testing daily compared with those testing less than daily between the trial arms at each time point.

TABLE 48 *Results of repeated measures ANOVAs on psychosocial data (continued)*

		df	Sum of squares	Mean square	F-statistic	*p*-value
Treatment seriousness						
Baseline to 3 months	Time	1, 149	6.663	6.663	2.258	0.135
	Arm	2, 149	38.820	19.410	1.095	0.336
	Time×arm	2, 149	5.396	2.698	0.914	0.403
Baseline to 6, 12 and 18 months	Time	3, 196	27.529	9.176	2.412	0.068
	Arm	3, 198	161.038	53.679	1.563	0.200
	Time×arm	9, 477	26.429	2.937	0.823	0.595
Self-care activities						
General diet						
Baseline to 3 months	Time	1, 146	0.004	0.004	0.003	0.959
	Arm	2, 146	5.447	2.724	0.502	0.606
	Time×arm	2, 146	11.892	5.946	3.927	0.022
Baseline to 6, 12 and 18 months	Time	3, 194	4.141	1.380	0.734	0.533
	Arm	3, 196	5.113	1.704	0.199	0.897
	Time×arm	9, 473	22.469	2.497	1.912	0.048
On how many of the last 7 days did you eat five or more servings of fruit and vegetables?						
Baseline to 3 months	Time	1, 147	1.260	1.260	0.841	0.360
	Arm	2, 147	17.040	8.520	1.155	0.318
	Time×arm	2, 147	4.347	2.174	1.452	0.237
Baseline to 6, 12 and 18 months	Time	3, 195	6.066	2.022	1.306	0.274
	Arm	3, 197	58.346	19.449	1.559	0.201
	Time×arm	9, 475	10.719	1.191	0.760	0.654
On how many of the last 7 days did you eat high-fat foods?						
Baseline to 3 months	Time	1, 148	0.484	0.484	0.293	0.589
	Arm	2, 148	16.252	8.126	1.515	0.223
	Time×arm	2, 148	1.796	0.898	0.544	0.582
Baseline to 6, 12 and 18 months	Time	3, 195	8.706	2.902	1.783	0.152
	Arm	3, 197	18.119	6.040	0.872	0.457
	Time×arm	9, 475	8.620	0.958	0.664	0.742
On how many of the last 7 days did you exercise?						
Baseline to 3 months	Time	1, 147	12.734	12.734	7.093	0.009
	Arm	2, 147	12.472	6.236	0.733	0.482
	Time×arm	2, 147	2.480	1.240	0.691	0.503
Baseline to 6, 12 and 18 months	Time	3, 194	9.878	3.293	1.534	0.207
	Arm	3, 196	31.766	10.589	0.722	0.540
	Time×arm	9, 472	9.666	1.074	0.602	0.796

In relation to the diabetes treatment satisfaction scale (DTSQc), the two single-item measures of satisfaction with perceived frequency of hypo- and hyperglycaemia were not analysed. Scores on the change in treatment satisfaction subscale were skewed with a left-hand tail, that is, the majority of respondents said that they were more satisfied with their diabetes care than they were 3 months ago. For this reason, a decision was taken to classify respondents at each assessment point as 'no change' in satisfaction with diabetes treatment, 'more satisfied' or 'less satisfied'. It is important

to remember that, each time this questionnaire was administered, participants were asked to compare their treatment now with their treatment 3 months ago. A chi-squared test was performed at each assessment point to determine whether the trial arms differed in the proportions of respondents in each of these categories (*Table 49*). This showed that there were no differences between the trial arms. In the total group, the majority of respondents (67–88%) reported improvements in their levels of satisfaction compared with 3 months ago at each assessment point.

Predictors of outcome

As part of a secondary exploratory analysis, relationships between baseline demographic, clinical and psychological characteristics and reductions in HbA1c were examined at each time point. These were analysed using HbA1c as a continuous and dichotomous variable (achieved versus did not achieve a 12.5% mean relative difference in HbA1c from baseline).

When HbA1c was analysed as a dichotomous variable at 3 months, a higher proportion of people in the lower social class category achieved a clinically significant reduction in HbA1c (41% vs 13%; $c^2 = 15.1$, df = 1, $p = 0.000$). Those who achieved a clinically significant reduction in HbA1c also scored higher on the 'significant others' locus of control subscale ($t = 2.47$, df = 146, $p = 0.008$). There were no other relationships between baseline variables and achievement of a 12.5% reduction in HbA1c at 3 months. At 6 and 12 months' follow-up, there was no relationship between achievement of a 12.5% reduction in HbA1c and baseline variables. At 18 months' follow-up, a higher proportion of people with microvascular complications achieved a 12.5% reduction in HbA1c (32% versus 17%, $c^2 = 6.1$, df = 1, $p = 0.014$); there were no other significant relationships, hence a predictor analysis was not deemed appropriate.

A series of partial correlations was carried out to determine whether there were any associations between baseline demographic, clinical and psychosocial characteristics and HbA1c levels at each time point. Baseline HbA1c was controlled for when running these partial correlations. At 6, 12 and 18 months HbA1c was positively correlated with the locus of control chance subscale ($r = 0.2$, df = 197, $p = 0.022$; $r = 0.2$, df = 199, $p = 0.020$; $r = 0.2$, df = 198. $p = 0.001$ respectively). At 18 months the diabetes-specific quality of life scale (ADDQoL) and BMI were also positively correlated with HbA1c ($r = 0.2$, df = 199, $p = 0.011$; $r = 0.2$, df = 199, $p = 0.033$ respectively). There were no other significant relationships and, because the reported correlations were low and not highly significant, it was not deemed appropriate to conduct a predictor analysis.

Summary

In the longitudinal analysis of the psychosocial data it must be acknowledged that bias has been introduced through the decision to focus on the group who completed questionnaires at all time points. This group were more satisfied with their diabetes treatment, reported slightly better diabetes-specific quality of life, exercised on significantly more days at baseline, were older, had lower baseline HbA1c values and had a higher proportion of people with macrovascular complications than the group who missed one or more questionnaire assessments. Importantly, when the different trial arms were compared there were no statistically significant differences at baseline on any of the factors that were assessed.

A series of repeated measures ANOVAs demonstrated reductions for the group as a whole in levels of fear of hypoglycaemia, which were significant at 3 and 12 months' follow-up. The relationship between fear and frequency of hypoglycaemia is complex, and it is recognised that the number of hypoglycaemic episodes in this study was only analysed descriptively. However, this result occurred without a corresponding reduction in the number of hypoglycaemic episodes reported.

Internal locus of control and level of exercise reduced significantly by 3 months' follow-up in the two device groups and the attention control group. There also appeared to be a deterioration in the level of general diet self-care behaviours in the GlucoWatch group compared with the other groups at 3 and 12 months' follow-up. Work by Clare Bradley and colleagues[124] has indicated that locus of control and other health beliefs are useful predictors of treatment choice amongst people with diabetes. In their study they found that lower internal locus of control predicted which patients chose insulin pump therapy. The results of the current study suggest that reliance on external devices to control diabetes may actually reduce perceptions of personal control over diabetes and lead to reductions in certain self-care behaviours. Treatment satisfaction did not differ between

TABLE 49 *Change in satisfaction with diabetes treatment (DTSQc)*

	Standard care control	Attention control	CGMS	GlucoWatch	Total	χ^2	df	*p*-value
3 months, n (%)								
No change		3 (5)	2 (4)	0	5 (3)	4.7	4	0.319
More satisfied		49 (88)	50 (91)	35 (85)	134 (88)			
Less satisfied		4 (7)	3 (6)	6 (15)	13 (9)			
6 months, n (%)								
No change	8 (16)	4 (7)	10 (18)	5 (12)	27 (13)	5.2	6	0.522
More satisfied	36 (71)	43 (77)	41 (75)	32 (78)	152 (75)			
Less satisfied	7 (14)	9 (16)	4 (7)	4 (10)	24 (12)			
12 months, n (%)								
No change	6 (12)	6 (11)	6 (11)	7 (17)	25 (12)	5.6	6	0.469
More satisfied	40 (78)	48 (86)	45 (82)	28 (68)	161 (79)			
Less satisfied	5 (10)	2 (4)	4 (7)	6 (15)	17 (8)			
18 months, n (%)								
No change	6 (12)	11 (20)	11 (20)	7 (17)	35 (17)	2.4	6	0.882
More satisfied	38 (75)	36 (64)	34 (62)	27 (66)	135 (67)			
Less satisfied	7 (14)	9 (16)	10 (18)	7 (17)	33 (16)			

the different trial arms during the course of the trial, but this may be due to ceiling effects of the questionnaire measure used. Quality of life was not compromised by use of the monitors.

Chapter 7
Health economic analysis

Economic results

Unit costs

Unit costs at 2005–6 prices, when they were available, were used to value the resource use measured in the trial. These were average costs. *Table 50* details the key unit costs together with their sources.

Missing data

As a consequence of participants missing appointments or missing responses in questionnaires there is a large proportion of data missing. The number of missing or incomplete forms/questionnaires in each trial arm for the EQ-5D questionnaires, CRFs and medication forms are shown in *Tables 51–53* respectively. For the EQ-5D, the proportion of questionnaires missing data ranges from 0.98% for the CGMS arm at baseline to 40.2% for the standard care control arm at week 52, although approximately 30% of the EQ-5D scores are missing. For the CRFs, the proportion of forms missing data ranges from 0% for three of the arms at baseline to 32.4% for the standard care control arm at week 52. Approximately 25% of the CRFs are missing. For the medication forms the proportion of forms missing data ranges from 0% for three of the arms at baseline to 31.4% for the standard care control arm at week 52. Again, approximately 25% of the medication forms are missing across all arms.

Resource use in natural units

Tables 68–72 in Appendix 10 provide a summary of the main areas of resource use measured in the trial at baseline and at 3, 6, 12 and 18 months respectively; results are presented separately for each trial arm. There appear to be no systematic differences in resource use between trial arms, although, as a consequence of the small number of people taking the medications, the standard deviations are very large. These results are based on the non-imputed data set, and at each period a participant's resource use is only included if both the CRF and the medication form were completed.

Resource costs

Complete case analysis

Tables 73–77 in Appendix 10 present resource costs for the 3-month period preceding baseline and 3, 6, 12 and 18 months respectively. The data relate to those individuals for whom at any particular time point we have both the CRF and the medication form. The costs are presented separately for each trial arm and include mean and median costs as well as the interquartile range and a 95% confidence interval for the mean cost.

It can be seen that the resource cost data for all cost categories at all time periods are positively skewed (as the mean is greater than the median). For the diabetes medicine, hospitalisation and other resources categories, the data are markedly skewed with the mean greater than the 75th percentile value. In some cases, for example the standard care control arm at week 78, this has resulted in the mean total cost also exceeding the 75th percentile total cost. The tables also show that for all resource categories at any time period there is no statistically significant difference between any of the trial arms (as the 95% confidence intervals overlap). It is interesting to note that the attention control arm fairs better in terms of mean and median total cost at all time periods during the trial (i.e. 12, 26, 52 and 78 weeks) with the exception of 12 weeks for which it does not have the lowest mean cost but does have the lowest median.

Figures 29–37 in Appendix 10 show the mean costs and 95% confidence intervals for insulin, diabetic medicine, other medication, hospitalisation, diabetes clinic costs, GP clinic costs, other resource costs, total costs and total costs excluding hospitalisation costs respectively, for each 3-month period by trial arm. Although costs cannot be negative, the full confidence intervals have been presented here to show the variability of some of the estimates.

Figure 29 shows that across trial arms there does not appear to be any marked difference in mean insulin cost at each period, and by 18 months the point estimates of insulin costs are very similar across the four arms.

TABLE 50 *Key unit costs relating to the trial*

Item of resource	Unit	Unit cost (£)	Source[a]	Notes
Hospital admission				
Admitted for DKA/HONK	Per day	463	NHS Ref	Based on diabetes mellitus HRG
Admitted for hypoglycaemia	Per day	272	NHS Ref	Average of two HRGs
Admitted for hyperglycaemia	Per day	235	NHS Ref	Average of two HRGs
Admitted to ICU	Per day	1424	NHS Ref and PSSRU	Average of two HRGs
General (unspecified admission)	Per day	243	PSSRU	
Diabetes clinic resources				
GP clinic visit	Per visit	27.5	PSSRU	Average of with and without training costs
Visit to nurse	Per visit	9.5	PSSRU	Average of with and without training costs
Telephone consultation with nurse	Per visit	9.5	PSSRU	Average of with and without training costs
Visit to dietician/podiatrist	Per visit	32	NHS Ref and PSSRU	Average of all costs/HRGs
GP clinic resources				
GP clinic visit	Per visit	27.5	PSSRU	Average of with and without training costs
Visit to nurse/telephone consultation with nurse	Per visit/ telephone consultation	9.5	PSSRU	Average of with and without training costs
Other resource usage				
Use of A&E facilities	Per use	84	NHS Ref	Average of all A&E-related HRGs
Paramedic assistance not in A&E	Per use	311	NHS Ref	Average of all diabetes-related paramedic HRGs
Outpatient appointment	Per appointment	104	NHS Ref	HRG for follow-up diabetic outpatient appointment
Insulin				
Short acting	Per unit	0.0103267	BNF	
Short-acting analogue	Per unit	0.0189043	BNF	
Long acting	Per unit	0.0155917	BNF	
Long-acting analogue	Per unit	0.0260000	BNF	
Mixture	Per unit	0.0177056	BNF	
Diabetic medicine				
Metformin	Per mg	0.0000367	BNF	
Glibenclamide	Per mg	0.0106429	BNF	
Gliclazide	Per mg	0.0005315	BNF	
Glimepiride	Per mg	0.1234167	BNF	
Acarbose	Per mg	0.0014667	BNF	
Repaglinide/nateglinide	Per mg	0.0346260	BNF	
Glitazones	Per mg	0.1136453	BNF	

TABLE 50 *Key unit costs relating to the trial (continued)*

Item of resource	Unit	Unit cost (£)	Source[a]	Notes
CGMS				
CGMS Starter Kit (less four sensors)	Monitor, transmitter, etc.	1973.5	Medtronic price list – September 2006	
Sensor	Per sensor	56.5	Medtronic price list – September 2006	
GlucoWatch				
GlucoWatch	Per watch	453	www.mendosa.com/glucowatch.htm	
Sensors	Per 16 sensor box	77.92	www.mendosa.com/glucowatch.htm	

DKA/HONK, diabetic ketoacidosis/hyperosmolar non-ketotic acidosis; HRG, health-care resource group; ICU, intensive care unit.
a BNF, *British National Formulary*; NHS Ref, *NHS Reference Costs*; PSSRU (Personal Social Services Research Unit), *Unit Costs of Health and Social Care*.

In *Figure 30* there also do not appear to be any marked differences in the mean cost of diabetic medicine across the trial arms, and by 18 months all of the point estimates of the mean cost of diabetic medicine lie between £6 and £12. In three of the arms, the CGMS arm, the attention control arm and the standard care control arm, the point estimate of the mean cost of diabetic medicine was lower at 18 months than at baseline. However, over the trial period the mean cost of diabetic medicine for the CGMS arm was very variable, as indicated by the wide confidence interval and variable point estimate.

Figure 31 indicates that there are no marked differences in the mean cost of other medication across the trial arms, although the point estimate of the mean cost of other medication for the standard care control arm is higher at all times than that of the other three arms. As the standard care control arm mean cost was also higher at baseline, it is likely that the higher cost in this arm during the trial was not a result of the trial interventions but instead depended on differences in participants that were already present at baseline.

Figure 32 presents the mean hospitalisation cost and 95% confidence interval for each arm at each trial period. The confidence intervals are much smaller for the GlucoWatch and attention control arms; however, this is most likely a consequence of the small sample size, implying that one or two long hospital stays can result in very large changes in the mean cost and have resulted in the very wide confidence interval estimates. As can be seen from *Tables 73–77,* the median and upper and lower quartiles are zero for all of the trial arms at all time periods. *Figure 32* also shows that there are no significant differences in the mean cost of hospitalisation across the arms.

Figures 33 and 34 present the mean costs and 95% confidence intervals for the diabetic clinic and GP clinic resource use respectively. Again, there appear to be no marked differences between the mean costs for the different arms across all time periods. It is worth noting that in *Figure 33* the mean cost of diabetic clinic resource use was lower at all time periods during the trial than at baseline in all of the trial arms. This may reflect that, as a result of going to the clinic for trial appointments (for

TABLE 51 *Summary of missing data: utilities*

	GlucoWatch, *n* (%)	CGMS, *n* (%)	Attention control, *n* (%)	Standard care control, *n* (%)
n	100	102	100	102
Baseline	9 (9)	1 (0.98)	2 (2)	3 (2.9)
Week 12	38 (38)	24 (23.5)	25 (25)	
Week 26	34 (34)	29 (28.4)	24 (24)	30 (29.4)
Week 52	37 (37)	31 (30.4)	22 (22)	41 (40.2)
Week 78	32 (32)	32 (31.4)	23 (23)	29 (28.4)

TABLE 52 *Summary of missing data: resource use – case record forms*

	GlucoWatch, *n* (%)	CGMS, *n* (%)	Attention control, *n* (%)	Standard care control, *n* (%)
n	100	102	100	102
Baseline	0 (0)	0 (0)	1 (1)	0 (0)
Week 12	26 (26)	21 (20.6)	19 (19)	
Week 26	30 (30)	23 (22.5)	18 (18)	24 (23.5)
Week 52	31 (31)	27 (26.5)	16 (16)	33 (32.4)
Week 78	27 (27)	26 (25.5)	19 (19)	25 (24.5)

TABLE 53 *Summary of missing data: resource use – medication forms*

	GlucoWatch, *n* (%)	CGMS, *n* (%)	Attention control, *n* (%)	Standard care control, *n* (%)
n	100	102	100	102
Baseline	1 (1)	0 (0)	0 (0)	0 (0)
Week 12	26 (26)	21 (20.6)	20 (20)	
Week 26	31 (31)	24 (23.5)	19 (19)	24 (23.5)
Week 52	31 (31)	28 (27.5)	15 (15)	32 (31.4)
Week 78	26 (27)	27 (26.5)	19 (19)	25 (24.5)

which the cost is not included in the diabetes clinic resource cost component), trial participants were less likely to visit the diabetes clinics at other times.

Figure 35 presents the same results for the other resource costs (which include outpatient visits, A&E visits and use of paramedics). There are no marked differences between the trial arms, although the point estimate of the mean cost for the standard care control group at 18 months does appear to be considerably higher.

Figure 36 presents the mean costs and 95% confidence intervals for the total costs (including trial-specific costs). The attention control arm has the lowest point estimate for mean costs at all time periods except 3 months, at which point CGMS has the lowest point estimate. However, again there are no marked differences in mean costs between trial arms at any time period. It is interesting to note the large total mean cost for the CGMS arm at 18 months and also the very large confidence interval. These are most likely driven by the hospitalisation costs and again present the problem that a small subset of one or two individuals with lengthy hospital stays can increase the mean cost considerably. In *Table 77* the skewness of the total costs for CGMS is shown by the large difference between median and mean total costs.

Figure 37 presents the mean costs and 95% confidence intervals for total costs excluding

hospitalisation costs. When hospitalisation costs are excluded, the attention control arm has the lowest point estimate at all time periods. This may indicate that the trial intervention of the attention control arm results in lower costs. However, it must also be noted that the attention control arm also has the lowest total costs, excluding hospital costs at baseline, and thus the lower costs over the trial might not be reflecting a trial effect but instead a more favourable (in terms of costs) group of participants in the attention control arm. As with the other cost components, there are no marked differences in total costs excluding hospitalisation costs between trial arms at any time period.

Post-imputation

Tables 54–58 present resource costs for the 3-month period preceding baseline and 3, 6 12 and 18 months respectively, based on the data sets imputed using ICE. The costs are presented separately for each trial arm and include mean costs and a 95% confidence interval for the mean cost. The costs have been calculated using a GLM regression with an identity link, and a gamma distribution function with the dependent variable being the cost component and the explanatory variables being dummy variables for each trial arm.

Figures 14–22 show the mean costs and 95% confidence intervals for insulin, diabetic medicine, other medication, hospitalisation, diabetes clinic costs, GP clinic costs, other resources costs and total costs respectively, for each 3-month period by trial arm.

It is worth noting that the confidence intervals are wider for the imputed estimates than for the complete case estimates, shown in Appendix 10, as the methods used for estimation take account of both the within and the between data set variability.

Figure 14 shows the imputed mean insulin costs and 95% confidence intervals for all four trial arms at baseline and 3, 6, 12 and 18 months (with the exception of the standard care control arm for which resource use was not collected at 3 months). The mean cost is greater at 18 months than at baseline in three of the four trial arms, with only the CGMS arm showing a very small decrease in cost. The two control arms also appear to show a trend for an increase in insulin cost over the trial period, with the mean insulin cost in both arms increasing from each period to the next. However, the differences in mean insulin costs between trial arms are not statistically significant at any of the trial periods.

Figure 15 shows the imputed mean diabetic medicine costs and 95% confidence intervals for all four trial arms at baseline and 3, 6, 12 and 18 months (with the exception of the standard care control arm for which resource use was not collected at 3 months). In all but one trial arm (the GlucoWatch arm), the mean cost at 18 months was lower than at baseline.

Figure 16 shows the imputed mean other medicine costs and 95% confidence intervals for all four trial arms at each trial period. As with the complete case results, the mean cost in the standard care control arm is higher at all periods. However, as it is also higher at baseline it might not indicate any trial intervention effect. *Figure 17* shows the same statistics for the hospitalisation costs. As with the complete case results, there appear to be no marked differences in hospitalisation costs between trial arms at any period during the trial.

Figures 18 and *19* show the imputed diabetes clinic and GP clinic resource costs respectively. As with the complete case results, the mean diabetic clinic resource cost for all arms at 18 months is lower than at baseline. This could indicate a trial effect with participants visiting the diabetes clinic less often at other times, as they already visit for their trial appointment. *Figure 19* shows increasing GP clinic costs for both the attention control and the CGMS arms over the trial period; however, the differences in GP clinic costs between arms do not appear to be significant for any period.

Figure 20 shows the imputed mean other resource use costs and 95% confidence intervals for all four trial arms at each trial period. There does not appear to be any systematic change or trial effect in any of the arms with the mean costs being variable within each trial arm across time. Again, there appears to be no marked difference between arms at any time period.

The imputed means and confidence intervals for total costs are plotted in *Figure 21*. As with the complete case results, the point estimates for mean total costs are lower in the attention control arm in all but one period. It also appears that for all arms except the attention control arm the mean total cost is increasing over the trial period. This may indicate that the attention control intervention was superior in terms of lower costs. However, there appear to be no marked differences between trial arms at any time period.

The imputed means and confidence intervals for total costs excluding hospitalisation are plotted in

TABLE 54 *Resource use costs (£) over the previous 3 months measured at baseline: imputed data*

	GlucoWatch	CGMS	Attention control	Standard care control
Insulin				
Mean	107.3435	100.9353	99.38991	101.1763
Standard error	5.874875	5.440187	5.4102	5.453179
95% CI lower	95.82892	90.27269	88.78611	90.48827
95% CI upper	118.858	111.5978	109.9937	111.8643
Diabetes medicine				
Mean	9.837156	17.43855	10.81231	9.887928
Standard error	3.436183	5.808304	3.637121	3.2934
95% CI lower	3.102361	6.054478	3.683687	3.432984
95% CI upper	16.57195	28.82261	17.94094	16.34287
Other medication				
Mean	70.0818	66.50027	60.35454	78.35383
Standard error	7.382328	6.849548	6.278394	8.070464
95% CI lower	55.6127	53.0754	48.04912	62.53601
95% CI upper	84.55089	79.92514	72.65997	94.17165
Hospitalisation				
Mean	134	114.4706	159.073	95.06863
Standard error	70.95057	60.01294	84.23463	49.84117
95% CI lower	47.46888	40.96742	56.34511	34.02373
95% CI upper	378.2688	319.8521	449.0937	265.6394
Diabetes clinic				
Mean	56.74499	42.11275	44.466	56.2647
Standard error	6.473944	4.757239	5.082315	6.355905
95% CI lower	44.05629	32.78873	34.50485	43.80736
95% CI upper	69.43369	51.43676	54.42715	68.72205
GP clinic				
Mean	39.24999	34.72059	32.32789	34.47549
Standard error	5.609484	4.913269	4.624789	4.878584
95% CI lower	28.2556	25.09076	23.26347	24.91364
95% CI upper	50.24437	44.35042	41.39231	44.03734
Other resources				
Mean	110.23	82.63725	90.328	106.6569
Standard error	23.78668	17.65671	19.49875	22.78887
95% CI lower	63.60896	48.03073	52.11114	61.9915
95% CI upper	156.851	117.2438	128.5449	151.3222

Figure 22. The point estimates for the attention control arm are lower for all trial periods, perhaps suggesting that the attention control intervention was superior in terms of lower costs. However, as the attention control arm also has lower costs at baseline this might simply suggest a difference

TABLE 54 *Resource use costs (£) over the previous 3 months measured at baseline: imputed data (continued)*

	GlucoWatch	CGMS	Attention control	Standard care control
Clinic appointments				
Mean	9.5	9.5	9.5	9.5
Standard error	0	0	0	0
95% CI lower	9.5	9.5	9.5	9.5
95% CI upper	9.5	9.5	9.5	9.5
Total cost				
Mean	536.988	468.3129	506.2547	491.3838
Standard error	85.85418	74.12285	80.94718	77.7748
95% CI lower	368.7168	323.0348	347.6012	338.948
95% CI upper	705.2591	613.5911	664.9083	643.8196
Total cost excluding hospital costs				
Mean	402.988	353.8447	347.1788	396.3152
Standard error	30.49603	26.47573	26.24504	29.6535
95% CI lower	343.2168	301.9532	295.7394	338.1954
95% CI upper	462.7591	405.7362	398.6181	454.435

CI, confidence interval.

in baseline covariates of participants between the arms driving costs. This possibility will be further explored in the regression analysis section.

Total trial costs over trial period using imputed data

For the purpose of comparing the trial arms over the whole trial period it is useful to examine the total cost over the entire period. However, as the data on resource use were only collected for the preceding 3 months at each trial appointment, no data were recorded for the periods from 6 to 9 months and from 12 to 15 months with the exception of data on device use, which covered the whole period between trial appointments. Therefore, it has been assumed that these costs were identical to the costs for the periods from 9 to 12 months and from 15 to 18 months respectively. The costs for each period during the trial (therefore excluding baseline costs) were then summated along with the cost of the device hardware for the GlucoWatch and CGMS trial arms, to give total costs. These figures are presented in *Table 59*.

As with the various cost components, there appear to be no significant differences in total trial costs between trial arms. However, the point estimate for the attention control arm is much lower than that for the other three trial arms. The results suggest that the attention control arm has lower costs, but, as discussed previously, this may be due to differences in baseline covariates of participants between arms driving the difference in costs rather than being an effect of the trial interventions.

Table 60 presents the total costs over the trial period excluding hospitalisation costs. The table shows that the total costs excluding hospitalisation costs for the attention control arm are markedly lower than those for the GlucoWatch and CGMS arms. It is worth noting that this difference will be partially driven by the device hardware costs. It can also be seen that the standard care control arm total costs excluding hospitalisation costs are also markedly lower than those for the CGMS arm.

Regression

For the regression analysis, the relationships between the costs at each stage and various covariates were examined. The analysis undertaken is presented below. This will focus on the results relating to total resource costs (both with and excluding hospitalisation) in week 78 and over the whole trial period.

Table 78 in Appendix 10 shows the results of the GLM regression of total cost of all resource use at 18 months on a constant, age, BMI and dummy variables representing type of diabetes, gender and

TABLE 55 *Resource use costs (£) over the previous 3 months measured at week 12 follow-up: imputed data*

	GlucoWatch	CGMS	Attention control
Insulin			
Mean	101.802	103.6891	97.03148
Standard error	13.12481	6.162946	7.580568
95% CI lower	76.07788	91.60991	82.17384
95% CI upper	127.5262	115.7682	111.8891
Diabetes medicine			
Mean	8.489535	11.65215	5.74076
Standard error	2.880365	3.621721	2.409841
95% CI lower	2.844123	4.553708	1.017559
95% CI upper	14.13495	18.75059	10.46396
Other medication			
Mean	76.13885	65.47226	66.08158
Standard error	11.10534	7.20601	7.616416
95% CI lower	54.37278	51.34874	51.15368
95% CI upper	97.90492	79.59578	81.00948
Hospitalisation			
Mean	2.43	40.5	158.0503
Standard error	1.859095	30.67964	123.6691
95% CI lower	0.542483	9.17595	34.1003
95% CI upper	10.88495	178.7553	732.5418
Diabetes clinic			
Mean	34.575	17.61765	22.513
Standard error	8.665417	4.306048	6.012282
95% CI lower	17.5911	9.177947	10.72914
95% CI upper	51.5589	26.05734	34.29685
GP clinic			
Mean	35.657	31.29804	31.63999
Standard error	5.795436	5.412168	4.243967
95% CI lower	24.29815	20.69038	23.32197
95% CI upper	47.01584	41.90569	39.95801
Other resources			
Mean	104.422	61.84706	70.704
Standard error	28.77106	14.05273	23.78885
95% CI lower	48.03176	34.30421	24.07871
95% CI upper	160.8122	89.38991	117.3293

trial arm. This analysis assumes that the effects of age, BMI, gender and type of diabetes on the total cost at 18 months are constant across treatment arms. The results indicate that the mean total costs at week 78 were lower in the attention control and the GlucoWatch arms than in the standard care control arm, as both have negative coefficients. The coefficients also indicate that those trial participants with higher BMI scores had higher costs. However, only one of the coefficients was found to be statistically significant in this regression (the coefficient for BMI).

TABLE 55 *Resource use costs (£) over the previous 3 months measured at week 12 follow-up: imputed data (continued)*

	GlucoWatch	CGMS	Attention control
Trial specific (not imputed)			
Device cost			
Mean	23.5708	110.2304	
Standard error	3.932771	5.534447	
95% CI lower	15.86271	99.38308	
95% CI upper	31.27889	121.0777	
Clinic appointments			
Mean	21.85	24.96078	23.275
Standard error	0.7564189	1.064481	1.069738
95% CI lower	20.36745	22.87444	21.1783524
95% CI upper	23.33255	27.04713	25.371648
Total cost			
Mean	408.9352	467.2671	476.5238
Standard error	60.25488	60.90088	75.50108
95% CI lower	290.8378	347.9036	328.5444
95% CI upper	527.0326	586.6306	624.5032
Total cost excluding hospital costs			
Mean	406.5052	426.7674	316.9858
Standard error	37.00741	26.67922	26.02178
95% CI lower	333.972	374.4771	265.9841
95% CI upper	479.0384	479.0577	367.9876

CI, confidence interval.

Table 79 in Appendix 10 shows the results of the GLM regression of total cost of all resource use excluding hospitalisation at 18 months on a constant, age, BMI and dummy variables representing type of diabetes, gender and trial arm. This analysis assumes that the effects of age, BMI, gender and type of diabetes on the total cost excluding hospitalisation at 18 months are constant across treatment arms. These results show that participants with type 1 diabetes had lower mean costs than those with type 2 or other type diabetes. In contrast to the previous GLM regression patients with higher BMI had lower mean costs, although the coefficient was not statistically significant. The point estimates of the coefficients indicate that total costs excluding hospitalisation at week 78 were lower in the other three trial arms than in the standard care control arm. However, it is also worth noting that even after controlling for these other covariates there are no marked differences between trial arms, as the coefficients for the dummy variables for the trial arms remained statistically insignificant.

Table 61 shows the results of the GLM regression of total cost over the trial period on a constant, age, BMI and dummy variables representing type of diabetes, gender and trial arm. As with the previous two analyses, this assumes that the effects of the covariates included are constant across trial arms. The results suggest that the attention control arm had lower costs than the standard care control arm, with the coefficient for the former being statistically significant. The coefficients also indicate that the CGMS arm had higher costs than the standard care control arm and the GlucoWatch arm had lower costs than the standard care control arm, but neither of these coefficients were statistically significant. The results suggest that after controlling for particular participant covariates (i.e. age, type of diabetes, gender and BMI) the attention control arm was the trial arm with the lowest total costs during the trial period, and the GlucoWatch arm had the second lowest total costs. The regression results also indicate that those patients with type 1 diabetes are likely to have lower costs than those with other types of diabetes (a very large proportion of which are

TABLE 56 *Resource use costs (£) over the previous 3 months measured at week 26 follow-up: imputed data*

	GlucoWatch	CGMS	Attention control	Standard care control
Insulin				
Mean	114.869	102.0879	104.4741	106.4166
Standard error	9.720862	5.794127	6.113217	6.579507
95% CI lower	95.81646	90.73163	92.49239	93.52097
95% CI upper	133.9215	113.4442	116.4558	119.3122
Diabetes medicine				
Mean	10.40396	10.78032	5.046285	7.134068
Standard error	3.131587	3.171871	1.437941	2.478876
95% CI lower	4.266166	4.563562	2.227973	2.27556
95% CI upper	16.54176	16.99707	7.864597	11.99258
Other medication				
Mean	77.89434	64.50969	59.92775	85.39747
Standard error	8.249953	6.691694	6.214917	8.8643
95% CI lower	61.72472	51.39421	47.74674	68.02376
95% CI upper	94.06395	77.62517	72.10877	102.7712
Hospitalisation				
Mean	125.9135	291.1144	34.06372	104.8322
Standard error	104.9638	170.1495	31.08187	74.91472
95% CI lower	24.57507	92.58838	5.696426	25.83526
95% CI upper	645.1333	915.3156	203.6956	425.3795
Diabetes clinic				
Mean	23.06398	22.8392	30.616	35.41078
Standard error	3.998069	3.540355	5.409642	5.416871
95% CI lower	15.22791	15.90023	20.0133	24.79391
95% CI upper	30.90005	29.77816	41.2187	46.02765
GP clinic				
Mean	26.011	29.47647	27.571	31.38725
Standard error	5.237927	3.925805	3.655583	4.694702
95% CI lower	15.74485	21.78203	20.40619	22.18581
95% CI upper	36.27715	37.17091	34.73581	40.5887
Other resources				
Mean	83.352	85.89608	79.416	101.4941
Standard error	16.51828	14.7296	14.17797	16.98977
95% CI lower	50.97677	57.02659	51.62769	68.19478
95% CI upper	115.7272	114.7656	107.2043	134.7935

type 2 diabetics), that men have lower costs than women, that costs increase with a participant's age and that patients with higher BMI scores have higher costs.

Table 62 shows the results of the GLM regression of total costs excluding hospitalisation costs over the trial period on a constant, age, BMI and dummy variables representing type of diabetes, gender and

TABLE 56 *Resource use costs (£) over the previous 3 months measured at week 26 follow-up: imputed data (continued)*

	GlucoWatch	CGMS	Attention control	Standard care control
Trial specific (not imputed)				
Device cost				
Mean	23.5708	33.78922		
Standard error	1.777005	2.500715		
95% CI lower	20.08793	28.8879		
95% CI upper	27.05367	38.69053		
Clinic appointments				
Mean	6.65	7.357843	7.79	7.1715686
Standard error	0.404298	0.568954	0.5717638	0.5689541
95% CI lower	5.85759	6.242714	6.6693636	6.0564391
95% CI upper	7.44241	8.472973	8.910636	8.286698
Total cost				
Mean	509.531	652.4997	355.5846	488.4531
Standard error	132.6317	131.3207	68.78098	109.2579
95% CI lower	249.5776	395.1158	220.7764	274.3116
95% CI upper	769.4844	909.8836	490.3929	702.5946
Total cost excluding hospital costs				
Mean	365.8153	356.737	314.8412	374.4119
Standard error	24.24218	20.97203	20.12176	22.21793
95% CI lower	318.3015	315.6326	275.4033	330.8656
95% CI upper	413.3291	397.8414	354.2791	417.9583

CI, confidence interval.

trial arm. As with the previous three analyses, this assumes that the effects of the covariates included are constant across trial arms. The results indicate that patients with type 1 diabetes had lower costs over the trial period, and those with a higher BMI had higher costs. The regression results also indicate that the CGMS and GlucoWatch trial arm patients had higher costs over the trial period than those in the standard care control arm, whereas those in the attention control arm had lower mean costs. The coefficients on the dummy variables for both the CGMS and the attention control arms were found to be statistically significant. The results suggest that after controlling for particular participant covariates (i.e. age, type of diabetes, gender and BMI) and removing hospitalisation costs because of their high variability, the attention control arm is the lowest cost trial arm followed by the standard care control arm. Comparing the effects of the various covariates with the regression results in *Table 62*, the coefficients are generally consistent (e.g. participants with type 1 diabetes have lower costs).

Subgroup analysis

As part of the clinical analysis of this trial it was suggested that some pretrial self-management activities might affect the clinical effects of the devices. These included smoking, exercise regime, frequency of blood glucose testing and diet. All of these activities are related to questions asked in the patient's questionnaire. Using the results from these questions, we were able to perform subgroup analysis based on these self-management activities. For example, we tested whether total costs excluding hospitalisation costs over the trial period differed between arms if an individual was a smoker. This was achieved through the use of dummy variable interaction terms. The results from these GLM regressions using total costs excluding hospitalisation costs over the trial period are presented in *Tables 80–83* in Appendix 10.

TABLE 57 *Resource use costs (£) over the previous 3 months measured at week 52 follow-up: imputed data*

	GlucoWatch	CGMS	Attention control	Standard care control
Insulin				
Mean	108.8186	102.6015	106.7777	103.0638
Standard error	6.450854	6.379535	6.302591	6.257993
95% CI lower	96.17513	90.09782	94.42486	90.79839
95% CI upper	121.462	115.1051	119.1306	115.3293
Diabetes medicine				
Mean	10.80737	13.62209	5.526643	6.83043
Standard error	3.150534	3.974746	1.484508	3.199883
95% CI lower	4.632434	5.831733	2.617061	0.5587747
95% CI upper	16.9823	21.41245	8.436225	13.10209
Other medication				
Mean	84.6521	66.396	72.60394	92.5903
Standard error	10.59642	7.276544	7.58664	10.43298
95% CI lower	63.8835	52.13424	57.73439	72.14204
95% CI upper	105.4207	80.65777	87.47348	113.0386
Hospitalisation				
Mean	103.664	235.2693	67.13931	359.6727
Standard error	55.13703	135.8248	39.2646	171.637
95% CI lower	36.55014	75.88442	21.33903	141.1599
95% CI upper	294.0132	729.4204	211.2414	916.4391
Diabetes clinic				
Mean	43.04496	26.33725	25.849	34.79998
Standard error	6.601656	4.55739	4.48586	6.314041
95% CI lower	30.10595	17.40493	17.05688	22.42469
95% CI upper	55.98397	35.26957	34.64112	47.17527
GP clinic				
Mean	31.99399	34.68921	36.61	25.23823
Standard error	5.058502	4.539769	5.588541	4.166525
95% CI lower	22.07951	25.79143	25.65666	17.07199
95% CI upper	41.90847	43.58699	47.56334	33.40447
Other resources				
Mean	80.27191	83.17839	64.10999	105.4255
Standard error	16.694	18.39381	12.21165	20.3189
95% CI lower	47.55228	47.12719	40.1756	65.60119
95% CI upper	112.9915	119.2296	88.04439	145.2498

Table 80 presents the results for the regression, including an interaction between those who answered from 4 to 7 in the exercise question (i.e. they take more exercise than those who answered from 0 to 3) and the various treatment arms. The results indicate that taking more exercise reduced costs, and also that the biggest mean cost reduction was for those in the attention control arm, as

TABLE 57 *Resource use costs (£) over the previous 3 months measured at week 52 follow-up: imputed data (continued)*

	GlucoWatch	CGMS	Attention control	Standard care control
Trial specific (not imputed)				
Device cost				
Mean	23.5708	31.57353		
Standard error	1.791039	2.520465		
95% CI lower	20.06043	26.63351		
95% CI upper	27.08117	36.51355		
Clinic appointments				
Mean	6.46	6.79902	7.79	6.5196078
Standard error	0.4228185	0.595017	0.5979557	0.5950173
95% CI lower	5.631291	5.632807	6.6180283	5.353395
95% CI upper	7.288709	7.965232	8.961972	7.68582
Total cost				
Mean	495.639	611.5951	389.6114	736.1378
Standard error	91.29345	150.4711	73.54258	135.342
95% CI lower	316.7072	316.6771	245.4706	470.8724
95% CI upper	674.5709	906.5131	533.7522	1001.403
Total cost excluding hospital costs				
Mean	389.6202	365.1971	319.2676	374.4679
Standard error	28.03671	26.55077	20.86932	26.6885
95% CI lower	334.6693	313.1585	278.3645	322.1594
95% CI upper	444.5712	417.2356	360.1707	426.7764

CI, confidence interval.

this has the largest negative coefficient. As the interaction coefficients are negative for the CGMS and GlucoWatch arms, more exercise appears to lead to a larger cost reduction for the GlucoWatch and CGMS arms than for the standard care control arm. However, none of the interaction coefficients was statistically significant.

Table 81 presents the results when treatment interactions based on the diet question in the questionnaire were considered (in which answering from 4 to 7 indicates a healthier diet). The results indicate that a healthier diet led to a larger cost reduction in the CGMS arm than in the standard care control arm, whereas the cost was actually increased for the GlucoWatch and attention control arms. However, none of the interaction coefficients was statistically significant.

Table 82 presents the results when treatment interactions based on the before trial glucose monitoring activities in the questionnaire were considered. The results indicate that testing for blood glucose daily decreased costs the most in the GlucoWatch trial arm. However, none of the interaction coefficients was statistically significant.

Table 83 presents the results when treatment interactions based on the patient's smoking status were considered. The results indicate that smoking increases costs for all arms, but the largest increase was for the CGMS trial arm. However, again none of the interaction coefficients was statistically significant.

EQ-5D

Health states

As discussed earlier, the EQ-5D questionnaire is based on five dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression), with each dimension having three levels (no problem, some problem or extreme problem). *Figures 23–27* present the percentages of the different responses to each question, respectively,

TABLE 58 *Resource use costs (£) over the previous 3 months measured at week 78 follow-up: imputed data*

	GlucoWatch	CGMS	Attention control	Standard care control
Insulin				
Mean	111.0251	98.97778	108.331	105.5302
Standard error	7.051135	5.389997	6.585783	6.686293
95% CI lower	97.20513	88.41358	95.42309	92.42527
95% CI upper	124.8451	109.542	121.2389	118.6351
Diabetes medicine				
Mean	13.03354	9.131367	6.847391	6.162883
Standard error	3.373174	2.386007	1.762625	1.599234
95% CI lower	6.422239	4.454879	3.392709	3.028443
95% CI upper	19.64484	13.80785	10.30207	9.297323
Other medication				
Mean	81.79268	66.47772	71.72795	80.43685
Standard error	8.121694	6.974437	7.154682	7.805403
95% CI lower	65.87445	52.80807	57.70503	65.13854
95% CI upper	97.71091	80.14736	85.75087	95.73516
Hospitalisation				
Mean	377.7721	538.739	148.5103	446.3265
Standard error	223.4398	269.826	82.7758	230.573
95% CI lower	118.5147	201.8629	49.81029	162.1513
95% CI upper	1204.17	1437.806	442.7864	1228.527
Diabetes clinic				
Mean	24.006	22.64216	23.38399	34.12353
Standard error	4.66343	6.545115	5.015855	6.515717
95% CI lower	14.86584	9.813967	13.5531	21.35296
95% CI upper	33.14615	35.47035	33.21489	46.8941
GP clinic				
Mean	41.151	42.35588	51.18899	32.46665
Standard error	7.145437	5.290734	7.962711	5.324044
95% CI lower	27.1462	31.98623	35.58236	22.03171
95% CI upper	55.1558	52.72552	66.79562	42.90158
Other resources				
Mean	91.02399	118.3313	89.79999	161.3666
Standard error	17.72144	26.47183	18.64563	33.24471
95% CI lower	56.29061	66.44751	53.25523	96.20814
95% CI upper	125.7574	170.2152	126.3448	226.525

in the different arms at baseline, 3 months (with the exception of the standard care control arm for which EQ-5D was not recorded), 6 months, 12 months and 18 months.

In all dimensions and across all time points, the majority of the patients have no problems (with the exception of the pain/discomfort dimension at 12 and 18 months for the standard care control

TABLE 58 *Resource use costs (£) over the previous 3 months measured at week 78 follow-up: imputed data (continued)*

	GlucoWatch	CGMS	Attention control	Standard care control
Trial specific (not imputed)				
Device cost				
Mean	23.5708	28.80392		
Standard error	1.798668	2.531201		
95% CI lower	20.04548	23.84286		
95% CI upper	27.09612	33.76498		
Clinic appointments				
Mean	7.03	6.705882	7.695	7.0784314
Standard error	0.4118527	0.579586	0.5824477	0.5795855
95% CI lower	6.222784	5.569916	6.5534235	5.942465
95% CI upper	7.837216	7.841849	8.836577	8.214398
Total cost				
Mean	783.9762	936.7379	511.4022	880.1099
Standard error	222.9824	242.5524	132.4582	242.051
95% CI lower	346.9388	461.344	251.789	405.6987
95% CI upper	1221.014	1412.132	771.0154	1354.521
Total cost excluding hospital costs				
Mean	392.6332	393.4261	358.9744	427.1652
Standard error	29.28408	28.22599	29.43711	33.17706
95% CI lower	335.2375	338.1042	301.2787	362.1394
95% CI upper	450.029	448.7481	416.67	492.191

CI, confidence interval.

arm and at 3 months for the CGMS arm and the anxiety/depression dimension at 18 months for the attention control arm).

Figure 23 shows that very few patients face extreme problems with mobility, with only a very small percentage, and at some periods for some trial arms 0%, falling into the 'unable' group (which corresponds to a response of confined to bed).

Figure 24 indicates that very few patients face extreme problems with self-care, with only a very small percentage, and at some periods for some trial arms 0%, responding that they were unable to wash and dress themselves.

Figure 25 presents the results for the activity question. A higher percentage of people fell into the unable category (which corresponds to a response of 'I am unable to perform my usual activities') than in the self-care and mobility questions, but the majority of people in all trial arms at all time points experienced no problem.

Figure 26 presents the results for the responses to the pain/discomfort question. For this question more patients responded at the worst level than for any of the other questions, with the percentage categorised as 'extreme' falling between 10% and 20% for most time points across all arms (in which extreme corresponds to a response of 'I have extreme pain or discomfort'). A high proportion of patients also fell into the moderate level, which corresponds to a response of 'I have moderate pain or discomfort'.

Figure 27 presents the results for the anxiety/depression dimension. A higher proportion of participants than in the mobility, self-care and activity dimensions responded at the worst level for this dimension (which corresponds to a response of 'I am extremely anxious or depressed'). However, with the exception of the attention control arm at

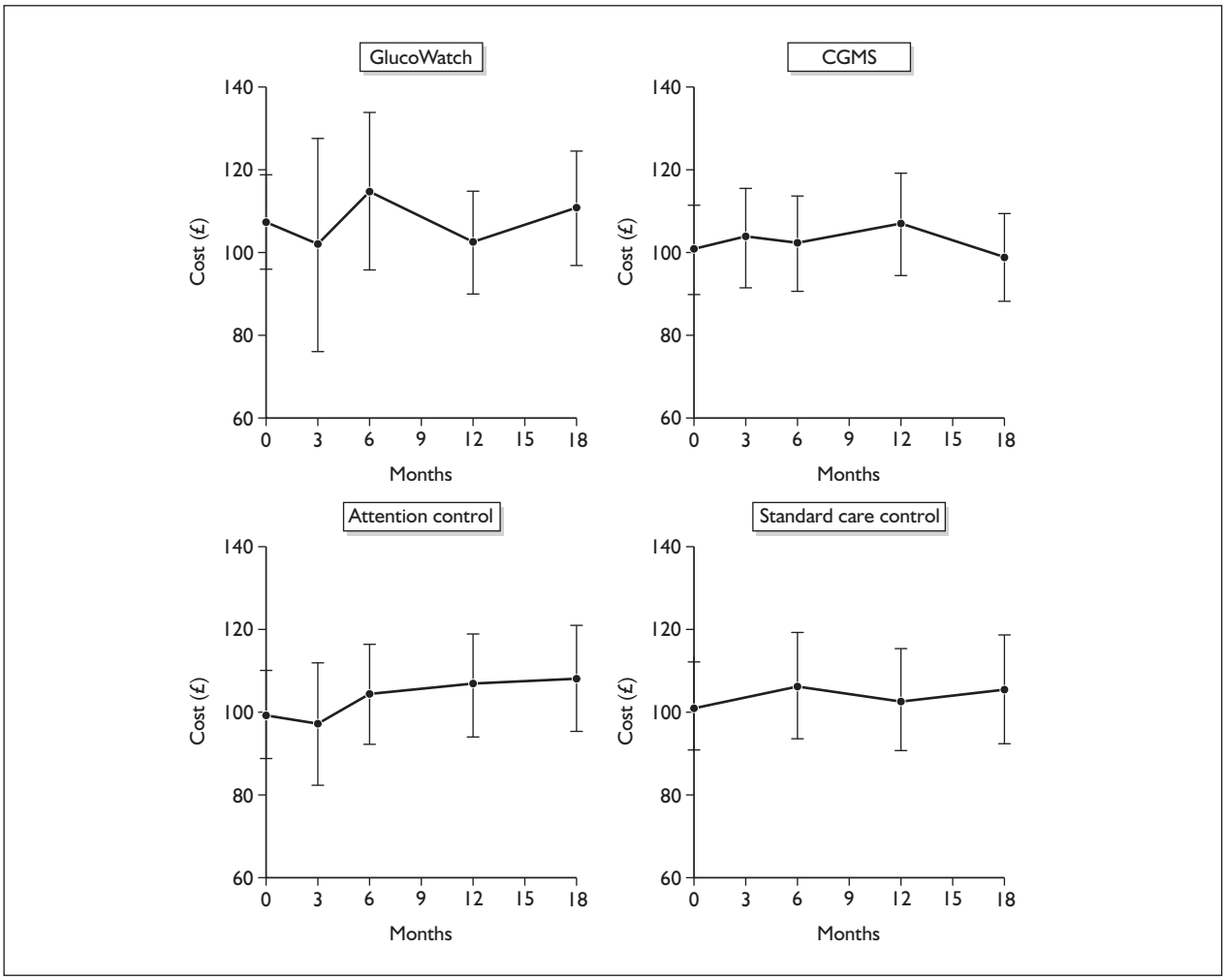

FIGURE 14 *Imputed mean insulin costs.*

18 months, the majority of patients experienced no problem with depression or anxiety.

With regards to change over time there does not appear to be any systematic pattern of change within arms, with the percentage of participants within each response for each question staying reasonably constant over time.

EQ-5D scores

Complete case EQ-5D scores

Table 84 in Appendix 10 shows the results for the EQ-5D scores at baseline, 3, 6, 12 and 18 months by the different trial arms for the non-imputed data. The table includes the mean, standard error and 95% confidence intervals. The results suggest that utility has increased from baseline to 18 months in all four arms of the trial, with the largest increase occurring in the attention control arm.

Figure 38 in Appendix 10 shows the mean EQ-5D scores and 95% confidence intervals for each trial arm at baseline, 3, 6, 12 and 18 months (with the exception of the standard care control arm for which there is no 3-month score). There are no marked differences in the mean EQ-5D score between trial arms at each time point. Across time there do not seem to be any systematic changes in mean EQ-5D score, although in the attention control arm the higher mean score in month 18 than at baseline may indicate improving HRQoL.

Imputed EQ-5D scores

Table 63 shows the results for the EQ-5D scores at baseline, 3, 6, 12 and 18 months by the different trial arms for the imputed data sets. *Figure 28* shows the mean EQ-5D scores and 95% confidence intervals for each arm for each period. As with the non-imputed data there are no significant differences between mean EQ-5D scores for each trial arm at each period. None of the trial arms appears to have a marked effect on participants' EQ-5D scores, with the mean estimates being fairly constant across time. The exception is the CGMS

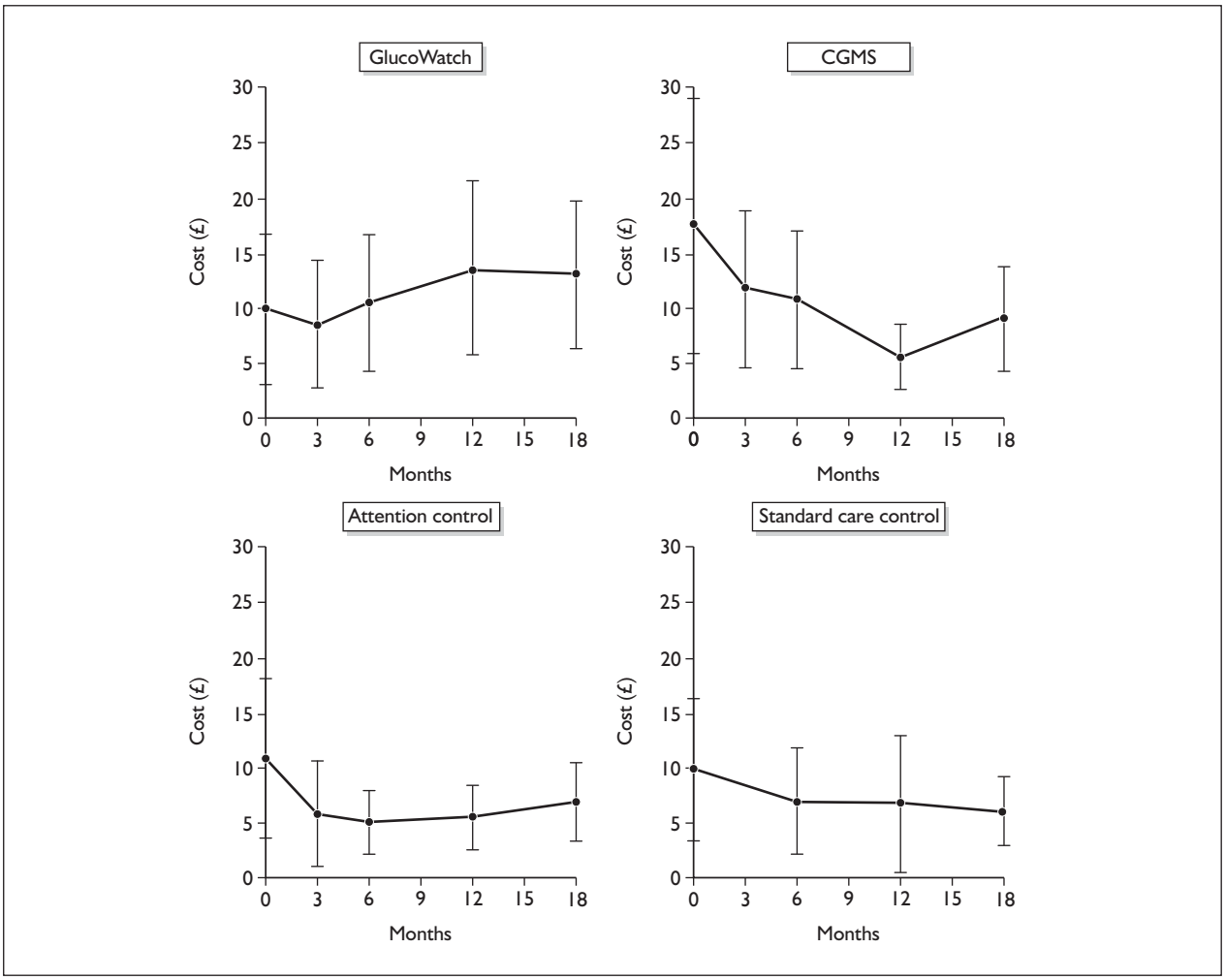

FIGURE 15 *Imputed mean diabetic medicine costs.*

arm in which there appears to be a dip in EQ-5D scores in the first two trial periods (3 months and 6 months). This dip could be due to the CGMS device, as it was in this period that it was worn most often. The gain in utility that was indicated in the attention control arm using the complete case data also appears to hold when the imputed data are used.

EQ-5D regression

Using the data sets imputed using ICE regression, analyses were undertaken on the EQ-5D scores to investigate whether by controlling for other important covariates there was a difference between arms. The results of one of the ordinary least squares regressions undertaken are shown in *Table 64*, in which the dependent variable is the EQ-5D score at 18 months. The regression assumes that the effects of age, type of diabetes, BMI, baseline EQ-5D and gender are constant across treatment arms. The results indicate that none of the treatment arms has a statistically significant effect on EQ-5D score at 18 months once important covariates and the baseline EQ-5D score have been controlled for. With regards to point estimates, the attention control arm and GlucoWatch arm dummy coefficients are both positive thus indicating a higher EQ-5D score in these two arms than in the standard care control arm; however, the point estimates are very small. The regression results indicate that, after controlling for particular covariates (i.e. age, type of diabetes, BMI and gender) and the baseline EQ-5D score, the attention control arm results in the highest utility at 18 months compared with the other three trial arms. Therefore, the results indicate that the attention control arm fares better in terms of the outcome of interest. With regards to the other trial arms, the GlucoWatch arm resulted in better outcomes than the standard care control arm, and the standard care control arm fared better than the CGMS arm.

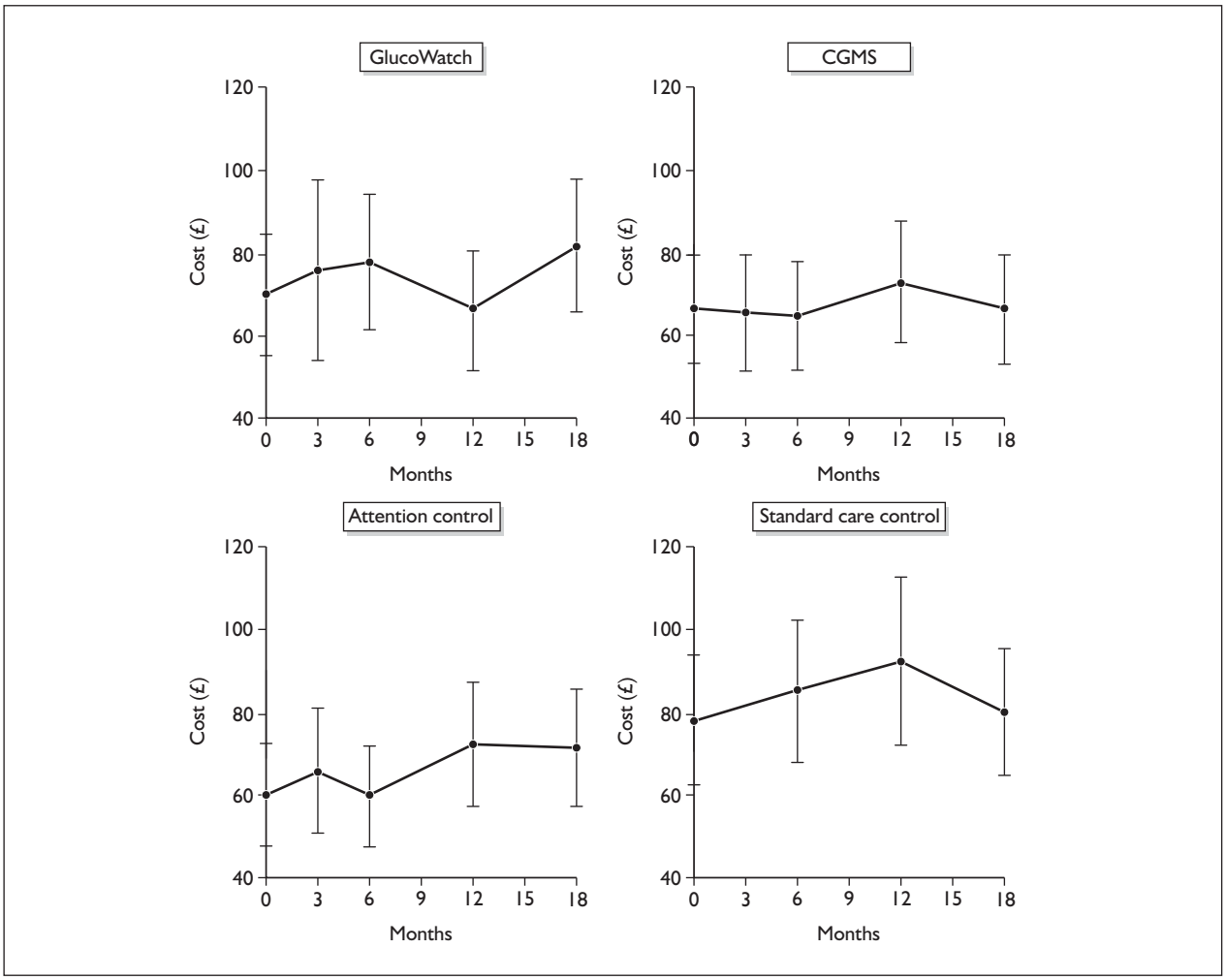

FIGURE 16 *Imputed mean other medication costs.*

The regression results also indicate that the EQ-5D score at 18 months decreases with the age of the participant and the participant's BMI score. The results also indicate that the EQ-5D score at 18 months is higher for those with type 1 diabetes than for those with other types of diabetes, and that men on average have higher EQ-5D scores than women.

As with the cost regressions, the pretrial self-management activities that might affect the clinical effects of the devices were included as interaction terms in regression analyses. The results from these regression analyses are presented in *Tables 85–88* in Appendix 10. As with the cost regressions there are no statistically significant interaction terms.

Days missed from paid employment

Table 65 presents the average number of days of paid employment missed for each trial arm during each trial period. This is based on a complete case analysis. There do not appear to be any systematic differences between the trial arms in terms of the average number of days of paid employment missed during the trial period.

Summary

The MITRE trial has not shown any consistent or marked differences between trial arms with regards to both mean costs and EQ-5D scores. No differences are formally statistically significant at the usual error probabilities. In terms of point estimates it appears that the participants in the attention control arm fared better in terms of both higher EQ-5D scores at 18 months and lower overall costs than the other three arms.

With other covariates and baseline EQ-5D scores controlled for when examining the 18-month EQ-5D scores, the attention control arm still fared better in terms of higher EQ-5D scores. When controlling for other covariates, the attention

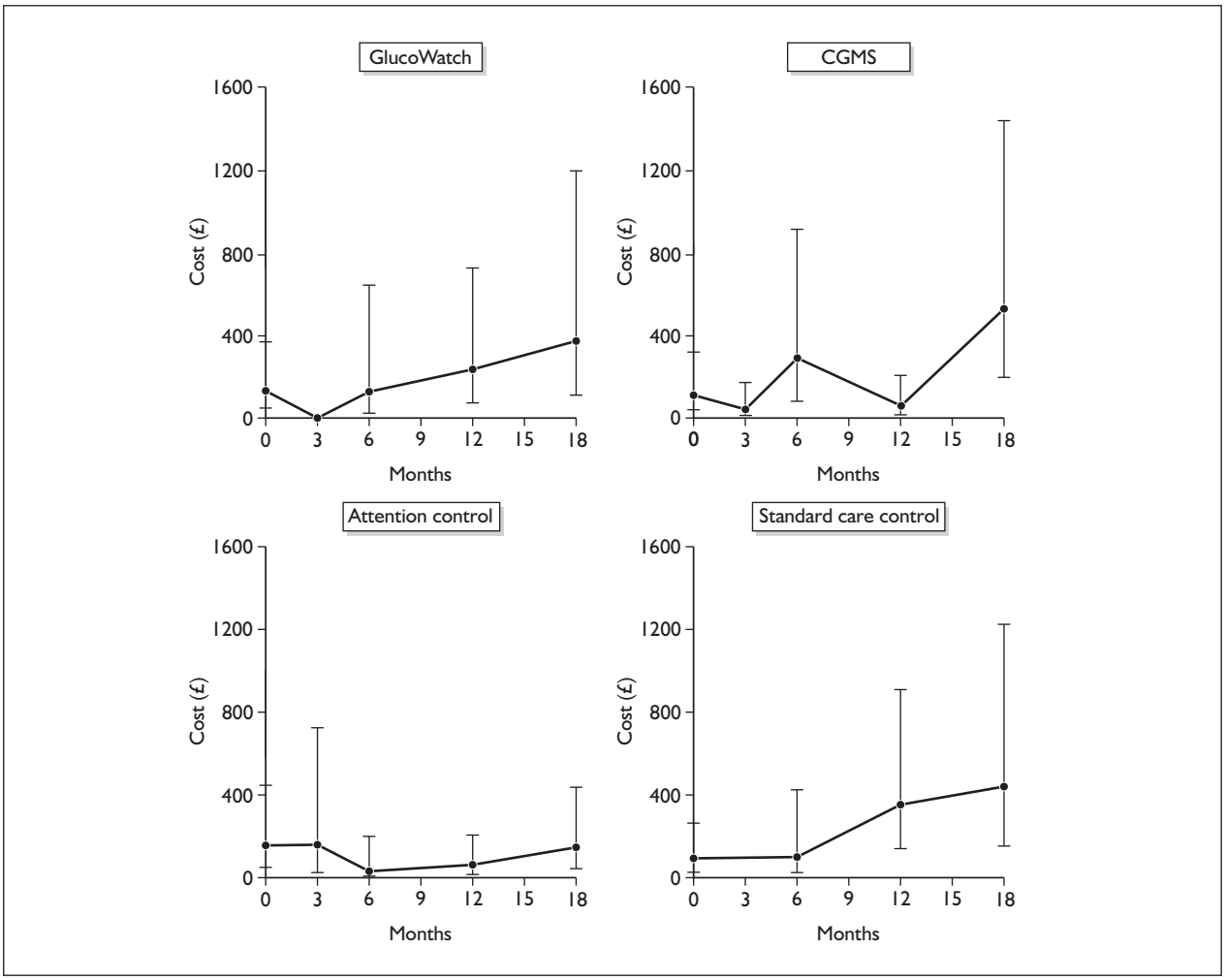

FIGURE 17 *Imputed mean hospitalisation costs.*

control arm also fared better in terms of lower total costs over the trial period than the other three arms. This suggests that after controlling for covariates the attention control arm still dominated the other trial arms in that it has better outcomes (in terms of EQ-5D scores) and lower costs.

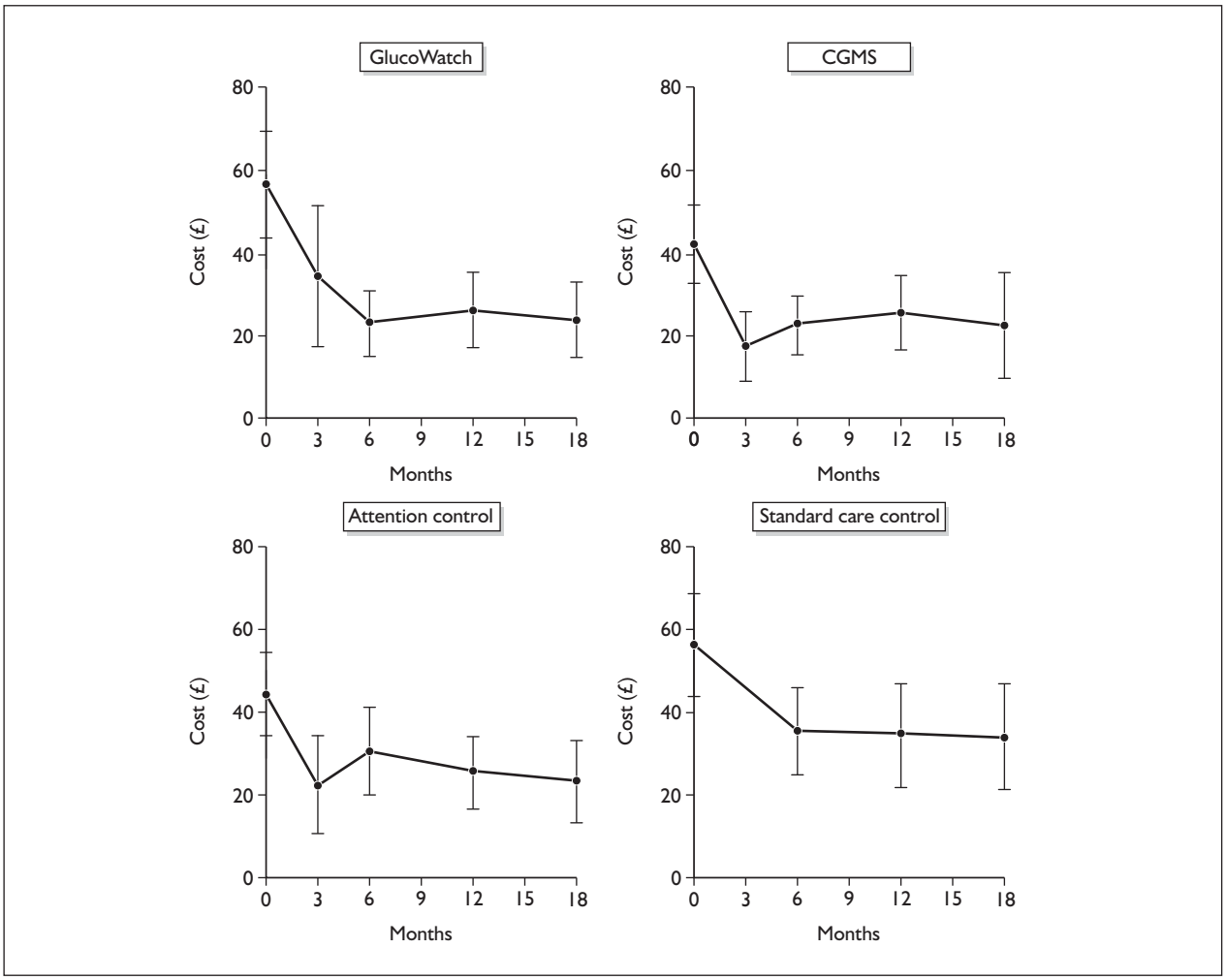

FIGURE 18 *Imputed mean diabetes clinic costs.*

TABLE 59 *Total costs (£) over the trial period*

	GlucoWatch	CGMS	Attention control	Standard care control
Mean	3883.56	6129.556	2634.136	4209.403
Standard error	536.6498	769.6195	324.6382	577.9442
95% CI lower	2831.745	4621.129	1997.857	3076.653
95% CI upper	4935.374	7637.982	3270.416	5342.153

CI, confidence interval.

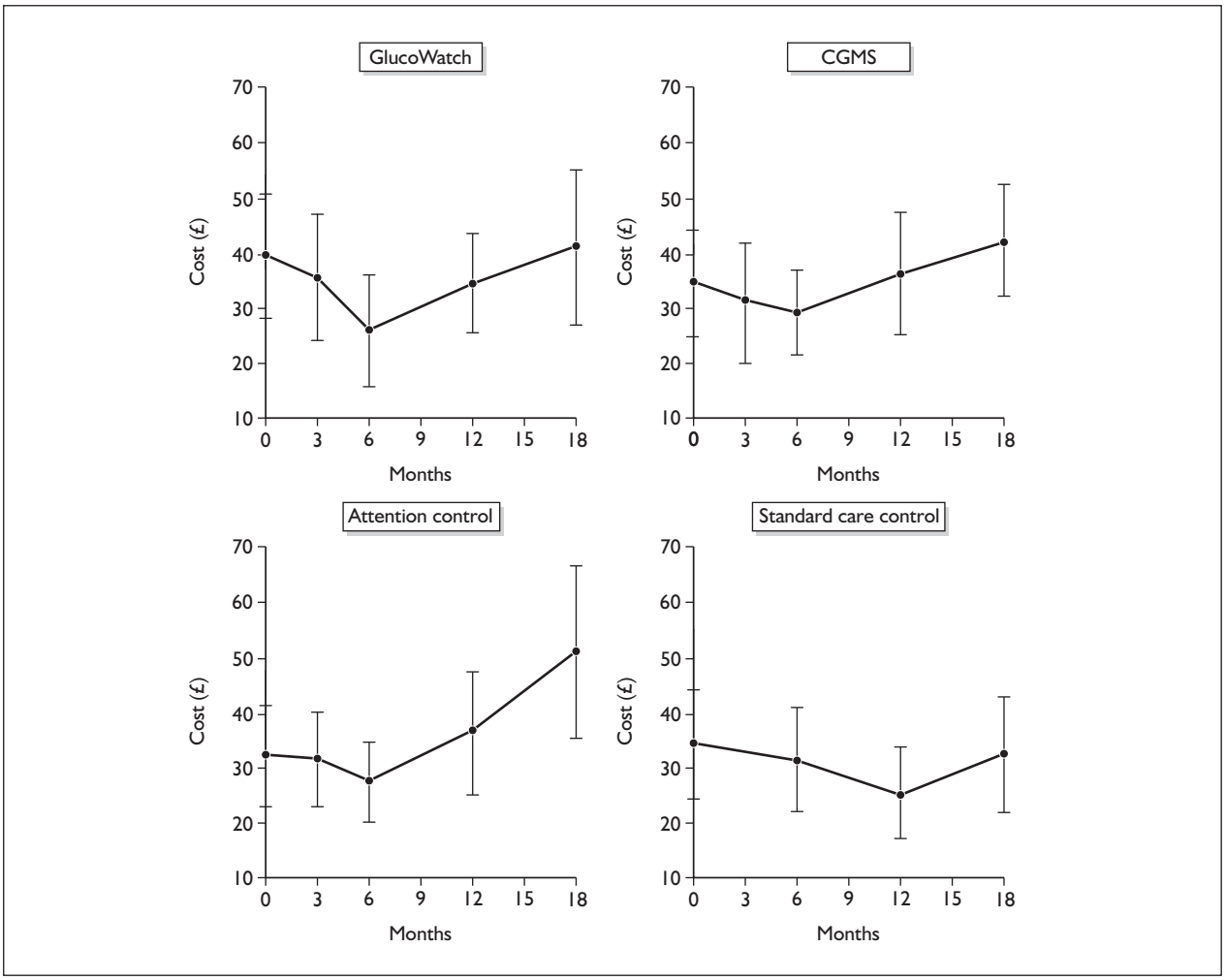

FIGURE 19 *Imputed mean GP clinic costs.*

TABLE 60 *Total costs (£) excluding hospitalisation costs over the trial period*

	GlucoWatch	CGMS	Attention control	Standard care control
Mean	2742.686	4213.873	1988.311	2352.084
Standard error	129.8799	186.2296	98.21064	104.4833
95% CI lower	2488.126	3848.869	1795.822	2147.3
95% CI upper	2997.246	4578.876	2180.8	2556.867

CI, confidence interval.

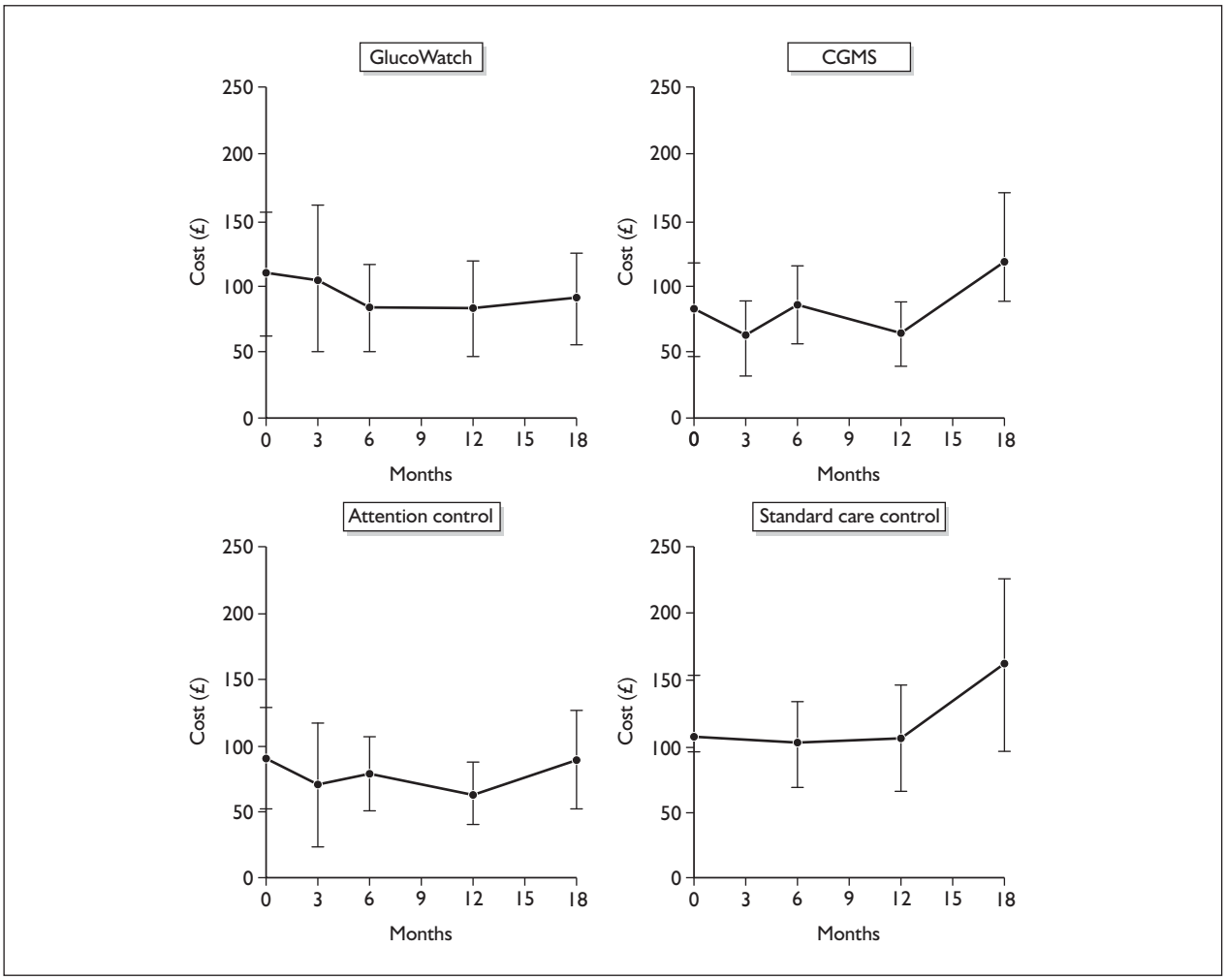

FIGURE 20 *Imputed mean other resources costs.*

TABLE 61 *Total costs over the trial period: regression results*

	Coefficient	Standard error	*p*-value
Age	9.137	15.934	0.566
Type 1 diabetes	–1676.031	621.56	0.007
Body mass index	15.291	38.380	0.690
Male	–278.069	438.241	0.526
Attention control	–1410.619	626.7615	0.024
CGMS	1731.656	1009.538	0.086
GlucoWatch	–531.8688	807.1885	0.510
Constant	4432.978	1448.12	0.002

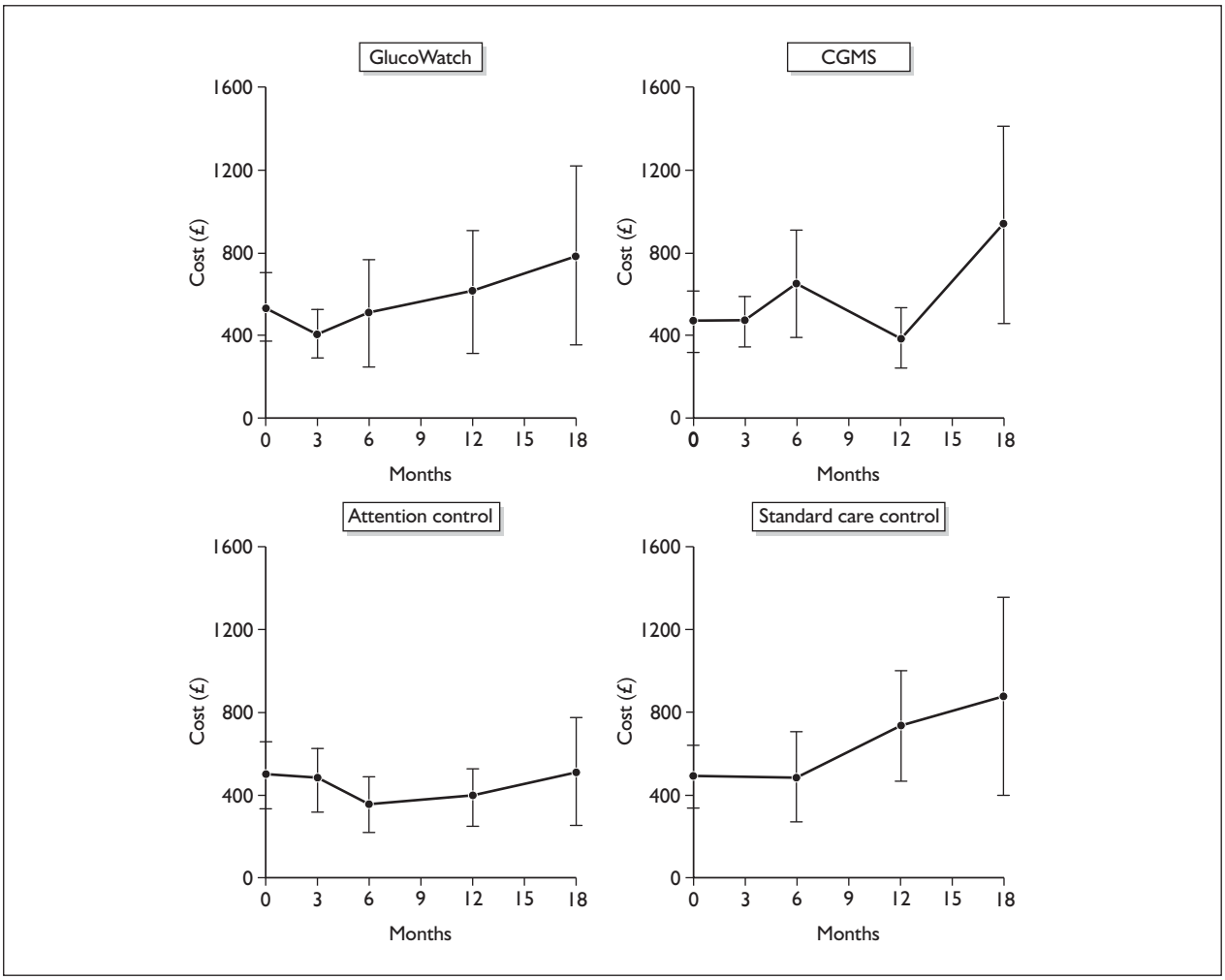

FIGURE 21 *Imputed mean total costs.*

TABLE 62 *Total costs excluding hospitalisation costs over the trial period: regression results*

	Coefficient	Standard error	*p*-value
Age	5.62664	4.358787	0.197
Type 1 diabetes	–364.3221	145.0538	0.012
Body mass index	73.03396	14.0117	0.000
Male	–42.78638	113.9083	0.707
Attention control	–387.7803	132.2323	0.003
CGMS	1790.103	206.3235	0.000
GlucoWatch	295.9567	168.1541	0.078
Constant	227.9488	476.4788	0.632

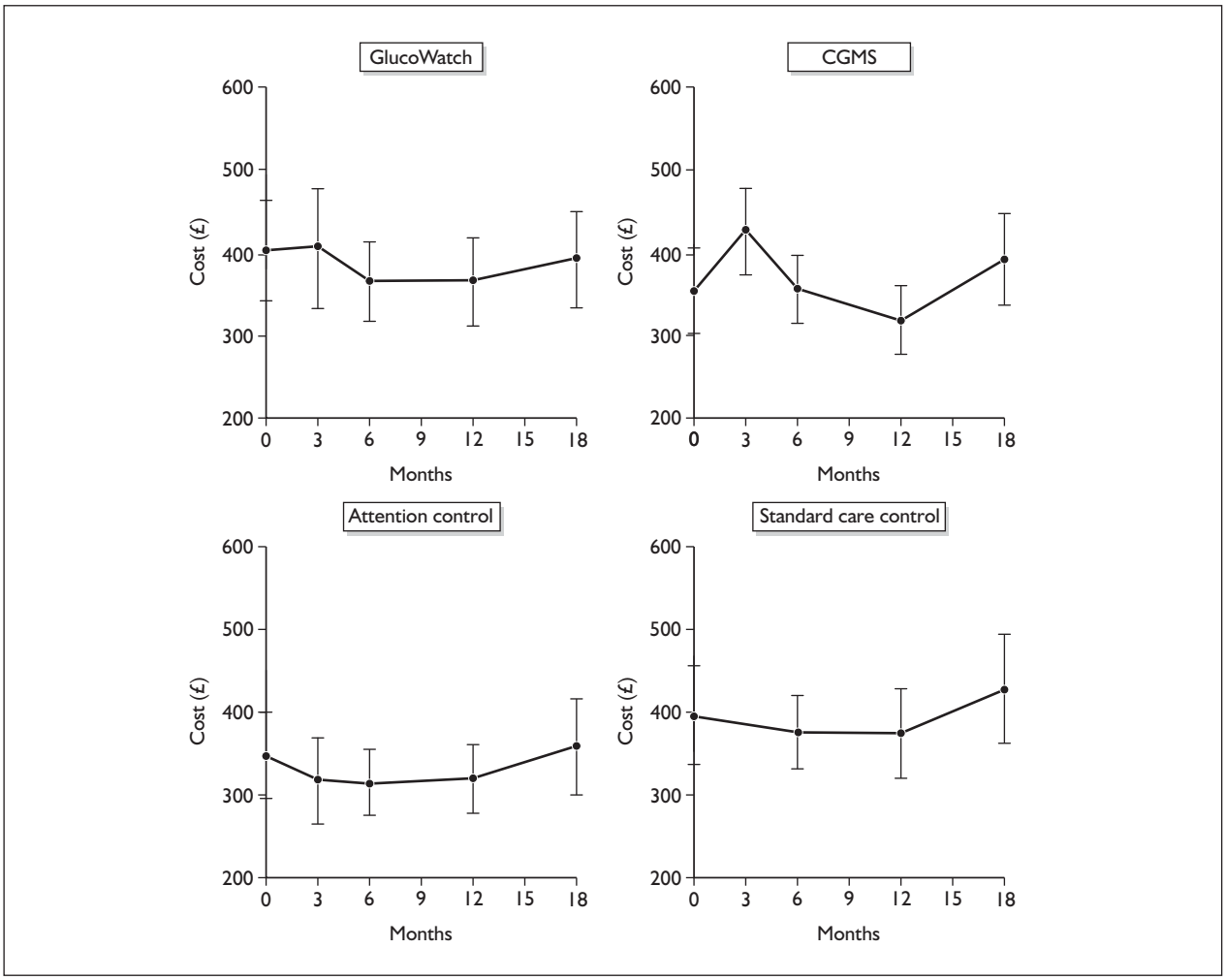

FIGURE 22 *Imputed mean total costs (excluding hospitalisation costs).*

TABLE 63 *Imputed EQ-5D scores*

	GlucoWatch	CGMS	Attention control	Standard care control
Baseline EQ-5D				
Mean	0.6717181	0.7001939	0.721989	0.6694628
Standard error	0.0349358	0.032986	0.0337425	0.0332896
95% CI lower	0.6030373	0.6353462	0.6556543	0.6040182
95% CI upper	0.7403989	0.7650416	0.7883237	0.7349073
3-month EQ-5D				
Mean	0.6671868	0.6609587	0.7224398	
Standard error	0.0390989	0.037934	0.0362096	
95% CI lower	0.5902429	0.5863073	0.6511819	
95% CI upper	0.7441307	0.7356101	0.7936976	
6-month EQ-5D				
Mean	0.7137618	0.6228653	0.7198611	0.6690004
Standard error	0.0375189	0.039232	0.0371481	0.0404423
95% CI lower	0.6400028	0.5457387	0.6468312	0.5894944
95% CI upper	0.7875208	0.6999919	0.7928911	0.7485064
12-month EQ-5D				
Mean	0.689628	0.6592545	0.7225261	0.6901344
Standard error	0.0377827	0.0379356	0.0349086	0.0363606
95% CI lower	0.6153504	0.5846764	0.6538989	0.6186526
95% CI upper	0.7639055	0.7338327	0.7911533	0.7616161
18-month EQ-5D				
Mean	0.6923357	0.6927319	0.7476758	0.6662872
Standard error	0.0343566	0.0362188	0.0343509	0.0353696
95% CI lower	0.6247937	0.6215288	0.6801451	0.5967538
95% CI upper	0.7598777	0.7639349	0.8152066	0.7358206

CI, confidence interval.

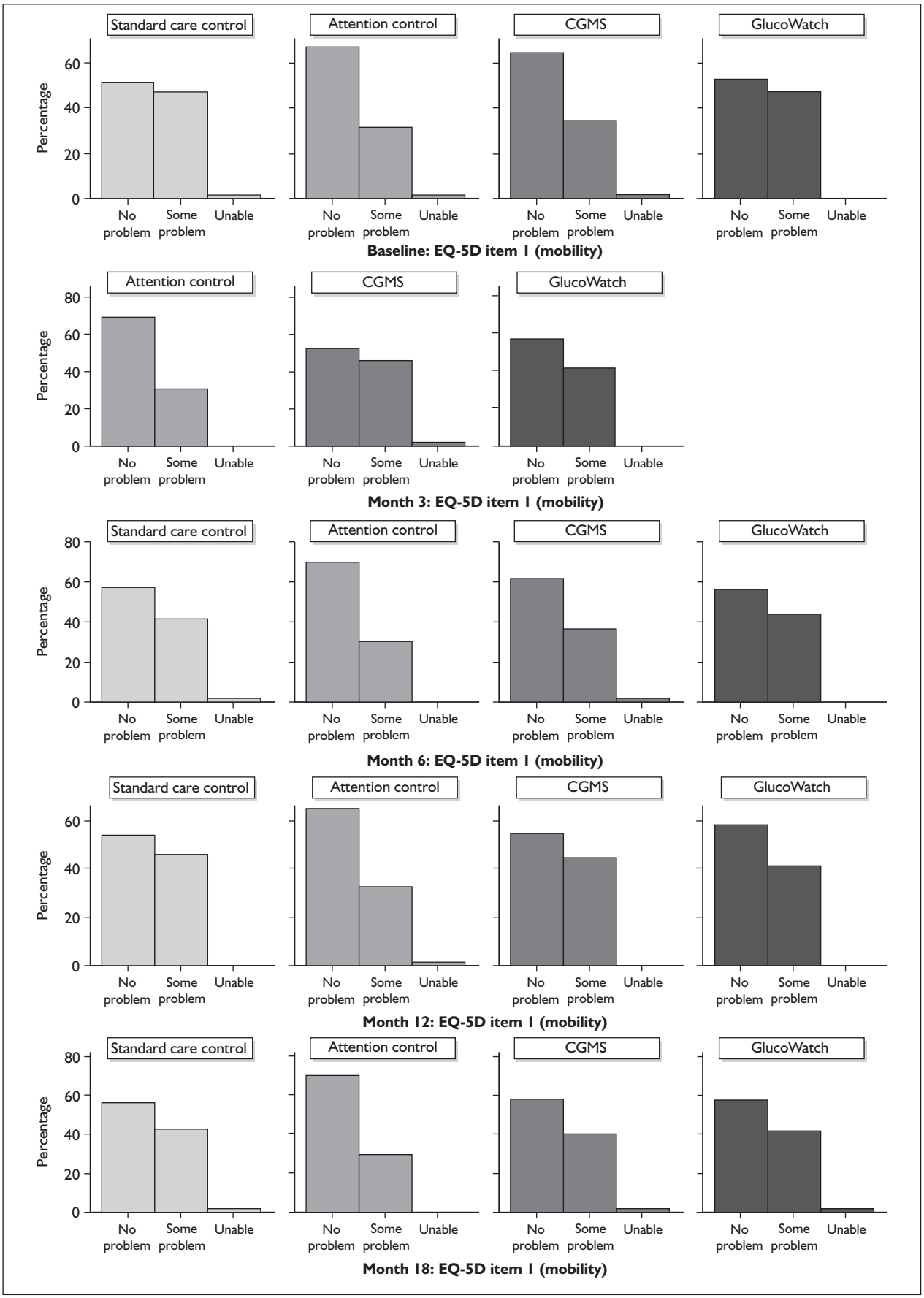

FIGURE 23 *EQ-5D responses to the mobility question by trial arm.*

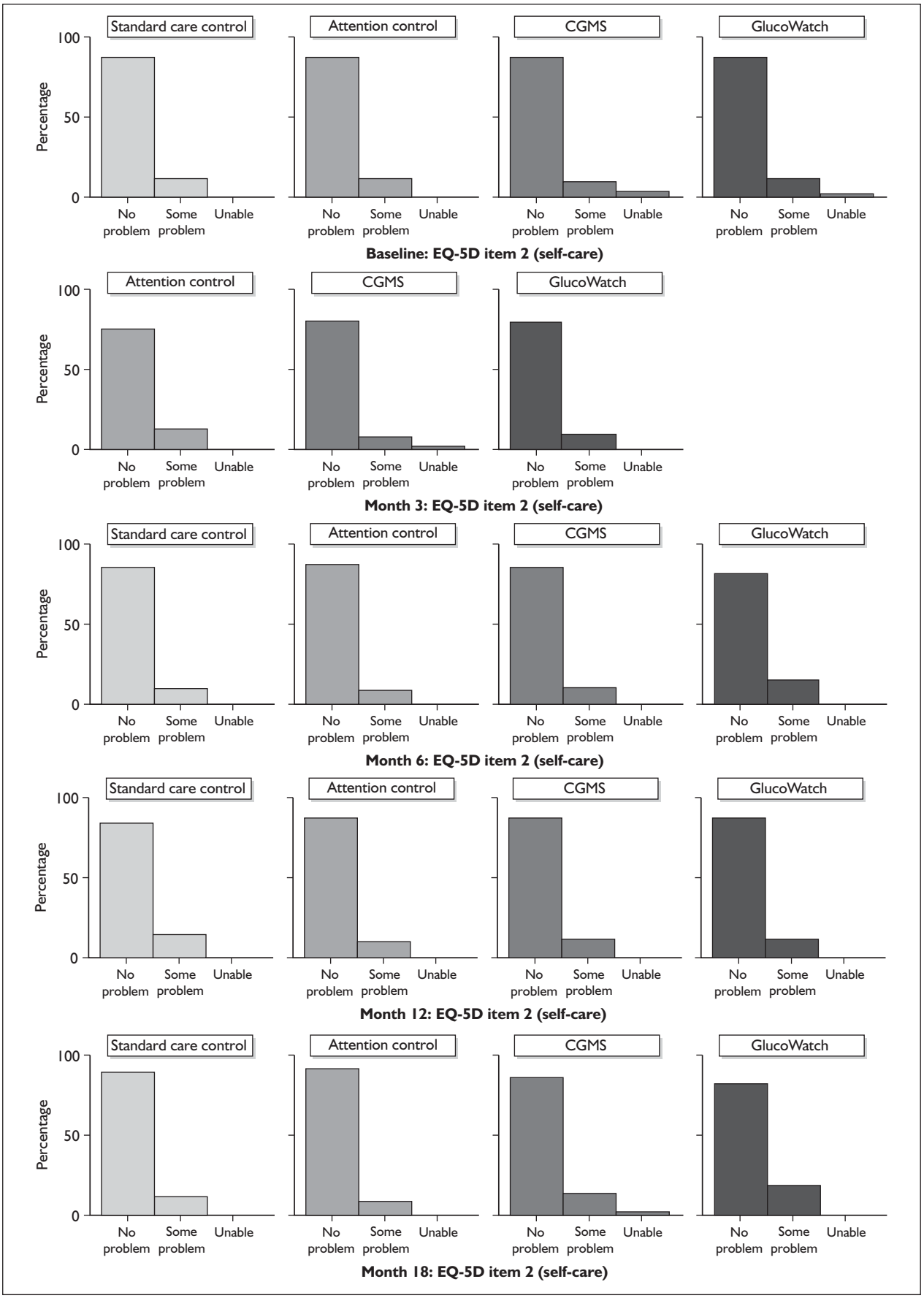

FIGURE 24 *EQ-5D responses to the self-care question by trial arm.*

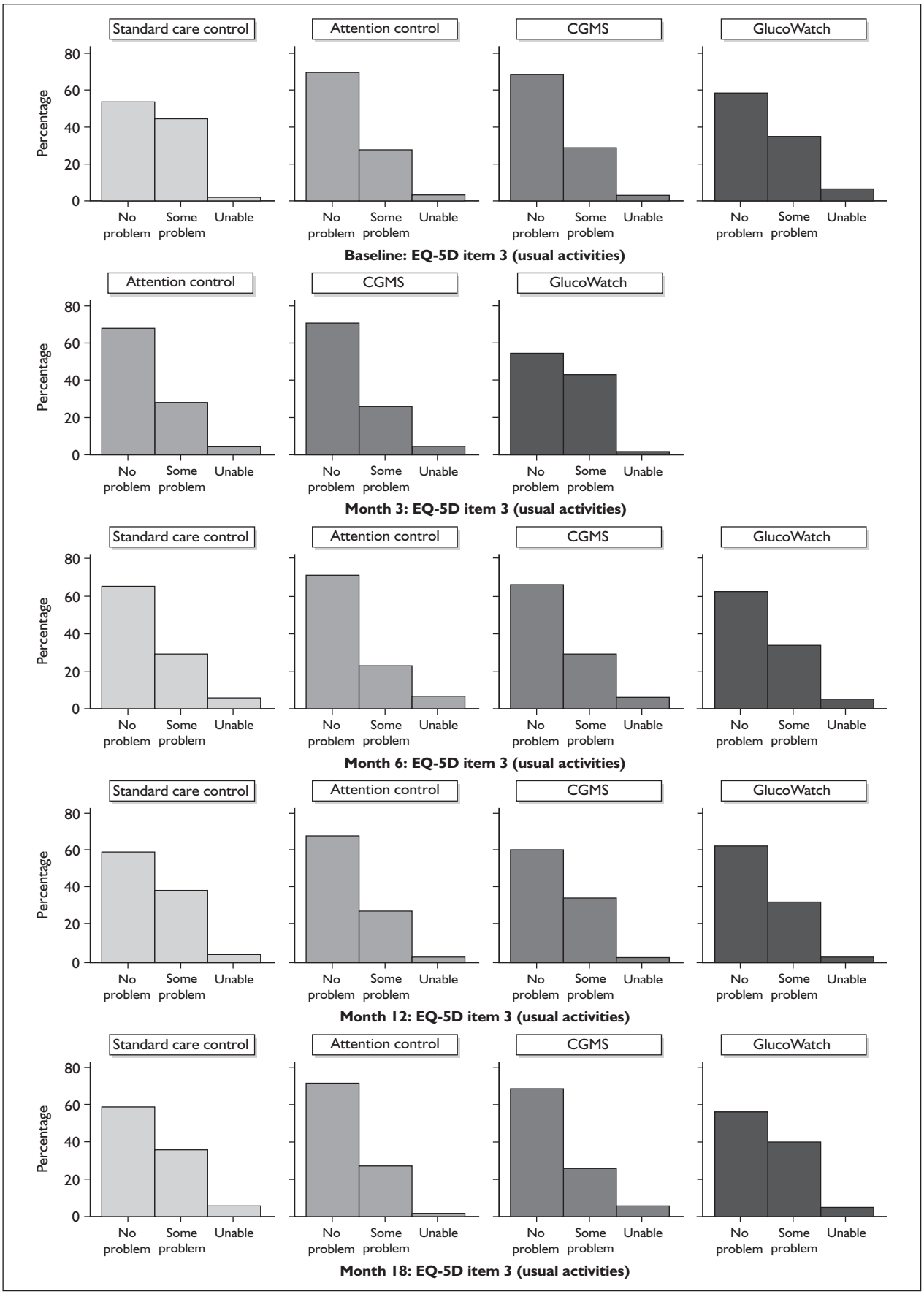

FIGURE 25 *EQ-5D responses to the usual activity question by trial arm.*

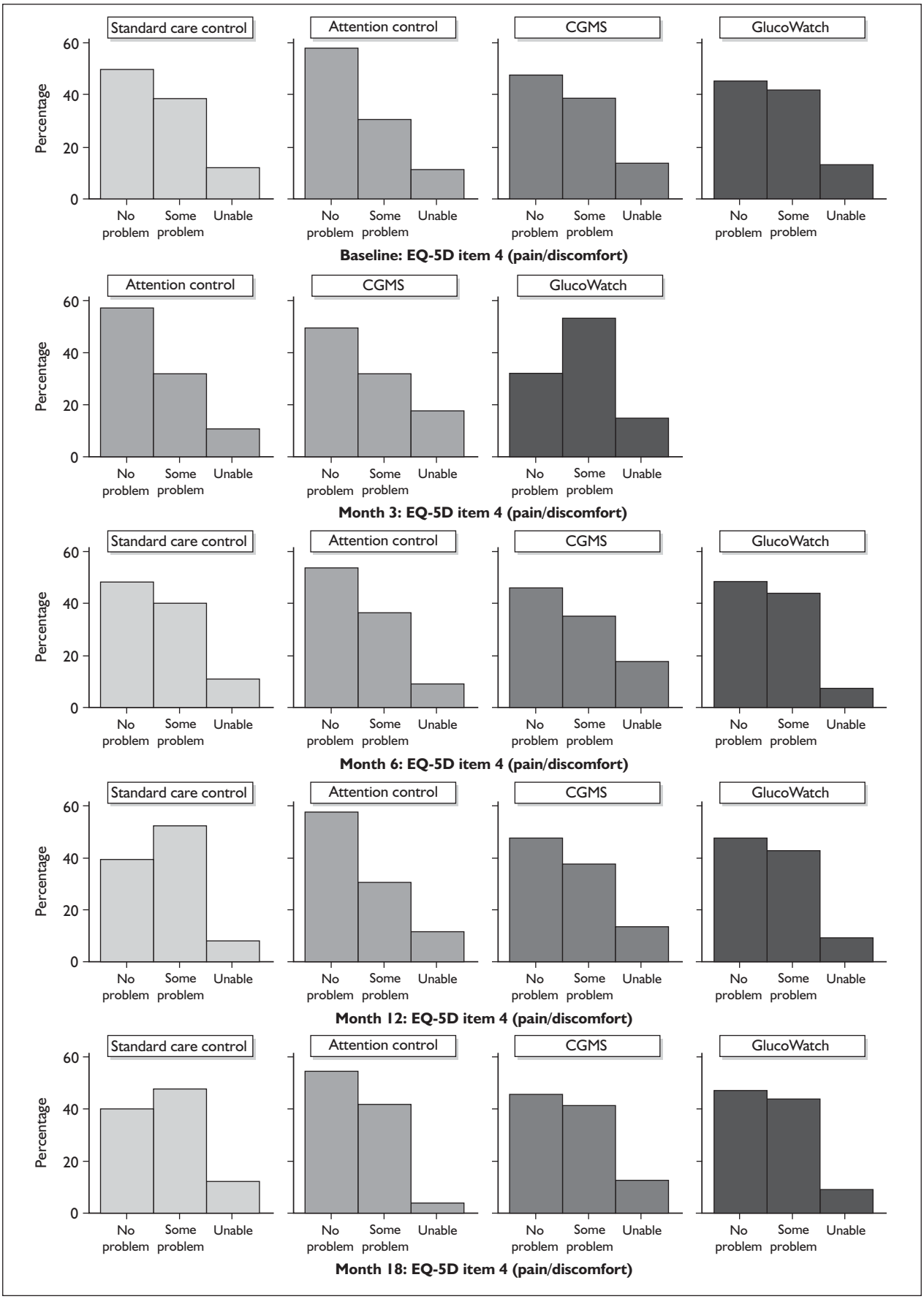

FIGURE 26 *EQ-5D responses to the pain/discomfort question by trial arm.*

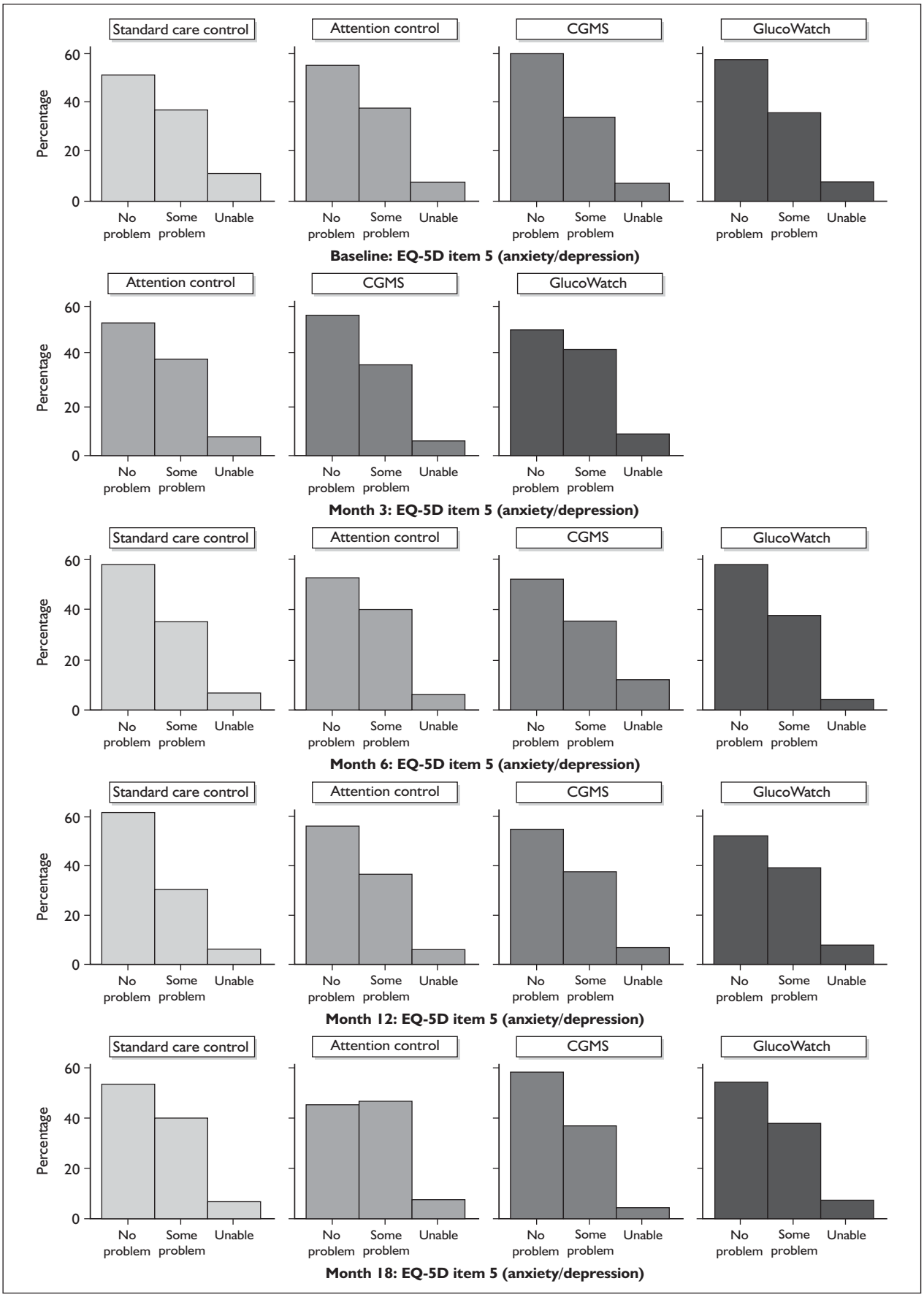

FIGURE 27 *EQ-5D responses to the anxiety/depression question by trial arm.*

TABLE 64 *EQ-5D score at 18 months: ordinary least squares regression*

	Coefficient	Standard error	*p*-value
Age	–0.0002	0.0009781	0.827
Type 1 diabetes	0.0311	0.0340573	0.361
Body mass index	–0.0079	0.0028112	0.005
Male	0.01461	0.0231845	0.529
Baseline EQ-5D score	0.65223	0.0568754	0.000
Attention control	0.01265	0.0352433	0.720
GlucoWatch	0.00708	0.0381882	0.853
CGMS	–0.0007	0.034312	0.983
Constant	0.4552	0.1117797	0.000

TABLE 65 *Average number of days of paid employment missed during the trial period for employed participants*

	GlucoWatch	CGMS	Attention control	Standard care control
Baseline				
Mean	5.590909	3.9434	3.557692	1.18
SD	17.54372	11.7807	13.5667	2.5769
12 weeks				
Mean	0.8571429	0.33333	1.578947	
SD	2.031268	0.78606	3.507764	
26 weeks				
Mean	2.6	0.65854	1.309524	3.5946
SD	6.907796	1.9699	3.196706	15.4299
52 weeks				
Mean	3.411765	4.47368	2.5	3.27273
SD	15.45299	16.0704	9.534515	14.9086
78 weeks				
Mean	2.314286	8	1.95	0.91667
SD	5.109227	21.7486	4.506121	3.58867

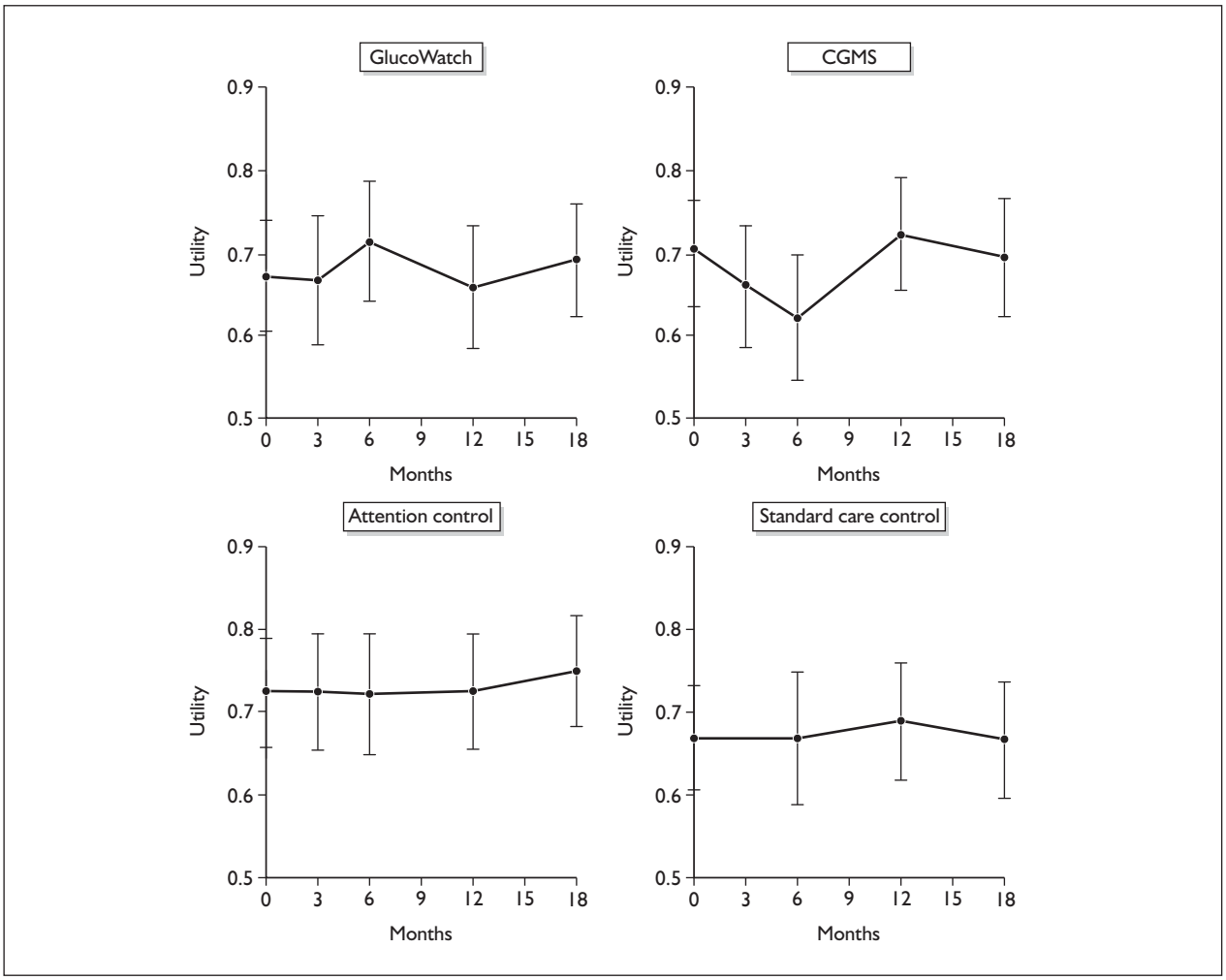

FIGURE 28 *Imputed mean EQ-5D utility scores.*

Chapter 8
Discussion

Clinical outcomes

As reported in the literature review, the clinical value of the additional information provided by continuous glucose monitoring devices remains to be established. The studies reported in the literature have used diverse designs and a variety of samples.

Although some single group studies have demonstrated changes in HbA1c over time, the lack of a control group renders these findings insufficient to provide clear evidence of the effectiveness of continuous glucose monitoring devices.[45,46,48,50,54,57,59,61,62,65] The studies that have included a control group have produced contradictory findings on HbA1c.[49,52,53,60,64,66] It is of note that many of these studies did not have sufficient power. A number of these studies also examined participants younger than those in this study, which set out to investigate the clinical impact of continuous glucose monitoring devices in poorly controlled insulin-requiring adults. The current study is also one of only a few that have included adults with type 2 diabetes within their sample.

The percentage change in HbA1c from baseline to 18 months was the primary indicator of long-term efficacy in this study, and percentage change in HbA1c from baseline to 6 months and baseline to 12 months assessed efficacy in the medium term. The change to 3 months assessed the short-term effects, as this covered the period of relatively intensive use of the devices. No significant differences between any of the groups were found in the percentage changes in HbA1c at any of the assessment times. The findings of the intention to treat analysis clearly indicated no advantage of having a continuous glucose monitoring device in relation to HbA1c change in the group of insulin-dependent people with diabetes studied. This finding complements that reported in a study of device use in children and adolescents[53] and suggests little clinical value of these devices in relation to HbA1c change in the group of insulin-requiring poorly controlled people with diabetes in this study.

Overall changes in HbA1c were found for all groups throughout the course of the study. This was highest in the early phases of the study (5.8%) and declined to 18 months (4.0%). In addition, approximately 25% of participants achieved what was defined as a clinically important change of 12.5% in HbA1c at each of the assessment times. These findings suggest that participation in the study did lead to some improvement in HbA1c but that this was not specific to the groups who received the devices. Importantly, at the times when the standard care control group was assessed, this group showed an improvement that was no different to the improvements of the other groups in the study who had greater contact with health-care professionals and of whom two received continuous glucose monitoring devices. It is also of note that, although not significant, one of the device groups (GlucoWatch) produced the smallest change in HbA1c and the lowest numbers achieving a clinically meaningful reduction in HbA1c at all time points.

Previous research on the effects of continuous glucose monitoring devices on the frequency of hypo- and hyperglycaemic events has been equivocal. In this study, no significant differences were found between the groups in the number of hypo- and hyperglycaemic events.

A per protocol analysis was applied to determine if a minimum use of the devices led to any improvement in clinical outcomes. The rationale behind this was to examine the efficacy of the devices given the 'underusage' in relation to the protocol, especially in the case of the GlucoWatch. The minimum specification of use was for the CGMS to be worn at least once and the GlucoWatch to be worn at least three times during the 3-month intensive period of study. In addition, the attention control group needed to attend at least one clinic visit. The per protocol analysis included approximately 80% of those recruited in the 6-, 12- and 18-month analyses and 70% of the three groups assessed at 3 months. Overall, this per protocol analysis indicated no particular advantage at any of the time points of having access to the additional information provided by the continuous glucose monitoring devices.

As it has been suggested that these devices and the additional information they provide may be of particular value in specific groups, an exploratory analysis of subgroups was undertaken. Comparisons were made according to age, the number of injections, BMI, SMBG, exercise, diet and smoking. In none of these analyses did any subgroup appear to receive any particular benefit from having the additional information provided by the devices. It is important to note, however, that the study was not powered to perform these analyses and the findings must be considered as exploratory and tentative.

As the role of continuous glucose monitoring devices in this study was to provide more detailed information for the trained research nurses, it may be expected that this would have resulted in an increase in the number and nature of their treatment recommendations to the participants. The findings, however, indicated that participants with the devices did not receive more or different types of treatment recommendations than those in the attention control group. This finding raises a number of issues as to the value of the additional information provided by continuous glucose monitoring devices to trained health-care professionals and the extent to which it should add to or alter the information already provided. It is often assumed that the additional information provided by continuous glucose monitoring devices is better. Although it may offer some insights into the timing and reasons for blood glucose excursions, these do not appear to be translated into more or different treatment recommendations compared with those with similar contact with health-care professionals. In this study the nurses underwent detailed training in the interpretation of the additional information, and regular meetings were held to ensure consistency of their analysis and resulting advice. It does remain possible, however, that different training provided to the nurses in the analysis of the records may have resulted in different advice being offered to those who wore the devices.

Overall, in relation to clinical measures, the conclusion to be drawn from the findings of the study is that, for unselected individuals with poorly controlled insulin-requiring diabetes, the provision of continuous glucose monitoring devices produces no perceivable clinical advantage either by intention to treat analysis or by per protocol analysis. Furthermore, the availability of the additional information provided by continuous glucose monitoring devices did not in this study lead to trained nurses offering more or different advice to the unselected individuals with poorly controlled insulin-requiring diabetes.

Health economic evaluation

The MITRE trial has not shown any consistent or marked differences between trial arms with regards to both mean costs and EQ-5D scores. No differences are formally statistically significant at the usual error probabilities. In terms of point estimates it appears that the participants in the attention control arm fared better in terms of both higher EQ-5D scores at 18 months and lower overall costs than participants in the other three arms. Once other covariates, and baseline EQ-5D scores when examining 18-month EQ-5D scores, had been controlled for the attention control arm, it still fared better in terms of higher EQ-5D scores at 18 months and lower total costs over the trial period than the other three arms. This indicates that the two intervention arms, the CGMS arm and the GlucoWatch arm, were dominated by the attention control arm as they had worse outcomes in terms of EQ-5D scores and were more costly. The CGMS arm was also dominated by the standard care control arm, although the GlucoWatch arm was not as it had marginally better outcomes but also a higher cost.

Given that the attention control arm dominated the two intervention arms in the economic analysis and that it also performed better in terms of the clinical analysis, it was considered that an extrapolation of results was not necessary and therefore only a within-trial analysis is presented. As the results indicated a lower cost and higher benefit for the attention control arm in the trial period, the attention control arm appears to be the optimal treatment strategy, and an extrapolation of the results over the participants' lifetimes would not be expected to alter this based on the evidence produced from the MITRE trial (i.e. we would still expect the costs of participants in the attention control arm to be lower and their outcomes to be better than those in the other arms over the participants' lifetimes and thus the attention control arm would still be expected to dominate the other trial arms). It might be assumed that the costs in the standard care control arm would have been the lowest given that it had the lowest trial-specific resource use associated with it. However, this arm was associated with higher non-trial-specific resource use costs than the attention control arm, suggesting that it was less effective

at reducing other health-care resource use. In particular, it is worth noting that the standard care control arm had the highest non-trial-specific diabetes clinic costs. This might have been a result of patients in the other arms saving any problems that they had which required a visit to the diabetes clinic until their trial-specific appointments.

A search of the NHS Economic Evaluation Database was performed to see if there were any other relevant economic evaluations of the GlucoWatch and CGMS that could help to further inform this evaluation. Only one full economic evaluation was identified, that of Eastman *et al*.[125] However, this study focused on the use of the GlucoWatch in children and adolescents (aged 7–17) with type 1 diabetes, whereas the MITRE study excluded individuals below 18 years of age; therefore, the Eastman *et al*. study is not considered to be relevant to the decision problem considered.

Given the absence of other relevant economic evaluations of the devices and the results shown in the MITRE trial, it appears that neither the CGMS device nor the GlucoWatch device should be considered for use in the management of diabetes.

This economic evaluation has attempted to consider all NHS resource costs during the trial; this is considered to be the most appropriate cost perspective within the UK, as highlighted by the NICE reference case.[80] The analysis has also used the EQ-5D score to measure a patient's utility, which is considered to be the most appropriate valuation method for health states by NICE. The EQ-5D questionnaire may not be sensitive enough to capture changes in HRQoL in this patient population. However, the findings in terms of EQ-5D scores were mimicked by those of the clinical analysis, which did not show any benefits related to the CGMS or GlucoWatch arms compared with the attention control arm using other measurement instruments.

The economic evaluation also suffers from problems caused by missing data. In an attempt to overcome these problems, multiple ICE has been used. However, this method is only valid if it is assumed that the data are missing at random or missing completely at random. This clearly may not be the case and hence the validity of using ICE can be called into question.

The economic evaluation of the MITRE trial has found that, based on the point estimates of cost and HRQoL, the attention control arm dominated the other trial arms (i.e. it had the lowest cost and the highest HRQoL). However, this result has several caveats. Issues surrounding missing data and poor device compliance leave the results open to question.

Participant-reported outcomes

Acceptability

Most studies have focused on the clinical efficacy of medical devices, and relatively little attention has been directed towards patients' or health professionals' acceptability of the devices. This area is of particular importance in considering the introduction of new health technologies into clinical practice. Devices may demonstrate clinical value, but if potential users find them unacceptable or choose not to use them then it is unlikely that they will become incorporated into routine care. In this trial particular attention was directed to acceptability in its broadest sense. To this end a number of assessment tools were developed specifically for the study to explore relative levels of and factors involved in use and acceptability of the devices. Some of these assessments were directed towards specific features of the devices. Acceptability of the two devices was compared, and factors influencing acceptability were also investigated.

Although not simply an assessment of the devices, the first level of acceptability involved an examination of participation rates in the intervention. As part of the process of informed consent, potential participants in this study received information on randomisation and the probability of being allocated to any arm (0.25), to one that had a device (0.5) and to an arm that required increased attendance at the hospital (0.75). In addition, they were given some information on the devices, and some invitees may have had previous knowledge of the devices. A decision to participate in this study obviously involved more than an evaluation of the devices. For studies to have external validity, high levels of patient participation are required, but there are increasing concerns that recruitment to trials is often much lower than anticipated.[126] The overall participation rate in this trial was not high at 25%. This is not dissimilar to other diabetes trials, for example the Dose Adjustment for Normal Eating trial sent invitation letters to 1016 eligible participants and randomised 169 (17%).[127] The nature of this trial and the demands made of

participants are not strictly comparable, but many studies, particularly in the area of continuous glucose monitoring devices, do not report participation rates.

A number of factors have been identified in systematic reviews that affect participation in RCTs, including the additional demands that the trial entails, patient preferences for particular treatments, worry caused by uncertainty and the possible risks associated with the trial, and concerns about information and consent. The findings in this study are in line with a systematic review[129] of reasons for non-participation in clinical trials that identified additional demands on the patient as being the main reason for refusal. When reasons were elicited in this study, time commitments and increased frequency of visits were the prime reasons given for non-participation.

The third most frequently reported reason in this study involved concerns about being randomised to one of the device arms (CGMS). Randomisation concerns have been identified in qualitative studies of non-participants,[129] but the issue here may have been specific to what was 'perceived' before participation as being the most invasive of the devices rather than to the process of randomisation itself.

Once allocated to groups, a more specific assessment of the acceptability and perceived value of the devices is their continued use and frequency of use. Lack of acceptability, as evidenced in the failure to continue to use devices, will limit the likelihood of their widespread roll-out in a health-care system. In this study the two devices had different levels of control and flexibility for patients. The GlucoWatch could be worn at will by patients whereas the CGMS required fitting by the nurse. Despite its flexibility, the GlucoWatch showed a more rapid decline in use over the study, with 57% continuing to use the device after the intensive period (3 months) and only 20% continuing to use the device by the end of the study (18 months). The comparable usage for the CGMS was 88% after the intensive period and 67% at 18 months.

During the 3-month intensive phase of the study the frequency with which participants were asked to use the two devices was different, in line with their relative levels of flexibility of use. The CGMS patients were asked to attend a visit to have the device fitted three times, whereas those with the GlucoWatch were recommended to wear it on a minimum of 12 occasions. The findings showed that participants used the devices significantly less than requested. The per protocol assessment, which specified a lower minimum use, showed that 96% of the CGMS group had it fitted at least once and 68% of the GlucoWatch group used the device at least three times. These findings emphasise that the likelihood of patients using these devices relatively intensively is low.

The GlucoWatch is commonly associated with skin irritation.[39,40,82–86,99] The declining use of the GlucoWatch in studies of children and adolescents has been attributed to skin irritation.[99] In the study by the DirecNet group that had a follow-up period of 6 months,[53] skin irritation was reported in all patients. Similarly, in this study skin reactions were reported in almost all of the GlucoWatch patients (84–98%) at each assessment point, and a number (9–23%) removed the device because of a skin reaction. It was also the most common reason given for stopping use of the device in this study. For the CGMS, skin irritations occurred in 14% of participants in the intensive period, declining to 6% at 18 months. Very few of the patients were still using the devices at the 18-month assessment and so the proportions reporting skin reactions are based on very small numbers.

Side effects as assessed by self-report questionnaire occurred with a greater frequency in the GlucoWatch group, with itching, redness, soreness and bruising being reported by over 70% of participants, and blisters being reported by 65% of participants in the intensive period (0–3 months). In the same period 34% of those who wore the CGMS reported each of itching, red marks and discomfort. This is higher than the frequency of side effects reported in some other adult studies.[64]

The occurrence of side effects is clearly more common in the GlucoWatch group, but it is important to consider whether participants felt that having these side effects was something that made the devices unacceptable to use. In health care, patients are often able to tolerate discomfort if they feel that they can manage this and that it will benefit them. An additional consideration in this study is that of altruism, i.e. participants may have felt that they were content to deal with the side effects as they were contributing to knowledge regarding care for people with diabetes. Over 40% of those who experienced soreness and red marks while wearing the GlucoWatch found these side effects 'not at all acceptable', with the figure for blisters the highest at 57%. Extrapolating from

these findings (the proportion who had blisters and the number finding these not at all acceptable) suggests that approximately 36% of all patients provided with the GlucoWatch would experience a side effect that was not at all acceptable to them. The figure would increase significantly if all of the other side effects for the GlucoWatch were taken into account. In the case of the CGMS, side effects were better tolerated, with 4% finding the itching and 8% finding the red marks and discomfort 'not at all acceptable'. The most unacceptable side effect in the CGMS group was bruising, experienced by 11% of the sample; of these, 38% found the bruising to be 'not at all acceptable'. For bruising, this would extrapolate to 4% of those provided with the CGMS.

A further issue limiting the acceptability of any device in health care is the extent to which it interferes with everyday life. In this study, sleep, exercise and washing were the areas in which over 60% of participants reported that both instruments interfered at least a little with daily activities. The two devices differed, particularly on washing, with the GlucoWatch interfering more; the reverse was found with mobility, for which the CGMS interfered more.

As with side effects it is important to establish not only the level of interference but also whether the interference experienced is something that is unacceptable. More participants in the GlucoWatch group found the interference unacceptable in all of the nine areas assessed. Over 15% found the interference with work, travel, social life, mobility, exercise and sleep completely unacceptable. The same figures for the CGMS group were much lower, with only exercise and travel having 5% of those experiencing interference rating it as completely unacceptable. Participants reported having to make more changes to their travel activities while wearing the GlucoWatch than with the CGMS.

The final area of acceptability that was examined was participants' attitudes towards the two devices. Factor analysis of an exploratory questionnaire yielded three components or subscales, two of which (ease of use and value) differed between the two devices. The GlucoWatch was viewed as being less easy to use and less valuable than the CGMS. The latter difference approached significance ($p = 0.01$).

Overall, the data on monitor use, side effects and interference with daily activities, as well as the perceived ease of use and value of the devices, suggest that any widespread application of the GlucoWatch technology will result in a significant proportion not being used. Its use appears to be driven by the relatively high occurrence and unacceptability of side effects. The CGMS on the other hand would be more likely to be widely used in clinical practice, although the barrier to use of this instrument appears to be related to participants' concerns about the device and possibly its invasive nature.

Psychosocial findings

Besides the assessment of acceptability, which focused on those receiving the devices, participants were asked to complete a series of questionnaires at baseline and at follow-up to assess the psychosocial impact of having the devices and receiving feedback on the basis of the information that they provide. These questionnaires were the AddQoL scale,[108] the SDSCA scale,[109] the worry subscale of the Fear of Hypoglycaemia questionnaire,[110] the DTSQ,[111,112] the ADDLoL[113] and the Personal Models of Diabetes questionnaire.[114]

Some baseline differences were found between the participants who completed all of the questionnaires at all time points ($n = 203$) and those who failed to complete at least one of the questionnaire assessments ($n = 201$). Those who completed all assessments were found to be significantly older, had better blood glucose control (HbA1c), had more macrovascular complications, showed marginally higher levels of satisfaction with their diabetes care, had a better quality of life and reported exercising slightly more frequently than those who failed to complete the questionnaires on all occasions. Although it is not possible to establish the reasons for completion versus non-completion, one may speculate that better adherence, blood glucose control and treatment satisfaction among the completing group implies that they showed greater attention to their diabetes, possibly because of the increased presence of macrovascular complications. In addition, it may have been the case that the older age of those who completed all of the questionnaires reflects the fact that more people in this group were no longer working and simply had more time to complete the questionnaires. It is important to note that the different characteristics between the two groups make any generalisations to the group studied overall questionable.

Amongst the 203 who completed questionnaires at all time points, there were no significant

differences at baseline between the trial arms on any of the factors assessed. The two device arms and the attention control group were assessed on changes to 3 months following the most intensive period of the study and this analysis did indicate some changes; however, none of these findings discriminated between the attention placebo group and those who received the devices, suggesting no particular impact of the devices in the group studied. Although fear of hypoglycaemia was found to decline in all three groups to 3 months, this was coupled with a reduction in feelings of personal control and a decline in the number of days exercised. On only one finding were the three groups distinguished – the GlucoWatch group showed a deterioration in diet compared with the other two groups. That the changes were found in all three groups following the intensive period of contact suggests that this increased contact with health-care professionals and/or participation in the study led to the changes observed. It does imply a complex inter-relation between changes in fear of hypoglycaemia and reductions in control and self-management behaviours at times of increased health-care professional contact.

In the analysis of all four groups over the longer follow-up times all of the groups showed less fear of hypoglycaemia from baseline to 12 months' follow-up. This implies that participation in the study, with a possible greater sense of scrutiny of participants' diabetes and completion of the questionnaires, may be responsible for reductions in the fear of hypoglycaemia observed in this study. No other significant differences were found between the groups.

Overall, the findings suggest that the provision of the devices and the additional information available to the nurses when giving advice to unselected individuals with poorly controlled insulin-requiring diabetes did not influence any of the psychological variables assessed.

Implications for the NHS

The implications from this study for the NHS are that the widespread distribution of continuous glucose monitoring devices to unselected insulin-requiring people with diabetes who are poorly controlled is unsupported. Further research is required to establish whether certain subgroups may show clinical benefits from the additional information that continuous glucose monitoring devices provide.

Limitations of the study

1. The study findings are limited to the group studied. In this case, insulin-requiring people with diabetes who were poorly controlled were selected for study. This was a broad selection criteria, and drawing conclusions to other subsets of individuals with diabetes is clearly not warranted.
2. No particular benefit was found to accrue to any subgroup in the study; however, it is important to note that these analyses were not adequately powered.
3. A relatively small proportion of those approached were recruited to the study and although this is not dissimilar to comparable studies it does limit the generalisability of the findings.
4. In the study, a loss of statistical power occurred because of a greater than expected loss to follow-up.
5. The study specified a specific usage of the continuous glucose monitoring devices and it was clear that there was a lower than expected use of the devices. This was particularly the case in the GlucoWatch arm in which device usage was initiated by the participant without the involvement of a health-care professional. This device also produced a greater frequency of adverse events, in particular skin irritations.
6. It was intended at the outset to recruit and assess individuals from various ethnic minority and language groups. Although a small number of participants did come from ethnic minority groups, all had an adequate understanding of the English language. The study is therefore limited to individuals who have an adequate understanding of spoken English.
7. One question that remains in relation to the health economics analysis is whether the EQ-5D is a sensitive enough instrument to capture HRQoL differences in patients using these continuous glucose monitoring devices.

Strengths of the study

1. This area of work has been characterised by small studies often performed by enthusiastic clinical teams and participants. This is the largest study to be performed to date and importantly used random allocation to groups.
2. Most studies that have been performed have assessed the value of the information provided by a single continuous glucose monitoring device. The inclusion of two types of monitor

in this study allows a greater understanding regarding the information provided by devices in general as well as the impact of different types of device.
3. Many studies performed in this area have failed to account for the additional contact with health-care professionals for those provided with the devices by comparing device groups with a standard care group. One of the strengths of the design used in this study is the use of two control groups, a standard care control group and an attention control group. Those participants in the latter group received equivalent health-care professional contact to those in the two device arms, thus ruling out increased contact as a potential confounding factor.
4. Short-term effects of the use of devices in diabetes, as well as other types of intervention, are not uncommon. A strength of this trial was that the study had a long follow-up period up to 18 months after recruitment.
5. The study was not limited by diabetes type and included all insulin-dependent people with diabetes.
6. The study provided standardised feedback that was delivered by nurses trained to interpret and make recommendations on the basis of the extra information available through continuous glucose monitoring devices.
7. The inclusion of a health economics assessment enabled the possible clinical benefits to be translated into economic implications.
8. The inclusion of psychosocial variables enabled an assessment to be performed of attitudes of patients to the devices, as well as the impact of having a device on underlying beliefs regarding their diabetes.

Recommendations for future research

The research performed in this study is the first detailed large study with a long follow-up period of the potential impact of the additional information provided by continuous glucose monitoring devices on blood glucose control in diabetes. There are a number of directions in which research on the value of the additional information that continuous glucose monitoring devices provide can go.

1. Although this study performed a series of subgroup analyses it was not adequately powered for these. Future studies should target specific subgroups for study such as poorly controlled type 1 patients with hypoglycaemia unawareness.
2. The acceptability of these devices to participants and health-care professionals is an area that needs further research. The devices are unlikely to be widely used if they are not perceived as being of value to prospective participants, and this will increasingly be the case if they are seen as being difficult to use, being invasive and causing side effects.
3. It is recommended that, as newer continuous glucose monitoring products become available with different characteristics (e.g. real-time participant feedback), they and the additional features that they offer are subjected to detailed assessment as in this study. It is of note that the newer products provide real-time feedback to patients and this will raise important issues regarding patient education and ease of interpretation and altering regimens in relation to this information. This will make the design of such studies even more difficult than the study reported here in which a small group of health-care professionals was trained to interpret and provide recommendations regarding treatment on the basis of the additional information provided by continuous glucose monitoring devices.
4. The protocol reported in this study avoids a common difficulty of not accounting for the additional contact with a health-care professional in the intervention group(s). It is strongly recommended that an attention placebo group is included in any future studies.
5. Lack of recruitment into trials is becoming an increasing issue and was reflected in the MITRE study. Techniques to increase recruitment into studies such as this is an area of current study and warrants further research.
6. It would be useful to explore what caused the lack of compliance for the benefit of future trial designs.
7. This study had an ambitious long-term follow-up period of 18 months. Future studies need to consider carefully whether this duration of engagement in the study is appropriate. Although not evidenced here, it is feasible that the devices may show short-term effects in some groups that are not sustained without additional health-care input.

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Contribution of authors

All authors have been involved in the conception and design of the study and/or the analysis or interpretation of the data.They have all participated in the drafting and revising of the report, as well as approving the final draft.

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Appendix 1

Guidance on administration of insulin

Dose adjustment advice is not given for single high readings. Patterns of blood glucose levels over 2–7 days are observed before advising dose changes (depending on frequency of testing and level of blood glucose). Wait a further 2–7 days and reassess before advising further changes.

Adjusting insulin when glucose levels are running high

For BD self-mixed/premixed regimen: total daily dose ≤ 20 units:

Pre-breakfast glucose (mmol/l)	Pre-evening meal glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
> 7–9		Absent		↑ Long-acting or premixed by 1–2 units
> 9		Present		↓ Long-acting or premixed by 1–2 units
	> 7–9		↑ Long-acting or premixed by 1–2 units	

For BD self-mixed/premixed regimen: total daily dose 20–50 units:

Pre-breakfast glucose (mmol/l)	Pre-evening meal glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
> 7–9		Absent		↑ Long-acting or premixed by 2–4 units
> 9		Present		↓ Long-acting or premixed by 2–4 units
	> 7–9		↑ Long-acting or premixed by 2–4 units	

For BD self-mixed/premixed regimen: total daily dose ≥ 50 units:

Pre-breakfast glucose (mmol/l)	Pre-evening meal glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
> 7–9		Absent		↑ Long-acting or premixed by 2–8 units
> 9		Present		↓ Long-acting or premixed by 2–8 units
	> 7–9		↑ Long-acting or premixed by 2–4 units	

For three times daily regimens (split evening dose): total daily dose ≤ 20 units:

Pre-breakfast glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre-bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Dinner insulin	Bedtime insulin
> 7–9			Absent			↑ Long-acting by 1–2 units
> 9			Present			↓ Long-acting by 1–2 units
	> 7–9			↑ Premixed or long-acting by 1–2 units		
		> 7–9			↑ Short-acting by 1–2 units	

For three times daily regimens (split evening dose): total daily dose 20–50 units:

Pre-breakfast glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre-bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Dinner insulin	Bedtime insulin
> 7–9			Absent			↑ Long-acting by 2–4 units
> 9			Present			↓ Long-acting by 2–4 units
	> 7–9			↑ Premixed or long-acting by 2–4 units		
		> 7–9			↑ Short-acting by 2–4	

For three times daily regimens (split evening dose): total daily dose ≥ 50 units:

Pre-breakfast glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre-bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Dinner insulin	Bedtime insulin
> 7–9			Absent			↑ Long-acting by 2–8 units
> 9			Present			↓ Long-acting by 2–8 units
	> 7–9			↑ Premixed or long acting by 2–8 units		
		> 7–9			↑ Short-acting by 2–8 units	

For basal bolus regimens: total daily dose ≤ 20 units:

Pre-breakfast glucose (mmol/l)	Pre-lunch glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre-bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
> 7–9				Absent				↑ Long-acting by 1–2 units
> 9				Present				↓ Long-acting by 1–2 units
	> 7–9				↑ Short-acting by 1–2 units			
		> 7–9				↑ Short-acting by 1–2 units		
			> 7–9				↑ Short-acting by 1–2 units	

In regimens with two isophane doses consider increasing pre-breakfast isophane by 1–2 units as an alternative to increasing the lunchtime short-acting dose.

For basal bolus regimens: total daily dose 20–50 units:

Pre-breakfast glucose (mmol/l)	Pre-lunch glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre-bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
> 7–9				Absent				↑ Long-acting by 2–4 units
> 9				Present				↓ Long-acting by 2–4 units
	> 7–9				↑ Short-acting by 2–4 units			
		> 7–9				↑ Short-acting by 2–4 units		
			> 7–9				↑ Short-acting by 2–4 units	

In regimens with two isophane doses consider increasing pre-breakfast isophane by 2–4 units as an alternative to increasing the lunchtime short-acting dose.

For basal bolus regimens: total daily dose ≥ 50 units:

Pre-breakfast glucose (mmol/l)	Pre-lunch glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre-bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
> 7–9				Absent				↑ Long-acting by 2–8 units
> 9				Present				↓ Long-acting by 2–8 units
	> 7–9				↑ Short-acting by 2–8 units			
		> 7–9				↑ Short-acting by 2–8 units		
			> 7–9				↑ Short-acting by 2–8 units	

In regimens with two isophane doses consider increasing pre-breakfast isophane by 2–8 units as an alternative to increasing the lunchtime short-acting dose.

Adjusting insulin in hypoglycaemia or when blood glucose levels are running generally too low

For BD self-mixed/premixed regimen: total daily dose ≤ 20 units:

Pre-breakfast glucose (mmol/l)	Pre-evening meal glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
< 4–7		Absent		↓ Long-acting or premixed by 1–2 units
< 4–7		Present		↓ Long-acting or premixed by 1–2 units
	< 4–7		↓ Long-acting or premixed by 1–2 units	

For BD self-mixed/premixed regimen: total daily dose 20–50 units:

Pre-breakfast glucose (mmol/l)	Pre-evening meal glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
< 4–7		Absent		↓ Long-acting or premixed by 2–4 units
< 4–7		Present		↓ Long-acting or premixed by 2–4 units
	< 4–7		↓ Long acting or premixed by 2–4 units	

For BD self-mixed/premixed regimen: total daily dose ≥ 50 units:

Pre-breakfast glucose (mmol/l)	Pre-evening meal glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
< 4–7		Absent		↓ Long-acting or premixed by 2–8 units
< 4–7		Present		↓ Long-acting or premixed by 2–8 units
	< 4–7		↓ Long-acting or premixed by 2–8 units	

For three times daily regimens (split evening dose): total daily dose ≤ 20 units:

Pre-breakfast glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Dinner insulin	Bedtime insulin
< 4–7			Absent			↓ Long-acting by 1–2 units
< 4–7			Present			↓ Long-acting by 1–2 units
	< 4–7			↓ Premixed or long-acting by 1–2 units		
		< 4–7			↓ Short-acting by 1–2 units	

For three times daily regimens (split evening dose): total daily dose 20–50 units:

Pre-breakfast glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Dinner insulin	Bedtime insulin
< 4–7			Absent			↓ Long-acting by 2–4 units
< 4–7			Present			↓ Long-acting by 2–4 units
	< 4–7			↓ Premixed or long-acting by 2–4 units		
		< 4–7			↓ Short-acting by 2–4 units	

For three times daily regimens (split evening dose): total daily dose ≥ 50 units:

Pre-breakfast glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Morning insulin	Dinner insulin	Bedtime insulin
< 4–7			Absent			↓ Long-acting by 2–8 units
< 4–7			Present			↓ Long-acting by 2–8 units
	< 4–7			↓ Premixed or long-acting by 2–8 units		
		< 4–7			↓ Short-acting by 2–8 units	

For basal bolus regimens: total daily dose ≤ 20 units:

Pre-breakfast glucose (mmol/l)	Pre-lunch glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre-bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
< 4–7				Absent				↓ Long-acting by 1–2 units
< 4–7				Present				↓ Long-acting by 1–2 units
	< 4–7				↓ Short-acting by 1–2 units			
		< 4–7				↓ Short-acting by 1–2 units		
			< 4–7				↓ Short-acting by 1–2 units	
In regimens with two isophane doses consider decreasing pre-breakfast isophane by 1–2 units as an alternative to decreasing the lunchtime short-acting dose.								

For basal bolus regimens: total daily dose 20–50 units:

Pre-breakfast glucose (mmol/l)	Pre-lunch glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre-bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
< 4–7				Absent				↓ Long-acting by 2–4 units
< 4–7				Present				↓ Long-acting by 2–4 units
	< 4–7				↓ Short-acting by 2–4 units			
		< 4–7				↓ Short-acting by 2–4 units		
			< 4–7				↓ Short-acting by 2–4 units	

In regimens with two isophane doses consider decreasing pre-breakfast isophane by 2–4 units as an alternative to decreasing the lunchtime short-acting dose.

For basal bolus regimens: total daily dose ≥ 50 units:

Pre-breakfast glucose (mmol/l)	Pre-lunch glucose (mmol/l)	Pre-dinner glucose (mmol/l)	Pre-bedtime glucose (mmol/l)	Nocturnal hypoglycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
< 4–7				Absent				↓ Long-acting by 2–8 units
< 4–7				Present				↓ Long-acting by 2–8 units
	< 4–7				↓ Short-acting by 2–8 units			
		< 4–7				↓ Short-acting by 2–8 units		
			< 4–7				↓ Short-acting by 2–8 units	

In regimens with two isophane doses consider decreasing pre-breakfast isophane by 2–4 units as an alternative to decreasing the lunchtime short-acting dose.

Insulin adjustment advice during illness

Diabetes specialist nurses have the knowledge and skills to assess illness symptoms and duration, to advise on management, including testing urine for ketones, and to advise when to seek medical advice. These aspects of sickness advice are not addressed in this document.

Dose adjustment advice

If normal daily dose is < 50 units:

- if blood sugars are < 13 mmol/l continue with normal insulin dose
- if blood sugars are 13–22 mmol/l take four units extra of fast- or rapid-acting insulin (or mixed insulin if this is the only one available) with each injection
- if blood sugars are > 22 mmol/l take six units extra of fast- or rapid-acting insulin (or mixed insulin if this is the only one available) with each injection.

If normal daily dose is >50 units:

- if blood sugars are < 13 mmol/l continue with normal insulin dose
- if blood sugars are 13–22 mmol/l take six units extra of fast- or rapid-acting insulin (or mixed insulin if this is the only one available) with each injection
- if blood sugars are > 22mmol/l take eight units extra of fast- or rapid-acting insulin (or mixed insulin if this is the only one available) with each injection.

Appendix 2

Presentation of trial (prerandomisation and after randomisation)

Prerandomisation

Key points to cover when describing the trial (either in person or over the telephone):

Introduction

- Study looking at two new ways of measuring blood glucose levels.
- We are comparing these two new machines or devices with traditional finger prick blood glucose testing.
- Four-group study with one in four chance of being in any arm of the trial.

GlucoWatch (explain whilst showing device when possible)

- Worn on forearm.
- Sticks to skin and takes blood glucose readings through the skin.
- Worn for up to 15 hours at a time.
- Takes readings automatically every 10 minutes.
- Readings shown on screen.
- Alarms can be set to go off if glucose level is too high or too low.
- Still need to do finger prick tests while using the device.
- Watch gives additional/supplementary information to the finger prick tests, e.g. it can be worn whilst sleeping, driving, etc.
- Can cause skin reactions, especially if already susceptible.

CGMS (explain whilst showing device when possible)

- Slightly bigger than mobile phone, worn hooked over belt or waistband.
- Small probe put under skin in tummy. When it goes in, similar sensation to having an injection.
- Worn over 3 days.
- Takes readings automatically every 5 minutes.
- Unlike the GlucoWatch it does not show the readings on the screen.
- Come in to see research nurse to have the readings downloaded from the monitor.
- As with the GlucoWatch you still need to do finger prick tests while using this device.

Attention control group

- Do normal finger prick tests using a meter that we give you.
- See research nurse on a more regular basis to get extra help with diet, lifestyle, medication adjustment, etc.

Normal diabetes care

- Do normal finger prick tests using a meter that we give you.
- Come to clinic as you are at the moment. Do not get extra input from staff.
- Study comparing the first two groups (devices) with the second two groups to find out if devices can help to improve diabetes control and to see how people get on with using the devices.
- Assure confidentiality and anonymity of information.
- Study is an RCT.
- Do not get to choose the group you are in; one in four chance of getting the group you want.
- If you agree to take part you have to agree to this.

Time frame

- 18-month study.

GlucoWatch

- Worn twice a week for the first 3 months. Seen once a month during this time.
- For the next 15 months watch can be worn as often as you want.
- Come in for visits 6, 12 and 18 months into the study.

CGMS

- Worn once a month for the first 3 months. Seen once a month during this time.
- Worn again three times at 6, 12 and 18 months into the study.

Attention control group

- As well as receiving usual care, come in once a month for the first 3 months to see research nurse.

Normal diabetes care

- Receive normal diabetes care at the clinic.

Finally, ask if they have any questions about the study.

After randomisation

Key points to include (refer to instruction books when required):

OneTouch meter: demonstrate

- Calibration of meter.
- Testing blood (patients should do one test to familiarise themselves).
- Give letter to patient to take to GP for new test strips.
- Supply with one extra bottle of test strips.

CGMS: demonstrate/discuss

- Show table of how to convert from mmol/l to mg/dl.
- Calibration and importance of calibrating a minimum of four times per day, remembering to do it last thing at night and when blood glucose is stable, i.e. not after injection or a meal.
- Entering events and when this should be done.
- Initialise and ask patient to return in 1 hour to calibrate.
- Give instruction sheet and conversion chart.
- How to turn off meter and remove sensor.

GlucoWatch: demonstrate/discuss

- Demonstrate use of battery charger and emphasise need to insert freshly charged battery before each use and also on removal.
- Set date and time.
- Demonstrate changing high and low alerts, and discuss when it would be appropriate to change these.
- Demonstrate entering events.
- Demonstrate preparation of sensor and fitting to watch.
- Discuss best position of sensor and preparation of skin for best conductivity. Mention need to position biographer 1–2 inches away from wrist and elbow and that skin should be washed before fitting, and hair shaved if necessary (preferably the day before). Mention that before calibration the GlucoWatch should be at a constant temperature, not bumped or moved vigorously.
- Fit watch ensuring a good contact but avoiding having the strap too tight.
- Start watch.
- Ensure that individuals return after warm-up period to check calibration.
- Provide instruction book and video.
- Provide individuals with 16 sensors and highlight that they should use the monitor a minimum of four times per month and a maximum of four times per week.
- The sensors must be kept in the fridge.
- Stress to patients that the monitors must not be relied upon for estimating insulin requirements.
- Stress to patients that they should not just rely on the watch readings to alert them to hypoglycaemic episodes. A finger prick test should be done to confirm that glucose levels are low.
- Discuss the difference between the GlucoWatch readings and the finger prick readings. Emphasise that the GlucoWatch is for recognising trends rather than for individual readings. Stress that the readings are about 20 minutes behind real time and that interstitial glucose is different to capillary glucose.
- Show the log book and how to complete it.
- Explain skin reaction scale to patient and the requirement of contacting the clinical team if a rating of > 6 occurs.
- Emphasise that if reaction is > 6 then they will need to attend the clinic to have the reaction assessed and photographed.

Appendix 3

Consent form

Confidential

Use of non-invasive glucose monitoring in the management of diabetes

PATIENT CONSENT FORM version 2

Name _____

Date of birth _____ Hospital number _____

Address _____

_____

_____

Please initial each box in ALL the boxes below if you are in agreement:

I have read the information sheet ☐

I have had an opportunity to ask questions and discuss this study ☐

I agree to take part in this study ☐

I understand that I will be randomised to one of four groups in the study ☐

The study has been explained to me by _____

I understand that I can withdraw from the study at any time and that this will not affect my medical care at all

SIGNED _____ Dated_____

WITNESSED by_____

SIGNED_____ Dated_____

Appendix 4

Consent form for individuals requiring screening HbA1c

Confidential

Use of non-invasive glucose monitoring in the management of diabetes

PATIENT CONSENT FORM for SCREENING version 5

Name _____

Date of birth _____Hospital number_____

Address _____

_____

Please initial each box in the ALL boxes below if you are in agreement:

I have read the information sheet ☐

I have had an opportunity to ask questions and discuss this study ☐

I agree to take part in this study ☐

I agree to have a blood test performed to see if my HbA1c is greater than or equal to 7.5% ☐

If the blood test (HbA1c) is 7.5% I understand that I will be randomised to one of four groups in the study ☐

The study has been explained to me by_____

I understand that I can withdraw from the study at any time and that this will not affect my medical care at all

SIGNED_____ Dated_____

Appendix 5

Patient information sheets

Patient information sheet

This has been written according to the guidelines from the Central Office for Research Ethics Committees (www.corec.org.uk/). For each site participating in this MREC-approved study the patient information sheet should be printed on local hospital paper with local contact names and telephone numbers before it is submitted to the LREC. Unheaded paper is not acceptable.

Study comparing new minimal and non-invasive glucose monitoring systems with current glucose measuring methods
INFORMATION SHEET FOR PATIENTS
Version 5 (November 2004)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to participate.

What is the purpose of the study?

In diabetes regular checking of blood sugars (glucose) provides information on glucose levels throughout the day and can guide diet, exercise and adjustment of your insulin dosage. However, even if you test your sugar four or six times a day you only get a limited view of what your sugars are like. To obtain more readings of sugar levels new machines have been developed that, whilst worn, automatically record sugar levels every 5–10 minutes. There are currently two such devices available – the GlucoWatch 2, which can be worn for up to 15 hours, and the Continuous Glucose Monitoring System (CGMS), which can be worn for up to 72 hours. When using the devices you still need to do finger prick tests.

The main purpose of this study is to find out if these new devices may help improve diabetes control and how acceptable they are to patients.

Why have I been chosen?

You currently inject insulin and your clinic blood test (HbA1c) is higher than ideal. We would like to see whether the devices will benefit patients like you.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of your care.

What will happen to me if I take part?

To enable us to make comparisons people will be allocated to one of four groups.

Which group you are allocated to will be purely by chance and selected by a computer. The four groups are:

- Group A: Participants receive normal diabetes care. That means attending the clinic for 6-monthly appointments and any other appointments should you need them.
- Group B: In addition to normal diabetes care participants will be asked to see the diabetes nurse in clinic once a month for the first 3 months of the study.
- Group C: In addition to normal care participants will be asked to wear and use the GlucoWatch twice a week for the first 3 months. Participants will see the nurse in clinic once a month during this period to allow feedback to be provided on diabetes control. Over the next 15 months participants will be able to keep the meter and use it as often as they wish.
- Group D: In addition to normal care participants will use the CGMS. During the first 3 months the device will be fitted three times. After wearing the device participants will see the nurse in clinic to obtain a read-out for discussion. Over the next 15 months participants will have the device fitted three times at 6-month intervals.

All participants will be asked to provide a blood sample at the beginning of the study and at 6-month intervals to measure long-term blood

sugar control. Whenever possible these will be combined with normal clinic blood tests. You will also be asked to complete some questionnaires at the beginning of the study, after 3 months and then at 6 and 18 months. These will take approximately 30 minutes.

As there are four groups you have a one in four chance of being allocated to a particular group, i.e. only one-quarter of patients will receive the GlucoWatch and one-quarter will use the CGMS.

What are the devices being studied?
The GlucoWatch 2 is the size of a large watch and is worn on your wrist. It requires a 2-hour warm-up period and then a finger prick sugar must be measured and entered into the device. The device provides read-out as often as every 10 minutes for up to 13 hours. The device also has an alarm to warn you about high or low sugars. Once you know how to use the device you can fit it yourself.

The CGMS is worn on your waist and is about the size of a small mobile phone. A small probe is fitted under the skin and attached to the device by a wire. After a warm-up of 1 hour you enter a finger prick sugar and the device starts recording your sugars. This device measures your sugars every 5 minutes for 72 hours.

During this time you have to measure and enter your glucose level at least four times a day to ensure that the monitor measures your blood sugar correctly. This device has to be fitted in the diabetes clinic and you may return at the end of 72 hours to have the machine removed or remove it yourself and return to the clinic within 1 week to receive the read-out of your sugars. This device does not give you read-out while you wear it.

What are the side effects of using the devices?
The GlucoWatch is commonly associated with skin irritation. Some patients feel aware of the presence of the CGMS with some local discomfort.

What are the possible benefits of taking part in the study?
The information we get from this study may help us to use these devices more widely and manage diabetes more effectively in the future.

What if something goes wrong?
While we do not expect any problems to arise in this study, if you are harmed by taking part there are no special compensation arrangements. If you are harmed because of someone's negligence then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have concerns about any aspect of the way you have been approached or treated during the course of the study, the normal National Health Service complaints mechanism should be available to you.

Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital/surgery will have your name and details removed so that you cannot be recognised from it.

What will happen to the results of the research study?
The results will be published in the medical press. Copies of any publications will be available to you from the researchers.

Who is organising and funding the research?
The study is being funded by the National Health Service Health Technology Assessment commissioning agency. It is being organised by a collaboration of doctors based at University College London and hospitals around the country. The researchers are not being paid for this study.

Who has reviewed the study?
The study has been reviewed by the National Health Service Health Technology Assessment commissioning agency and both multiregional and local research ethics committees.

Contact for further information
If you have any concerns regarding the conduct within the study, please contact either your diabetes team or the local ethics committee (contact name and number to be supplied). If you have any further questions regarding the study, please contact Dr Steven Hurel at University College London Hospital on: 0207–380–9029.

Patient information sheet for individuals requiring screening HbA1c

This has been written according to the guidelines from the Central Office for Research Ethics Committees (www.corec.org.uk/). For each site participating in this MREC-approved study, the

patient information sheet should be printed on local hospital paper with local contact names and telephone numbers before it is submitted to the LREC. Unheaded paper is not acceptable.

Study comparing new minimal and non-invasive glucose monitoring systems with current glucose measuring methods
INFORMATION SHEET FOR PATIENTS REQUIRING SCREENING
Version 6 (November 2004)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to participate.

What is the purpose of the study?

In diabetes regular checking of blood sugars (glucose) provides information on glucose levels throughout the day and can guide diet, exercise and adjustment of your insulin dosage. However, even if you test your sugar four or six times a day you only get a limited view of what your sugars are like. To obtain more readings of sugar levels new machines have been developed that, whilst worn, automatically record sugar levels every 5–10 minutes. There are currently two such devices available – the GlucoWatch 2, which can be worn for up to 15 hours, and the Continuous Glucose Monitoring System (CGMS), which can be worn for up to 72 hours. When using the devices you still need to do finger prick tests.

The main purpose of this study is to find out if these new devices may help improve diabetes control and how acceptable they are to patients.

Why have I been chosen?

You currently inject insulin and your previous clinic blood test (HbA1c) is higher than ideal. We would like to see whether the devices will benefit patients like you. However, we first need to be sure that your clinic blood test is still higher than ideal, which for this study means 7.5% or over.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of your care.

What will happen to me if I take part?

As this is a study for people whose HbA1c is greater than or equal to 7.5% we will need first to establish by means of the blood test whether your HbA1c is at this level. If it is then we would like you to participate in the study. However, if it is not 7.5% or over the study will not be appropriate for you and your participation will cease at this point.

To enable us to make comparisons people will be allocated to one of four groups. Which group you will be allocated to will be purely by chance and selected by a computer. The four groups are:

- Group A: Participants receive normal diabetes care. That means attending the clinic for 6-monthly appointments and any other appointments should you need them.
- Group B: In addition to normal diabetes care participants will be asked to see the diabetes nurse in clinic once a month for the first 3 months of the study.
- Group C: In addition to normal care participants will be asked to wear and use the GlucoWatch twice a week for the first 3 months. Participants will see the nurse in clinic once a month during this period to enable feedback to be provided on diabetes control. Over the next 15 months participants will be able to keep the meter and use it as often as they wish.
- Group D: In addition to normal care participants will use the CGMS. During the first 3 months the device will be fitted three times. After wearing the device participants will see the nurse in clinic to obtain a read-out for discussion. Over the next 15 months participants will have the device fitted three times at 6-month intervals.

All participants will be asked to provide a blood sample at the beginning of the study and at 6-month intervals to measure long-term blood sugar control. Whenever possible these will be combined with normal clinic blood tests. You will also be asked to complete some questionnaires at the beginning of the study, after 3 months and then at 6 and 18 months. These will take approximately 30 minutes.

As there are four groups you have a one in four chance of being allocated to a particular group, i.e. only one-quarter of patients will receive the GlucoWatch and one-quarter will use the CGMS.

What are the devices being studied?

The GlucoWatch 2 is the size of a large watch and is worn on your wrist. It requires a 2-hour warm-up period and then a finger prick sugar must be measured and entered into the device. The device provides read-out as often as every 10 minutes for up to 13 hours. The device also has an alarm to warn you about high or low sugars. Once you know how to use the device you can fit it yourself.

The CGMS is worn on your waist and is about the size of a small mobile phone. A small probe is fitted under the skin and attached to the device by a wire. After a warm-up of 1 hour you enter a finger prick sugar and the device starts recording your sugars. This device measures your sugars every 5 minutes for 72 hours. During this time you have to measure and enter your glucose level at least four times a day to ensure the monitor measures your blood sugar correctly. This device has to be fitted in the diabetes clinic and you may return at the end of 72 hours to have the machine removed or remove it yourself and return to the clinic within 1 week to receive the read-out of your sugars. This device does not give you read-out while you wear it.

What are the side effects of using the devices?

The GlucoWatch is commonly associated with skin irritation. Some patients feel aware of the presence of the CGMS with some local discomfort.

What are the possible benefits of taking part in the study?

The information we get from this study may help us to use these devices more widely and manage diabetes more effectively in the future.

What if something goes wrong?

While we do not expect any problems to arise in this study, if you are harmed by taking part there are no special compensation arrangements. If you are harmed because of someone's negligence then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have concerns about any aspect of the way you have been approached or treated during the course of the study, the normal National Health Service complaints mechanism should be available to you.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital/surgery will have your name and details removed so that you cannot be recognised from it.

What will happen to the results of the research study?

The results will be published in the medical press. Copies of any publications will be available to you from the researchers.

Who is organising and funding the research?

The study is being funded by the National Health Service Health Technology Assessment commissioning agency. It is being organised by a collaboration of doctors based at University College London and hospitals around the country. The researchers are not being paid for this study.

Who has reviewed the study?

The study has been reviewed by the National Health Service Health Technology Assessment commissioning agency and both multiregional and local research ethics committees.

Contact for further information

If you have any concerns regarding the conduct within the study, please contact either your diabetes team or the local ethics committee (contact name and number to be supplied). If you have any further questions regarding the study, please contact Dr Steven Hurel at University College London Hospital on: 0207–380–9029.

Appendix 6

MITRE Skin Scale

Problems

0 = none

1 = fitting device

2 = calibration

3 = inaccurate results

4 = inaccurate alarm

5 = other (please comment)

Redness

0 = none

1 = mild, patchy red spots

2 = moderate/noticeable spots

3 = intense within site

4 = intense with flaring beyond site

Swelling

0 = no problem

1 = mild lumpiness

2 = moderate lumpiness

3 = severe lumps

4 = blisters

Total

ADD Redness score to Swelling score. If greater than or equal to 6, call nurse

Irritation

0 = none

1 = mild

2 = moderate

3 = severe

Appendix 7

Acceptability questionnaire

The following questionnaire asks you about your use of the MiniMed CGMS or GlucoWatch.

Section one: We are interested to know whether wearing the monitor interfered with or got in the way of any of your normal activities. To help us understand this we would like you to answer three sets of questions about how the monitor influenced your normal activities. The first set of questions refers to when you were actually wearing the monitor. For each question please circle how much the monitor interfered with the activity and then how happy you were to put up with this.

1(a). When wearing the monitor it interfered with my normal washing (e.g. bath/showering) routine:

Not at all	A little	Moderately	A lot	Completely

1(b). I found this:

Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Completely acceptable

2(a). When wearing the monitor it interfered with my skin care routine:

Not at all	A little	Moderately	A lot	Completely

2(b). I found this:

Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Completely acceptable

3(a). Do you exercise regularly? Yes/No If no please go to question 4.

3(b). When wearing the monitor it interfered with my normal exercise routine:

Not at all	A little	Moderately	A lot	Completely

3(c). I found this:

Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Completely acceptable

4(a). When wearing the monitor it interfered with my daily travel (e.g. using public transport, driving):

Not at all	A little	Moderately	A lot	Completely

4(b). I found this:

Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Completely acceptable

5(a). When wearing the monitor it interfered with my sleep:

Not at all	A little	Moderately	A lot	Completely

5(b). I found this:

Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Completely acceptable

6(a). When wearing the monitor it interfered with my ability to move around, e.g. bending down:

Not at all	A little	Moderately	A lot	Completely

6(b). I found this:

Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Completely acceptable

7(a). When wearing the monitor it interfered with my social life:

Not at all	A little	Moderately	A lot	Completely

7(b). I found this:

Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Completely acceptable

8(a). Do you regularly work? Yes/No If no please go to question 9

8(b). When wearing the monitor it interfered with my work activities:

Not at all	A little	Moderately	A lot	Completely

8(c). I found this:

Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Completely acceptable

9(a). When wearing the monitor it interfered with my choice of clothes:

Not at all	A little	Moderately	A lot	Completely

9(b). I found this:

Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Completely acceptable

Now please circle the appropriate box to indicate whether you avoided wearing the monitor in any of the following situations.

I avoided wearing the monitor when:	Not at all	Sometimes	Always	N/A
1. Exercising	0	1	2	
2. Travelling	0	1	2	
3. Sleeping	0	1	2	
4. Going out socially	0	1	2	
5. At work	0	1	2	
6. Meeting people I didn't know	0	1	2	
7. Going out for long periods of time	0	1	2	
8. Eating out	0	1	2	

Finally, please circle the appropriate box to indicate whether you changed any of your normal activities when wearing the monitor.

When I was wearing the monitor I changed my normal:	Not at all	Sometimes	Always	N/A
1. Exercise routine	0	1	2	
2. Travel arrangements	0	1	2	
3. Sleep routine	0	1	2	
4. Social plans	0	1	2	
5. Work routine	0	1	2	

Section two: The following statements relate more generally to the monitor and its impact. For each statement please indicate the extent that you agree or disagree by circling the appropriate number.

	Strongly disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Strongly agree
1. I was not worried about the way I looked when I was wearing the monitor	1	2	3	4	5
2. I found the use of the monitor required careful planning	1	2	3	4	5
3. I had no difficulty in calibrating the monitor	1	2	3	4	5
4. I was unhappy that the monitor reminded other people about my health problems	1	2	3	4	5
5. Wearing the monitor made me more confident that my blood sugars were under control	1	2	3	4	5
6. I thought the amount of training in the machine was sufficient	1	2	3	4	5
7. I was confident that the monitor would accurately record if I was going hypo	1	2	3	4	5
8. I felt more self-conscious of my appearance when I was wearing the monitor	1	2	3	4	5
9. I thought that generally the monitor was impractical	1	2	3	4	5
10. I was happy with the length of time that the monitor was meant to be worn for	1	2	3	4	5
11. I was confident that the blood glucose readings from the monitor were accurate	1	2	3	4	5
12. I found using the monitor took up too much time	1	2	3	4	5
13. I found it difficult to plan when to wear the monitor so that it fitted in with my normal day-to-day activities	1	2	3	4	5
14. I was unhappy with the number of finger prick tests that were needed for the monitor to work properly	1	2	3	4	5
15. I found the monitor unreliable in hot and cold environments	1	2	3	4	5
16. I was happy to explain what the monitor was to friends	1	2	3	4	5
17. I was concerned that the monitor would not record accurately if my blood sugars went too high	1	2	3	4	5
18. I would have found the monitor more useful if it could make recordings over longer periods of time	1	2	3	4	5
19. Wearing the monitor has not helped decrease the amount of time I have high blood glucoses	1	2	3	4	5
20. I found the warm-up period of the monitor frustrating	1	2	3	4	5

21. I made an effort to cover up the monitor so that other people would not see it	1	2	3	4	5
22. I found that the monitor made me more aware of symptoms of hypoglycaemia	1	2	3	4	5
23. I could not always enter information into the machine as instructed to	1	2	3	4	5
24. I felt the monitor missed too many readings	1	2	3	4	5
25. I was happy to explain what the monitor was to anyone who asked	1	2	3	4	5
26. I thought the read-outs from the monitor were straightforward and easy to understand	1	2	3	4	5
27. It was easy to understand how to work the monitor	1	2	3	4	5
28. Wearing the monitor has helped me reduce the number of hypos I experience	1	2	3	4	5
29. I found it difficult to understand when the monitor showed an error	1	2	3	4	5
30. I would be interested in using the machine in the future	1	2	3	4	5
31. I feel that the monitor has helped me improve my blood sugar control	1	2	3	4	5
32. I thought the time spent at the clinic for training and setting up the monitor was too long	1	2	3	4	5
33. I would recommend other people in a similar situation to me to wear the monitor	1	2	3	4	5

Please answer the final questions in section two only if you use the GlucoWatch.

	Strongly disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Strongly agree
34. I found the alarms for hypoglycaemia were useful	1	2	3	4	5
35. I thought the alarm for hypoglycaemia was accurate	1	2	3	4	5
36. I found it embarrassing when the alarm sounded at work	1	2	3	4	5
37. I did not find the alarms for high blood sugar useful	1	2	3	4	5
38. I did not think the alarms for high blood sugar were accurate	1	2	3	4	5

Section three: Finally, we would like to know whether you experienced any of the following side effects from wearing the monitor. If yes, please indicate how acceptable these were to you.

	Yes/No	Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Completely acceptable
Itching	Yes/No	0	1	2	3	4
Tingling	Yes/No	0	1	2	3	4
Soreness	Yes/No	0	1	2	3	4

Dry skin	Yes/No	0	1	2	3	4
Red marks	Yes/No	0	1	2	3	4
Discomfort	Yes/No	0	1	2	3	4
Bruising	Yes/No	0	1	2	3	4
Pain	Yes/No	0	1	2	3	4
Blisters	Yes/No	0	1	2	3	4

Appendix 8

The development of the acceptability questionnaire

In the preliminary phase of this RCT, a qualitative study was conducted with individuals who had previously used continuous glucose monitoring devices in order to understand the issues related to their acceptability (study one). This information was then used to develop an acceptability questionnaire according to the recommendations of Todd and Bradley[130] (study two). The process of developing this questionnaire is described, followed by the results from the analysis of this data.

At the time that this study commenced there was no published measure of acceptability available. The DirecNet group[53] have since published a questionnaire assessing satisfaction with and perceived therapeutic impact of the GlucoWatch, which can be used with other continuous glucose monitors. This questionnaire was developed solely through consultation with health-care professionals, without prior consultation with users of the device. This is in contrast to recommendations for the development of new psychological measurement tools, which state that consultation with the population of interest as well as with experts in the field is an important aspect of questionnaire development.[130] This classic method is particularly important for acceptability when the user perspective is the key construct to be assessed and when it may be unknown to experts in the field. The DirecNet measure is also potentially limited by being unidimensional and hence it is not possible to analyse separate aspects of satisfaction.

Study one

Methods

Design

The qualitative study consisted of interviews with individuals who had previously used a continuous glucose monitoring device, with the aim of increasing understanding of user acceptability and satisfaction.

Participants

All individuals who had used or were currently using either the GlucoWatch or the CGMS device at a London teaching hospital (UCLH) in the past 18 months were eligible for participation in the interview study unless they were currently undergoing any psychiatric treatment or were unable to communicate in fluent English.

Recruitment and consent procedure

Individuals fulfilling the inclusion/exclusion criteria were identified by the consultant diabetologist at UCLH. Information sheets and invitation letters were then sent to all of these individuals. Potential participants were contacted the following week to confirm interest in participation and to arrange an appointment for interview at their convenience. The consent procedure included confirmation that the information sheet had been read, an opportunity to ask questions and re-emphasis that the interview would be tape-recorded. All participants were assured of confidentiality and anonymity, and informed that the UCLH ethics committee had approved the study. Written consent was subsequently obtained.

Interview format

The interviews were exploratory and therefore a semistructured format was used. The discussion was facilitated by a topic guide, which had been elicited from the literature, and discussion with experts in the field. General topics addressed included practical, social and emotional impact and concerns related to the devices; however, there was full scope for other issues related to the devices to be raised, and the interviewer probed all areas of importance to the interviewee. No time limit was set for the interviews; however, it was anticipated that they would take approximately 30–60 minutes.

Analysis

All interviews were tape-recorded and transcribed. The transcripts were anonymised. Framework analysis[131] was used to identify themes relating to the acceptability of the GlucoWatch and the CGMS.

Results

Of eight eligible participants, six (75%) consented to take part in the study. *Table 66* shows the demographics of these participants, four of whom had used the GlucoWatch and two the CGMS.

Six broad themes were elicited through analysis, including:

TABLE 66 *Demographics of participants undergoing individual interviews*

	Device	Device last worn (months)	Number of times worn	Age at time of interview	Sex	Type of diabetes	Duration of diabetes (years)
1	GlucoWatch	18	15 times in 2 weeks	56	F	1	45
2	CGMS	3	Once	43	M	1	8
3	CGMS	1	Once	45	F	1	42
4	GlucoWatch	18	'Initially a lot, less since'	55	M	2	18
5	GlucoWatch	18	15–20 times	35	F	MODY	20
6	GlucoWatch	15	15–20 times in 2 weeks	25	F	1	15

MODY, maturity-onset diabetes mellitus of the young.

- Interference with daily activities: For example, disruption with washing and sleep routines, problems moving around and variously cited difficulties with travelling, at work, shopping and eating out:

  It sort of slowed things down like dressing, you had to take a bit more care.

  P2 (CGMS)

  The only thing I found is on the tube, because if you are standing and you are being jammed and pushed that would make it a problem ….

  P3 (CGMS)

- Reliability and accuracy of the device: Participants using the GlucoWatch reported that it did not always work in warm weather and that it skipped readings. They also expressed concern about the accuracy of readings:

  If you are sweaty or have some problem it will miss that reading.

  P5 (GlucoWatch)

  If you walked out into the cold, it would go off on occasions.

  P6 (GlucoWatch)

- Practicality and ease of use: Comments included the inconvenience of still needing to do finger prick tests when wearing the device; that it was time-consuming; difficulties with calibration; and the inconvenience of alarms on the GlucoWatch:

  It was extremely difficult to set up … you had to have it turned on for 3 hours beforehand, now as a working person that meant I had to get up at 4 o'clock in the morning to set it off, then to start it at 7 o'clock.

  P1 (GlucoWatch)

  I would have preferred one that vibrated discreetly, rather than bleeped all over the place, because working at what I do, it is usually a mixture of panic and everybody rushing under their shirts to look for their pagers.

  P4 (GlucoWatch)

- Improvements in glycaemic control: For some, the devices filled in the gaps in relation to the finger prick readings, increased perceptions of control and improved identification of hypoglycaemia:

  The feedback was good because we knew the blood sugars dropped around 3–4 o'clock in the morning and it confirmed that ….

  P3 (CGMS)

- Side effects: Those reported included dry skin, itchiness, soreness and tingling:

  You had to be quite careful about the way you peeled it off the skin, otherwise you would take the top layer with it.

P4 (GlucoWatch)

> I did react to the strips … it went a bit raw, but I am not sure whether I got little scabs, but it was like that, it was itchy … when I had a few on the same sort of area, it looked like I had some horrible disease.

P5 (GlucoWatch)

- Self-consciousness and disclosure: Concerns related to other people knowing about their diabetes; having to explain what the device was; worries about appearance and what to wear:

> I didn't really want to meet anyone to have to explain what it was … but I avoided, I think, actually seeing anyone where I might have to go into an explanation.

P5 (GlucoWatch)

This study highlighted the range of issues users considered important in assessing acceptability and potential satisfaction with continuous glucose monitoring devices. Although some themes identified by participants are similar to those reported by the DirecNet group,[53] other areas were identified, such as interference with daily activities. This study therefore provided a foundation on which to develop an acceptability measure.

Study two

Methods

Questionnaire design

Drawing upon the themes identified in study one, items were generated for the pilot questionnaire by one of the authors (LS). Items were divided into three sections: (1) interference with lifestyle, (2) attitudes to device (including reliability and accuracy of device, practicality and ease of use, perceived benefit to glycaemic control, self-consciousness) and (3) side effects. Individuals were asked to rate the acceptability of interference with specific aspects of lifestyle, and the acceptability of any side effects experienced. This draws upon related quality of life literature which indicates that evaluations of disruptions to lifestyle are only valid if individuals perceive those areas of life to be important to them.[132] For example, a patient's social life may be affected a lot by their diabetes but this aspect of their life may not be important to them. This principle was applied in the current study. People with diabetes may be willing to tolerate disruption to activities or particular side effects if they feel that they are benefiting from wearing the device, hence it is important to assess both of these aspects.

Following generation of the initial items, experts in the field, including diabetologists, diabetes specialist nurses, statisticians, clinical trialists and health psychologists, were consulted about the content of the questionnaire. Their comments on phrasing, format, etc. were incorporated into the questionnaire. In addition, it was advised that, within the section on interference, items assessing the extent to which behaviour was avoided or changed should also be included. The questionnaire was then piloted with the potential user group.

Participants

All individuals from two hospital diabetes clinics (UCLH, Bournemourth Royal Hospital) who had used either the GlucoWatch or CGMS in the previous 18 months, were sufficiently fluent in written English and were not currently undergoing any psychiatric treatment were invited to participate in piloting of the questionnaire.

Recruitment and consent procedure

Individuals fulfilling the inclusion/exclusion criteria were identified by the consultant diabetologists at UCLH and the Royal Bournemouth Hospitals Trust and an invitation letter, information sheet (including contact number in case of queries), consent form, pilot questionnaire and prepaid envelope were sent out to them.

Results

A total of 19 (95%) outpatient clinic attendees from the two hospitals completed a copy of the pilot questionnaire. Seven of these had used the GlucoWatch and 12 had used the CGMS. Five of these participants had already taken part in the individual interviews. There were 10 women (53%) and the majority of the respondents had type 1 diabetes (89%). The mean age of the participants was 41 years and the mean duration of diabetes was 18 years.

Comments from the user group included reference to phraseology, for example the meaning of calibration, advice to include 'not applicable' options and recommendations to clarify certain statements, for example 'my normal bathing routine' was changed to 'my normal washing routine (e.g. bath/showering), as well as advice on formatting. These changes were incorporated into the final version of the questionnaire.

TABLE 67 *Summary of the acceptability questionnaire*

	Example items	Response format
Section one		
Interference (9 items)	(a) When wearing the monitor it interfered with my normal exercise routine	5-point Likert scale: not at all –completely
	(b) I found this acceptable	
Avoidance (8 items)	I avoided wearing the monitor when exercising	3-point Likert scale: not at all – always
Section two		
Attitude to device (38 items)	I was not worried about the way I looked when wearing the monitor	5-point Likert scale: strongly disagree – strongly agree
	Wearing the monitor made me more confident that my blood sugars were under control	
	I was confident that the monitor would accurately record if I was going hypo	
	I thought that generally the monitor was impractical	
	I would recommend other people in a similar situation to me to wear the monitor	
Section three		
Side effects (9 items)	Did you experience itching?	Dichotomous scale – yes/no
	If yes, how acceptable was this to you?	5-point Likert scale: not at all – completely

Appendix 9

Principal components analysis for 'impact from wearing the monitor' questionnaire – pattern matrix: three-factor solution

	Component		
	1	2	3
24. I felt the monitor missed too many readings	**0.748**	–0.053	–0.228
13. I found it difficult to plan when to wear the monitor so that it fitted in with my normal day-to-day activities	**0.728**	0.011	0.082
15. I found the monitor unreliable in hot and cold environments	**0.716**	0.040	–0.072
12. I found using the monitor took up too much time	**0.709**	0.027	0.152
23. I could not always enter information into the machine as instructed to	**0.664**	0.074	–0.026
20. I found the warm-up period of the monitor frustrating	**0.635**	0.006	0.145
11. I was confident that that the blood glucose readings from the monitor were accurate	**0.629**	–0.252	–0.151
2. I found the use of the monitor required careful planning	**0.602**	–0.007	–0.094
10. I was happy with the length of time that the monitor was meant to be worn for	**0.529**	–0.116	0.092
9. I thought that generally the monitor was impractical	**0.501**	–0.207	0.025
3. I had no difficulty in calibrating the monitor	0.436	–0.038	0.179
29. I found it difficult to understand when the monitor showed an error	0.408	0.137	0.140
17. I was concerned that the monitor would not record accurately if my blood sugars went too high	0.404	–0.318	–0.137
14. I was unhappy with the number of finger prick tests that were needed for the monitor to work properly	0.380	–0.036	0.112
22. I found that the monitor made me more aware of symptoms of hypoglycaemia	–0.332	**–0.784**	–0.080
28. Wearing the monitor has helped me reduce the number of hypos I experience	–0.078	**–0.776**	–0.016
5. Wearing the monitor made me more confident that my blood sugars were under control	–0.018	**–0.688**	0.134
31. I feel that the monitor has helped me improve my blood sugar control	0.257	**–0.664**	0.028
7. I was confident that the monitor would accurately record if I was going hypo	0.169	**–0.603**	–0.014
33. I would recommend other people in a similar situation to me to wear the monitor	0.334	**–0.582**	0.083
30. I would be interested in using the machine in the future	0.258	**–0.553**	0.046
19. Wearing the monitor has not helped decrease the amount of time I have high blood glucoses	0.194	**–0.513**	–0.048
27. It was easy to understand how to work the monitor	0.314	–0.334	0.251
16. I was happy to explain what the monitor was to friends	–0.199	–0.215	**0.694**
21. I made an effort to cover up the monitor so that other people would not see it	0.009	0.158	**0.621**
25. I was happy to explain what the monitor was to anyone who asked	–0.135	–0.269	**0.607**
4. I was unhappy that the monitor reminded other people about my health problems	0.116	0.062	**0.602**
1. I was not worried about the way I looked when I was wearing the monitor	0.011	0.176	**0.572**
8. I felt more self-conscious of my appearance when I was wearing the monitor	0.135	0.113	**0.526**

continued

	Component		
	1	**2**	**3**
26. I thought the read-outs from the monitor were straightforward and easy to understand	0.000	–0.331	0.456
32. I thought the time spent at the clinic for training and setting up the monitor was too long	0.208	–0.043	0.389
6. I thought the amount of training in the machine was sufficient	0.190	–0.133	0.285

Extraction method: principal component analysis. Rotation method: oblimin with Kaiser normalisation (rotation converged in eight iterations).

Appendix 10

Health economic analyses

TABLE 68 *Key resource use in the four trial arms measured at baseline*[a]

	GlucoWatch (*n* = 100)		CGMS (*n* = 102)		Attention control (*n* = 100)		Standard care control (*n* = 102)	
Items of resource use	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Medication								
Insulin (number of units per day)								
Short acting			24 (*n* = 1)					
Short-acting analogue	36 (*n* = 3)	22.65	40.67 (*n* = 3)	9.02	40 (*n* = 1)		40.67 (*n* = 3)	3.06
Long acting	52.5 (*n* = 4)	28.72	65 (*n* = 1)		75 (*n* = 2)	1.41	56 (*n* = 4)	25.033
Long-acting analogue								
Mixture	68.5 (*n* = 92)	43.74	63.65 (*n* = 97)	33.69	61.79 (*n* = 97)	28.78	64.03 (*n* = 95)	32.90
Other diabetes medicine (mg per day)								
Metformin	468.18	907.43	499.50	934.42	731.5	1150.11	505.39	989.70
Glibenclamide								
Gliclazide	5.65	40.00	3.73	37.63	2.4	24	2.35	17.64
Glimepiride	0.24	1.12	0.40	1.33	0.16	0.88	0.25	1.18
Acarbose	1.01	7.07			1.5	15	0.98	9.90
Repaglinide/nateglinide					0.08	0.8		
Glitazones			0.29	2.97	0.27	1.73		
Hospitalisation (number of days admitted)								
DKA/HONK	0.01	0.1					0.01	0.10
Hypoglycaemia	0.02	0.14						
Hyperglycaemia					0.01	0.10		
ICU			0.01	0.10	0.06	0.60		
Other	0.4	1.63	0.31	1.89	0.17	0.69	0.28	2.16
Diabetes clinic (number of visits)								
Doctor	0.95	0.58	0.88	0.41	0.89	0.35	0.92	0.41
Nurse	0.49	0.97	0.31	0.64	0.37	0.71	0.42	1.10
Nurse (telephone)	0.51	1.64	0.34	1.09	0.13	0.47	0.32	1.01
Podiatrist/dietician	0.66	1.56	0.36	0.56	0.47	1.22	0.75	2.72
GP clinic (number of visits)								
Doctor	1.22	1.94	1.14	1.54	1.04	1.61	1.01	1.19
Nurse (visit/telephone)	0.6	1.33	0.36	0.97	0.40	1.35	0.7059	2.91

continued

TABLE 68 *Key resource use in the four trial arms measured at baseline[a] (continued)*

	GlucoWatch (*n* = 100)		CGMS (*n* = 102)		Attention control (*n* = 100)		Standard care control (*n* = 102)	
Items of resource use	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Other								
A&E (number of attendances/visits)	0.15	0.44	0.10	0.33	0.12	0.39	0.12	0.57
Paramedic (number of attendances/visits)	0.13	0.75	0.03	0.17	0.04	0.20	0.09	0.55
Outpatient (number of attendances/visits)	0.55	1.08	0.63	1.13	0.66	1.07	0.67	1.54
Trial appointments	1		1		1		1	

DKA/HONK, diabetic ketoacidosis/hyperosmolar non-ketotic acidosis; ICU, intensive care unit.
a All resource use relates to the previous 3 months unless explicitly stated.

TABLE 69 *Key resource use in the four trial arms measured at 12 weeks' follow-up*

	GlucoWatch (*n* = 74)		CGMS (*n* = 81)		Attention control (*n* = 80)	
Items of resource use	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Medication						
Insulin (number of units per day)						
Short acting			25 (*n* = 1)			
Short-acting analogue	20 (*n* = 1)		36 (*n* = 1)		30 (*n* = 1)	
Long acting	47 (*n* = 2)	18.38			80 (*n* = 2)	5.65
Long-acting analogue			40 (*n* = 1)			
Mixture	66.93 (*n* = 60)	40.25	64.15 (*n* = 78)	35.85	60.56 (*n* = 77)	28.95
Other diabetes medicine (mg per day)						
Metformin	611.49	1008.34	538.27	1004.90	785	1158.88
Glibenclamide						
Gliclazide	8.65	52.25			3	26.83
Glimepiride	0.365	1.40	0.54	1.52	0.2	1.04
Acarbose	0.68	5.81			1.88	16.77
Repaglinide/nateglinide					0.05	0.45
Glitazones	0.16	1.03	0.37	3.33		
Hospitalisation (number of days admitted)						
DKA/HONK					0.01	0.11
Hypoglycaemia						
Hyperglycaemia						
ICU					0.04	0.33
Other	0.014	0.12	0.21	1.24	0.48	2.86
Diabetes clinic (number of visits)						
Doctor	0.18	0.42	0.15	0.36	0.11	0.32
Nurse	0.28	0.71	0.17	0.519	0.25	0.60
Nurse (telephone)	0.28	1.37	0.39	1.39	0.47	1.42
Podiatrist/dietician	0.91	3.55	0.26	0.54	0.40	0.74
GP clinic (number of visits)						
Doctor	1.19	2.01	0.86	1.05	1.01	1.17
Nurse (visit/telephone)	0.45	0.95	0.53	1.05	0.60	1.66
Other						
A&E (number of attendances/visits)	0.04	0.20	0.10	0.30	0.04	0.19
Paramedic (number of attendances/visits)	0.03	0.16	0.012	0.11		
Outpatient (number of attendances/visits)	0.84	1.67	0.51	1.45	0.63	1.24
Trial appointments	2.45	0.91	2.631	0.70	2.58	0.81

DKA/HONK, diabetic ketoacidosis/hyperosmolar non-ketotic acidosis; ICU, intensive care unit.

TABLE 70 *Key resource use in the four trial arms measured at 26 weeks' follow-up*

Items of resource use	GlucoWatch (*n* = 68)		CGMS (*n* = 78)		Attention control (*n* = 81)		Standard care control (*n* = 78)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Medication								
Insulin (number of units per day)								
Short acting			26 (*n* = 1)					
Short-acting analogue	39 (*n* = 2)	21.21	30 (*n* = 2)		33 (*n* = 1)		50 (*n* = 1)	
Long acting	34 (*n* = 1)						52 (*n* = 2)	2.83
Long-acting analogue	70 (*n* = 1)		48 (*n* = 1)		51 (*n* = 2)	55.15		
Mixture	68.03 (*n* = 64)	42.89	66.97 (*n* = 74)	37.06	64.37 (*n* = 78)	29.58	66.59 (*n* = 75)	29.21
Other diabetes medicine (mg per day)								
Metformin	621.01	1025.68	618.59	1032.24	779.012	1182.42	539.10	964.18
Glibenclamide								
Gliclazide	9.28	54.08			2.96	26.67	4.10	25.45
Glimepiride	0.41	1.48	0.5	1.50	0.25	1.11	0.36	1.40
Acarbose	0.72	6.02			1.85	16.67	3.85	33.97
Repaglinide/nateglinide								
Glitazones	0.29	1.43	0.38	3.40				
Hospitalisation (number of days admitted)								
DKA/HONK	0.01	0.12						
Hypoglycaemia								
Hyperglycaemia					0.01	0.11		
ICU	0.03	0.24	0.09	0.79				
Other	0.19	0.64	0.77	3.67	0.07	0.34	0.44	1.77
Diabetes clinic (number of visits)								
Doctor	0.26	0.44	0.29	0.48	0.41	0.61	0.35	0.48
Nurse	0.19	0.57	0.19	0.62	0.11	0.54	0.38	0.86
Nurse (telephone)	0.19	0.62	0.19	0.85	0.12	0.60	0.36	1.31
Podiatrist/dietician	0.37	0.73	0.37	0.79	0.56	1.59	0.58	1.66
GP clinic (number of visits)								
Doctor	0.8	1.08	0.96	1.04	0.93	1.20	0.91	1.27
Nurse (visit/telephone)	0.37	0.84	0.41	0.78	0.37	0.84	0.64	2.14
Other								
A&E (number of attendances/visits)	0.03	0.17	0.14	0.38	0.10	0.37	0.13	0.37
Paramedic (number of attendances/visits)	0.03	0.24	0.03	0.16			0.04	0.25
Outpatient (number of attendances/visits)	0.73	1.47	0.68	1.26	0.70	0.95	0.81	1.16
Trial appointments	0.74	0.44	0.77	0.42	0.86	0.35	0.87	0.34

DKA/HONK, diabetic ketoacidosis/hyperosmolar non-ketotic acidosis; ICU, intensive care unit.

TABLE 71 *Key resource use in the four trial arms measured at 52 weeks' follow-up*

Items of resource use	GlucoWatch (*n* = 69)		CGMS (*n* = 74)		Attention control (*n* = 85)		Standard care control (*n* = 70)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Medication								
Insulin (number of units per day)								
Short acting			30 (*n* = 1)					
Short-acting analogue	30 (*n* = 2)		31 (*n* = 2)	7.07	40 (*n* = 1)		52 (*n* = 2)	2.83
Long acting					40 (*n* = 1)		68 (*n* = 3)	30.20
Long-acting analogue	32.5 (*n* = 2)	3.54	52 (*n* = 1)		14 (*n* = 1)			
Mixture	69.06 (*n* = 65)	41.64	66.1 (*n* = 70)	37.44	67.32 (*n* = 81)	31.78	63.94 (*n* = 65)	28.39
Other diabetes medicine (mg per day)								
Metformin	581.88	995.61	417.57	848.63	761.18	1141.80	536.43	1016.96
Glibenclamide								
Gliclazide	8.12	47.81			2.82	26.03	4	23.74
Glimepiride	0.46	1.50	0.68	1.77	0.24	1.09	0.29	1.19
Acarbose	0.72	6.02			1.76	16.27		
Repaglinide/nateglinide								
Glitazones	0.23	1.35	0.41	3.49				
Hospitalisation (number of days admitted)								
DKA/HONK	0.014	0.12					0.04	0.36
Hypoglycaemia	0.014	0.12	0.01	0.12			0.03	0.17
Hyperglycaemia			0.01	0.12	0.01	0.11		
ICU			0.03	0.23			0.06	0.48
Other	0.42	2.49	0.88	3.63	0.25	1.09	1.29	6.76
Diabetes clinic (number of visits)								
Doctor	0.48	0.50	0.44	0.50	0.42	0.50	0.45	0.56
Nurse	0.29	0.69	0.12	0.37	0.17	0.49	0.17	0.42
Nurse (telephone)	0.43	1.38	0.09	0.37	0.07	0.26	0.39	1.13
Podiatrist/dietician	0.81	2.30	0.35	0.65	0.42	1.20	0.61	1.07
GP clinic (number of visits)								
Doctor	0.97	1.27	1.09	1.65	1.10	1.26	0.75	0.99
Nurse (visit/telephone)	0.45	0.81	0.56	1.04	0.57	1.44	0.33	0.63
Other								
A&E (number of attendances/visits)	0.06	0.24	0.17	0.42	0.17	0.41	0.14	0.39
Paramedic (number of attendances/visits)			0.03	0.16			0.04	0.21
Outpatient (number of attendances/visits)	0.78	1.64	0.6	1.28	0.46	0.78	0.75	1.69
Trial appointments	0.72	0.45	0.72	0.45	0.86	0.35	0.79	0.41

DKA/HONK, diabetic ketoacidosis/hyperosmolar non-ketotic acidosis; ICU, intensive care unit.

TABLE 72 *Key resource use in the four trial arms measured at 78 weeks' follow-up*

	GlucoWatch (*n* = 74)		CGMS (*n* = 75)		Attention control (*n* = 81)		Standard care control (*n* = 77)	
Items of resource use	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Medication								
Insulin (number of units per day)								
Short acting			30 (*n* = 1)					
Short-acting analogue	15 (*n* = 1)		44 (*n* = 4)	19.34			48.33 (*n* = 3)	14.43
Long acting	38 (*n* = 1)				40 (*n* = 1)		40 (*n* = 1)	
Long-acting analogue	56 (*n* = 1)				14 (*n* = 1)			
Mixture	69.86 (*n* = 69)	41.86	66.13 (*n* = 70)	32.84	68.61 (*n* = 78)	32.09	67.32 (*n* = 73)	33.73
Other diabetes medicine (mg per day)								
Metformin	599.32	1035.78	610	949.64	841.98	1143.39	715.58	1100.70
Glibenclamide								
Gliclazide	7.57	46.19			2.96	26.67	6.75.	45.95
Glimepiride	0.55	1.73	0.51	1.55	0.20	1.03	0.29	1.24
Acarbose	0.68	5.81			1.85	16.67	3.90	34.19
Repaglinide/nateglinide					0.074	0.66		
Glitazones	0.22	1.31			0.05	0.44		
Hospitalisation (number of days admitted)								
DKA/HONK	0.01	0.12	0.13	1.15			0.01	0.11
Hypoglycaemia							0.01	0.11
Hyperglycaemia			0.01	0.11	0.01	0.11	0.04	0.34
ICU	1.16	5.22	0.25	1.96			0.09	0.46
Other			0.76	3.81	0.52	2.11	1.52	5.82
Diabetes clinic (number of visits)								
Doctor	0.22	0.42	0.26	0.47	0.27	0.52	0.38	0.73
Nurse	0.25	0.76	0.22	1.21	0.23	0.58	0.39	1.32
Nurse (telephone)	0.36	0.87	0.28	1.22	0.25	0.96	0.25	1.07
Podiatrist/dietician	0.40	0.78	0.30	1.20	0.36	0.78	0.61	1.41
GP clinic (number of visits)								
Doctor	1.26	1.44	1.37	1.83	1.49	1.91	0.90	1.19
Nurse (visit/telephone)	0.56	1.11	0.57	0.84	0.99	2.90	0.47	0.97
Other								
A&E (number of attendances/visits)	0.19	0.43	0.14	0.42	0.11	0.32	0.19	0.54
Paramedic (number of attendances/visits)			0.05	0.36	0.02	0.16	0.04	0.25
Outpatient (number of attendances/visits)	0.78	1.58	0.83	1.53	0.74	1.63	1.31	2.82
Trial appointments	0.79	0.41	0.71	0.46	0.85	0.36	0.85	0.36

DKA/HONK, diabetic ketoacidosis/hyperosmolar non-ketotic acidosis; ICU, intensive care unit.

TABLE 73 *Resource use costs (£) over the previous 3 months measured at baseline*

	GlucoWatch (*n* = 99)	CGMS (*n* = 102)	Attention control (*n* = 99)	Standard care control (*n* = 102)
Insulin				
Mean (SD)	107.3903 (69.64864)	100.9353 (53.97036)	99.05564 (46.00468)	101.1763 (52.24441)
Median (IQR)	93.70715 (64.62561–122.7887)	88.38041 (64.62561–119.5574)	87.24458 (67.8569–99.05564)	92.0915 (67.8569–114.7105)
Lower 95% CI	95.85499	90.25441	88.41606	90.46995
Upper 95% CI	118.9243	111.6161	109.6952	111.8827
Diabetes medicine				
Mean (SD)	9.538291 (35.10903)	17.43855 (50.71419)	10.92153 (33.60979)	9.887929 (36.90468)
Median (IQR)	0 (0–3.354806)	0 (0–5.032209)	0 (0–5.703171)	0 (0–3.354806)
Lower 95% CI	3.208481	6.037416	3.673773	3.423309
Upper 95% CI	15.8681	28.83968	18.16929	16.35255
Other medication				
Mean (SD)	69.6884 (65.26365)	66.50027 (70.54967)	59.36177 (66.19725)	78.35388 (82.26122)
Median (IQR)	62.196 (8.701326–116.7622)	60.99091 (5.6575–88.15534)	60.06212 (1.303598–93.88969)	63.87509 (1.857576–127.4893)
Lower 95% CI	55.36941	53.0388	47.16462	62.49288
Upper 95% CI	84.00735	79.96174	71.55892	94.21476
Hospitalisation				
Mean (SD)	135.3535 (490.1574)	114.4706 (552.5181)	160.1919 (934.0419)	95.06863 (610.7599)
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Lower 95% CI	47.7411	41.0036	56.50195	34.05378
Upper 95% CI	383.7486	319.5699	454.1693	265.405
Diabetes clinic				
Mean (SD)	56.17677 (65.06823)	42.11275 (27.1274)	44.43434 (42.81144)	56.26471 (89.85232)
Median (IQR)	37 (27.5–59.5)	32 (27.5–59.5)	27.5 (27.5–59.5)	37 (27.5–59.5)
Lower 95% CI	43.50276	32.75248	34.40954	43.75893
Upper 95% CI	68.85076	51.47301	54.45914	68.77048
GP clinic				
Mean (SD)	38.33333 (56.958)	34.72059 (44.09871)	32.44949 (54.14396)	34.47549 (44.37399)
Median (IQR)	27.5 (0–46.5)	27.5 (0–37)	27.5 (0–37)	27.5 (0–55)
Lower 95% CI	27.50394	25.05714	23.28223	24.88026
Upper 95% CI	49.16272	44.38403	41.61634	44.07072
Other resources[a]				
Mean (SD)	109.4444 (288.9773)	82.63725 (143.3519)	91.0303 (133.3113)	106.6569 (274.7831)
Median (IQR)	0 (0–104)	0 (0–104)	0 (0–104)	0 (0–104)
Lower 95% CI	62.74198	47.89649	52.18558	61.81823
Upper 95% CI	156.1469	117.378	129.875	151.4955

continued

TABLE 73 *Resource use costs (£) over the previous 3 months measured at baseline (continued)*

	GlucoWatch (*n* = 99)	CGMS (*n* = 102)	Attention control (*n* = 99)	Standard care control (*n* = 102)
Clinic appointments				
Mean (SD)	9.5 (0)	9.5 (0)	9.5 (0)	9.5 (0)
Median (IQR)	9.5 (9.5–9.5)	9.5 (9.5–9.5)	9.5 (9.5–9.5)	9.5 (9.5–9.5)
95% CI	9.5–9.5	9.5–9.5	9.5–9.5	9.5–9.5
Total cost				
Mean (SD)	535.4251 (706.9194)	468.3153 (626.8077)	506.945 (1016.425)	491.3838 (811.1197)
Median (IQR)	312.6697 (235.33–501.7001)	333.2448 (188.5574–449.0145)	323.2387 (192.419–504.01)	337.8497 (190.4853–496.9085)
Lower 95% CI	366.4371	322.6971	346.9457	338.5936
Upper 95% CI	704.4131	613.9288	666.9442	644.174
Total cost excluding hospitalisation costs				
Mean (SD)	400.0716 (358.7512)	353.8447 (201.3291)	346.7531 (208.3709)	396.3152 (357.2824)
Median (IQR)	297.3721 (235.3336–470.859)	324.3998 (188.557–431.9397)	313.8725 (190.2281–446.6711)	329.9094 (190.4853–473.7934)
Lower 95% CI	340.2965	301.7597	294.9444	337.9786
Upper 95% CI	459.8466	405.9297	398.5618	454.6517

CI, confidence interval; IQR, interquartile range.
a Other resources included A&E visits, use of paramedic services and outpatient visits.

TABLE 74 *Resource use costs (£) over the previous 3 months measured at week 12 follow-up*

	GlucoWatch (*n* = 74)	CGMS (*n* = 81)	Attention control (*n* = 80)
Insulin			
Mean (SD)	104.323 (65.51337)	102.0688 (57.68368)	97.28607 (46.14403)
Median (IQR)	90.47585 (64.62561–129.2512)	87.24458 (61.39433–122.7887)	84.0133 (70.28035–117.9417)
Lower 95% CI	91.07121	89.67621	85.40057
Upper 95% CI	117.5749	114.4614	109.1716
Diabetes medicine			
Mean (SD)	8.352051 (23.75591)	11.7642 (37.85964)	5.440307 (12.69146)
Median (IQR)	0 (0–5.032209)	0 (0–6.709612)	0 (0–5.36769)
Lower 95% CI	2.97977	4.531484	2.074728
Upper 95% CI	13.72433	18.99691	8.805887
Other medication			
Mean (SD)	71.94521 (73.46802)	70.48483 (73.69214)	70.51452 (71.37)
Median (IQR)	62.196 (1.303598–122.9412)	64.41602 (8.701326–107.3426)	64.4303 (1.857576–119.9456)
Lower 95% CI	55.11736	54.72702	54.65185
Upper 95% CI	88.77307	86.24264	86.37719
Hospitalisation			
Mean (SD)	3.283784 (28.24818)	51 (301.839)	179.375 (944.6939)
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)
Lower 95% CI	0.7145207	11.87073	41.37373
Upper 95% CI	15.09157	219.1103	777.6768
Diabetes clinic			
Mean (SD)	39.19595 (130.9039)	17.76543 (24.82427)	22.78125 (34.27964)
Median (IQR)	0 (0–32)	0 (0–32)	0 (0–41.5)
Lower 95% CI	19.31476	9.152516	11.66778
Upper 95% CI	59.07712	26.37835	33.89471
GP clinic			
Mean (SD)	36.93919 (58.04279)	28.80864 (32.50005)	33.31875 (40.45808)
Median (IQR)	27.5 (0–55)	27.5 (0–55)	27.5 (0–37)
Lower 95% CI	25.90807	20.58568	23.74919
Upper 95% CI	47.97031	37.03161	42.88831
Other resources[a]			
Mean (SD)	98.94595 (180.409)	64.77778 (155.9192)	69.45 (130.5649)
Median (IQR)	0 (0–104)	0 (0–84)	0 (0–104)
Lower 95% CI	52.47758	35.70016	38.08087
Upper 95% CI	145.4143	93.85538	100.8191

continued

TABLE 74 *Resource use costs (£) over the previous 3 months measured at week 12 follow-up (continued)*

	GlucoWatch (*n* = 74)	CGMS (*n* = 81)	Attention control (*n* = 80)
Trial specific			
Device cost			
Mean (SD)	29.74649 (21.92156)	133.9259 (62.17853)	
Median (IQR)	19.48 (19.48–38.96)	169.5 (113–169.5)	
95% CI	24.66767–34.8253	120.1771–147.6747	
Clinic appointments			
Mean (SD)	26.95946 (4.45507)	27.67901 (3.077447)	27.075 (3.733275)
Median (IQR)	28.5 (28.5–28.5)	28.5 (28.5–28.5)	28.5 (28.5–28.5)
95% CI	25.9273–27.99162	26.99853–28.35949	26.2442–27.9058
Total cost			
Mean (SD)	419.6911 (310.2753)	508.2746 (365.1272)	505.2409 (1028.736)
Median (IQR)	352.4226 (207.5634–541.8344)	418.1334 (340.8049–561.1271)	289.9698 (189.5366–416.4692)
Lower 95% CI	292.7515	361.3343	358.2682
Upper 95% CI	546.6307	655.212	652.2136
Total cost excluding hospitalisation costs			
Mean (SD)	416.4073 (310.1415)	457.2746 (188.2154)	325.8659 (194.7861)
Median (IQR)	341.1699 (207.5634–538.3796)	418.1334 (340.8049–524.5836)	283.8349 (185.6246–411.1677)
Lower 95% CI	359.9066	397.9703	283.3408
Upper 95% CI	472.9081	516.5789	368.391

CI, confidence interval; IQR, interquartile range.
a Other resources included A&E visits, use of paramedic services and outpatient visits.

TABLE 75 *Resource use costs (£) over the previous 3 months measured at week 26 follow-up*

	GlucoWatch (*n* = 69)	CGMS (*n* = 78)	Attention control (*n* = 81)	Standard care control (*n* = 78)
Insulin				
Mean (SD)	106.9819 (69.29126)	105.8066 (59.67397)	103.8667 (49.44549)	106.2188 (46.83577)
Median (IQR)	90.47585 (64.6256–129.2512)	96.1306 (64.62561–124.4043)	87.24458 (71.08817–135.7138)	99.36189 (72.70381–119.5574)
Lower 95% CI	93.50214	93.26762	91.78776	93.63095
Upper 95% CI	120.4616	118.3455	115.9457	118.8066
Diabetes medicine				
Mean (SD)	10.20616 (29.29028)	11.69475 (38.17898)	5.785674 (13.79335)	6.565005 (16.58462)
Median (IQR)	0 (0–6.709612)	0 (0–6.709612)	0 (0–5.032209)	0 (0–5.032209)
Lower 95% CI	3.521762	4.490842	2.288349	2.520994
Upper 95% CI	16.89057	18.89867	9.283	10.60902
Other medication				
Mean (SD)	69.43361 (70.60947)	68.38614 (65.69072)	61.48261 (64.39966)	90.42999 (90.66718)
Median (IQR)	64.41602 (0–122.9412)	63.16786 (8.701326–93.79195)	60.06212 (1.303598–115.8484)	68.76344 (8.701326–143.5115)
Lower 95% CI	52.92768	53.09585	47.99283	70.21097
Upper 95% CI	85.93955	83.67643	74.97238	110.649
Hospitalisation				
Mean (SD)	95.10145 (510.888)	321.9615 (1756.145)	20.90123 (87.34481)	105.9231 (430.062)
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Lower 95% CI	30.70776	111.1876	7.363017	36.57993
Upper 95% CI	294.5275	932.2903	59.33185	306.7171
Diabetes clinic				
Mean (SD)	22.41304 (28.70719)	23.66026 (32.71964)	31.60494 (51.08239)	35.04487 (56.346)
Median (IQR)	9.5 (0–32)	19 (0–32)	27.5 (0–37)	27.5 (0–41.5)
Lower 95% CI	14.5535	15.85669	21.37593	23.48646
Upper 95% CI	30.27259	31.46382	41.83394	46.60328
GP clinic				
Mean (SD)	25.89855 (33.3572)	30.69231 (31.52099)	28.98148 (36.06924)	31.12179 (42.45618)
Median (IQR)	27.5 (0–27.5)	27.5 (0–55)	27.5 (0–55)	27.5 (0–37)
Lower 95% CI	18.34648	22.27453	21.1815	22.58622
Upper 95% CI	33.45063	39.11009	36.78146	39.65737
Other resources[a]				
Mean (SD)	88.31884 (166.5115)	90.48718 (142.2582)	78.12346 (103.7325)	106.7308 (151.8163)
Median (IQR)	0 (0–104)	0 (0–104)	0 (0–104)	42 (0–208)
Lower 95% CI	55.94482	59.29056	51.69287	69.93396
Upper 95% CI	120.6929	121.6838	104.554	143.5276

continued

TABLE 75 *Resource use costs (£) over the previous 3 months measured at week 26 follow-up (continued)*

	GlucoWatch (*n* = 69)	CGMS (*n* = 78)	Attention control (*n* = 81)	Standard care control (*n* = 78)
Trial specific (not imputed)				
Device cost				
Mean (SD)	29.74649 (21.92156)	43.46154 (23.95894)		
Median (IQR)	19.48 (19.48–38.96)	56.5 (56.5–56.5)		
95% CI	24.22355–35.06341	38.05963–48.86345		
Clinic appointments				
Mean (SD)	9.5 (0)	9.5 (0)	9.5 (0)	9.5 (0)
Median (IQR)	9.5 (9.5–9.5)	9.5 (9.5–9.5)	9.5 (9.5–9.5)	9.5 (9.5–9.5)
95% CI	9.5–9.5	9.5–9.5	9.5–9.5	9.5–9.5
Total cost				
Mean (SD)	457.497 (561.7956)	705.6503 (1801.08)	340.2461 (200.8813)	491.4125 (502.2477)
Median (IQR)	329.4486 (210.5307–489.706)	364.8754 (247.1595–540.8842)	307.1031 (198.9022–482.7256)	370.5746 (208.6631–597.6501)
Lower 95% CI	291.6923	465.1169	226.4352	323.9058
Upper 95% CI	623.3017	946.1837	454.057	658.9191
Total cost excluding hospitalisation costs				
Mean (SD)	362.3956 (233.6655)	383.6888 (194.0919)	319.3449 (167.9698)	385.4894 (236.471)
Median (IQR)	317.323 (201.0105–463.0884)	356.9482 (243.2285–503.9083)	302.1329 (172.9229–422.8631)	346.0672 (197.5097–526.1445)
Lower 95% CI	313.417	334.9158	279.5099	336.4875
Upper 95% CI	411.3741	432.4617	359.1799	434.4913

CI, confidence interval; IQR, interquartile range.
a Other resources included A&E visits, use of paramedic services and outpatient visits.

TABLE 76 *Resource use costs (£) over the previous 3 months measured at week 52 follow-up*

	GlucoWatch (*n* = 69)	CGMS (*n* = 74)	Attention control (*n* = 84)	Standard care control (*n* = 69)
Insulin				
Mean (SD)	108.902 (66.24)	104.5704 (60.12698)	104.7882 (52.55685)	101.703 (45.02058)
Median (IQR)	93.70715 (64.6256–137.3294)	92.89932 (64.4517–123.37)	90.47585 (71.08817–125.2121)	93.70715 (69.47253–121.173)
Lower 95% CI	95.14949	91.81899	92.79501	88.85988
Upper 95% CI	122.6536	117.3215	116.7813	114.5461
Diabetes medicine				
Mean (SD)	10.07033 (28.93296)	13.21438 (40.04223)	5.642944 (13.54682)	5.286804 (14.50967)
Median (IQR)	0 (0–5.032209)	0 (0–6.709612)	0 (0–5.870911)	0 (0–3.354806)
Lower 95% CI	3.515276	4.908458	2.313873	1.845479
Upper 95% CI	16.62538	21.52031	8.972015	8.728128
Other medication				
Mean (SD)	74.85209 (78.74908)	69.11092 (72.08633)	71.82547 (73.57283)	90.25136 (87.82544)
Median (IQR)	65.71961 (1.30359–109.5652)	65.34481 (3.161174–92.45578)	60.43684 (1.857576–117.53)	68.76344 (10.00492–132.3125)
Lower 95% CI	56.76703	52.98697	56.09725	68.44567
Upper 95% CI	92.93715	85.23486	87.55368	112.057
Hospitalisation				
Mean (SD)	112.7826 (610.2315)	263.3108 (1006.337)	63.54762 (266.8934)	426.6667 (1858.157)
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Lower 95% CI	39.35484	95.26697	24.47298	148.8829
Upper 95% CI	323.2109	727.7715	165.0106	1222.736
Diabetes clinic				
Mean (SD)	46.00725 (85.99677)	25.56081 (25.97522)	27.05357 (42.29899)	37.2029 (42.339)
Median (IQR)	27.5 (0–41.5)	27.5 (0–32)	27.5 (0–32)	27.5 (0–46.5)
Lower 95% CI	30.39457	17.18486	18.73286	24.578
Upper 95% CI	61.61992	33.93676	35.37428	49.82779
GP clinic				
Mean (SD)	30.97101 (38.59022)	35.12162 (47.49079)	35.54762 (39.2071)	23.8913 (30.75375)
Median (IQR)	27.5 (0–37)	27.5 (0–55)	27.5 (0–55)	9.5 (0–27.5)
Lower 95% CI	21.87104	25.15684	26.08132	16.87151
Upper 95% CI	40.07098	45.08641	45.01391	30.9111

continued

TABLE 76 *Resource use costs (£) over the previous 3 months measured at week 52 follow-up (continued)*

	GlucoWatch (*n* = 69)	CGMS (*n* = 74)	Attention control (*n* = 84)	Standard care control (*n* = 69)
Other resources[a]				
Mean (SD)	86.26087 (170.4961)	86.40541 (147.1258)	62.28571 (84.00639)	104.0725 (201.6886)
Median (IQR)	0 (0–104)	0 (0–104)	0 (0–104)	0 (0–104)
Lower 95% CI	50.85023	52.1547	39.11212	61.35005
Upper 95% CI	121.6715	120.6561	85.45929	146.7949
Trial specific (not imputed)				
Device cost				
Mean (SD)	29.74649 (21.92156)	43.52027 (23.92947)		
Median (IQR)	19.48 (19.48–38.96)	56.5 (56.5–56.5)		
95% CI	24.22355–35.06341	37.97626–49.06428		
Clinic appointments				
Mean (SD)	9.5 (0)	9.5 (0)	9.5 (0)	9.5 (0)
Median (IQR)	9.5 (9.5–9.5)	9.5 (9.5–9.5)	9.5 (9.5–9.5)	9.5 (9.5–9.5)
95% CI	9.5–9.5	9.5–9.5	9.5–9.5	9.5–9.5
Total cost				
Mean (SD)	508.852 (733.7279)	650.1862 (1085.374)	379.8519 (354.4342)	798.5745 (1995.022)
Median (IQR)	314.4025 (218.740–496.3476)	364.5415 (238.9077–511.8788)	300.3122 (155.545–441.7924)	347.5139 (218.8747–527.1156)
Lower 95% CI	305.0318	398.7069	241.9548	478.7061
Upper 95% CI	712.6722	901.6655	517.7489	1118.443
Total cost excluding hospitalisation costs				
Mean (SD)	396.0694 (280.9253)	386.8754 (179.2374)	316.3043 (186.3885)	371.9078 (257.977)
Median (IQR)	306.2508 (218.740–496.3476)	357.0795 (238.9077–500.429)	289.3006 (152.5102–430.8362)	309.3441 (203.6944–458.6702)
Lower 95% CI	338.3413	332.4257	274.5207	317.7013
Upper 95% CI	453.7975	441.3251	358.0879	426.1143

CI, confidence interval; IQR, interquartile range.
a Other resources included A&E visits, use of paramedic services and outpatient visits.

TABLE 77 *Resource use costs (£) over the previous 3 months measured at week 78 follow-up*

	GlucoWatch (*n* = 73)	CGMS (*n* = 74)	Attention control (*n* = 81)	Standard care control (*n* = 77)
Insulin				
Mean (SD)	107.9953 (69.41531)	104.7006 (53.0956)	107.7652 (53.42913)	107.1132 (53.79766)
Median (IQR)	87.24458 (64.62561–132.4825)	93.70715 (67.8569–129.2512)	96.93842 (71.08817–142.1763)	90.47585 (71.08817–129.2512)
Lower 95% CI	94.64915	91.84937	95.12228	94.22446
Upper 95% CI	121.3414	117.5519	120.4082	120.0019
Diabetes medicine				
Mean (SD)	11.09998 (30.02979)	7.857158 (17.91067)	6.186931 (13.61149)	6.467282 (15.78746)
Median (IQR)	0 (0–5.703171)	0 (0–5.032209)	0 (0–6.709612)	0 (0–5.032209)
Lower 95% CI	4.965533	3.544309	2.940939	2.987187
Upper 95% CI	17.23443	12.17001	9.432922	9.947374
Other medication				
Mean (SD)	75.35487 (69.88329)	67.49416 (61.29162)	74.13741 (69.57445)	83.67282 (79.00392)
Median (IQR)	67.45985 (8.994604–111.8608)	66.38447 (8.701326–89.06657)	68.53532 (4.464771–118.0645)	64.72234 (8.701326–132.3125)
Lower 95% CI	59.27851	53.19244	59.12215	66.29174
Upper 95% CI	91.43124	81.79587	89.15267	101.0539
Hospitalisation				
Mean (SD)	289.2877 (1310.078)	633.6351 (3816.325)	128.9012 (523.7314)	521.5714 (1935.147)
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Lower 95% CI	99.66971	219.8923	46.87454	184.8108
Upper 95% CI	839.6468	1825.864	354.4681	1471.975
Diabetes clinic				
Mean (SD)	24.46575 (33.45346)	21.02027 (56.97364)	23.5 (33.10721)	35.93506 (63.48049)
Median (IQR)	0 (0–37)	0 (0–27.5)	9.5 (0–32)	27.5 (0–37)
Lower 95% CI	13.89565	12.00031	13.86154	20.81841
Upper 95% CI	35.03586	30.04023	33.1384	51.05158
GP clinic				
Mean (SD)	39.99315 (45.77272)	43.2973 (50.90913)	50.46296 (62.23744)	29.08442 (36.90871)
Median (IQR)	27.5 (0–55)	27.5 (9.5–56)	37 (0–64.5)	27.5 (0–37)
Lower 95% CI	28.90807	31.37775	37.18458	21.23514
Upper 95% CI	51.07823	55.21684	63.74131	36.93369
Other resources[a]				
Mean (SD)	97.31507 (166.4559)	103.7838 (180.3439)	94.04938 (177.595)	164.8961 (323.7527)
Median (IQR)	0 (0–104)	42 (0–104)	0 (0–104)	84 (0–188)
Lower 95% CI	56.43631	60.48331	56.5441	97.45199
Upper 95% CI	138.1938	147.0843	131.5547	232.3402

continued

TABLE 77 *Resource use costs (£) over the previous 3 months measured at week 78 follow-up (continued)*

Trial specific (not imputed)				
Device cost				
Mean (SD)	29.74649 (21.92156)	38.93919 (26.32814)		
Median (IQR)	19.48 (19.48–38.96)	56.5 (0–56.5)		
95% CI	24.22355–35.06341	32.83945–45.03892		
Clinic appointments				
Mean (SD)	9.5 (0)	9.5 (0)	9.5 (0)	9.5 (0)
Median (IQR)	9.5 (9.5–9.5)	9.5 (9.5–9.5)	9.5 (9.5–9.5)	9.5 (9.5–9.5)
95% CI	9.5–9.5	9.5–9.5	9.5–9.5	9.5–9.5
Total cost				
Mean (SD)	687.0337 (1366.573)	1029.714 (3854.674)	494.5031 (608.7462)	958.1169 (2056.001)
Median (IQR)	306.8568 (229.7793–622.3994)	351.4037 (233.404–534.8004)	358.4832 (214.7412–502.6199)	379.2524 (216.901–624.457)
Lower 95% CI	303.8276	459.2653	232.6593	437.7748
Upper 95% CI	1070.239	1600.163	756.347	1478.459
Total cost excluding hospitalisation costs				
Mean (SD)	397.746 (253.3182)	396.079 (232.992)	365.6019 (241.9009)	436.5455 (380.6667)
Median (IQR)	306.8568 (229.7793–485.6231)	345.5013 (233.4048–511.6154)	329.2203 (214.20–434.9224)	323.5288 (215.7505–508.2052)
Lower 95% CI	333.9219	332.9533	309.9082	368.3392
Upper 95% CI	461.5701	459.2046	421.2956	504.7518

CI, confidence interval; IQR, interquartile range.
a Other resources included A&E visits, use of paramedic services and outpatient visits.

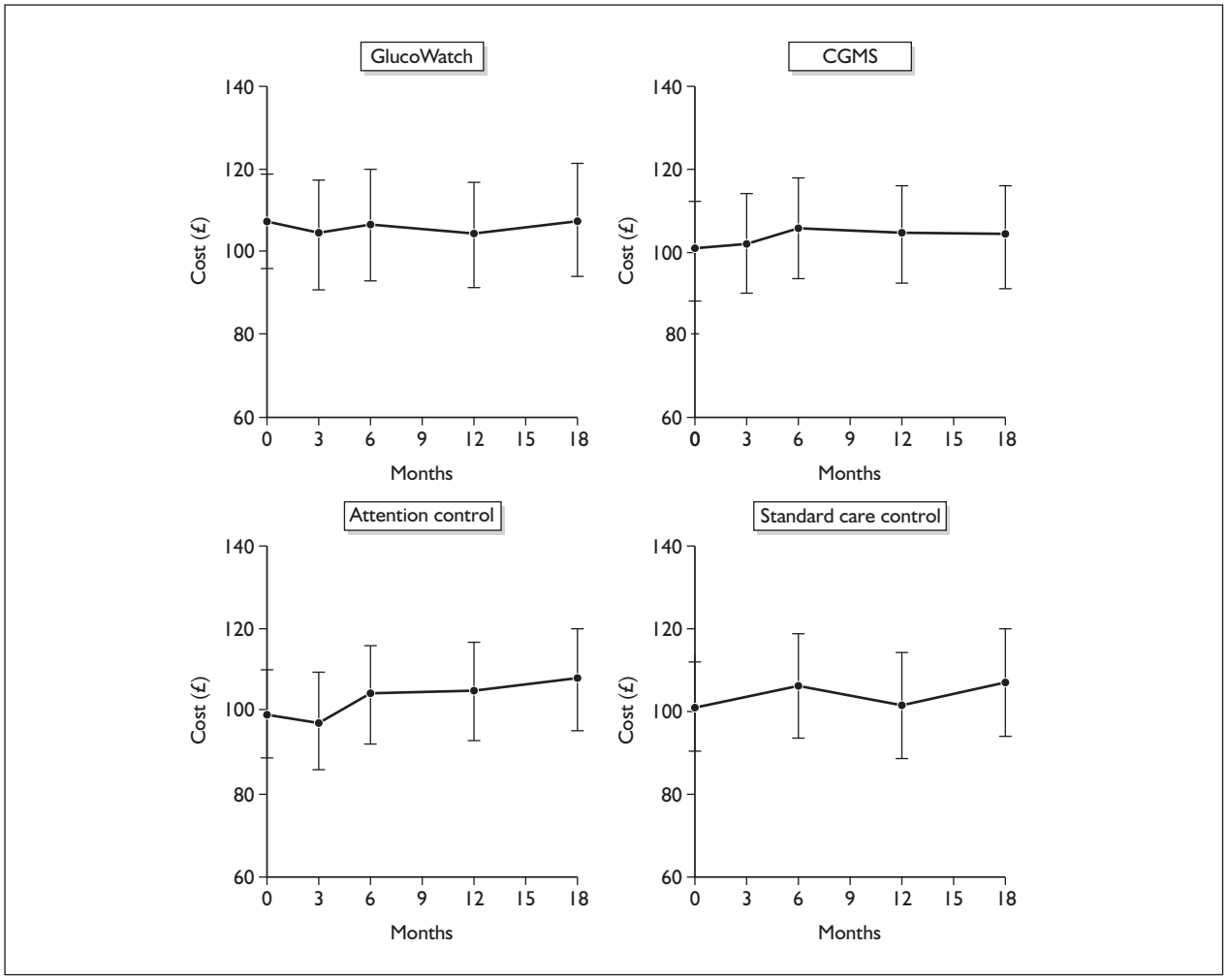

FIGURE 29 *Mean insulin costs.*

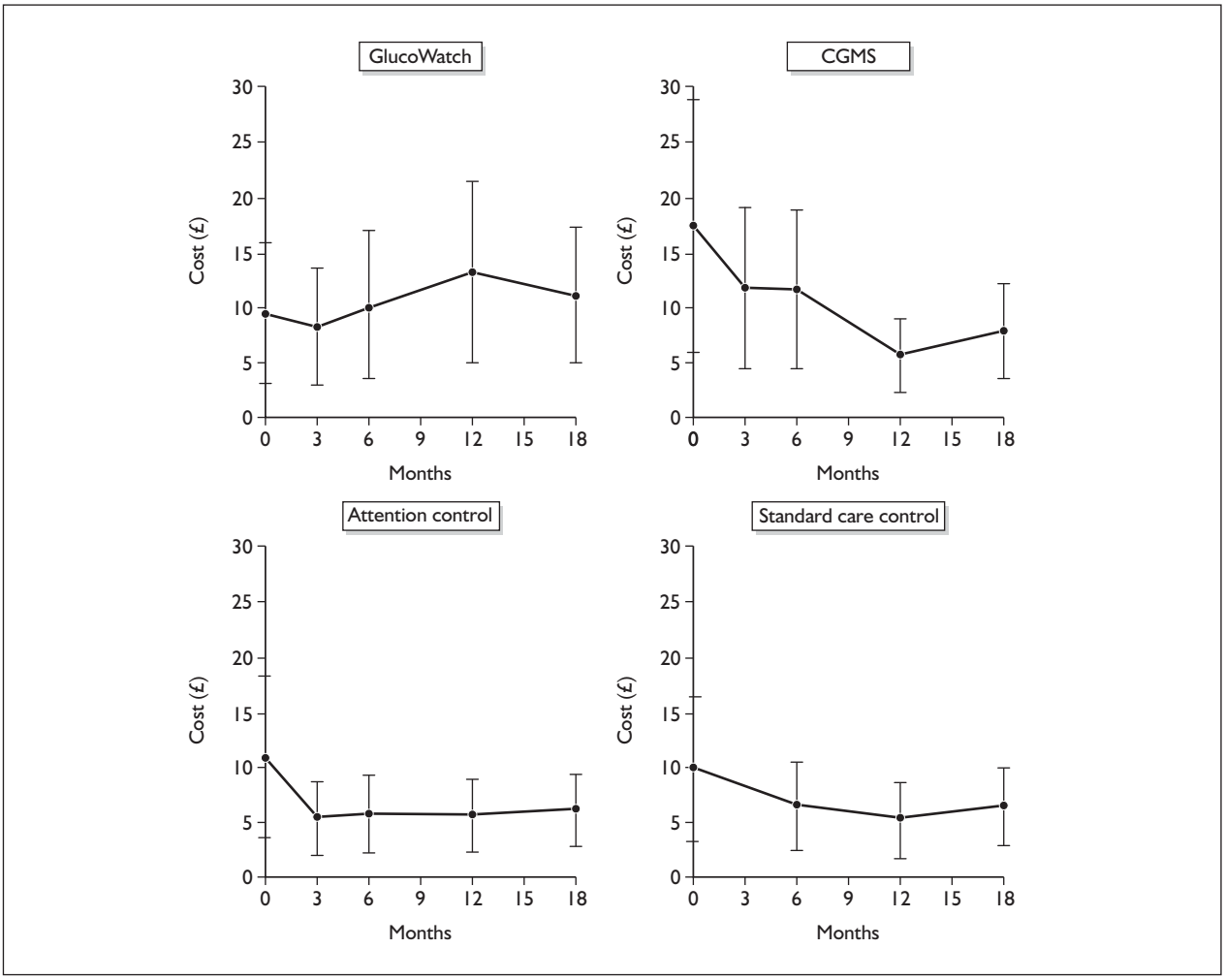

FIGURE 30 *Mean diabetic medicine costs.*

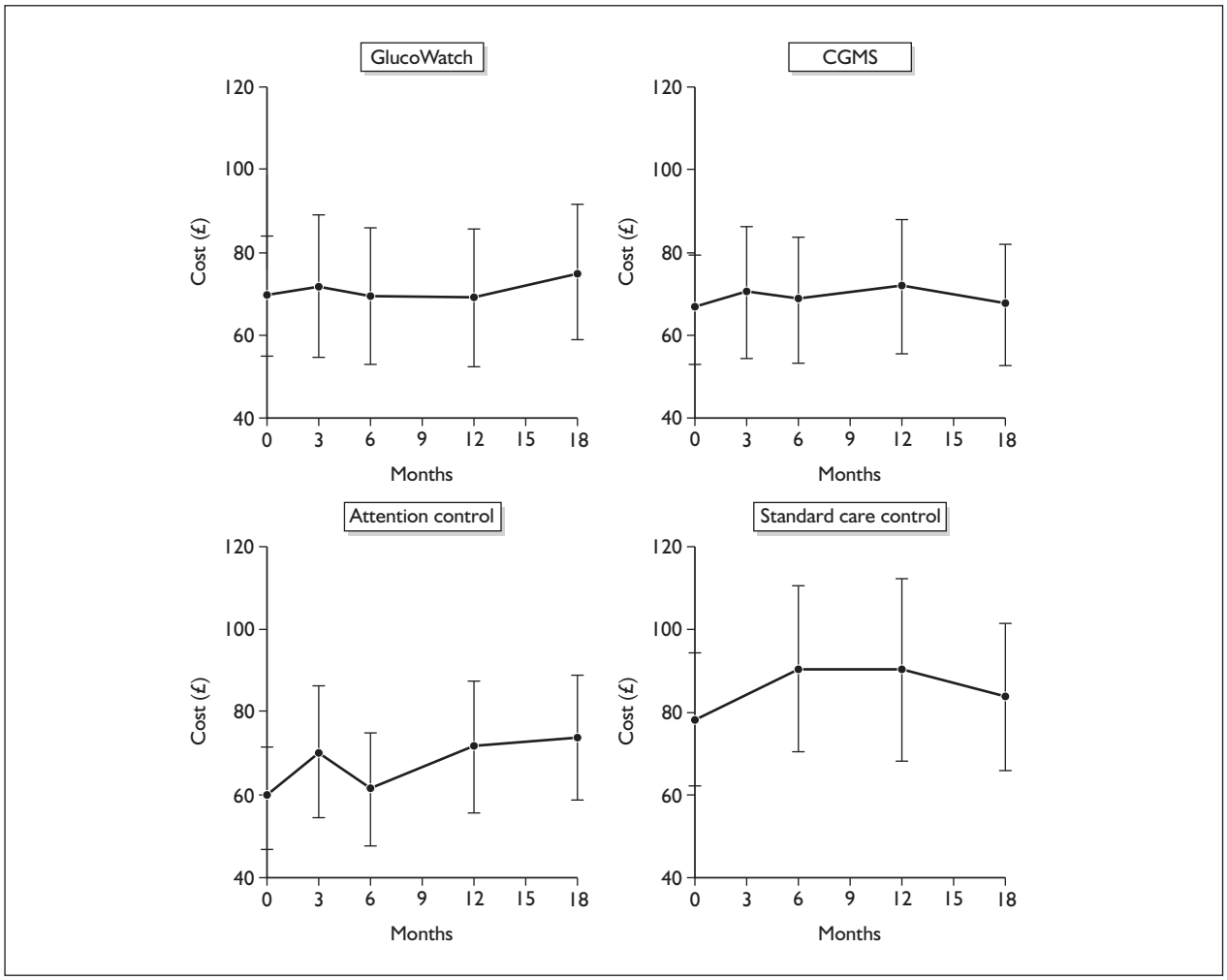

FIGURE 31 *Mean other medication costs.*

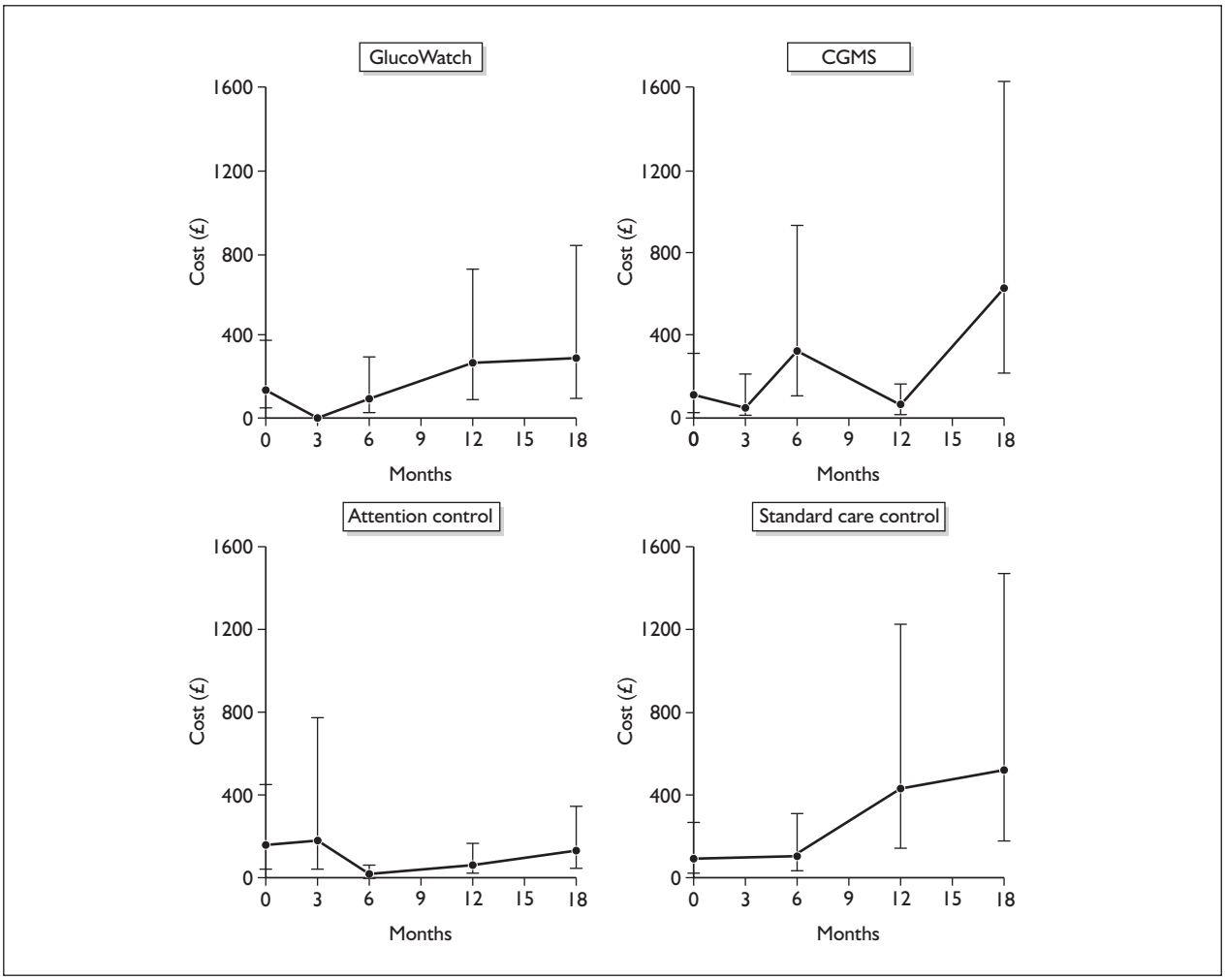

FIGURE 32 *Mean hospitalisation costs.*

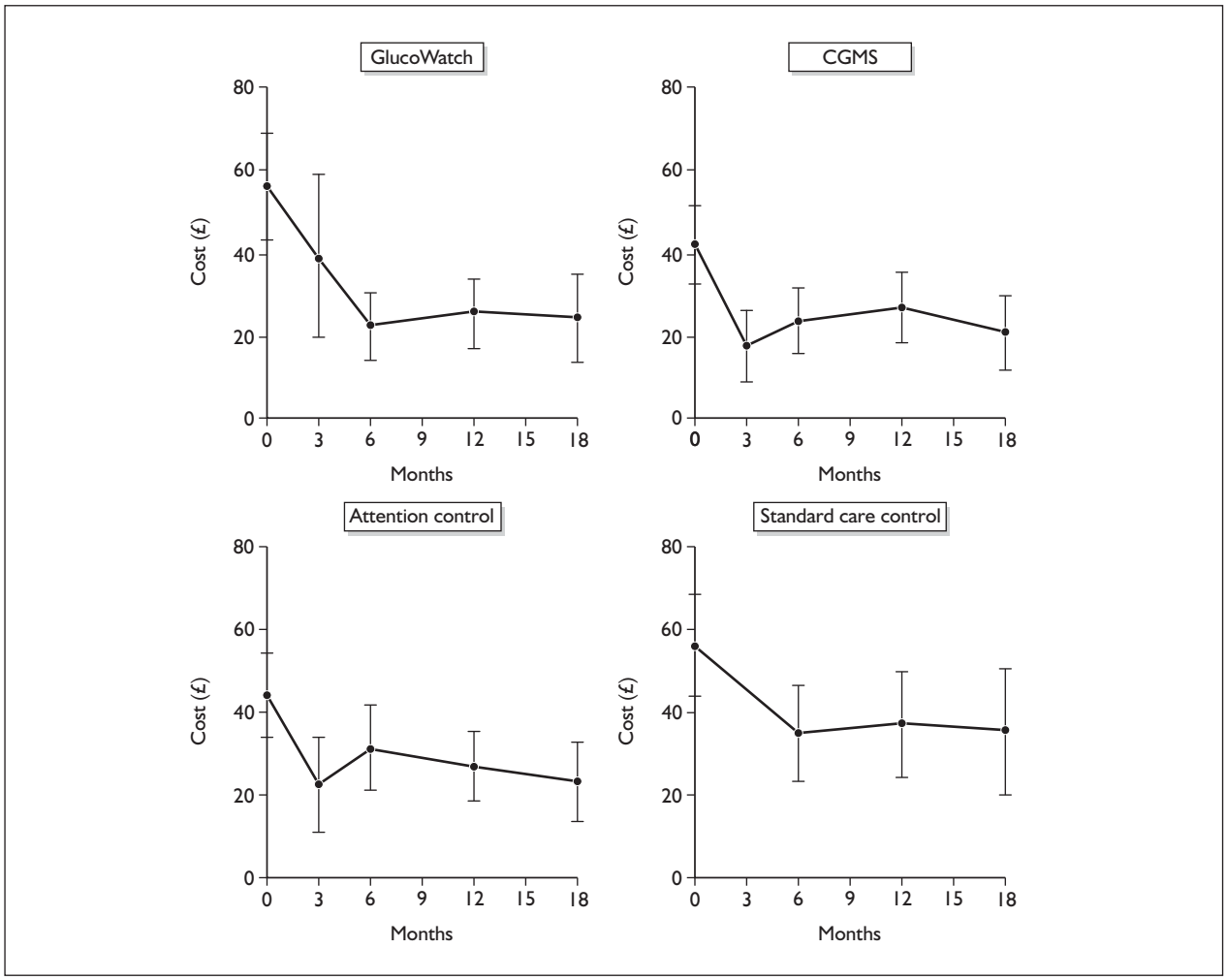

FIGURE 33 *Mean diabetes clinic costs.*

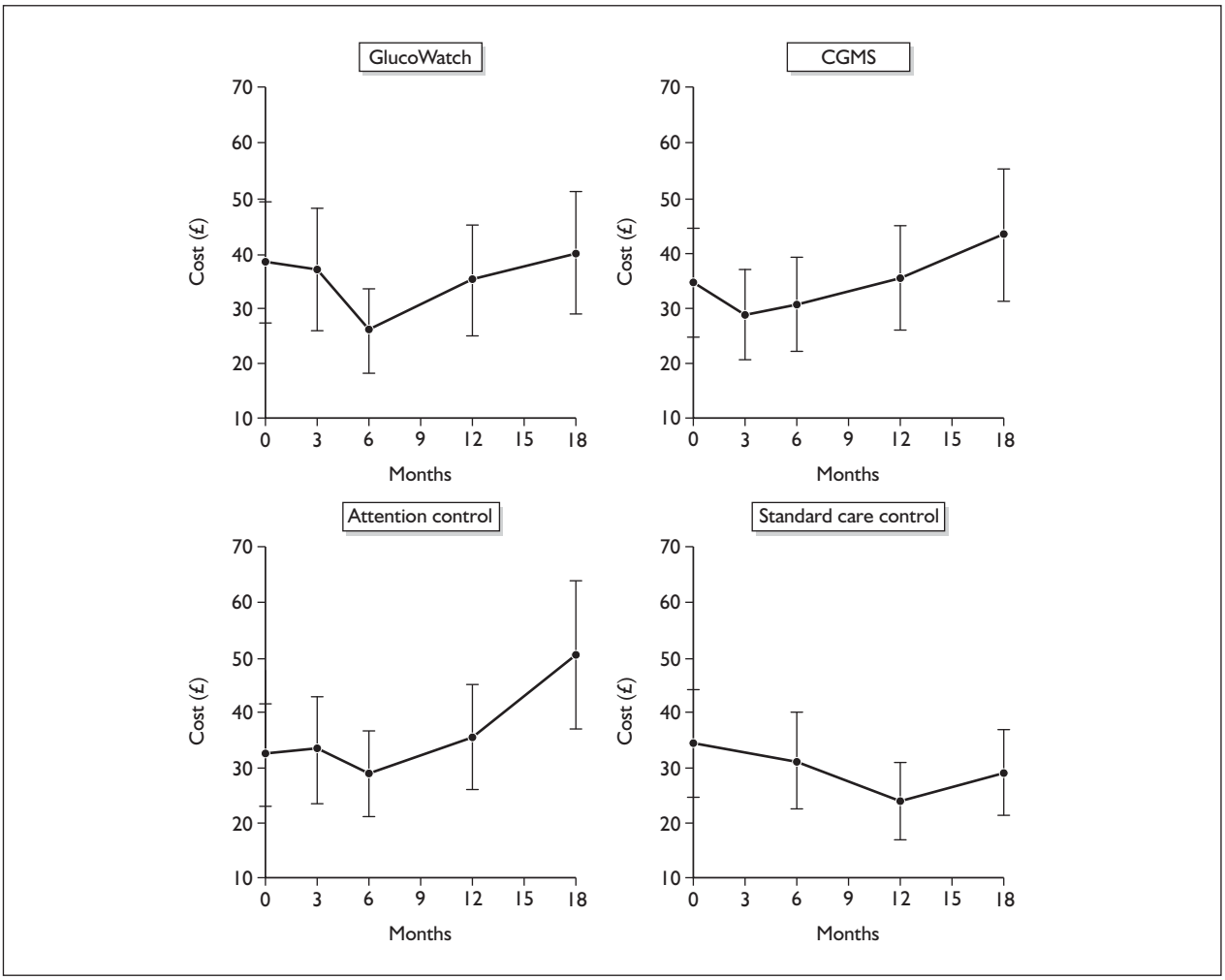

FIGURE 34 *Mean GP clinic costs.*

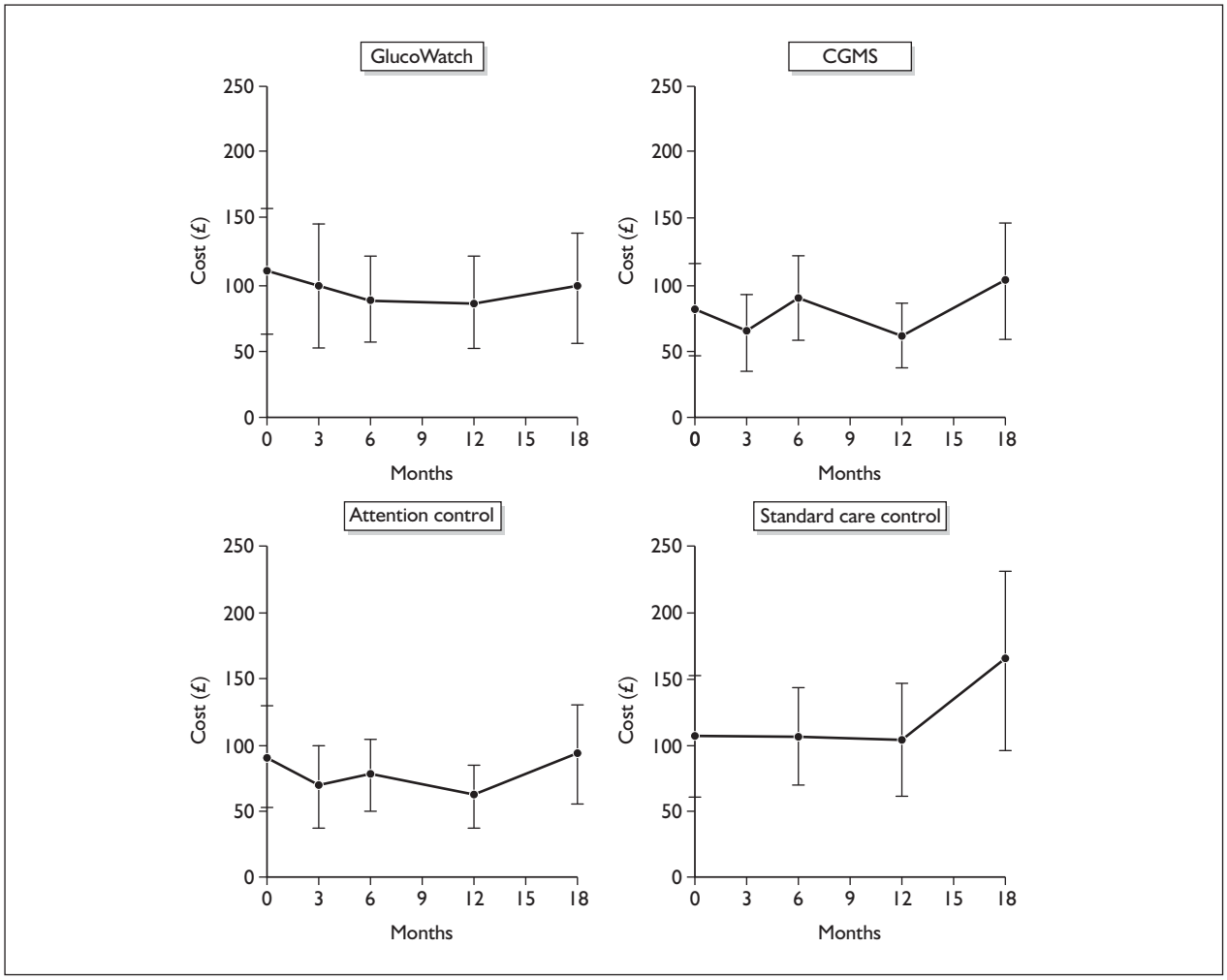

FIGURE 35 *Mean other resources costs.*

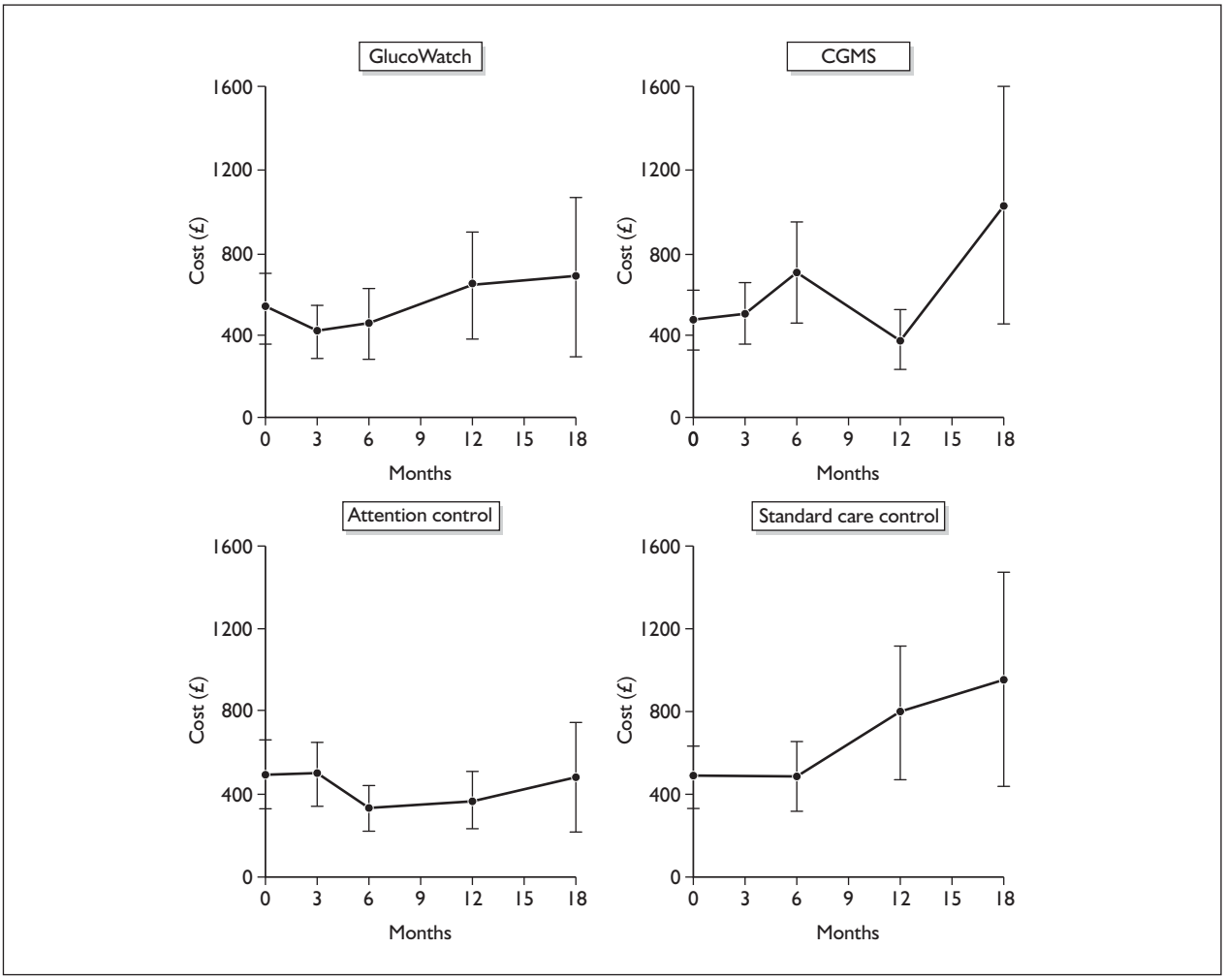

FIGURE 36 *Mean total costs.*

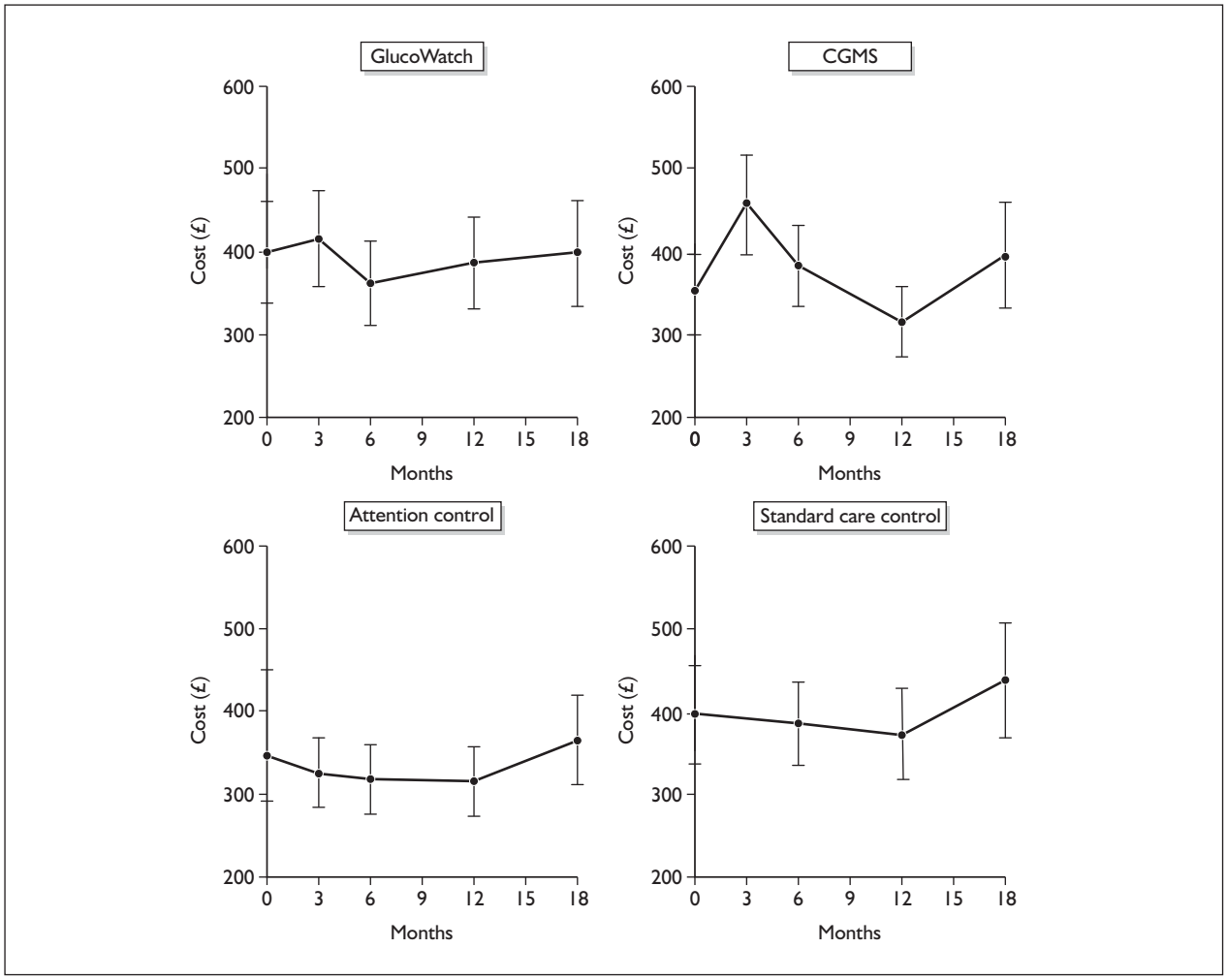

FIGURE 37 *Mean total costs excluding hospitalisation costs.*

TABLE 78 *Total costs at week 78: regression results*

	Coefficient	Standard error	*p*-value
Age	0.2552213	1.213237	0.833
Type 1 diabetes	–77.6445	40.21793	0.054
Body mass index	10.86376	3.489198	0.002
Male	–11.64437	31.89776	0.715
Attention control	–58.74848	42.36369	0.166
GlucoWatch	–33.81361	41.6757	0.417
CGMS	–47.29945	43.7304	0.279
Constant	151.9971	124.7873	0.223

TABLE 79 *Total costs excluding hospitalisation at week 78: regression results*

	Coefficient	Standard error	*p*-value
Age	2.696141	5.80318	0.642
Type 1 diabetes	–514.3562	253.2142	0.042
Body mass index	–2.403295	12.30161	0.845
Male	–77.56625	156.72	0.621
Attention control	–307.2976	255.1442	0.228
GlucoWatch	–82.45775	335.485	0.806
CGMS	–223.5118	269.2317	0.406
Constant	1195.273	507.0164	0.018

TABLE 80 *Total costs excluding hospitalisation costs over trial period: regression results using exercise subgroups*

	Coefficient	Standard error	*p*-value
Age	5.689998	4.342725	0.190
Type 1 diabetes	–348.6062	148.6917	0.019
Body mass index	74.15337	14.60962	0.000
Male	–51.0078	114.1686	0.655
Exercise score 4–7	–11.74044	206.9217	0.955
Attention control	–421.5133	159.0791	0.008
GlucoWatch	306.607	195.3599	0.117
CGMS	1844.851	249.9034	0.000
Exercise score 4–7 – attention control	94.31581	253.0587	0.709
Exercise score 4–7 – GlucoWatch	–38.42935	324.8824	0.906
Exercise score 4–7 – CGMS	–179.6108	444.7126	0.686
Constant	192.457	523.9669	0.713

TABLE 81 *Total costs excluding hospitalisation costs over trial period: regression results using diet subgroups*

	Coefficient	Standard error	*p*-value
Age	5.133873	4.299325	0.232
Type 1 diabetes	–352.9775	144.4978	0.015
Body mass index	73.85978	14.07969	0.000
Male	–43.81862	112.8181	0.698
Diet score 4–7	56.14283	199.3265	0.778
Attention control	–457.6673	200.6207	0.023
GlucoWatch	287.3236	234.9324	0.221
CGMS	2005.711	331.9112	0.000
Diet score 4–7 – attention control	96.95208	252.5268	0.701
Diet score 4–7 – GlucoWatch	18.71196	292.5013	0.949
Diet score 4–7 – CGMS	–342.136	420.6827	0.416
Constant	187.8347	479.1325	0.695

TABLE 82 *Total costs excluding hospitalisation costs over trial period: regression results using blood glucose test daily subgroups*

	Coefficient	Standard error	*p*-value
Age	6.55559	4.284977	0.126
Type 1 diabetes	–367.918	144.191	0.011
Body mass index	72.76064	14.01085	0.000
Male	–32.3283	114.7347	0.778
Blood glucose test daily	190.3029	208.6937	0.362
Attention control	–261.334	160.7296	0.104
GlucoWatch	481.2176	211.1496	0.023
CGMS	1988.976	297.7032	0.000
Blood glucose test daily – attention control	–294.969	249.9996	0.238
Blood glucose test daily – GlucoWatch	–449.821	303.8542	0.139
Blood glucose test daily – CGMS	–424.789	409.4608	0.300
Constant	101.5287	497.7958	0.838

TABLE 83 *Total costs excluding hospitalisation costs over trial period: regression results using smoker subgroups*

	Coefficient	Standard error	*p*-value
Age	7.732037	4.421205	0.080
Type 1 diabetes	–336.6606	148.5614	0.023
Body mass index	79.60763	14.89585	0.000
Male	–57.01366	114.6122	0.619
Smoker	156.5748	250.3943	0.532
Attention control	–417.7887	185.1574	0.024
GlucoWatch	284.7399	198.6748	0.152
CGMS	1756.154	239.4647	0.000
Smoker – attention control	104.2476	316.1562	0.742
Smoker – GlucoWatch	78.98562	335.7703	0.814
Smoker – CGMS	279.0655	533.2503	0.601
Constant	–115.7293	508.9477	0.820

TABLE 84 *EQ-5D scores: complete case*

	GlucoWatch	CGMS	Attention control	Standard care control
Baseline EQ-5D				
Mean	0.6708681 ($n = 91$)	0.6998317 ($n = 101$)	0.7216735 ($n = 98$)	0.6689394 ($n = 99$)
Standard error	0.0339246	0.0334928	0.032564	0.0347244
95% CI lower	0.6034711	0.6333829	0.657043	0.6000299
95% CI upper	0.7382652	0.7662804	0.7863039	0.7378489
3-month EQ-5D				
Mean	0.6540161 ($n = 62$)	0.6663333 ($n = 78$)	0.71728 ($n = 75$)	
Standard error	0.0401901	0.0407534	0.0380716	
95% CI lower	0.573651	0.585183	0.6414207	
95% CI upper	0.7343812	0.7474837	0.7931393	
6-month EQ-5D				
Mean	0.7166818 ($n = 66$)	0.6486301 ($n = 73$)	0.7317105 ($n = 76$)	0.7046945 ($n = 72$)
Standard error	0.0338	0.0441721	0.03619	0.0395782
95% CI lower	0.6491786	0.5605747	0.6596164	0.6257777
95% CI upper	0.784185	0.7366856	0.8038047	0.7836112
12-month EQ-5D				
Mean	0.7123175 ($n = 63$)	0.6957747 ($n = 71$)	0.7266667 ($n = 78$)	0.704459 ($n = 61$)
Standard error	0.0388167	0.0393283	0.0378713	0.0381535
95% CI lower	0.6347241	0.6173368	0.6512553	0.6281406
95% CI upper	0.7899109	0.7742125	0.8020781	0.7807775
18-month EQ-5D				
Mean	0.7006177 ($n = 68$)	0.7046572 ($n = 70$)	0.7542598 ($n = 77$)	0.6768082 ($n = 73$)
Standard error	0.0381302	0.040309	0.0301506	0.0385209
95% CI lower	0.6245094	0.6242429	0.6942096	0.6000182
95% CI upper	0.7767259	0.7850714	0.8143099	0.7535982

CI, confidence interval.

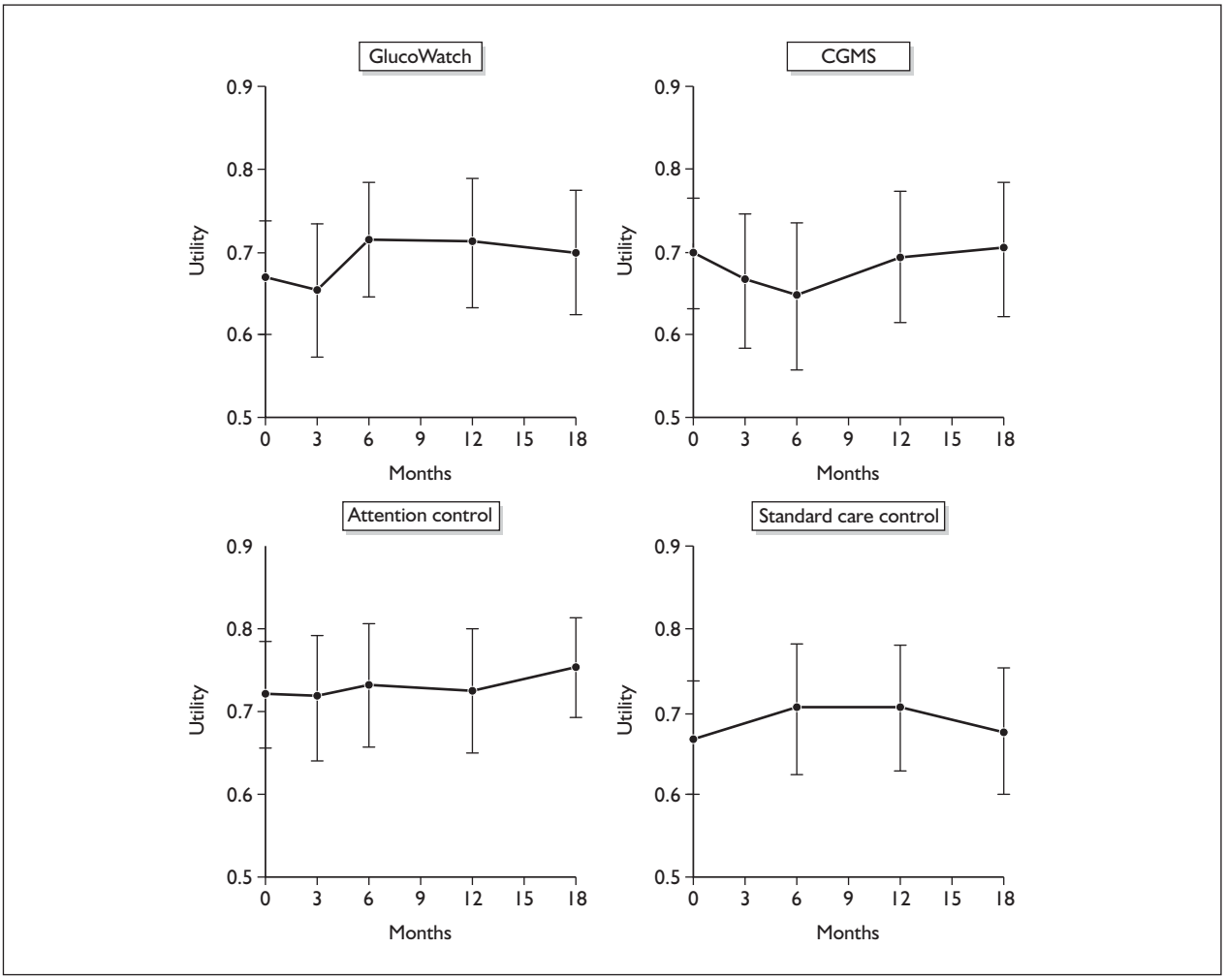

FIGURE 38 *Mean EQ-5D utility scores.*

TABLE 85 *EQ-5D scores at 18 months: regression results using exercise subgroups*

	Coefficient	Standard error	*p*-value
Age	–0.0003	0.0009765	0.748
Type 1 diabetes	0.03111	0.0343357	0.365
Body mass index	–0.0077	0.0028304	0.006
Male	0.01571	0.0232124	0.498
Baseline EQ-5D score	0.65204	0.0565114	0.000
Exercise score 4–7	–0.0209	0.0532081	0.694
Attention control	–0.0076	0.0464975	0.871
GlucoWatch	–0.0101	0.0448549	0.822
CGMS	–0.0102	0.0429121	0.812
Exercise score 4–7 – GlucoWatch	0.05555	0.0743366	0.455
Exercise score 4–7 – attention control	0.05541	0.0717412	0.440
Exercise score 4–7 – CGMS	0.0258	0.074778	0.730
Constant	0.46322	0.1169368	0.000

TABLE 86 *EQ-5D scores at 18 months: regression results using diet subgroups*

	Coefficient	Standard error	*p*-value
Age	–0.0002	0.0009859	0.842
Type 1 diabetes	0.02997	0.034985	0.392
Body mass index	–0.0078	0.002787	0.005
Male	0.01344	0.023443	0.567
Baseline EQ-5D score	0.65176	0.0570727	0.000
Diet score 4–7	–0.0298	0.0492662	0.545
Attention control	–0.0097	0.0583352	0.868
GlucoWatch	–0.0034	0.0609341	0.956
CGMS	–0.0199	0.05828	0.733
Diet score 4–7 – attention control	0.03408	0.068208	0.617
Diet score 4–7 – GlucoWatch	0.01524	0.0803002	0.849
Diet score 4–7 – CGMS	0.02958	0.0706621	0.676
Constant	0.47322	0.1160119	0.000

TABLE 87 *EQ-5D scores at 18 months: regression results using blood glucose test daily subgroups*

	Coefficient	Standard error	*p*-value
Age	–0.0007	0.0010308	0.495
Type 1 diabetes	0.02303	0.0341674	0.500
Body mass index	–0.0078	0.0027757	0.005
Male	0.01875	0.0235038	0.425
Baseline EQ-5D score	0.65381	0.0570799	0.000
Blood glucose test daily	0.06585	0.0525093	0.210
Attention control	0.01063	0.0428001	0.804
GlucoWatch	0.02335	0.0514364	0.650
CGMS	0.01683	0.0460868	0.715
Blood glucose test daily – attention control	0.00999	0.0655135	0.879
Blood glucose test daily – GlucoWatch	–0.033	0.0704527	0.639
Blood glucose test daily – CGMS	–0.0391	0.068178	0.567
Constant	0.4504	0.1156285	0.000

TABLE 88 *EQ-5D scores at 18 months: regression results using smoking status subgroups*

	Coefficient	Standard error	*p*-value
Age	–0.0003	0.0010326	0.749
Type 1 diabetes	0.02717	0.0347052	0.434
Body mass index	–0.0079	0.0027174	0.004
Male	0.01347	0.0232806	0.563
Baseline EQ-5D score	0.66053	0.0569767	0.000
Smoker	0.02402	0.0591024	0.684
Attention control	0.04125	0.038201	0.280
GlucoWatch	0.00188	0.0392045	0.962
CGMS	0.01193	0.0365801	0.744
Smoker – attention control	–0.1157	0.0799983	0.148
Smoker – GlucoWatch	0.03396	0.0930997	0.715
Smoker – CGMS	–0.0528	0.0859339	0.539
Constant	0.45089	0.1090405	0.000

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