NCCHTA

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MITRE
Minimally-Invasive Technology Role and Evaluation

A randomised controlled trial to compare minimally invasive glucose monitoring devices to conventional monitoring in the management of insulin treated diabetes mellitus.

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Authorised by: Dr Steven Hurel

Signature …….. Date ……..

General Information

This document describes a NHS Health Technology Assessment (HTA) funded trial being conducted in collaboration between the Royal Free and University College Medical School, the Medical Research Council Clinical Trials Unit (MRC CTU), the Centre for Health Economics at the University of York and five collaborating NHS trusts (University College Hospital, The Whittington, Queen Elizabeth 2, Gateshead and Royal Bournemouth Hospital). This trial protocol provides information about procedures for entering patients. It is not intended the protocol be used as an aide-memoire or guide for treatment of other patients. Amendments may be necessary; these will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact Dr Hurel or Debbie Cooke at University College London to confirm the details of the protocol in their possession. Clinical problems relating to this trial should be referred to the local clinical investigator.

Person authorised to sign final protocol and amendments: Dr Steven Hurel

The trial will be carried out in accordance with this protocol, Data Protection Act (MRC CTU DPA number: G0027154, UCL DPA number: Z6364106) and the MRC guidelines for Good Clinical Practice (GCP).

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Glossary and Abbreviations

ADDQOL	Audit of Diabetes Dependent Quality of Life
ADE	Adverse Device Event
CGMS	Continuous Glucose Monitoring System
CRF	Case Report Form
CTU	Clinical Trials Unit
DCCT	Diabetes Control and Complications Trial
DMC	Data Monitoring Committee
DSMC	Data and Safety Monitoring Committee
DSN	Diabetes Specialist Nurse
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EQ-5D	Euroqol
ERC	Endpoint Review Committee
HbA1c	Glycosylated Haemoglobin
HTA	Health Technology Assessment
LI	Local Investigator
LREC	Local Research Ethics Committee
MRC	Medical Research Council
MREC	Multi Centre Research Ethics Committee
PI	Principal Investigator
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
TC	Trial Co-ordinator

TMG Trial Management Group

TSC Trial Steering Committee

UCL University College London

UKPDS United Kingdom Prospective Diabetes Study

1 Summary

1.1 Abstract

This multi-centre randomised controlled trial (RCT) compares two minimally invasive glucose monitoring systems, the Cygnus GlucoWatch® G2™ Biographer (Biographer) and the MiniMed continuous glucose monitoring system (CGMS), with standard monitoring with more frequent nurse visits (Attention Control) and standard monitoring (Standard Control) in insulin treated Diabetes Mellitus. The trial will assess the following:

1) the acceptability of the devices 2) glycaemic control, 3) quality of life and 4) health care utilisation in relation to standard treatment. It will also model 5) the long-term cost-effectiveness of such devices. The trial is intended to investigate how the devices could be incorporated into routine diabetes care in the NHS. Evaluations will be clinical, psychological and address the cost effectiveness of the devices. To gain a geographically broad based sample, 600 patients will be recruited from centres in London, the South West and the North East.

Following recruitment and consent patients will be randomised to one of four groups. One group will be provided with and shown how to use the Biographer. One group will be fitted with the CGMS on a regular basis. Both these groups will attend the clinic for consultations with a nurse specialist 3 times in 3 months. To provide a control for the additional attention a third group will be asked to attend clinic for advice at a frequency similar to the two intervention groups. Finally one group will act as a standard control group with no intervention and will be followed up at routine visits every six months. All patients will also be provided with a standard capillary glucose meter.

The trial will be conducted in two phases for each patient. During the first phase (0-3 months) Biographer patients will be asked to wear the device 2-3 times weekly, CGMS patients will have the device fitted on up to three occasions and attention control patients will monitor their blood glucose with a capillary meter at their usual frequency. Patients in these three groups will be seen by a diabetes specialist nurse at either 4 (Biographer, Attention Control) or 6 (CGMS) week intervals. At these visits glucose profiles will be downloaded from the devices and will provide the basis for adjustment to current treatment regimes. The nurse will also record details of any side-effects and patients' experiences of using the monitors. During the second phase of the trial (3-18 months) use of the Biographer will be at patients' discretion and the CGMS will be fitted at 6-monthly intervals. All patients will be followed up at 6 monthly intervals to assess clinical, quality of life outcomes and resource use.

1.2 Summary flowchart and Trial Overview

The flow chart indicates time periods of visits to the clinic. For details of assessments completed at each visit refer to table 1.3.

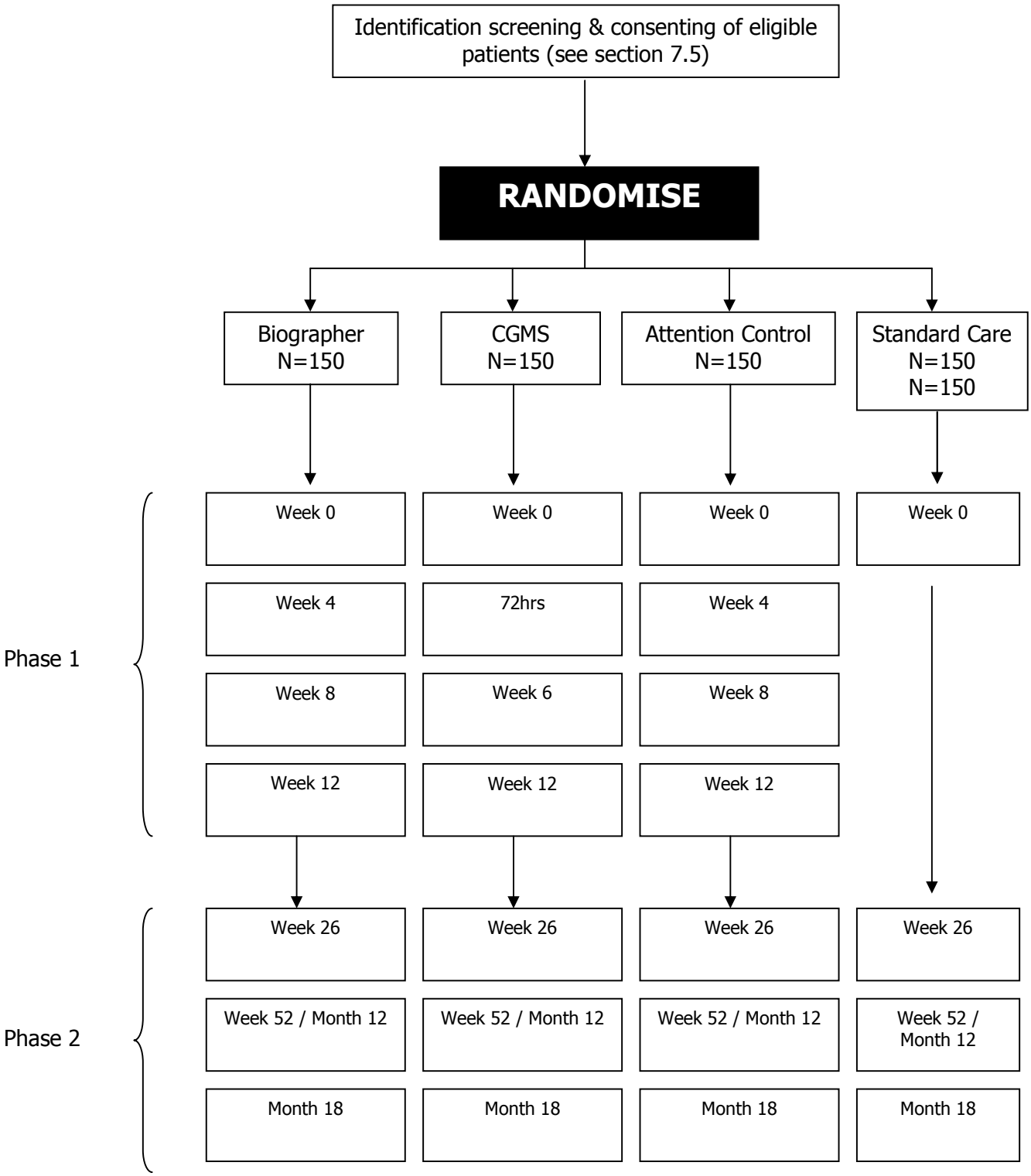

Table 1.3. TRIAL OVERVIEW

Biographer

	Baseline	Wk 4	Wk 6	Wk 8	Wk 12	Mth 6	Mth 12	Mth 18
Nurse Sessions								
Nurse visit	y	y	-	y	y	y	y	y
Assessments								
Baseline Assessment Form	y	-	-	-	-	-	-	-
Diabetes Follow-up Form	-	y	-	y	y	y	y	y
MITRE Outcome form	-	-	-	-	y	y	y	y
Meter Acceptability	-	-	-	-	y	y	y	y
HbA1c	y	-	-	-	y	y	y	y
Illness Perception	y	-	-	-	y	y	y	y
Self-Management Behaviours	y	-	-	-	y	y	y	y
DTSQ	y	-	-	-	y	y	y	y
Locus of Control	y	-	-	-	y	-	-	-
ADDQOL	y	-	-	-	y	y	y	y
Fear of Hypo's	y	-	-	-	y	y	y	y
EQ-5D	y	-	-	-	y	y	y	y

CGMS

	Baseline	72 hrs	Wk 4	Wk 6	Wk 8	Wk 12	Mth 6	Mth 12	Mth 18
Nurse Sessions									
Nurse visit	y	y	-	y	-	y	y	y	y
Assessments									
Baseline Assessment Form	y	-	-	-	-	-	-	-	-
Diabetes Follow-up Form	-	y		y		y	y	y	y
MITRE Outcome form	-	-	-	-	-	y	y	y	y
Meter Acceptability	-	-	-	-	-	y	y	y	y
HbA1c	y	-	-	-	-	y	y	y	y
Illness Perception	y	-	-	-	-	y	y	y	y
Self-Management Behaviours	y	-	-	-	-	y	y	y	y
DTSQ	y	-	-	-	-	y	y	y	y
Locus of Control	y	-	-	-	-	y	-	-	-
ADDQOL	y	-	-	-	-	y	y	y	y
Fear of Hypo's	y	-	-	-	-	y	y	y	y
EQ-5D	y	-	-	-	-	y	y	y	y

Attention Control

	Baseline	Wk 4	Wk 6	Wk 8	Wk 12	Mth 6	Mth 12	Mth 18
Nurse Sessions								
Nurse visit	y	y	-	y	y	y	y	y
Assessments								
Baseline Assessment Form	y	-	-	-	-	-	-	-
Diabetes Follow-up Form	-	y	-	y	y	y	y	y
MITRE Outcome form	-	-	-	-	y	y	y	y
Meter Acceptability	-	-	-	-	-	-	-	-
HbA1c	y	-	-	-	y	y	y	y
Illness Perception	y	-	-	-	y	y	y	y
Self-Management Behaviours	y	-	-	-	y	y	y	y
DTSQ	y	-	-	-	y	y	y	y
Locus of Control	y	-	-	-	y	-	-	-
ADDQOL	y	-	-	-	y	y	y	y
Fear of Hypo's	y	-	-	-	y	y	y	y
EQ-5D	y	-	-	-	y	y	y	y

Standard Control

	Baseline	Wk 4	Wk 6	Wk 8	Wk 12	Mth 6	Mth 12	Mth 18
Nurse Sessions								
Nurse visit	y	-	-	-	-	y	y	y
Assessments								
Baseline Assessment Form	y	-	-	-	-	-	-	-
Diabetes Follow-up Form	-	-	-	-	-	y	y	y
MITRE Outcome form	-	-	-	-	-	y	y	y
Meter Acceptability	-	-	-	-	-	-	-	-
HbA1c	y	-	-	-	-	y	y	y
Illness Perception	y	-	-	-	-	y	y	y
Self-Management Behaviours	y	-	-	-	-	y	y	y
DTSQ	y	-	-	-	-	y	y	y
Locus of Control	y	-	-	-	-	-	-	-
ADDQOL	y	-	-	-	-	y	y	y
Fear of Hypo's	y	-	-	-	-	y	y	y
EQ-5D	y	-	-	-	-	y	y	y

2. Background

2.1 Introduction

2.1.1 Role of Glycaemic Control

Diabetes mellitus is associated with significant morbidity including 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 (DCCT, 1993; UKPDS, 1998). In addition, both studies demonstrated a reduction in macrovascular disease such as heart disease although this did not reach statistical significance.

To achieve improved glycaemic control in the DCCT (1993), patients with Type 1 diabetes received intensive therapy with four insulin injections daily. In the UKPDS (1998) patients with Type 2 diabetes received intensive therapy with both oral agents and insulin. The availability of capillary blood glucose measurements is a key element in such intensive therapy. The patient is responsible for obtaining these measurements by fingerprick tests several times daily. The readings are an important tool for recognising patterns in blood glucose concentrations that can lead to adjustment in insulin therapy. (Kirk and Rheney, 1998). Hence, patients may be advised to test their blood glucose before meals, at bedtime and in the morning, and readings may be helpful in identifying the effect of exercise and diet on blood glucose. In addition, in both the DCCT and the UKPDS studies intensive therapy was associated with greater risk of hypoglycaemia. Self-monitoring can identify hypoglycaemia and therefore testing may be desirable before driving or undertaking any dangerous sport or activity, or at night for those patients who are prone to frequent hypoglycaemia.

It has been shown, however, that even testing seven times daily may miss debilitating episodes of hypo- and hyperglycaemia (Bolinder et al, 1997). The average number of fingerprick blood glucose measurements performed by a patient with type 1 diabetes is however estimated to be only two per day. Despite encouragement to perform more, many patients are reluctant because of the pain, inconvenience and discomfort experienced using finger pricks (Ginsberg, 1992). In addition, not all patients perform blood glucose testing accurately or make appropriate use of the information. Ideally, the patients should use the information obtained to adjust their therapy and should record the information for review with healthcare professionals in order to provide the basis for further changes to their therapy. Unfortunately, this is not always done as frequently or accurately as desired. It is difficult to envisage how such limited data can be realistically used to modify insulin regimes to optimise glycaemic control (Ginsberg, 1992). There is, therefore, a need to obtain detailed information on individual glucose excursions in a more patient friendly manner.

2.1.2 Non-and minimally invasive devices

The knowledge that home blood glucose monitoring is useful but with limitations has led to the development of non- and minimally invasive glucose monitoring techniques. Several

techniques have been developed involving local radiation or body fluid sampling (Klonoff 1997).

Despite intensive interest in this area developments have been slow by nature of the complexity of measurement of glucose across a dynamic multilayer consisting of lipids, protein, water and other biomolecules. The only approved non-invasive device currently available, the Diasensor 2000 (Biocontrol Technologies, California), employs near-infrared spectroscopy (Gabriely I et al, 1999). This instrument is currently undergoing efficacy studies in the United States. The device is similar in size to an office laser printer. Calibration for one individual takes approximately two months. Hence, whilst offering the advantage of being non-invasive the device is not portable or practicable and it is expensive.

Two minimally invasive devices are now available for clinical use. These are the Biographer, which extracts fluid electro-osmotically through the skin, and the MiniMed Continuous Glucose Monitoring System (CGMS) that harvests interstitial fluid. The devices offer portable frequent estimations of glucose over a period of 12-15 and 72 hours respectively. The usable accurate range is reported to be very similar between 2.2 - 22.0 mmol/L. There are however few other similarities between the devices. Previous research with both the Biographer and MiniMed systems has been limited but the devices and research to date is summarised below.

2.1.3 The GlucoWatch biographer

The Biographer 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 i) a reusable portion, which contains the microprocessor, electronics and output display, ii) 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 Biographer requires a two-hour warm up period followed by a single capillary glucose estimation for calibration. Following the warm-up period the device is then worn for up to 13 hours providing the patient with up to 78 estimates over that period. A measurement is made every ten minutes and the device averages the last two recordings to provide a digital readout to the patient every 10 minutes. Over 8,500 recordings can be stored in the memory. This information can be downloaded to any PC to provide information for the patient on profiles and trends in glucose. This information can then be shared with the healthcare professionals either by download at a clinic visit or to a patient's own PC. The latter option could allow patients feedback on their glucose profiles without attendance at a clinic.

The device can also be programmed to provide audible warnings should the glucose level rise above or fall below pre-set values. However, the device will not record if the skin has excess perspiration or has rapidly changed in temperature, as these will confound the recording. It is not clear at present what frequency of use is ideal for the Biographer. It is envisaged that use should be about twice weekly.

Most studies on the Biographer have focussed on the correlation between the Biographer and capillary blood glucose values. Studies by Garg et al (1999) and Tamada et al (1999)

have shown this to be acceptable with an r value of 0.85-0.90. The Biographer readings do lag behind blood glucose concentrations by approximately 18 minutes. To date, no trial has evaluated the impact of the Biographer on health outcomes. However, the use of the Biographer for detection of hypoglycaemia has been examined, and is reported to be more effective than current medical practice (Pitzer et al, 2001). This study demonstrates that the Biographer can effectively detect hypoglycaemia but to allow for the difference between interstitial level and blood patients are advised to set the low glucose alert at an appropriate level such as 5.6mmol/L.

The acceptability of the Biographer has also been examined in a pilot study of 10 type 1 patients. Although no patients dropped out during the trial problems were reported in relation to the cost of the device and sensors, difficulty with calibration, skin reactions and practical intrusiveness (Chan et al. 2001). Similar problems with use were also seen in two smaller studies with up to 20% dropout (Krimholtz et al. 2001, Lenzen et al. 2001). These problems mean the acceptability of the device must be systematically assessed.

2.1.4 The MiniMed CGMS

The MiniMed CGMS is a Holter style device equal 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. 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. 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. A total of two weeks of results can be stored in the device.

The patient is asked to perform frequent capillary glucose testing, if possible, in addition to those 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 the healthcare professional and adjustments to treatment made as appropriate. The device may then be refitted at intervals to review the change in trends. The optimal frequency of use of the device is not known although it is thought that use should be 4-6 weekly during initial treatment changes and 4-6 monthly during review.

Studies have confirmed that the interstitial fluid glucose measured with the device reflects the plasma glucose across a broad concentration of glucose (Rebrin et al, 1999; Gross et al, 2000). Two pilot studies have evaluated the impact on glycaemic control. In one study nine adults with type 1 diabetes wore the CGMS for two 1-week periods and the information obtained was used to adjust diet and insulin treatment (Bode et al, 1999). At the end of this period HbA1c had fallen from 9.9%±1.1% to 8.8%±1.0% ($p = 0.0006$). The second study was a randomised controlled trial with eleven children using the meter 6 times for three days over a 30-day period (Chase et al, 2001). The intervention group showed a significant reduction in HbA1c 1 month after baseline that was not seen in the control group. In addition there was a significant difference in the number of hypoglycaemic events detected at 1 month with the MiniMed group reporting less events than the control group. This study also assessed quality of life and fear of hypoglycaemia in both groups but found no

differences either between groups or over time. This is not surprising however given the small sample size within this study.

2.2 Rationale

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 Biographer provides a constant source of information to the patient and provides a rapid readout of glucose levels. The CGMS records more information over a longer period but does not offer this information to the patients, and requires a visit to the diabetes clinic for download. Hence whilst the Biographer provides the patients with an opportunity for regulation of their own glycaemic control and may promote empowerment the CGMS relies on feedback from the diabetes team.

What is not clear to date is what impact the devices have on diabetes control and whether the costs incurred are justifiable. These devices may also be differentially acceptable to patients and may have different effects on patient health outcomes and their perceptions of their diabetes. It is important, therefore, to assess the physical, biochemical and psychological impact of these devices before they become more widely available.

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

The most appropriate way to address these aims is in a sufficiently powered, well-designed randomised controlled trial. It is appropriate to include both forms of continuous glucose meters within a trial in order to compare the respective efficacy and acceptability of both meters for patients. It is also important to include an attention control group to account for the additional input from the DSN that will be received by patients in the meter groups. The current trial is designed to address these issues.

It is important to note that this trial is 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.

3 Objectives

1. To compare the benefits of using the Biographer and CGMS on glycaemic control, in terms of glycosylated haemoglobin levels, relative to an attention control and standard treatment.
2. To assess patient acceptability and ease of use of the two minimally invasive glucose monitors.
3. To assess the impact of the devices on patients' quality of life.
4. To assess the impact of the devices on health care utilisation for diabetes-related illnesses and number of diabetes-related patient sick days / absenteeism.
5. To model the long-term health benefits, costs and cost-effectiveness of these technologies.

4 Design

This trial will be a 4 arm randomised controlled trial

Group 1 (Biographer) will receive the GlucoWatch Biographer.
Group 2 (CGMS) will receive the MiniMed Continuous Glucose Monitoring System.
Group 3 (Attention Control) will receive standard treatment but with frequency of nurse feedback sessions matched to group 1 and 2.
Group 4 (Standard Control) will be seen at treatment intervals reflecting common practice within the United Kingdom, i.e. every 6 months.

After randomisation, the treatment and follow-up period will consist of two phases:

Phase 1 (0-3 months for each patient) will address short-term acceptability and patient perception of the devices. All patients will attend clinic for baseline assessment. Patients in groups 1 and 2 will then be provided with the Biographer or CGMS monitors and asked to use them as described in section 9.1. Patients in groups 1-3 will also attend three nurse feedback sessions in this phase (see section 9.3).

Phase 2 (3-18 months for each patient) is designed to principally assess the short-term (6 months) medium-term (12 months) and long-term (18 months) clinical efficacy, quality of life and economic impact of the devices. During this phase patients in Group 1 will use the Biographer as desired and group 2 will be fitted with the CGMS at 6,12 and 18 months. Patients in groups 1-3 will also attend nurse feedback sessions at 6,12 and 18 months. Patients in all groups will complete assessments at 6,12 and 18 months.

The trial outline and overview are shown in Figure 1.2 and Table 1.3.

5 Project Timetable and Milestones

Planning	0 - 2 months
Recruitment	2 - 30 months
Trial	2 - 48 months
Analysis and write up	48 - 51 months

6 Study Endpoints

6.1 Primary endpoints

1. The primary endpoint for long-term efficacy of the devices is change in glycosylated haemoglobin from baseline to 18 months.

2. Medium term efficacy will be assessed by change in glycosylated haemoglobin from baseline to 12 months.

3. Short-term efficacy will be assessed by change in glycosylated haemoglobin from baseline to 6 months.

4. Acceptability of the devices for patients in Biographer and CGMS arms will be assessed both by patients inability to comply with the protocol, and by means of a questionnaire at 3, 6, 12 and 18 months.

6.2 Secondary endpoints

1. Number and severity of hypoglycaemia events.
2. Frequency of adverse device events.
3. Change in glycosylated haemoglobin from baseline to 3 months in groups 1-3.
4. Change in quality of life of participants in the 4 groups.
5. Change in perception of diabetes.
6. Differential resource use, cost and quality-adjusted life years between the 4 groups.
7. Frequency of use of the Biographer during Phase 2 of the trial.

7 Selection of Patients

7.1 Population

The trial population is adults (18 years of age or more) who have had insulin-treated diabetes mellitus (type 1 or 2) for at least six months and who attend diabetes clinics in the four participating centres. Patients who speak English, Bengali, Cantonese or Turkish will be included to ensure individuals from different ethnic backgrounds are evaluated.

7.2 Inclusion criteria

1. All patients with insulin-treated diabetes mellitus (type 1 or type 2) receiving two or more injections daily (including continuous subcutaneous insulin infusion (CSII) pump users).
2. Aged over 18 years.
3. Duration of diabetes over six months.
4. Patients fluent in English, Bengali, Cantonese or Turkish.
5. a) Two HbA1c's greater than or equal to 7.5%, one in the last 3 months and another within the previous 15 months. *Follow normal consent procedure (see 7.5.3 below)*

   b) Individuals with one HbA1c greater than or equal to 7.5% in the last three months and either i) a second over 15 months previously or ii) no other HbA1c's, can be invited to have a screening blood done in 3 months time. If this is greater than or equal to 7.5% and the participant consents to the study this can be used as the baseline HbA1c. *Follow consent procedure for individuals requiring a screening blood (see 7.5.4 below).*

   c) If a participant has an HbA1c greater than or equal to 7.5% but more than 3 months previously they can be invited to have a screening blood done as soon as possible. If this is greater than or equal to 7.5% and the participant consents to the study this can be used as the baseline HbA1c. *Follow consent procedure for individuals requiring a screening blood (see 7.5.4 below).*

   <u>In all cases, the two HbA1c results must be a minimum of 12 weeks apart.</u>

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

7.3 Exclusion criteria

1. Previous inability to use a capillary glucose meter
2. Previous use of the Biographer or CGMS sensor
3. Presence of abnormal haemoglobin (presence of elevated levels of HbF or HbS)

4. Pregnancy or planned pregnancy in next 18 months
5. Skin Conditions – e.g. eczema, psoriasis or other skin irritation at the sites of monitor use
6. Patient is on dialysis
7. Visual or physical impairment limiting ability to use monitors
8. Planned major surgery (e.g. CABG, hip replacement) within 3 months of consent
9. Participation in any other ongoing trial.

7.4 Trial Site location

Patients will be enrolled from:

1. Royal Bournemouth Hospital
2. Queen Elizabeth Hospital, Gateshead
3. University College London Hospitals
4. The Whittington Hospital, London

Further sites may be enlisted at a later date if necessary to obtain satisfactory accrual rates.

7.5 Recruitment Procedure

7.5.1 Identification of Patients

Patients will be identified from 3 sources:

i) local diabetes databases
ii) posters advertising the trial in the waiting areas of trial sites
iii) scanning of clinic notes

This will be performed primarily by the trial DSNs but may be assisted by the LI. Patients identified as potentially suitable will be provided with an information sheet and invited to discuss the trial in more detail with the DSN or LI. Discussion can be held in person, by telephone contact or through the approved invitation letter (Appendix 1).

7.5.2 Screening of Patients

Any patients identified and interested in the trial must be screened to ensure they fulfil inclusion/ exclusion criteria (see 7.2 & 7.3). Screening will primarily be the responsibility of the DSN but may be assisted by the LI or their appointee.

7.5.3 Consent of Patients

Patients will be provided with a full explanation of each arm of the trial, including the potential problems with use of the devices. It will be clearly explained that patients have a 1 in 4 chance of being in any arm of the trial. Patients will be asked to provide verbal agreement that they will not use a non-invasive or minimally invasive blood glucose monitor independent of the trial, regardless of which trial arm they are randomised to. Patients should however be informed that if they are allocated to the standard treatment or attention control groups and if the results indicate either of the monitors to be of benefit that they will be given priority for use of the Biographer or CGMS on completion of the trial. Following explanation a period of at least 24 hours but no more than 4 weeks must elapse prior to written consent and subsequent randomisation. Written consent will then be obtained. This will normally be by the LI but can be assisted by the DSN or the appointee of the LI where appropriate. The original consent form will be inserted in the site folder and a copy placed in the patients' clinical notes. A copy of the consent form should be given to the patient (Appendix 4). It is the responsibility of the DSN to ensure that this is performed.

7.5.4 Consent of Patients Requiring a Screening Blood Test

If a patient requires a screening blood (i.e. they fit inclusion criteria 7.2 5b or 5c) the following procedure should be followed:

- Give the patient information sheet for screening version 6 (November 2004, Appendix 3).
- Explain to patient that to take part in the study they will have to have a blood test to confirm their HbA1c is greater than or equal to 7.5%.
- If patient agrees to take part in study and have a screening blood make an appointment for either 3 months time (criteria b) or as soon as possible (criteria c)
- At screening appointment consent patient into the study as usual but using Consent Form for Screening (version 6, appendix 5). Explain that if their screening HbA1c is greater than or equal to 7.5% they will be randomised into one of the four arms of the study, but that if less than 7.5% they will not be asked to continue in the study.
- Take screening blood (3 samples as would be done for baseline blood).
- If ≥7.5%, randomise as normal and use this as the baseline HbA1c.
- If <7.5% inform patient that they will not be eligible to continue the study.

If patient fits inclusion criteria 2.1 5 (a) follow the normal consent procedure (above).

7.5.5 Randomisation and Enrolment

Following written consent from participants, the DSN will telephone the MRC Clinical Trials Unit Randomisation Line. Randomisation will be site specific and will ensure balanced allocation in terms of age and type of diabetes by use of the minimisation method. Following telephone randomisation, the MRC Clinical Trials Unit will fax notification of allocation and study number to the centre. The screening, randomisation form and fax notification will be placed in the CRF by the DSN. The study number will be 4 digits: the first number will correspond to centre number (1, 2, 3, 4 or 9 if a new centre is enlisted) the following 3 digits will be the next number in sequence, e.g. 1001, 1002, 1003, 9001. The DSN will be responsible for enrolling individuals into the trial. Randomisation will occur immediately before the baseline clinic visit and assessment. A facility for randomisation of patients before 9am will also be available. DSN must notify the MRC Clinical Trials Unit at least one day prior to randomisation if they wish to use this facility.

RANDOMISATIONS
020 7670 4711 (Mon - Fri, 9am – 5pm)
07771 942372 (Mon-Fri, pre-9am)
(FAX 020 7670 4829)

7.5.6 Recruitment Log

A record of all individuals approached to take part in the trial should be maintained. This should record demographic data and any data on lack of suitability or reasons for refusal. It is the responsibility of the DSN and LI or their appointee to enter details in the log of any individual that they approach to take part in the trial. The recruitment log should be completed weekly and faxed to the trial coordinator monthly. Any queries concerning recruitment should be referred directly to the PI.

7.6 Rate of Recruitment

A total of 400 patients will be recruited into the trial: Hence 100 patients from each hospital. The target rate of recruitment will be 5 patients per centre per month from July 2004 such that recruitment is expected to be completed in 24 months.

The Trial Steering Committee will monitor recruitment rates and if these fail to achieve target accrual rates then other centres may be invited to participate. Other centres may be approached if recruitment falls below target for 2 consecutive months. In this instance resources will be transferred to other centres to achieve the required recruitment rates.

8 Withdrawal of Patients

There are two types of withdrawal: 1) from treatment 2) from trial.

8.1 TREATMENT WITHDRAWAL

Patients should be withdrawn from treatment if any of the following events occur:

i) Skin reaction or other side effect intolerable to patient or clinically unacceptable
ii) Development of co-morbid conditions preventing use of monitors e.g. stroke

Where patients are withdrawn from treatment follow-up data should still be collected wherever possible. The DSN should record full details of reason for withdrawal from treatment on the appropriate form in the CRF. This form will be coded with participant's date of birth and participant number.

8.2 TRIAL WITHDRAWAL

Patients will only be withdrawn from the trial if they withdraw their consent or become pregnant.

Withdrawn participants will not be replaced by new recruits. Full details of reason for withdrawal from trial should be recorded on the appropriate trial withdrawal forms by the DSN. If a participant wishes to withdraw from the trial the DSN will ask them whether they consent to routine clinic assessments (ie. HbA1c) being used for the purposes of the trial. Where a withdrawn patient no longer attends the hospital clinic they will be asked whether routine assessments (i.e. HbA1c) taken at either a new hospital clinic or GP surgery may be used for the purposes of the trial.

Patients who no longer wish to use the devices will not be withdrawn from the trial. They will be asked to continue to attend for the trial visits. Nurse feedback will use the clinical data that is available. These patients will be included in the intention to treat analysis.

9 Treatment of Patients

9.1 Trial Treatment

All patients will be provided with a One Touch Ultra (Lifescan, United Kingdom) self-monitoring glucose meter, and trained in use at the baseline clinic visit. Patients will be asked to use this device in preference to their usual glucose meter and at their normal frequency. Data (ie the last 150 recorded values) will be downloaded and stored in clinic. All patients will receive normal clinical treatment. This typically takes the form of 6 monthly clinic visits with access to diabetes advice when required. This will be alongside any specific treatment required for the trial.

Specific treatment for each group is described below.

9.1.1 Group 1: Biographer

Phase one: At a baseline clinic visit the DSN will train and provide patients with the One Touch Ultra monitor and will train participants in use of the Biographer. All patients will then be provided with a Biographer monitor and asked to use it at times of their choice, but with a minimum attempted use of 4 times per month and a maximum attempted use of 4 times per week. In addition they will be told to continue to perform capillary blood glucose monitoring as desired. They will also be advised to check a capillary glucose should the Biographer sound a high or low alarm. It must be explained to patients that the monitors must not be relied upon for estimating insulin requirements. During this period patients will be reviewed by the DSN at 4, 8 and 12 weeks at which point the results from both the Biographer and the One Touch Ultra meter will be downloaded, saved and printed. Print outs will be added to the CRF and patients notes and will be stored on the local PC. The results from the Biographer and One Touch Ultra meter will be used to provide feedback and as the basis for adjustment of their treatment regime (see section 9.3).

Phase two: Patients will be asked to continue using the Biographer as often as they wish to do so, but will be recommended to use the device at least twice per week. At a minimum they will be reviewed by the DSN and provided with feedback on results at 6, 12 and 18 months. The device will store approximately 8,500 recorded values which equates to 108 completed 13 hour profiles i.e. 4 per week over a six month interval. Patients who choose to use the Biographer more frequently will be offered appointments at the clinic to download the output, but they will not receive nurse feedback at that time. Throughout the 18-month period the DSN will be available via the telephone to discuss any problems. If the Biographer fails at any point during the 18 months the patient should notify the DSN who will replace it.

9.1.2 Group 2: CGMS

Phase one: At a baseline clinic visit the DSN will train and provide patients with the One Touch Ultra monitor and will train participants in use of the CGMS. The device will be fitted by the DSN and patients will be requested to wear it for 72 hours. In addition to wearing the CGMS patients will continue to perform capillary blood glucose monitoring as desired. Patients may return to the clinic 72 hours later for the device to be removed, or alternatively may remove the device themselves and return to the clinic as soon as possible, but no more than one week after device removal. On the return visits both the CGMS and One Touch Ultra meter recordings will be downloaded, saved and printed. Print outs will be added to the CRF and patients notes and will be stored on the local PC. The results from the CGMS and One Touch Ultra meter will be reviewed by the DSN and used to provide patients with feedback and adjustment in therapy (see section 9.3). Patients will also be fitted with the device and receive nurse feedback sessions at 6 and 12 weeks.

Phase two: Patients will be fitted with the CGMS and receive nurse feedback sessions at 6, 12 and 18 months. During the 'fitting visits' discussion concerning diabetes control will be avoided. Participants will be told that this will be discussed in detail at their visit for downloading of glucose readings, which will occur within the following week. Throughout the 18-month period the DSN will be available via the telephone to discuss any problems. At each fitting patients will be requested to wear the CGMS for 72 hours. If the device fails

within 24 hours of fitting then the patient will be encouraged to return to the clinic for a refitting. If the device fails more than 24 hours after fitting the available data will be reviewed in the nurse feedback session.

9.1.3 Group 3: Attention Control
Phase one: At a baseline clinic visit the DSN will train and provide patients with the One Touch Ultra monitor. Patients will be asked to monitor capillary blood glucose at their normal frequency for 3 months. Patients will attend nurse feedback sessions at 4, 8 and 12 weeks at which point the results from the One Touch Ultra meter will be downloaded and saved on the local PC. The results from this will be used to provide feedback (see section 9.3).

Phase two: Patients will be asked to continue using the One Touch Ultra monitor at their normal frequency. They will be reviewed by the DSN and provided with feedback on results at 6, 12 and 18 months. Throughout the 18-month period the DSN will be available via the telephone to discuss any problems.

9.1.4 Group 4: Standard Treatment Control
Phases one and two: At a baseline clinic visit the DSN will train and provide patients with a One Touch Ultra monitor. Patients will be asked to monitor capillary blood glucose at their normal frequency. Patients will then receive standard treatment; this typically consists of 6 monthly clinic visits and access to diabetes advice when required. Patients will receive no feedback sessions with the DSN although they will attend clinic at 0, 6, 12 & 18 months for assessments.

9.2 Baseline Nurse Session
The purpose of the baseline clinic visit is to train participants in use of the One Touch Ultra meter and Biographer and CGMS systems where appropriate. Training for each of these should be as described in the respective manuals. Where patients are non-English speakers the session should be held with the assistance of an appropriately trained translator.

9.3 Nurse Feedback sessions
At each feedback session the DSN will be expected to download and review glucose results from both standard and minimally invasive glucose monitors, provide appropriate lifestyle advice and make any appropriate adjustments to medication according to the protocol (see appendix 8). Print outs of glucose results from all monitors should be placed in the CRF. Any alterations to medications should be recorded in the CRF and patients' notes. If any adverse device event, or serious adverse event is identified during a nurse feedback session the appropriate form should be completed and the PI contacted as described in section 14. During each nurse feedback session the DSN will also be expected to complete the sections of the CRF relating to use and any difficulties of use of the monitors and frequency of hypoglycaemic and hyperglycaemic episodes. One Touch Ultra meters will have a quality control check at each visit.

Where patients are non-English speakers the session should be held with the assistance of an appropriately trained translator.

Two weeks prior to each follow-up appointment, participants will be sent an approved reminder letter to prompt them to come in for their visit (see Appendix 6). They will be asked to bring with them:

- Completed questionnaire (Attention, Standard, Biographer)
- Lifescan Meter
- Glucowatch (where necessary)
- Diaries
- Reading glasses (where necessary)

9.4 Patient travel

Reimbursement of patient expenses incurred for travel to the Investigating Centre will be met for visits that are additional to usual care. Travel will be reimbursed at local second class public transport rates. Expenses will be initially met locally and application for reimbursement with due receipt made to the PI on a quarterly basis.

9.5 Risks and Discomforts

9.5.1 Biographer

The risks and discomforts associated with the Biographer have been described by the manufacturers as:

i) Mild tingling sensation.

ii) Mild to moderate skin irritation, erythema, oedema and small blisters.

iii) Small blisters may occur around or under the biographer band, and around the edges of the biographer. This occurs when the band is fastened too tightly. Similar blisters may occur if the skin is not flat when the biographer is applied.

iv) Blisters that break open can become infected. Subjects should be advised to avoid breaking the blister, to keep the area clean and dry, and to call the DSN if they are worried that a blister may have become infected. Pigmentation of the skin may occur at the blister site(s) during the healing process and usually resolves within 6 months. Small scars may occur at blister sites, but resolve within a year in most cases.

v) Allergic reaction to one or more of the components in the biographer or AutoSensor.

9.5.2 CGMS

The CGMS may be associated with mild discomfort at the site of insertion and possible skin reaction. These reactions however are thought to be mild.

9.5.3 One Touch Ultra

Home capillary glucose estimation by fingerprick may produce pain and/or ecchymosis at the site.

10 Trial product(s)

The standard capillary glucose monitors to be used by all patients are the One Touch Ultra (Lifescan) meters. For calibration of the meter a capillary glucose will be measured concurrently with laboratory glucose at each visit. These monitors will be sent directly to individual sites from Lifescan as will a supply of 100 strips per patient. The contact is:

Mr Paul Shackleford
Lifescan
Enterprise House
Station Road
Loudwater, High Wycombe
HP10 9UF
Tel: 01494 450 423
Fax: 01494 463 299
Mobile: 07850570180

The Biographer and autosensors will be sent directly to sites from Cygnus. The contact for this is:

Barbara Montgomery
Director of Product Management
Animas Corporation
200 Lawrence Drive
West Chester, PA 19380
610-644-8990, extension 1238

The CGMS monitors and sensors will be sent directly to sites from Minimed. The contact for this is:

Mr Ian Tilly
Medtronic MiniMed
Hillthorpe
Ashstead Woods Road
Ashstead
Surrey
KT21 2ER
Tel: 01372 278 945
Fax: 01372 278 976
e-mail ian.tilly@meditronic.com

It should be noted that the autosensors for the Biographer and sensors for the CGMS must be stored at 4°C

It is the local investigators responsibility to ensure that adequate supplies of materials are available and they will be expected to liase directly with the contacts listed above. Problems

concerning supplies should be referred to the Principal Investigator. All invoicing should be directed to the Principal Investigator.

10.1 Dispensing

At the baseline clinic visit the DSN will provide each patient with a One Touch Ultra monitor and a starter supply of strips. The patient's General Practitioner should provide additional supplies of strips.

For patients in the Biographer group a Biographer device will be provided by the DSN at baseline. Patients will be given 16 autosensors at the first baseline visit. At subsequent visits patients will be given sufficient autosensors to enable them to use the Biographer a maximum of 4 times per week. Patients will be advised to check the expiry date on autosensors before use and asked to return any that are out of date to the DSN.

During Phase 2 of the trial they will be given 24 autosensors (based on 12 weeks supply using two sensors per week). They will contact the DSN if further supplies are required.

For patients in the CGMS group the DSN will fit the device and monitor at a clinic visit. No additional materials will be dispensed to patients.

Serial numbers of the devices used by each patient will be recorded in the CRF by the DSN. The number of strips and autosensors supplied to each participant should also be recorded in the CRF and a local log.

10.2 Accountability

Local investigators will take responsibility for the equipment supplied to them. However, throughout the trial period the PI maintains the right to reallocate equipment to ensure optimal use and that recruitment rates are maintained. At the end of the trial equipment will be equitably distributed between all participating centres at the discretion of the PI.

11 Non-trial treatment

Patients in all arms of the trial will receive medication for diabetes and other co-morbid conditions as required.

Concomitant medication will be recorded in the CRF. Qualitative changes in such medication will be recorded but dose changes will not routinely be recorded unless they are expected to impact directly on glycaemic control, or the DSN considers that they may impact on trial outcomes e.g. quality of life.

12 Efficacy and Outcome Assessments

For overview of assessments and clinic visits see Figure 1.2 and Table 1.3.

Patient-completed questionnaire assessments should be completed in clinic during the baseline assessment and training session. For the Biographer and CGMS groups this may occur during the calibration phase of the training. The DSN will mark questionnaires with patient study number and then distribute them and allow the participant to complete these in privacy, although where necessary the DSN may provide instruction if the patient is unclear on how to complete an assessment. On completion the questionnaires should be returned to the DSN in a sealed envelope. These will then be forwarded to the trial co-ordinator who will be responsible for following up missing data. Nurse completed sections of the CRF will be filled in by the DSN during a brief patient interview prior to the baseline training session.

For subsequent assessments nurse completed sections of the CRF will be completed either during the nurse feedback session (groups 1-3) or during a brief patient interview (group 4). Participants will be requested to complete patient questionnaires prior to the assessment session. Where requested, participants may be sent the questionnaires to complete at home in the week prior to the clinic visit. These should be brought to the clinic in a sealed envelope. If these are not returned at the visit the participant will be requested by the DSN to complete a copy in clinic. Again these will be returned to the DSN in a sealed envelope and forwarded to the trial co-ordinator.

12.1 Primary Efficacy Measures

12.1.1 Glycaemic Control

Change in glycosylated haemoglobin from baseline to 18 months is the primary indicator of efficacy. Assessment is by blood sample. Three samples will be taken at each assessment. One will be analysed at the local site, the second will be sent in clinical packaging for standardisation and via royal mail freepost to the Department of Diabetes and Endocrinology at University College London Hospitals. All samples sent for standardisation should be accompanied by two completed copies of the sample form, this is the responsibility of the local DSN. The third sample will be retained in case of damage or loss to the standardised sample. All samples will be coded by patient initials, date of birth and study number and week number. It will be the responsibility of the London based DSN to transfer all received samples and accompanying sample forms to the Chemical Pathology department of University College Hospitals. Mark Buckley Sharp will be responsible for samples at the Chemical Pathology Department at UCH.

Measurement Periods: 0, 3, 6, 12, 18 months

12.1.2 Patient Perceived Acceptability of Non-Invasive Monitoring Devices

Acceptability will be measured in biographer and CGMS groups by self-report questionnaire (see appendix 9) at 3, 6, 12 and 18 months. Inability of patients to comply with the protocol for using the devices will also provide an indirect indicator of acceptability.
Measurement Periods: 3, 6, 12,18 months

12.2 Other Outcome Measures

12.2.1 Clinical Assessments

i) Hypoglycaemic episodes (defined as blood sugar <3.5mmol/L). Frequency and time of hypoglycaemic episodes, together with how they were detected will be recorded in the CRF by the DSN. To collect this data patients will be asked to keep diaries. Where possible incidence of hypoglycaemic events will be confirmed by the One Touch Ultra (Lifescan) meters and recorded as such in the CRF. In the case of Groups 1 & 2 downloaded data from the Biographer and CGMS will also be used. A hypoglycaemic episode will be recorded if i) blood glucose <3.5mmol for >20 minutes (i.e. two or more readings for the biographer, four or more readings for the CGMS), ii) blood glucose of <3.5 followed by one or more skipped readings followed by reading of <3.5 for the biographer, or iii) blood glucose of <3.5 followed by two or more skipped readings coded PRSP (perspiration) on the biographer.

Awareness of hypoglycaemia will be recorded by completion of the Edinburgh Hypoglycaemia Symptoms Scale and the Hypoglycaemia Symptoms Awareness Questionnaire (McAulay et al. 2001). Undetected hypoglycaemia will be calculated by comparison of patient self-reports with the downloaded data in the biographer and CGMS groups.
Measurement Periods: Data will be recorded in the CRF by the DSN at baseline and each assessment visit.

ii) Hyperglycaemic episodes (defined as blood sugar >10.0mmol). The percentage of finger prick blood glucose values higher than 10.0mmol will be recorded in the CRF by the DSN. This data will be drawn from patient diaries. In the case of Groups 1 & 2 downloaded data from the Biographer and CGMS will also be used and recorded as the number of glucose readings >10mmol/l for >20 minutes (two or more readings for the biographer, four or more readings for the CGMS).

iii) Skin Reactions (Biographer & CGMS groups). During nurse feedback sessions the DSN will record the extent of skin irritation for each application of the monitor. This data will be drawn from patients' ratings and recordings in their diaries using the Mitre Skin Scale.
Measurement Periods: Data will be recorded in the CRF by the DSN at baseline and each feedback session for groups 1 and 2. Adverse Device Event forms will be completed if reactions are severe (i.e. > 6 on MITRE Skin Scale).

iv) Side Effects. Any side effects reported by patients from either the minimally invasive glucose monitors or standard monitors should be recorded in the CRF by the DSN.

Measurement Periods: Data will be recorded at baseline and each feedback session for groups 1,2 and 3. In the event that patients contact the nurse to report with side effects outside of these times the details will be recorded and the dates logged.

12.2.2 Psychosocial Assessments

The following assessments will be carried out at measurement periods of 0,3*,6,12,18 months. *The Standard Control (SC) arm will not be assessed at 3 months.

i) Quality of Life – This will be assessed by the patient self-report questionnaire the ADDQOL (Bradley 1999).

ii) Self-Management Behaviours - The Summary of Diabetes Self-Care Activities scale will be used to assess the frequency with which patients perform diet, exercise, blood glucose monitoring and foot-care behaviours over the prior week (Toobert 2000).

ii) Fear of Hypoglycaemia - This will be assessed by the patient self-report 'Fear of Hypoglycaemia questionnaire' (Worry subscale) (Cox 1987).

iii) Satisfaction with Treatment - This will be assessed by the patient self-report questionnaire the Diabetes Treatment Satisfaction Questionnaire at baseline and Change in Satisfaction Treatment Questionnaires at follow-up (Bradley 1994).

iv) Diabetes Beliefs - This will be assessed by two patient self-report questionnaires the patient perceived locus of control and diabetes perceptions questionnaire (Hampson 2000). Self-efficacy shall also be assessed by two trial-developed items.

12.2.3 Health Economic Evaluation

Data will be collected prospectively, from all patients, on the utilisation of health service resources over the period of the trial. These data will include types and number of glucose monitors employed, numbers of visits to GPs, diabetic clinics, hospital out-patient clinics, in-patient days in hospital for diabetes-related problems, drug use for management of diabetes and its complications and other treatments for diabetic complications. These data will be collected using a mixture of patient questionnaires and case-report forms completed in clinic. Resource use will be valued using unit costs relevant to the UK health service at the time of analysis. Where possible, these will be taken from routine and national sources such as the British National Formulary, NHS Reference costs (NHS Executive, 1999), hospital cost returns (CIPFA, 2000) and the University of Kent routine survey of unit costs in primary and community care (Netten A et al. 2001). If necessary, additional unit costs will be collected from participating centres using a standardised costing protocol. As a part of the follow-up questionnaires, patients will be asked for details of time lost from usual activities (e.g. paid work) due to diabetes-related ill-health, which will facilitate an estimate of productivity costs.

The DSNs will also complete a Weekly Contact Diary documenting the amount of contact time (telephone or face-to-face) with trial participants and purpose of contact (see Appendix 10).

The EQ-5D will also be completed by participants to provide preference data for the estimation of Quality Adjusted Life Years (QALYS) that will be supplemented from published sources. All health economic data will be recorded in the CRF by the DSN or as part of self-completed questionnaires.
Measurement Periods: 0, 3, 6, 12, 18months (SC arm not measured at 3 months)

13 Recording of data

The DSN will be responsible for recording all treatment and assessment data in the CRF and weekly backing-up of downloaded monitor results stored on the computer. Instructions for completing the CRF are given in appendix 11. They will also be responsible for ensuring the CRF is completed at each assessment, with no missing data, including checking that the correct date of completion and patient identifiers are present. Two copies of the CRF should be present. The original will be collected at monthly visits by the trial coordinator, who will take responsibility for the forwarding of data to the MRC CTU where they will be entered into a database via TELEforms scanning software. A copy of all data is also to be kept at the local centres.

For non-English speakers DSN recorded sections of the CRF will be completed by the DSN with the assistance of a translator. For sections of the CRF that are patient completed (e.g. self-report questionnaires) patients will complete a copy of the forms in their own language.

The chemical pathology department at UCLH will forward HbA1c results to the DSN at the central site. The DSN will take responsibility for forwarding the chemical pathology results to the MRC CTU who will store them in an appropriate database.

14 Adverse events

14.1 Adverse Device Event (ADE)

An adverse device event will be defined as an event occurring after any exposure to the Biographer or CGMS where there is a reasonable possibility that the device caused or contributed to the event. This is classified on the MITRE Skin Scale as a score greater than or equal to 6 (appendix 12). In this instance patients should be instructed to attend the diabetes clinic for review by the DSN. The DSN should review and photograph the site and where appropriate consider the patient for withdrawal from treatment.

The DSN will record all ADE's in the CRF and complete and send the ADE form to the PI. A monthly report on ADE's will be provided by the DSN to the LI and PI. The PI will provide an ongoing report of adverse device events from all trial centres to the DSMC.

14.2 Serious adverse events (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that results in death, is life-threatening, requires unplanned inpatient hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability.

The DSN will record all SAE's in the CRF. In addition if a SAE occurs within any trial arm, a SAE form must be completed and faxed by the DSN, or when not available by the LI, to the PI and CTU within 72 hours of identifying the event. It is the PI's responsibility to inform the DSMC. Skin reactions will be recorded in the CRF.

15 Statistical Considerations

15.1 Sample Size

The original sample size calculation was based on the proportion of patients achieving a 1% absolute drop in glycosylated haemaglobin. 150 patients would be needed in each arm to detect an increase in the proportion achieving a 1% drop for 30% to 50%, with 90% power. In June 2004 the sample size was re-evaluated in light of advances in diabetes and current clinical targets. It was decided to measure the percentage change of HbA1c from baseline instead of an absolute change and look for a clinically important difference of 12.5%. This proportional change takes into account the starting HbA1c of the patients, and equates to an absolute drop of 1% in patients entering the study with the original 8% HbA1c minimum value. Based on clinical data, we estimated a 5% mean change from baseline in the standard control group, with a standard deviation of 15.5%. Allowing for 10% drop-out rate, 100 patients per arm provide 90% power to detect a 12.5% reduction from the starting HbA1c, at the 5% significance level.

We therefore plan to enrol a total of 400 patients from 4 centres.

15.2 Analysis plan

Primary Efficacy Outcome – Glycaemic Control

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

All analyses will be by intention to treat, comparing each of the monitors to control; the trial is not powered to make a direct comparison between the monitors. To assess whether the increased attention given to the patients allocated monitors is itself responsible for any change in observed outcome, the attention control arm will be compared to standard control. If there is no difference in outcome (within defined limits) the two control arms may be combined. The initial analyses will be uncorrected; subsequent analysis correcting for possible differences between the treatment arms will be conducted.

The primary outcome, the percentage change in HbA1c from baseline, will be calculated looking for a clinically important difference of 12.5% at the 5% significance level e.g. a baseline HbA1c of 14% improving to 12.25% at 18-months follow-up. This equates to an absolute drop in HbA1c of 1% in patients entering the study with an HbA1c of 8%, the criteria on which the original sample size calculation was based.

Exploratory analyses of the characteristics of patients who remain on their allocated trial treatment throughout and which patients have a successful outcome at 18 months will also be performed to identify which patients may benefit from use of the interventions.

Primary Efficacy Outcome – Acceptability
Comparison of Biographer and CGMS will be by parametric/non-parametric tests depending on the type of data and will assess whether the two non-invasive devices differ in acceptability. Acceptability will be assessed by questionnaire as well as inability to use the devices according to the protocol.

Psychosocial Outcomes
Groups will be compared on quality of life, self-management behaviours, fear of hypoglycaemia, illness beliefs and satisfaction using repeated measures analysis of variance. Predictors of outcome will also be examined using multiple regression. Factors to be entered into the equation will be determined by correlation analysis, with demographic variables forced into the regression at step one.

Health Economic Evaluation
Within-trial analysis
A within-trial cost-effectiveness analysis will relate differential mean costs to a range of measures of effectiveness such as change in glycosylated haemoglobin, number of either hypo- or hyperglycaemia events and frequency of acute infective complications. A cost-utility analysis, relating differential mean costs to differential mean QALYs (based on EQ-5D responses), will also be conducted, although it is unlikely that any modest short-term differences in health outcomes will manifest themselves in terms of QALYs. A fully stochastic analysis will be undertaken using cost-effectiveness acceptability curves to present the probability that each of the management strategies is the most cost-effective. Sensitivity analysis will be undertaken to explore the effect on results of sources of variability such as unit costs and effectiveness in different patient sub-groups.

Longer-term modelling
The second stage of the economic evaluation will seek to express changes in the primary endpoint (change from baseline in glycosylated haemoglobin achieved at the 18 month assessment) in terms of longer-term costs and health-related outcomes. This will be undertaken using decision modelling which will be structured around the relationship between differences in glycosylated haemoglobin and differential complication rates. The data necessary to quantify this relationship will be taken from published sources, but is likely to rely on studies such as the UKPDS (1998). The costs and health related effects of complications will also be estimated based on published data. The ultimate aim of the modelling will be to estimate differential long-term costs and quality-adjusted survival conditional on the form of monitoring used. The EQ-5D instrument, which will be completed as part of the trial, will provide preference data for the estimation of QALYs that will be supplemented from published sources.

16 Monitoring

16.1 Direct Access to Data

The local investigators will permit trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents. Patient consent will be obtained at baseline for data to be used to this effect.

16.2 Confidentiality

Patient data will be identified by study number alone. The CTU will have no access to patients' names and addresses. The trial coordinator at UCL will however have access to patients' names, addresses and telephone numbers to allow for data monitoring purposes.

16.3 Quality Assurance and Quality Control

The trial coordinator will visit each of the 4 centres on a monthly basis for the purpose of data verification. Each centre will ensure source data is available for these visits. The TC will validate 10% of the CRF information against the source data. Following data verification the TC will be responsible for forwarding data to the MRC CTU for data entry.

16.4 Monitoring and Stopping Rules/ Discontinuation Criteria

An independent Data Monitoring Committee has been set up to monitor the progress of the trial. Data on patient intake and trial safety will be reviewed in strict confidence every 6 months, which may initiate an interim analysis. There will be no formal stopping rule but the DMC will advise the Chairman of the Steering Committee that the trial should be stopped or a particular arm should be dropped if, in their view, there is:

a) Proof beyond reasonable doubt that either of the minimally invasive monitors cause harm to all, or some, types of patients.

b) Evidence from other studies that render use of the devices inappropriate or inadvisable.

17 Regulatory and Ethics Approval

The protocol has received Multi-Centre Research Ethics Committee (MREC) approval (Ref 02/2083) and Local Research Ethics Committee (LREC) approval. Patients consent to participate in the trial will be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. The patient information sheet and patient consent form are attached (appendices 1-4).

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded in the CRF and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

18 Indemnity

The HTA and NHS are both publicly funded bodies and are not allowed to purchase advance insurance to cover indemnity because they are backed by the resources of the Treasury.

"The HTA will give sympathetic consideration to claims for non-negligent harm suffered by a person as a result of trial or other work supported by the HTA. This does not extend to liability for non-negligent harm arising from conventional treatment where this is one arm of a trial. The HTA acts as its own insurer and does not provide cover for non-negligent harm in advance for participants in HTA-funded studies.

Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within the hospital, whether or not the patient is participating in a HTA supported trial. The HTA does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is a NHS Trust or not."

19 Trial Committees

The following committees provide the core management and independent supervision of trial:

19.1 TMG

The Trial Management Group (TMG) will consist of Steven Hurel, Stanton Newman, Debbie Cooke, Andrew Nunn, Sarah Meredith, Angela Casbard, Ann Gerrard and Margaret Band. Its remit is to consider day to day management issues and the overall progress of the trial.

19.2 TSC

The Trial Steering Committee will provide overall supervision of the trial on behalf of the Trial Sponsor (HTA) and ensure that the trial is conducted following the principles of MRC Guidelines for good clinical practice. The following individuals have agreed to sit on the committee. The HTA have approved their membership:

Chair
Dr James Ahlquist, Consultant Physician, Southend Hospital, Prittlewell Chase, Westcliffe on Sea, Essex, SS0 0RY

Independent Members
Judith Hunt (Patient Representative), 10 St Ann's Gardens, London, NW1
Dr David Girling

Investigators
Professor Andrew Nunn (Trial Statistician)
Angela Casbard (Trial Statistician)
Dr S J Hurel (Principal Investigator)

Professor Stanton Newman (Investigator)
Debbie Cooke (Trial Co-ordinator)

Health Technology Assessment Representatives
A representative of the Trial Sponsor will be invited to attend each meeting

The TSC will concentrate on the progress of the trial, adherence to protocol, patient safety and consider new information with relevance to the research question. Frequency of meetings will be at least annually and preferably six monthly. Responsibility for calling and organising the TSC lies with the PI.

19.3 DSMC

A DSMC has been established that will report to the TSC. It is the responsibility of the TSC Chair to submit a suggested membership of the DSMC. The DSMC will have access to all trial data. The role of the DSMC is to monitor these data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. Membership of the DSMC is completely independent. This consists of:

Chair
Professor John Betteridge (UCLH)

Independent Members
Pamela Clifton (Patient Representative)
Linda Morison (London School of Hygiene & Tropical Medicine)

Clinical Trials Unit, MRC
Professor Andrew Nunn (Trial Statistician)
Angela Casbard (Trial Statistician)

20 Publication

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications.

All publications shall include a list of participating investigators, and if there are named authors, these should include the Principal Investigator(s), Clinical Trial Manager(s), and Statistician(s) involved in the trial. The ISRCTN number allocated to this trial 33678610 will be attached to any publications resulting from this trial.

21 Protocol Amendments

- Updated contact details
- Removal of St Mary's Hospital as collaborator throughout document
- Trial Co-ordinator changed from Liz Steed to Debbie Cooke throughout document

- Project Timetable and Milestones amended to account for 2 project extensions granted (5)
- Inclusion criteria amended re HbA1c (7.2, 5)
- Identification of patients: use of invitation letter (7.5.1)
- Consent of patients requiring a screening blood test: additional consent procedure introduced because of amended HbA1c inclusion critieria (7.5.4)
- Randomisation and Enrolment: Details included about facility for pre-9am randomisation (7.5.5)
- Rate of recruitment: amended following approval of 1-year extension for recruitment (7.6)
- Trial Treatment amended to include delivery of reminder letter to prompt participants to attend their research visit (9.1)
- Nurse Feedback Session: amended to include details on patient reminder letter (9.3)
- Trial Products: contact details updated (10)
- Health Economic Evaluation: text regarding administration of questionnaire to estimate patients' travel costs removed. This was no longer regarded as essential data. Measures amended to include Weekly Contact Diary documenting time spent with patients and purpose of contact (12.2.3)
- Sample Size: changed from 600 to 400 (15.1)
- Analysis Plan: Primary Efficacy Outcome amended as now looking at percentage change in HbA1c from baseline rather than absolute reduction (15.2)
- Updated membership of trial committees (19.1, 19.2, 19.3)
- Appendix 1: Invitation letter - now included (p43)
- Appendix 2: Patient Information Sheet for Normal Consent Procedure (previously Appendix 1) – Version 5 now included. Section on side-effects updated from Version 4 in previous protocol. Previous wording (Version 4): The GlucoWatch has been associated with skin irritation in some patients. Wording in Version 5: The Glucowatch is commonly associated with skin irritation (p45)
- Appendix 3: Patient Information Sheet for Individuals Requiring Screening - now included (p48)
- Appendix 4: Consent Form (previously Appendix 2), p51
- Appendix 5: Consent Form for Individuals Requiring Screening (version 5) - now included. Previous versions amended to correct HbA1c criteria from 8.0% to 7.5%, to remove space for witness signature and to remove space for health care professional signature (p52)
- Appendix 6: Reminder Letter (version 2) – now included. Previous version amended to remove paragraph stressing the importance of the research to participants as this was considered too coercive by MREC (p53)
- Appendix 7: GP Letter (previously Appendix 3), p54
- Appendix 8: Guidance for Administration of Insulin (previously Appendix 4), p55
- Appendix9: Patient Questionnaires (previously Appendix 5) – Acceptability questionnaires developed for the purpose of the study are now included (p64)
- Appendix 10: Weekly Contact Diary – now included (p85)
- Appendix 11: Guidance for CRF Completion (previously Appendix 7), p87
- Appendix 12: MITRE Skin Scale (previously Appendix 6), p89

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APPENDIX 1: Invitation Letter

University College London Hospitals NHS Trust

[patients' name and address]

[date]

Patient Invitation Letter, Version 1: 2004

Dear [patient's name]

A research study is being carried out here in the [insert name of Department] that you may be interested in taking part in. The Department of Diabetes & Endocrinology at the University College London Hospitals NHS Trust are the lead centre for this project [and we are working together with them - *insert for Bournemouth, Gateshead and Chelsea & Westminster only*].

Regular checking of blood glucose (sugars) gives information on your glucose levels throughout the day and can guide diet, exercise and adjustment of insulin dosage. There are now new monitors that can automatically record your sugar levels whilst they are being worn.

This study is looking at two of these new blood glucose testing monitors. It will find out whether these can improve diabetes control and how acceptable they are to patients.

I am enclosing an information sheet giving you some more details about the research.

If you decide you do not want to take part, this will not affect your future medical care in any way.

If you are interested in taking part or if you would just like some more information please contact me on the following number: **Tel [insert number of Diabetes Research Nurse]**

Thank you for your time and interest.

Yours sincerely,

[name of Diabetes Research Nurse]
Diabetes Research Nurse

Enc.

Appendix 2: Patient Information sheet for Normal Consent Procedure

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. Un-headed 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 4 or 6 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 15hours 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 fingerprick 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 4 groups.

Which group you will be allocated to will be purely by chance and selected by a computer. The 4 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. Particpants will see the nurse in clinic once a month during this period to see to provide feedback 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 Continuous Glucose Monitoring System. During the first three months the device will be fitted three times. After wearing the device participants will see the nurse in clinic obtain a read out for discussion.. Over the next 15 months particpants 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 months intervals to measure long-term blood sugar control. Wherever 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, 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 readout 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 devices you can fit them 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 one 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 4 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 one week to receive the readout of your sugars. This device does not give you readout 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, which 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 recognized 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 organizing and funding the research?
The study is being funded by the National Health Service Health Technology Assessment Commissioning agency. It is being organized 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 3: 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. Un-headed 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 4 or 6 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 15hours 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 fingerprick 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 4 groups. Which group you will be allocated to will be purely by chance and selected by a computer. The 4 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 see to provide feedback 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 Continuous Glucose Monitoring System. During the first three months the device will be fitted three times. After wearing the device participants will see the nurse in clinic 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 months intervals to measure long-term blood sugar control. Wherever 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, 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?
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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 one 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 4 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 one week to receive the readout of your sugars. This device does not give you readout 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, which 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 recognized 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 organizing and funding the research?
The study is being funded by the National Health Service Health Technology Assessment Commissioning agency. It is being organized 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.

University College London Hospitals NHS
NHS Trust

APPENDIX 4: 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 5: Consent Form for Individuals Requiring Screening HbA1c

University College London Hospitals NHS Trust

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 6: Reminder Letter

University College London Hospitals NHS
NHS Trust

Minimally Invasive Technology: Role & Evaluation (MITRE) Study
Reminder Letter: Version 2 (November 2005)

[insert date]

Dear [insert name]

Thank you very much for continuing to take part in the diabetes study. Your next appointment is

[insert date / time of appointment] at the Diabetes Centre.

Please remember to bring:

- Your blood glucose testing meter (Onetouch Ultra)
- Your diary of blood glucose readings
- The glucowatch (where appropriate)
- Your reading glasses (if necessary)

I have enclosed a copy of the questionnaire for this research visit. I would be very grateful if you would also fill this in and bring it with you.

If for any reason you are unable to attend, please contact me to rearrange this appointment:

Tel:
Email:

We are able to refund travel expenses on public transport (on production of tickets) and also on car mileage. Please let me know if you would like to claim these expenses.

I look forward to seeing you

With best wishes

[insert name of nurse]
Diabetes Research Nurse

Enc.

University College London Hospitals NHS
NHS Trust

APPENDIX 7: GP Letter

Confidential

GENERAL PRACTITIONER LETTER version 2

Dr.....
.....
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Dear Dr.....

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

RE:

Your patient has kindly agreed to participate in the above study. A copy of the information sheet is enclosed. The study will run over an eighteen month period. Please do not hesitate to contact me if you have any concerns or questions.

Yours sincerely,

Appendix 8:
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 mmol/L	Pre-evening meal mmol/l	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
>7-9		absent		↑ Long acting or premixed by 1-2
>9		present		↓ Long-acting or premixed by 1-2
	>7-9		↑ Long-acting or premixed by 1-2	

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

Pre breakfast mmol/l	Pre-evening meal mmol/l	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
>7-9		absent		↑ Long acting or premixed by 2-4
>9		present		↓ Long-acting or premixed by 2-4
	>7-9		↑ Long acting or premixed by 2-4	

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

Pre breakfast mmol/l	Pre-evening meal mmol/l	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
>7-9		absent		↑ Long acting or premixed by 2-8
>9		present		↓ Long-acting or premixed by 2-8
	>7-9		↑ Long acting or premixed by 2-4	

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

Pre breakfast mmol/l	Pre-dinner mmol/l	Pre bedtime	Nocturnal hypo-glycaemia	Morning insulin	Dinner insulin	Bedtime insulin
>7-9			absent			↑ long-acting by 1-2
>9			present			↓ long-acting by 1-2
	>7-9			↑premixed or longacting by 1-2		
		>7-9 mmol/l			↑short-acting by 1-2	

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

Pre breakfast mmol/l	Pre-dinner mmol/l	Pre bedtime	Nocturnal hypo-glycaemia	Morning insulin	Dinner insulin	Bedtime insulin
>7-9			absent			↑ long-acting by 2-4
>9			present			↓ long-acting by 2-4
	>7-9			↑premixed or long acting by 2-4		
		>7-9			↑ short-acting by 2-4	

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

Pre breakfast mmol/l	Pre-dinner mmol/l	Pre bedtime	Nocturnal hypo-glycaemia	Morning insulin	Dinner insulin	Bedtime insulin
>7-9			absent			↑long-acting by 2-8
>9			present			↓long-acting by 2-8
	>7-9			↑premixed or long acting by 2-8		
		>7-9			↑short-acting by 2-8	

For basal bolus regimens: total daily dose **< 20 units**

Pre breakfast glucose	Pre lunch glucose	Pre dinner glucose	Pre bedtime glucose	Nocturnal hypo-glycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
>7-9				absent				↑ long- acting by 1-2
>9				present				↓ long- acting by 1-2
	>7-9				↑ short acting by 1-2			
		>7-9 mmol/l				↑ short acting by 1-2		
			>7-9 mmol/l				↑ short acting by 1-2	

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

For basal bolus regimens: total daily dose **20-50 units**

Pre breakfast	Pre lunch	Pre dinner	Pre bedtime	Nocturnal hypo-glycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
>7-9				absent				↑ long-acting by 2-4
>9				present				↓ long-acting by 2-4
	>7-9				↑ short acting by 2-4			
		>7-9				↑ short acting by 2-4		
			>7-9				↑ short acting by 2-4	

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

For basal bolus regimens: total daily dose **>-50 units**

Pre breakfast glucose	Pre lunch glucose	Pre dinner glucose	Pre bedtime glucose	Nocturnal hypo-glycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
>7-9				absent				↑ long- acting by 2-8
>9				present				↓ long- acting by 2-8
	>7-9				↑ short acting by 2-8			
		>7-9				↑ short acting by 2-8		
			>7-9				↑ short acting by 2-8	

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

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	Pre-evening meal glucose	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
<4-7 mmol/l		absent		↓ Long acting or premixed by 1-2 units
<4-7 mmol/l		present		↓ Long-acting or pre-mixed by 1-2 units
	<4-7 mmol/l		↓ Long-acting or premixed by 1-2 units	

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

Pre breakfast Glucose	Pre-evening meal glucose	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
<4-7 mmol/l		absent		↓ Long acting or premixed by 2-4 units
<4-7mmol/l		present		↓ Long-acting or pre-mixed by 2-4 units
	<4-7 mmol/l		↓ Long acting or premixed by 2-4 units	

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

Pre breakfast Glucose	Pre-evening meal glucose	Nocturnal hypoglycaemia	Morning insulin	Evening insulin
<4-7 mmol/l		absent		↓ Long acting or premixed by 2-8 units
<4-7mmol/l		present		↓ Long-acting or pre-mixed by 2-8 units
	<4-7 mmol/l		↓ Long-acting or pre-mixed by 2-8 units	

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

Pre breakfast Glucose	Pre-dinner glucose	Pre bedtime glucose	Nocturnal hypo-glycaemia	Morning insulin	Dinner insulin	Bedtime insulin
<4-7 mmol/l			absent			↓long-acting by 1-2 units
<4-7mmol/l			present			↓ long-acting by 1-2 units
	<4-7 mmol/l			↓premixed or long-acting by 1-2 units		
		<4-7mmol/l			↓short-acting by 1-2 units	

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

Pre breakfast Glucose	Pre-dinner glucose	Pre bedtime glucose	Nocturnal hypo-glycaemia	Morning insulin	Dinner insulin	Bedtime insulin
<4-7 mmol/l			absent			↓ long-acting by 2-4 units
<4-7 mmol/l			present			↓ long-acting by 2-4 units
	<4-7 mmol/l			↓premixed or long-acting by 2-4 units		
		<4-7 mmol/l			↓ short-acting by 2-4 units	

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

Pre breakfast Glucose	Pre-dinner glucose	Pre bedtime glucose	Nocturnal hypo-glycaemia	Morning insulin	Dinner insulin	Bedtime insulin
<4-7 mmol/l			absent			↓ long-acting by 2-8 units
<4-7mmol/l			present			↓ long-acting by 2-8 units
	<4-7 mmol/l			↓premixed or long acting by 2-8 units		
		<4-7 mmol/l			↓short-acting by 2-8 units	

For basal bolus regimens: total daily dose **< 20 units**

Pre breakfast glucose	Pre lunch glucose	Pre dinner glucose	Pre bedtime glucose	Nocturnal hypo-glycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
< 4-7 mmol/l				absent				↓ long- acting by 1-2 units
< 4-7 mmol/l				present				↓ long- acting by 1-2 units
	< 4-7 mmol/l				↓ short acting by 1-2 units			
		< 4-7 mmol/l				↓short acting by 1-2 units		
			< 4-7 mmol/l				↓ short acting by 1-2 units	

In regimens with 2 isophane doses, consider decreasing pre-breakfast isophane by 1-2 units as an alternative to decreasing the lunchtime short acting

For basal bolus regimens: total daily dose **20-50 units**

Pre breakfast glucose	Pre lunch glucose	Pre dinner glucose	Pre bedtime glucose	Nocturnal hypo-glycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
< 4-7 mmol/l				absent				↓long-acting by 2-4 units
< 4-7 mmol/l				present				↓ long-acting by 2-4 units
	< 4-7 mmol/l				↓short acting by 2-4 units			
		< 4-7 mmol/l				↓short acting by 2-4 units		
			< 4-7 mmol/l				↓short acting by 2-4 units	

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

For basal bolus regimens: total daily dose **> 50 units**

Pre breakfast glucose	Pre lunch glucose	Pre dinner glucose	Pre bedtime glucose	Nocturnal hypo-glycaemia	Breakfast insulin	Lunch insulin	Dinner insulin	Bedtime insulin
< 4-7 mmol/l				absent				↓long- acting by 2-8 units
< 4-7 mmol/l				present				↓ long- acting by 2-8 units
	< 4-7 mmol/l				↓short acting by 2-8 units			
		< 4-7 mmol/l				↓short acting by 2-8 units		
			< 4-7 mmol/l				↓short acting by 2-8 units	

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

Insulin Adjustment Advice During Illness

DSNs 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 4units 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 6units 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 6units 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 8units extra of fast or rapid acting insulin(or mixed insulin if this is the only one available) with each injection

Appendix 9: Patient Questionnaires

Questionnaire Instructions

The following questions help us to understand your experience of having diabetes, and how it affects your life.

All your answers are strictly confidential and will only be seen by the research assistant (Liz Steed) involved in this study.

- Please read each question carefully and then answer by circling the response that is closest to your situation, as shown below.

A) If I did not have diabetes, my quality of life would be:

very much better	much better	a little better	the same	a little worse	much worse	very much worse

- Work through the questions quite quickly. Don't spend too long on any one question.
- Respond to each question separately. Try not to worry about your previous choices.
- Answer according to your own beliefs and experiences and not how you think we want you to answer.
- Remember that there are no right or wrong answers to the questions.
- Complete the questionnaire on your own. Try not to ask for help from family and friends. If you have any queries call Liz Steed on 020 7679 9421.
- When you have completed the questionnaire please check that you haven't missed any questions.
- Place and seal in the brown envelope, and return to your diabetes specialist nurse.

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE
For further information or queries pleas contact Liz Steed (020- 7679-9421)

1. QUALITY OF LIFE

The following questions ask about your quality of life and the effects of your diabetes on your quality of life. Your quality of life is how good or bad you feel your life to be. Please circle the answer which best indicates your response on each scale.

There are no right or wrong answers, we just want to know how you feel about your life now.

A) In general, my present quality of life is:

as good as it could possibly be	very good	good	neither good nor bad	bad	very bad	as bad as it could possibly be

For the next statement, please consider the effects of your diabetes, its management and any complications you may have.

B) If I did not have diabetes, my quality of life would be:

very much better	much better	a little better	the same	a little worse	much worse	very much worse

For each of the following 13 statements please consider the effects of your diabetes, its management and any complications you may have on the aspect of life described by the statement.

In each of the following boxes:

a) Circle the answer that shows how diabetes affects this aspect of your life

b) Circle the answer that shows how important this aspect of your life is to your quality of life

Some statements have a "not applicable " option. Please circle the N/A box if this aspect of life does not apply to you.

1. If I did not have diabetes, my working life and work-related opportunities would be:

very much better	much better	a little better	the same	a little worse	much worse	very much worse	N/A
This aspect of my life is *(please circle the answer that applies to you)*							
very important		important		somewhat important		not at all important	

2. If I did not have diabetes, my social life would be:

very much better	much better	a little better	the same	a little worse	much worse	very much worse
This aspect of my life is *(please circle the answer that applies to you)*						
very important	important	somewhat important	not at all important			

3. If I did not have diabetes my family life would be:

very much better	much better	a little better	the same	a little worse	much worse	very much worse	N/A
This aspect of my life is *(please circle the answer that applies to you)*							
very important	important	somewhat important	not at all important				

4. If I did not have diabetes, my friendships would be:

very much better	much better	a little better	the same	a little worse	much worse	very much worse
This aspect of my life is *(please circle the answer that applies to you)*						
very important	important	somewhat important	not at all important			

5. If I did not have diabetes, my sex life would be:

very much better	much better	a little better	the same	a little worse	much worse	very much worse	N/A
This aspect of my life is *(please circle the answer that applies to you)*							
very important	important	somewhat important	not at all important				

6. If I did not have diabetes, my holidays or leisure activities would be:

very much better	much better	a little better	the same	a little worse	much worse	very much worse
This aspect of my life is *(please circle the answer that applies to you)*						
very important	important	somewhat important	not at all important			

7. If I did not have diabetes, problems with travelling (either local or long distance) would be:

very much decreased	Much decreased	a little decreased	the same	a little increased	much increased	very much increased
This aspect of my life is *(please circle the answer that applies to you)*						
very important	important	somewhat important	not at all important			

8. If I did not have diabetes, my worries about my future (e.g. health, independence, income) would be:

very much decreased	much decreased	a little decreased	the same	a little increased	much increased	very much increased
This aspect of my life is *(please circle the answer that applies to you)*						
very important	important	somewhat important	not at all important			

9. If I did not have diabetes, my worries about the future of my family and close friends (e.g. their health, independence, income) would be:

very much decreased	much decreased	a little decreased	the same	a little increased	much increased	very much increased	N/A
This aspect of my life is *(please circle the answer that applies to you)*							
very important	important	somewhat important	not at all important				

10. If I did not have diabetes my motivation to achieve things would be:

very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased
This aspect of my life is *(please circle the answer that applies to you)*						
very important	important	somewhat important	not at all important			

11. If I did not have diabetes, the things I could do physically would be:

very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased
This aspect of my life is *(please circle the answer that applies to you)*						
very important	important	somewhat important	not at all important			

12. If I did not have diabetes, the extent to which people would fuss or worry about me too much would be:

very much decreased	much decreased	a little decreased	the same	a little increased	much increased	very much increased
This aspect of my life is *(please circle the answer that applies to you)*						
very important	important	somewhat important	not at all important			

13.If I did not have diabetes, my enjoyment of food would be:

very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased
This aspect of my life is *(please circle the answer that applies to you)*						
very important	important	somewhat important	not at all important			

2. SELF-CARE BEHAVIOURS

The questions below ask you about your diabetes self-care activities ***during the past 7 days***. If you were sick during the past 7 days, please think back to the last 7 days that you were not sick.

Diet

1) How many of the last SEVEN DAYS have you followed a healthy eating plan?

0 1 2 3 4 5 6 7

2) On average, over the past month, how many DAYS PER WEEK have you followed your eating plan?

0 1 2 3 4 5 6 7

3) On how many of the last SEVEN DAYS did you eat five or more servings of fruits and vegetables?

0 1 2 3 4 5 6 7

4) On how many of the last SEVEN DAYS did you eat high fat foods such as red meat or full-fat dairy products?

0 1 2 3 4 5 6 7

Exercise

5) On how many of the last SEVEN DAYS did you participate in at least 30 minutes of physical exercise? (Total minutes of continuous activity, including walking).

0 1 2 3 4 5 6 7

6) On how many of the last SEVEN DAYS did you participate in a specific exercise session (such as swimming, walking, biking) other than what you do around the house or as part of your work?

0 1 2 3 4 5 6 7

Blood Sugar Testing

7) On how many of the last SEVEN DAYS did you test your blood sugar?

0 1 2 3 4 5 6 7

8) On how many of the last SEVEN DAYS did you test your blood sugar the number of times recommended by your health care provider?

0 1 2 3 4 5 6 7

Foot Care

9) On how many of the last SEVEN DAYS did you check you feet?

0 1 2 3 4 5 6 7

10) On how many of the last SEVEN DAYS did you inspect the inside of your shoes?

0 1 2 3 4 5 6 7

Smoking

11) Have you smoked a cigarette – even one puff – during the last SEVEN DAYS?

0. No

1. Yes *If yes,* how many cigarettes did you smoke on an average day?

Number of cigarettes: _____

3. THOUGHTS ABOUT DIABETES

1. How serious is your diabetes?

Not at all serious	*Slightly serious*	*Fairly serious*	*Very Serious*	*Extremely serious*

2. How worried are you about developing complications of diabetes (like eye problems, foot ulcers or heart attacks)?

Not at all worried	*Slightly worried*	*Fairly worried*	*Very worried*	*Extremely worried*

3. How important is following your self-care recommendations (for example, diet, exercise and glucose testing) for controlling your diabetes?

Not at all Important	*Slightly important*	*Fairly important*	*Very important*	*Extremely important*

4. How frustrated do you feel when trying to take care of your diabetes?

Not at all frustrated	*Slightly frustrated*	*Fairly frustrated*	*Very frustrated*	*Extremely frustrated*

5. How important is controlling your blood sugar levels for avoiding complications from your diabetes?

Not at all Important	*Slightly important*	*Fairly important*	*Very important*	*Extremely important*

6. How much has having diabetes changed your activities (that is your family and social events, work, and hobbies)?

Not at all	*Slightly*	*Moderately*	*A lot*	*Completely*

7. How important do you believe healthy eating is for controlling your diabetes?

Not at all Important	*Slightly important*	*Fairly important*	*Very important*	*Extremely important*

8. How likely do you think it is that healthy eating will prevent future complications of your diabetes?

Not at all Likely	*Slightly likely*	*Fairly likely*	*Very likely*	*Extremely likely*

9. How important do you believe physical activity is for controlling your diabetes?

Not at all Important	*Slightly important*	*Fairly important*	*Very important*	*Extremely important*

10. How likely do you think it is that physical activity will prevent future complications of your diabetes?

Not at all Likely	*Slightly likely*	*Fairly likely*	*Very likely*	*Extremely likely*

11. How much control do you feel you have over your blood sugar levels?

None	*Slightly*	*Moderately*	*A lot*	*Completely*

4. WORRIES ABOUT DIABETES

I worry about	Never	Rarely	Sometimes	Often	Always
1. Not recognising/ realising I am having low blood sugar	0	1	2	3	4
2. Not having food, fruit, or juice with me	0	1	2	3	4
3. Passing out in public	0	1	2	3	4
4. Embarrassing myself or my friends in a social situation	0	1	2	3	4
5. Having a reaction while alone	0	1	2	3	4
6. Appearing stupid or drunk	0	1	2	3	4
7. Losing control	0	1	2	3	4
8. No one being around to help me during a reaction	0	1	2	3	4
9. Having a reaction while driving	0	1	2	3	4
10. Making a mistake or having an accident	0	1	2	3	4
11. Getting a bad evaluation or being criticised	0	1	2	3	4
12. Difficulty thinking clearly when responsible for others	0	1	2	3	4
13. Feeling light-headed or dizzy	0	1	2	3	4

Please tick one box in each group below, to indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual activities **(e.g. work, study, housework, family or leisure activities)**

I have no problems with performing my usual activities	❑
I have some problem with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/ discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/ depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

6. DIABETES TREATMENT

Please answer the following questions in relation to your treatment in the last few weeks.

1. How satisfied are you with your current treatment?

Very satisfied	6	5	4	3	2	1	0	Very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

Most of the time	6	5	4	3	2	1	0	None of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

Most of the time	6	5	4	3	2	1	0	None of the time

4. How convenient have you been finding your treatment to be recently?

Very convenient	6	5	4	3	2	1	0	Very inconvenient

5. How flexible have you been finding your treatment to be recently?

Very flexible	6	5	4	3	2	1	0	Very inflexible

6. How satisfied are you with your understanding of your diabetes?

Very satisfied	6	5	4	3	2	1	0	Very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

Very satisfied	6	5	4	3	2	1	0	Very dissatisfied

The following questions are concerned with your present treatment for your diabetes compared with your experience of treatment 3 months ago (before you used the GlucoWatch orCGMS monitor). We would like to know how, if at all, your experience of treatment has changed. Please answer by circling a number on each of the scales to indicate the extent to which you have experienced changes. If you have experienced no change, circle '0'.

1. How satisfied are you with your current treatment?

much more satisfied now 3 2 1 0 -1 -2 -3 much less satisfied now

2. How often have you felt that your blood sugars have been unacceptably high recently?

much more of the time now 3 2 1 0 -1 -2 -3 much less of the time now

3. How often have you felt that your blood sugars have been unacceptably low recently?

Much more of the time now 3 2 1 0 -1 -2 -3 Much less of the time now

4. How convenient have you been finding your treatment to be recently?

Much more convenient now 3 2 1 0 -1 -2 -3 Much less convenient now

5. How flexible have you been finding your treatment to be recently?

Much more flexible now 3 2 1 0 -1 -2 -3 Much less flexible now

6. How satisfied are you with your understanding of your diabetes?

Much more satisfied now 3 2 1 0 -1 -2 -3 Much less satisfied now

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Much more likely to recommend the treatment now 3 2 1 0 -1 -2 -3 Much less likely to recommend the treatment now

8. How satisfied would you be to continue with your present form of treatment?

Much more satisfied now 3 2 1 0 -1 -2 -3 Much less satisfied now

7. BELIEFS ABOUT DIABETES

This questionnaire looks at how individuals view different aspects of their life. Please circle one number to show how much you agree or disagree with each statement. The more strongly you agree with a statement then the higher will be the number you circle.

	Strongly disagree	Moderately disagree	Slightly disagree	Slightly agree	Moderately agree	Strongly agree
1. It's within my power to achieve acceptable diabetes control.	1	2	3	4	5	6
2. If I remain free of complications, or their progress is delayed, it will be largely due to good fortune.	1	2	3	4	5	6
3. If my blood sugars get too high, it's usually because I haven't taken enough care	1	2	3	4	5	6
4. If I am to have a good quality of life as well as control of my diabetes, I need the support of those around me	1	2	3	4	5	6
5. If my blood sugar is unacceptably low, it will be because I haven't take the necessary steps to avoid it.	1	2	3	4	5	6
6. If I remain free of complications, or existing complications get no worse, it's because of my own efforts.	1	2	3	4	5	6
7. Living with diabetes is made more difficult because some people are inconsiderate.	1	2	3	4	5	6
8. If my blood sugar levels fluctuate widely, I'm just unlucky.	1	2	3	4	5	6
9. Health care professionals play a key role in making a success of my diabetes management	1	2	3	4	5	6
10. When problems arise with my diabetes, it's just bad luck.	1	2	3	4	5	6
11. Those closest to me help me to enjoy meals, while keeping good diabetes control in mind.	1	2	3	4	5	6
12. If my quality of life is impaired by my diabetes, it will be because of the treatment recommended.	1	2	3	4	5	6
13. People's lack of understanding of my diabetes creates difficulties in managing my condition.	1	2	3	4	5	6
14. When things go wrong with my diabetes, it is quite possibly due to inappropriate treatment or advice given by health care professionals.	1	2	3	4	5	6

	Strongly disagree	Moderately disagree	Slightly disagree	Slightly agree	Moderately agree	Strongly agree
15. When things go badly with my diabetes control, it's likely to be due to my own actions or lack of action.	1	2	3	4	5	6
16. For me to have good diabetes control depends a great deal on doctors, nurses and other health professionals	1	2	3	4	5	6
17. Good diabetes management is largely a matter of chance.	1	2	3	4	5	6
18. Health care professionals are important in preventing or limiting complications of my diabetes.	1	2	3	4	5	6
19. I might just as well say 'what will be will be' where complications of my diabetes are concerned.	1	2	3	4	5	6
20. Successful management of my diabetes depends a great deal on those close to me.	1	2	3	4	5	6
21. If my blood sugar levels are unstable, it probably means I need better care from the diabetes team.	1	2	3	4	5	6
22. If I have the quality of life I wish while also having good diabetes control, it will be due to good luck	1	2	3	4	5	6
23. When things go wrong with my diabetes management, it's often because those close to me haven't helped enough.	1	2	3	4	5	6
24. If my diabetes is successfully managed, while I also live life as I wish, it will be because I have made it happen.	1	2	3	4	5	6

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 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.

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

Not at all	A little	Moderately	A lot	Completely

1b. I found this

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

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

Not at all	A little	Moderately	A lot	Completely

2b. I found this

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

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

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

Not at all	A little	Moderately	A lot	Completely

3c. I found this

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

4a. 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

4b. I found this

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

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

Not at all	A little	Moderately	A lot	Completely

5b. I found this

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

6a. 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

6b. I found this

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

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

Not at all	A little	Moderately	A lot	Completely

7b. I found this

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

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

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

Not at all	A little	Moderately	A lot	Completely

8b. I found this

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

9a When wearing the monitor it interfered with my choice of clothes

Not at all	A little	Moderately	A lot	Completely

9b. 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	Strong 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	1	2	3	4	5

prick tests that were needed for the monitor to work properly					
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 readouts 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	Strong 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

Thank you for completing these questionnaires. Please seal in envelope provided and return to your diabetes specialist nurse.

APPENDIX 10: WEEKLY CONTACT DIARY

Please email or fax every Friday to Ann Gerrard (Fax: 020 7670 4829) and Debbie Cooke (Fax: 020 7679 9028)

Week beginning: …….
Site: ……..

						Purpose of contact*							
						In Person - time spent in minutes			Telephone - tick all that apply				
Date	**ID No.**	**Week No.**	**Type of contact**	**Questionnaires retuned to nurse**	**Questionnaires to be posted back**	**Monitor training/fitting**	**Downloading data from monitors**	**Clinical advice/feedback**	**Trial management**	**Patient management**	**Monitor problems**	Total time	**Comments**

*1=phone, 2=face-to-face as part of routine research visit, 3=face-to-face outside of routine research visit, 4=other

Guidelines for Completing Weekly Contact Diary

1. **First Six Columns:** Please complete for all patients.
2. **Log of Time Spent with Patient (purpose of contact and total time columns)**
   This part of the form is to be completed for patients who were newly randomised into the study when this form was introduced:

   - Bournemouth: 1064 onwards
   - Gateshead: 2079 onwards
   - UCLH: 3085 onwards
   - Whittington: 4039 onwards

Please complete the time log every time you have contact with these patients by phone or in person.

Type of contact: in each case, please use 1 of the codes listed

Purpose of contact:
In person: please insert the approximate time (minutes) spent for each task listed. If you do not do one of these tasks when you see the patient e.g. monitor training, then please insert a cross in those columns rather than leaving them blank.

For the 'total time' column, please add up the time spent on each of the tasks.

Telephone contact: From the three columns, please tick all that apply for each phone call you have with the patient

Definitions
Trial Management: discussion of visit times, rearranging appointments
Patient Management: clinical / lifestyle advice
Monitor Problems: troubleshooting of problems with Lifescan, Biographer or CGMS

For the ‘total time’ column, please record the length of the phone call

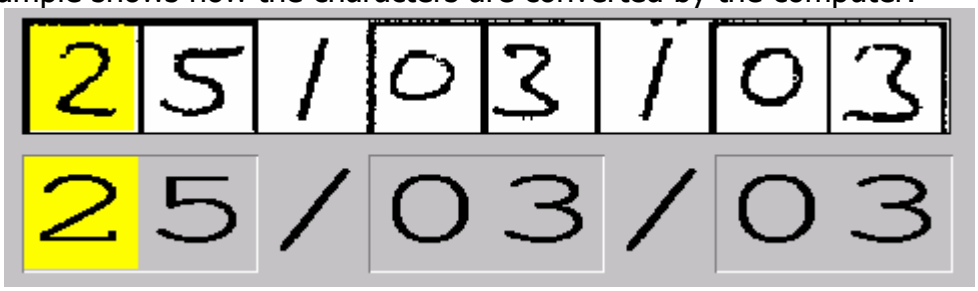
APPENDIX 11:
Guide to completing the CRFs

These forms were designed using TELE*forms* software. TELE*forms* are a special type of form which can be scanned into the computer, which saves the data in a database, minimising manual data entry.

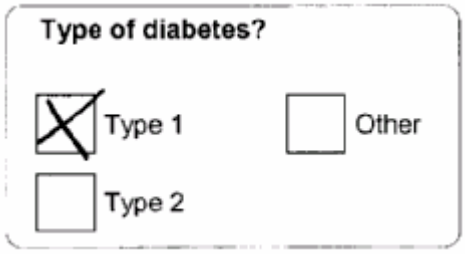
The form should be completed in BLOCK CAPITALS with a **black ballpoint pen.** To enable maximum accuracy of the scanning procedure, the forms must be completed with more care than would normally be required. Examples are given below. The CRFs have been designed so that the majority of fields are either multiple choice options or confined to one character per box.

EXAMPLES

1. **One character per box field -** Try not to touch the edges of the individual boxes. This example shows how the characters are converted by the computer.



2. **Multiple choice fields -** These must be filled in with an X, filling the whole box, rather than a tick. It doesn't matter if you go over the edge of the box slightly.



3. **Free text fields –** These occur less often and are used to record extra information. The writing should be in block capitals and as clear as possible to maximise the chance of correct interpretation by the software.
4. **Signature fields –** The software only detects that the box has been signed and does not try to interpret the signature.

Appendix 12:

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