CLINICAL TRIAL PROTOCOL

Clinical Assessment of a Novel Advanced Bolus Calculator for Type 1 Diabetes (ABC4D)

Principal investigator: Dr Nick Oliver

General Information

Authors:	Professor D Johnston, Dr N Oliver and Dr M Reddy
Title:	Clinical Assessment of a Novel **A**dvanced **B**olus **C**alculator **f**or Type 1 **D**iabetes (ABC4D)
Identifying Number:	Imperial College Joint Research Office 13SM0091
Date:	1st of May 2014 (amended 15.06.15 and 12.08.16)
Sponsor:	Imperial College London Joint Research Compliance Office Imperial College London and Imperial College Healthcare NHS Trust Room 510A, 5th floor Lab Block Charing Cross Hospital, Fulham Palace Road, W6 8RF
Sponsor Contact:	Ruth Nicholson Research Governance Manager Joint Research Compliance Office Imperial College London and Imperial College Healthcare NHS Trust, Room 5L10D, 5th Floor, Lab Block, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF Email: r.nicholson@imperial.ac.uk Telephone: 0203 311 0212
Principal Investigator:	Dr Nick Oliver St. Mary's Hospital Medical School Building, Imperial College, London, W2 1PG Nick.oliver@imperial.ac.uk 0207 594 2460
Other departments:	Institute of Biomedical Engineering Bessemer Building, South Kensington Campus, Imperial College, London, SW7 2AZ

Background

Type 1 diabetes mellitus (T1DM) is caused by a T-cell mediated autoimmune destruction of the pancreatic beta cells resulting in an inability of the pancreas to produce insulin, which is required for maintaining glucose homeostasis. 5% of the UK population have diabetes and of those 10% have T1DM. It is expected that the prevalence and incidence of diabetes will continue to increase worldwide (1).

The majority of subjects with T1DM are on multiple daily injections (MDI) of insulin (a basal-bolus regimen), to mimic physiological insulin secretion in response to glucose levels. The insulin dosages are determined by intermittent capillary blood glucose measurements. Continuous subcutaneous insulin infusion (CSII) via a pump provides an alternative form of insulin therapy with the advantage of delivering variable basal rates throughout the day and less injections (2). In additions, there is evidence supporting benefit of subcutaneous continuous glucose monitoring (CGM) with regards to reductions in hypoglycaemia (3, 4)
It is well-established that intensive treatment of T1DM reduces the risk of microvascular complications including retinopathy, nephropathy and neuropathy (5). Achieving optimal glycaemic control with intensive insulin treatment is challenging for many T1DM subjects due to the associated risk of recurrent hypoglycaemia (5) which can result in reduced hypo awareness. Severe hypoglycaemia is associated with seizures and death (6, 7).

Structured education is an important and recommended component of the management plan for people diagnosed with T1DM (8). Self-monitoring of blood glucose, carbohydrate (CHO) counting and insulin dose-adjustment are integral parts of the structured education provided.

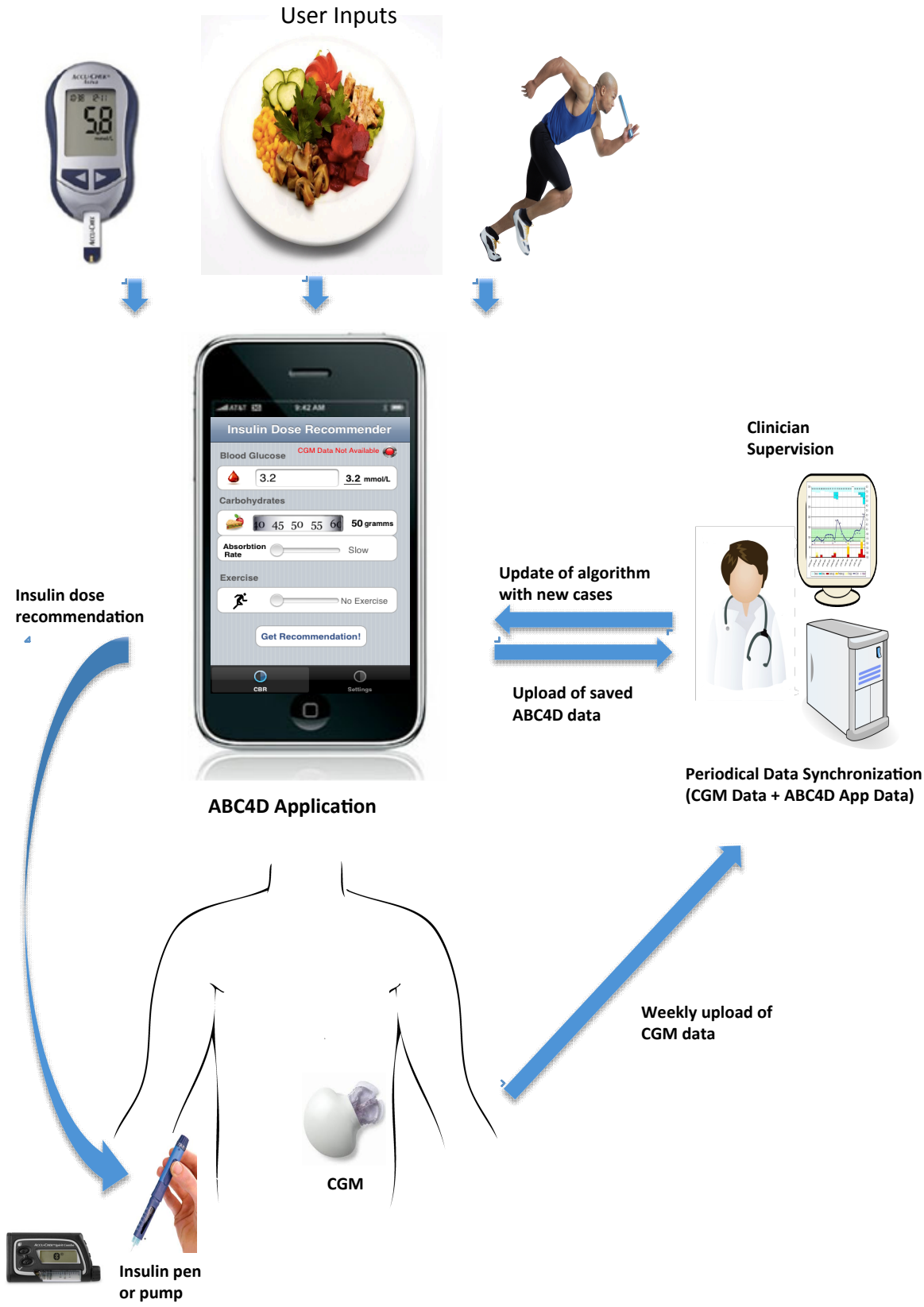
Insulin bolus calculators have been developed to aid insulin dose adjustment, and are currently incorporated in most of the latest commercially available insulin pumps (9) and some glucose meters. The standard insulin bolus calculator consist of a simple algorithm that requires five subject-specific parameters as input to generate a recommended bolus insulin dose:

(i) current blood glucose (mmol/L)
(ii) target blood glucose (mmol/L)
(iii) insulin-to-carbohydrate ratio (grams of carbohydrate per 1 unit of insulin)
(iv) total grams of carbohydrate in meals
(v) insulin sensitivity factor (reduction in glucose per 1 unit of insulin)

Other features such as insulin-on-board (amount of active insulin still in the body from previous injections) are often taken into account, and are important in prevention of delivering excess insulin leading to hypoglycaemia.

This clinical trial protocol assesses a novel Advanced Bolus Calculator for Diabetes (ABC4D). The complete integrated system consists of a smartphone that holds the advanced decision support algorithm. The system requires regular updates of cases derived from continuous glucose monitoring (CGM) data. Each new case includes information about the problem (e.g. capillary blood glucose, meal information and physical exercise), solution (recommended insulin dose) and outcome (post-prandial blood glucose).

ABC4D System



The novel decision support algorithm is based on case-based reasoning (CBR). CBR is an artificial intelligence technique that tries to solve newly encountered problems by applying the solutions learned from solved problems encountered in the past (10).
The CBR algorithm requires the following input for each insulin dose recommendation:

- Time of day
- Capillary blood glucose
- Meal carbohydrate intake (g)
- Type of meal CHO (fast, medium or slow absorption)
- Pre- or post-meal exercise if within 4 hours of the meal (intensity: moderate or intense)

These parameters make up the case problem presented to the CBR algorithm. Using this information the algorithm will find a similar case scenario from the pool of previously encountered cases and recommend an improved solution (insulin dose) to achieve the best possible outcome (post-prandial blood glucose).

The insulin recommendation application runs locally on a standard operating system such as iOs5.x or Android within a commercially available smartphone. It contains the CBR based decision support algorithm as well as information of past successful cases. Opening the decision support application on the smartphone leads to the main menu, which provides a link to the submenu for requesting a new recommendation. Every calculated recommendation needs to be accepted or declined manually, and the latter option requires the user to enter the adjusted amount of insulin that has been delivered. In addition, the main menu enables the user to view logged data such as recent glucose levels, meal/exercise events and previous insulin dose advices. If subjects are having snacks in between main meals they will have the option to introduce this information in the ABC4D graphical user interface, however no insulin recommendation will be given by the ABC4D.

The glucose sensors that will be used throughout the clinical validation studies are the Enlite sensor (CE marked,manufactured by Medtronic) or the Dexcom sensor (CE marked, manufactured by Dexcom). They are subcutaneous sensor which sit just under the skin and sample interstitial fluid using an enzyme electrode. A small voltage is applied across the sensor and a current is fed back to the sensor instrumentation. This current is proportional to the glucose concentration in interstitial fluid and is calibrated against blood glucose a minimum of 12-hourly. In phase 2 and 3 the CGM will be blinded and either calibrated retrospectively using the iPro2 system (CE marked, manufactured by Medtronic) or calibrated in real-time using the Dexcom CGM system (however the CGM will be blinded to the subject). The iPro2 consist of a recorder that will be attached to the Enlite sensor and at the end of 6 days the data will be downloaded to the Medtronic Carelink iPro software. The Dexcom CGM data will be downloaded to the DiaSend/Dexcom Studio software. In phase 4 Dexcom real-time CGM (i.e subjects will be able to see their CGM data at all times) will be used continuously throughout the study. All data will be anonymised.

In order to demonstrate safety and efficacy of the CBR algorithm, an *in-silico* study using the UVa-Padova T1DM simulator (11) was done and showed good results. The simulator was developed from human data and takes into account sensor errors, sensor placement, route of insulin administration and meal-time glucose absorption.

Trial Objectives, Purpose and Design: The principal research objectives are to assess the safety, technical proof of concept and efficacy of the ABC4D device in subjects with T1DM. Safety will be assessed by measuring post-prandial glucose for hypo- and hyperglycaemia. This will initially be assessed over 8 hours with two meal challenges, in a controlled clinical environment. Phase 2 will take place over 6 weeks where subjects will be using the ABC4D for bolus calculations in their normal environment. Subjects will have blinded CGM (Enlite sensor, iPro2, Medtronic) throughout the study and the data will be downloaded every week allowing the research team to update the algorithm's case base with new cases from the preceding week. The algorithm will have the capacity to retrieve new cases in an automatic process, but for safety the research team will accept each case manually in phase 1 and 2.
The primary outcome in the third and final phase of the study is the change in HbA1c after subjects have used the ABC4D for 6 months. In the 3rd phase of the study, the subjects will have 4 weeks of consecutive CGM, followed by one week of blinded retrospective CGM each month for the remainder time of the study. The CGM data will be downloaded and calibrated retrospectively, allowing the researcher to update the algorithm's case base with new cases on a monthly basis. In phase 3 and phase 4 the retrieval of new cases derived from combined CGM data and data from the ABC4D application will be a semi-automatic process without the research team approving each case. However, the research team will approve the revision summary before updating the case-base.
The final phase (Phase 4) will aim to investigate the efficacy of ABC4D with RT-CGM compared to standard bolus calculator (defined as the bolus wizard within insulin pumps, bolus calculator in glucose meter or the ABC4D app as a standard bolus calculator (without CBR adaptation)) with RT-CGM where the primary outcome is HbA1c at 6 months. RT-CGM will be used throughout the study period in both the intervention and control group.
The study will be conducted over four phases as outlined below:

Phase 1

Objective: To demonstrate safety and technical proof of concept of the ABC4D in a controlled clinical environment

Methodology Non-randomised open label study

Primary outcome:
Post-prandial hypoglycaemia within 2 hours of insulin administration

Secondary outcomes:
Post-prandial glucose at 60 and 120 minutes
Post-prandial area under the curve (AUC) at 120 minutes
Hypoglycaemia at 4-hours post-prandially
Glycaemic risk: LBGI and HBGI
Glycaemic variability: MAGE and CONGA-2

These are validated, published metrics

Timescale: Each subject will be in the study for 8 hours. It is anticipated that it will take 2 months to complete the 1st phase.
Population: 6 adults with T1DM

Subject inclusion criteria:

- Adults ≥18 years of age
- Diagnosis of T1DM for > 1 year
- On MDI using a basal-bolus insulin regime
- Structured education in previous 3 years
- HbA1c ≤ 86mmol/mol
- No severe hypoglycaemia (defined as needing 3rd party assistance) in previous year

Subject exclusion criteria:

- Recurrent severe hypoglycaemia
- Pregnant or planning pregnancy
- Breastfeeding
- Enrolled in other clinical trials
- Have active malignancy or under investigation for malignancy
- Addison's Disease
- Gastroparesis
- Autonomic neuropathy
- Concomitant use of GLP-1 analogues and gliptins
- Visual impairment
- Reduced manual dexterity

Subject withdrawal criteria:

- Loss of capacity to give informed consent
- Cessation of MDI of insulin as usual care for T1DM
- Recurrent severe hypoglycaemia
- Terminal illness

Withdrawal will be immediate and subjects will be followed up in the appropriate out-patient diabetes clinic within 4 weeks of withdrawal

Recruitment Recruiting will be undertaken in the T1DM clinics at St Mary's Hospital and Charing Cross Hospital campuses of Imperial College Healthcare. Participant information sheets will be given to potential subjects and, after a minimum of 48 hours and following any questions, informed consent will be taken.

Visit 1: Screening

- Attend the clinical research unit at 08:00-09:00
- Routine clinical examination
- ECG
- Non-fasting venous blood taken for HbA1c, creatinine, lipids
- Urine for albumin/creatinine ratio
- Urine pregnancy test in female subjects of childbearing age
- CHO counting and hypoglycaemia education revision by a qualified health care professional.
- The basal insulin dose will be reviewed and adjusted if needed.

- Continuous glucose monitor (CGM retrospective/blinded iPro2, Medtronic) placed in the anterior abdominal wall according to manufacturer's instructions. CGM sensor to be worn for 6 continuous days.
- Instructions to subjects to ensure:
    - Capillary blood glucose measurements fasting, pre-meals, post-meals and pre-bed.
    - Food diaries and physical activity record to be kept for 6 days.

Visit 2: CGM review

- Attend 7 days following visit 1
- Remove CGM, upload data to Medtronic Carelink iPro software, calibration data and review data with subject.
- Recalculate insulin sensitivity factor (ISF) and insulin:CHO ratio (ICR).
- Update the CBR algorithm with subject's clinical parameters and cases derived from the CGM data and diary.

Visit 3: Assessment of the ABC4D

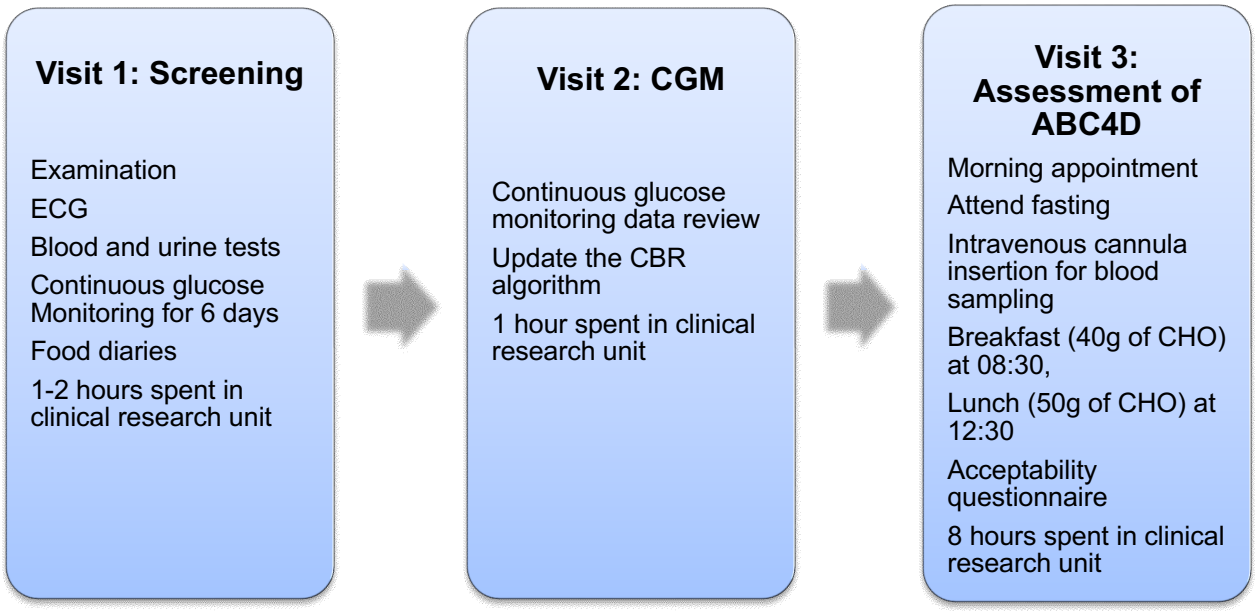
- Attend the clinical research unit fasting at 08:00. Subjects should take their basal insulin as normal the evening before the appointment.
- Clean area and site intravenous 18g or 20g cannula in peripheral vein
- Subject to have breakfast (40g of CHO) at 08:30, lunch (50g of CHO) at 12:30
- The insulin bolus dose for each meal will be calculated using the ABC4D and given to the subject as a subcutaneous injection (Novorapid or Humalog) in the anterior abdominal wall, immediately before the meal.
- Throughout the study period (08:30-16.30) 2.5mL venous blood will be taken every 15 minutes during the first 2 hours post meal and every 30 minutes for the remaining time. The samples will be analysed immediately for glucose concentration using the YSI glucose analyser.
- The ABC4D study will be terminated if venous blood glucose concentrations fall below 3.0mmol/L or above 15mmol/L, or if the subject experiences hypoglycaemia symptoms. Hypoglycaemia will be confirmed by an additional venous blood plasma glucose sample and will be treated according to Imperial College Hospitals NHS Trust Guidelines.
- After 8 hours (at 16:30) of the study the subject can be discharged if glucose concentrations are stable.
- Acceptability questionnaire to be completed.

Usual care will be maintained for diabetes throughout the study. No concomitant medical therapies are contra-indicated, except GLP-1 analogues and gliptins. Support will be offered to any participants who have concerns about their diabetes management.

Statistics 6 subjects planned to be enrolled. This is not a randomised study and there are no comparison or control groups. Outcomes from the study are absolutes as described above. The sample size is a realistic number for recruitment and provides robust clinical validation and safety data. The study is not powered to show a change in the primary or secondary outcomes compared with usual care but is an assessment of a new technology.

Missing, unused, and spurious data will be assessed on an individual basis and may be ignored, withdrawn or the visit may be removed from the analysis with appropriate justification adjudicated by the Principal Investigator.

Phase 1 of ABC4D study: Summary of visits



Phase 2

Objective: To demonstrate safety, technical proof of concept and efficacy of the ABC4D in the subject's own environment

Methodology Non-randomised open label study

Primary outcome:
Post-prandial hypoglycaemia

Secondary outcomes:
Post-prandial glucose at 60 and 120 minutes
Post-prandial AUC at 120 minutes
Hypoglycaemia at 4-hours post-prandial
Glycaemic risk: LBGI and HBGI
Glycaemic variability: MAGE and CONGA-2
Acceptability questionnaire (non-validated)

These are validated, published metrics.

Timescale: Each subject will be in the study for 6 weeks. It is anticipated that it will take 4 months to complete the 2nd phase.

Population 20 adults with T1DM

Subject inclusion criteria:

- Adults ≥18 years of age
- Diagnosis of T1DM for > 1 year
- On MDI using a basal-bolus insulin regime
- Structured education in previous 3 years
- HbA1c ≤ 86mmol/mol
- No severe hypoglycaemia (defined as needing 3rd party assistance) in previous year

Subject exclusion criteria:

- Recurrent severe hypoglycaemia
- Pregnant or planning pregnancy
- Breastfeeding
- Enrolled in other clinical trials
- Have active malignancy or under investigation for malignancy
- Addison's Disease
- Gastroparesis
- Autonomic neuropathy
- Concomitant use of GLP-1 analogues and gliptins
- Visual impairment
- Reduced manual dexterity

Subject withdrawal criteria:

- Loss of capacity to give informed consent
- Cessation of MDI of insulin as usual care for T1DM
- Recurrent severe hypoglycaemia
- Terminal illness

Withdrawal will be immediate and subjects will be followed up in the appropriate out-patient diabetes clinic within 4 weeks of withdrawal

Recruitment.

Recruiting will be undertaken in the diabetes clinics at Imperial College Healthcare NHS Trust, from registered research databases and from interested subjects who contact us. Participant information sheets will be given to potential subjects and, after a minimum of 48 hours and following any questions, informed consent will be taken.

Subjects who have already participated in phase 1 of the study can also be recruited for phase 2 and they will be re-consented. These subjects will not need re-screening, however they may need to repeat 1 week of CGM using iPRO2 for initializing of the ABC4D at the start of the Phase 2 study, this is at the discretion of the Principal Investigator.

Visit 1: Screening

- Attend the clinical research unit at 08:00-09:00
- Routine clinical examination

- ECG
- Non-fasting venous blood taken for HbA1c, creatinine, lipids
- Urine for albumin/creatinine ratio
- Urine pregnancy test in female subjects of childbearing age
- CHO counting and hypoglycaemia education revision by a qualified health care professional.
- The basal insulin dose will be reviewed and adjusted if needed.
- Continuous glucose monitor (CGM retrospective/blinded iPro2, Medtronic) placed in the anterior abdominal wall according to manufacturer's instructions. CGM sensor to be worn for 6 continuous days.
- Instructions to subjects to ensure:
    - Capillary blood glucose measurements fasting, pre-meals, post-meals and pre-bed.
    - Food record and physical activity record to be kept for 6 days. The subject will be provided with an ABC4D device and will be instructed to enter information about meals and physical activity directly in the ABC4D application. The insulin dose recommendation button will be disabled and subjects will be advised to use their normal insulin regimen.

Visit 2: CGM review and ABC4D start

- Attend 7 days following visit 1
- Remove CGM, upload data to the Medtronic Carelink iPro software, enter calibration data and review data with subject.
- Recalculate ISF and ICR after CGM and review of different types of carbohydrates.
- Initialize CBR algorithm case base with cases derived from the CGM data.
- Switch on the ABC4D device
- Instructions to subjects to ensure:
    - Capillary blood glucose measurements fasting, pre-meals, post-meals and pre-bed.
    - Accurate subject input of pre-meal capillary blood glucose, pre- or post-meal exercise (moderate or intense), type of meal absorption (fast, medium, slow), carbohydrate (CHO) amount (g) and insulin given if CBR algorithm advice not taken.
    - No correction boluses for 2 hours post-meal unless clinically indicated (CBG >15mM or ketosis)
- A detailed ABC4D user guide will be given to the subject
- CGM (retrospective/blinded iPro2, Medtronic) placed in the anterior abdominal wall according to manufacturer's instructions.
- 24-hour contact numbers for medical and technical enquires and support will be given to subjects.

Visits 3-7: Weekly download of CGM data and algorithm update

- Attend clinical research unit on day 7 following visit 2 and then day 14, 21, 28 and 35.
- Upload data from the smartphone ABC4D application to the desktop PC and store it in the corresponding folder.
- Remove CGM, upload data to Medtronic Carelink Pro software, enter calibration data. The CGM data will not be disclosed to the subject.

- Export uploaded CGM data to a text file (i.e. csv) and store it in the corresponding folder.
- Using the ABC4D PC application, update the CBR algorithm case base with the uploaded data from the CGM and the data from ABC4D smartphone application. The medical and engineering team will jointly approve the revised case base before being updated in the smartphone ABC4D application.
- New CGM (retrospective/blinded iPro2, Medtronic) placed in the anterior abdominal wall according to manufacturer's instructions.

Visit 8: Final visit at the end of 6 weeks
Attend clinical research unit
Remove CGM, upload data to Medtronic Carelink iPro software, enter calibration data.
Switch off ABC4D and return device
Acceptability questionnaire to be completed.

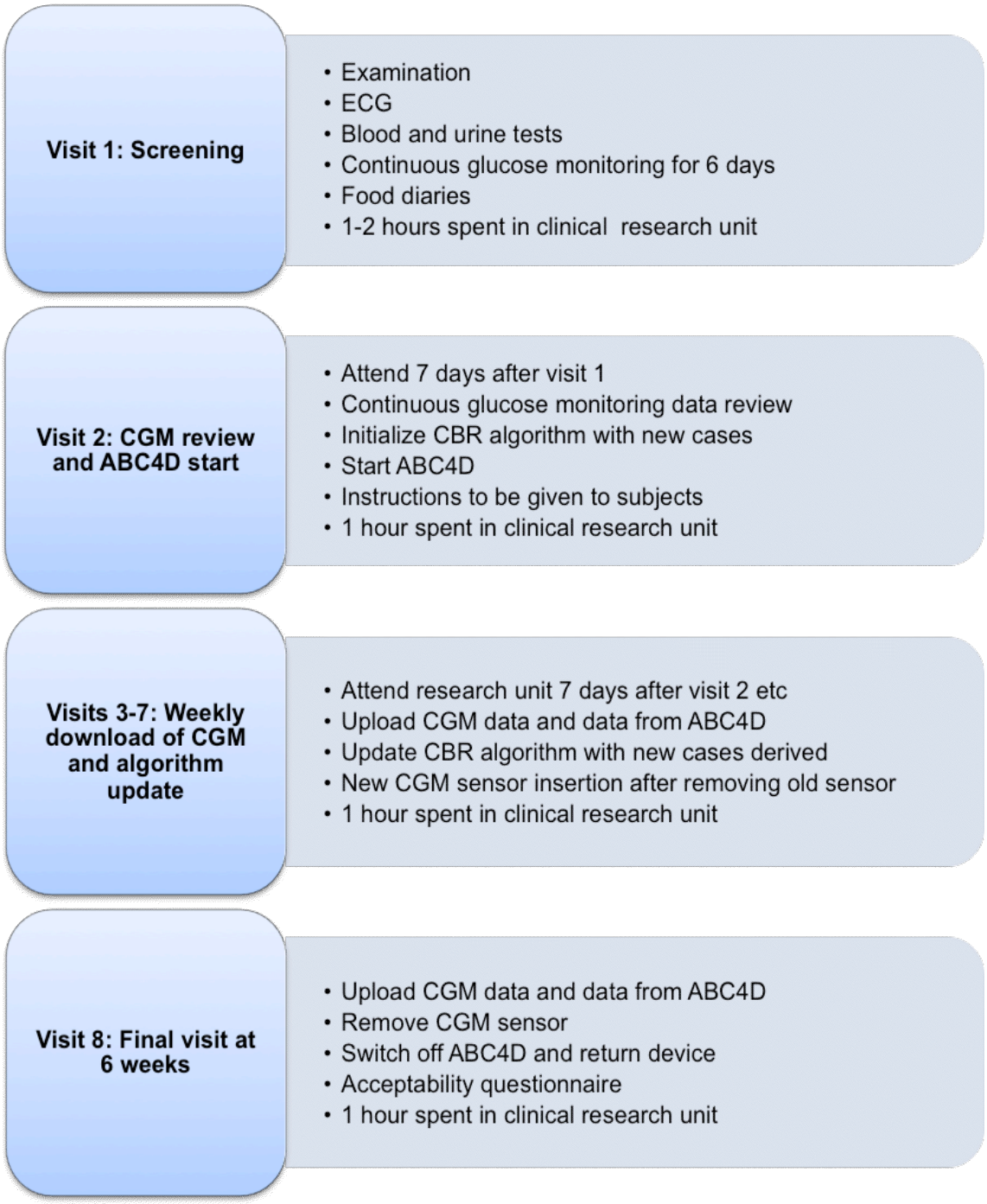
Usual care will be maintained for diabetes throughout the study. No concomitant medical therapies are contra-indicated, except GLP-1 analogues and gliptins. Support will be offered to any participants who have concerns about their diabetes management.

Subjects using the ABC4D will have the opportunity to call a physician for medical support and an engineer for technical support 24 hours a day throughout the study.

Statistics 20 subjects planned to be enrolled. This is not a randomised study and there are no comparison or control groups. Outcomes from the study are absolutes as described above. The sample size is comparable to other technology transfer studies, is a realistic number for recruitment and provides robust clinical validation and safety data. The study is not powered to show a change in the primary or secondary outcomes compared with usual care but is an assessment of a new technology.

Missing, unused, and spurious data will be assessed on an individual basis and may be ignored, withdrawn or the visit may be removed from the analysis with appropriate justification adjudicated by the Principal Investigator.

Phase 2 of ABC4D study: Summary of visits



Phase 3

Objective: To demonstrate efficacy of the ABC4D

Methodology Randomised open-label study

Primary outcome:

HbA1c at 6 months

Secondary outcomes:
HbA1c at 3 months
Post-prandial AUC at 4 hours and 6 hours
Post-prandial AUC (<3.9) at 4 hours and 6 hours
Episodes of hypoglycaemia within 4- and 6-hours post-prandially
% time in target glucose (3.9-10mmol/l)
% time in hypo- (<3.9mmol/l) and hyperglycaemia (>10mmol/l)
Glycaemic risk: LBGI and HBGI
Glycaemic variability: MAGE and CONGA-2
Change in weight (kg)
Number achieving target HbA1c (≤ 53 mmol/mol)
24-hours insulin dose requirements
PAID score questionnaire
DQOL questionnaire
DTSQ Questionnaire
Acceptability questionnaire (non-validated)

These are validated, published metrics.

Timescale: Each subject will be in the study for 6 months. It is anticipated that it will take 15 months to complete the 3rd phase.

Population: 142 subjects with T1DM, are required to demonstrate an HbA1c difference of 0.6% with α of 0.05 and 90% power (two-tailed). We aim to screen n=160 and randomise n=80 in each group. This power calculation is based on using a population mean HbA1c of 7.9% with a standard deviation of 1.1.

Subject inclusion criteria:
- Adults ≥18 years of age
- Diagnosis of T1DM for > 1 year
- On MDI using a basal-bolus insulin regime or continuous subcutaneous insulin infusion (insulin pump)
- Structured education
- HbA1c ≥ 48mmol/mol and ≤ 86mmol/mol
- No severe hypoglycaemia (defined as needing 3rd party assistance) in previous year

Subject exclusion criteria:
- Recurrent severe hypoglycaemia
- Pregnant or planning pregnancy
- Breastfeeding
- Enrolled in other clinical trials
- Have active malignancy or under investigation for malignancy
- Addison's Disease
- Gastroparesis
- Autonomic neuropathy

- Concomitant use of GLP-1 analogues, sodium-glucose co-transporter-2 (SGLT2) inhibitors and gliptins
- Visual impairment
- Reduced manual dexterity

Subject withdrawal criteria:

- Loss of capacity to give informed consent
- Cessation of MDI of insulin as usual care for T1DM
- Recurrent severe hypoglycaemia
- Terminal illness

Withdrawal will be immediate and subjects will be followed up in the appropriate out-patient diabetes clinic within 4 weeks of withdrawal

Recruitment

Recruiting will be undertaken in the diabetes clinics at Imperial College Healthcare NHS Trust, from registered research databases and from interested subjects who contact us. Participant information sheets will be given to potential subjects and, after a minimum of 48 hours and following any questions, informed consent will be taken.

Subjects who have already participated in phase 1 and/or 2 of the study can also be recruited for phase 3 and they will be re-consented. These subjects will not need re-screening, however they may need to repeat 1 week of CGM using iPRO2 for initializing of the ABC4D at the start of the Phase 3 study, this is at the discretion of the Principal Investigator.

Visit 1: Screening

- Attend the clinical research unit
- Routine clinical examination
- ECG
- Non-fasting venous blood taken for HbA1c, creatinine, lipids.
- Urine for albumin/creatinine ratio
- Urine pregnancy test in female subjects of childbearing age
- CHO counting and hypoglycaemia education revision by a qualified health care professional.
- The basal insulin dose will be reviewed and adjusted if needed.
- Questionnaires to be completed
- Continuous glucose monitor (CGM retrospective/blinded iPro2, Medtronic or Dexcom) placed in the anterior abdominal wall according to manufacturer's instructions. CGM sensor to be worn for 6-7 continuous days.
- Instructions to subjects to ensure:
    - Capillary blood glucose measurements fasting, pre-meals, post-meals and pre-bed.
    - Food diaries and physical activity record to be kept for 6 days

Randomisation

Subjects who fit the inclusion criteria will be randomized to either ABC4D (intervention group) or standard care (control group) in a 1:1 ratio

Standard care is defined as the bolus wizard within insulin pumps, bolus calculator in glucose meter or the ABC4D app as a standard bolus calculator (without CBR adaptation)

Intervention group:

Intervention: ABC4D for 6 months

Visit 2: CGM review and ABC4D start

- Attend 7 days following visit 1
- Remove CGM, upload data to Medtronic Carelink Pro software or DiaSend/Dexcom Studio, enter and review data with subject.
- Recalculate ISF and ICR after CGM and review of different types of carbohydrates.
- Initialize CBR algorithm case base with cases derived from the CGM data and diary.
- Switch on the ABC4D device
- Instructions to subjects to ensure:
    - Capillary blood glucose measurements fasting, pre-meals, post-meals and pre-bed.
    - Accurate subject input of pre-meal capillary blood glucose, pre- or post-meal exercise (moderate or intense), type of meal absorption (fast, medium, slow), carbohydrate (CHO) amount (g) and insulin given if CBR algorithm advice not taken
    - No correction boluses for 2 hours post-meal unless clinically indicated (CBG >15mM or ketosis)
- A detailed ABC4D user guide will be given to the subject
- CGM (blinded iPro2, Medtronic or Dexcom) placed in the anterior abdominal wall according to manufacturer's instructions.

Visits 3-6: Weekly CGM and update of CBR algorithm

- Attend clinical research unit on day 7 following visit 2 and then day 14, 21 and 28.
- Upload data from the smartphone ABC4D application to the desktop PC and store it in the corresponding folder.
- Remove CGM, upload data to Medtronic Carelink Pro software or DiaSend/Dexcom Studio.The CGM data will not be disclosed to the subject.
- Export uploaded CGM data to a text file (i.e. csv) and store it in the corresponding folder.
- Using the ABC4D PC application, update the CBR algorithm case base with the uploaded data from the CGM and the data from ABC4D smartphone application. The algorithm update with new cases will be an automatic process without the research team approving each case.
- New CGM (blinded iPro2, Medtronic or Dexcom) placed in the anterior abdominal wall according to manufacturer's instructions.

Visits 7-16: Monthly CGM and update of CBR algorithm

- Blinded CGM for the last 6 days of every month for the remaining 5 months of the study

- Subject to attend the clinical research unit for insertion of the sensor at the start of blinded CGM and for upload of CGM data and update of CBR algorithm with new cases 7 days later**:**

  Visits 7, 9, 11, 13, 15:
  - Attend clinical research unit at start of week 8, 12, 16, 20 and 24 of the study
  - New CGM (blinded iPro2, Medtronic or Dexcom) placed in the anterior abdominal wall according to manufacturer's instructions.
  - All subjects will be offered the opportunity to insert the CGM themselves at home, with appropriate training, rather than attending the clinical research unit for these visits (visits 7, 9, 11, 13, 15)

  Visit 8, 10, 12, 14, 16:
  - Attend clinical research unit at end of week 8 (7 days after insertion of CGM), 12, 16, 20 and 24 of the study
  - Upload data from the smartphone ABC4D application to the desktop PC and store it in the corresponding folder.
  - Remove CGM, upload data to Medtronic Carelink Pro software or DiaSend/Dexcom Studio. The CGM data will not be disclosed to the subject.
  - Export uploaded CGM data to a text file (i.e. csv) and store it in the corresponding folder.
  - Using the ABC4D PC application, update the CBR algorithm case base with the uploaded data from the CGM and the data from ABC4D smartphone application. The algorithm update with new cases will be an automatic process without the research team approving each case.

Clinical review at 1 month, 3 months and 6 months:

Review at 1 month (coincides with visit 6):
- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.

Review at 3 months (coincides with visit 10):
- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.
- Random venous blood taken for HbA1c
- Weight (kg)

Review at 6 months (coincides with visit 16):
- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.
- Random venous blood taken for HbA1c
- Weight (kg)
- PAID score, DQOL, DTSQ and acceptability questionnaires to be completed

Control group:

Intervention: Standard care for 6 months

Visit 2: CGM review and ABC4D start

- Attend 7 days following visit 1
- Remove CGM, upload data to Medtronic Carelink Pro software or DiaSend/Dexcom Studio and review data with subject.
- Recalculate ISF and ICR after CGM and review of different types of carbohydrates.

Visits 3-8: CGM at 1, 3 and 6 months

Visits 3, 5, and 7:

- Attend clinical research unit at start of week 4, 12 and 24 of the study
- New CGM (retrospective/blinded iPro2, Medtronic or Dexcom) placed in the anterior abdominal wall according to manufacturer's instructions.

Visits 4, 6 and 8:

- Attend clinical research unit at end of week 4 (7 days after insertion of CGM), 12 and 24 of the study.
- Remove CGM, upload data to Medtronic Carelink Pro software or DiaSend/Dexcom Studio. The CGM data will not be disclosed to the subject.

Clinical review at 1 month, 3 months and 6 months:

Review at 1 month (coincides with visit 4):

- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.

Review at 3 months (coincides with visit 6):

- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.
- Random venous blood taken for HbA1c
- Weight (kg)

Review at 6 months (coincides with visit 8):

- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.
- Random venous blood taken for HbA1c
- Weight (kg)
- PAID score, DQOL and DTSQ questionnaires to be completed

Usual care will be maintained for diabetes throughout the study. No concomitant medical therapies are contra-indicated, except GLP-1 analogues, SLGT2 inhibitors and gliptins. Support will be offered to any participants who have concerns about their diabetes management.

Subjects in the intervention group using the ABC4D will have the opportunity to call a physician for medical support and an engineer for technical support 24 hours a day throughout the study.

Statistics This is a randomised study with an intervention group and a control group. Outcomes from the study are absolutes as described above.142 subjects with T1DM, are required to demonstrate an HbA1c difference of 0.6% with α of 0.05 and 90% power (two-tailed). We aim to screen n=160 and randomise n=80 in each group. This power calculation is based on using a population mean HbA1c of 7.9% with a standard deviation of 1.1.
The sample size is comparable to other technology transfer studies, is a realistic number for recruitment and provides robust clinical validation and safety date of a new technology.

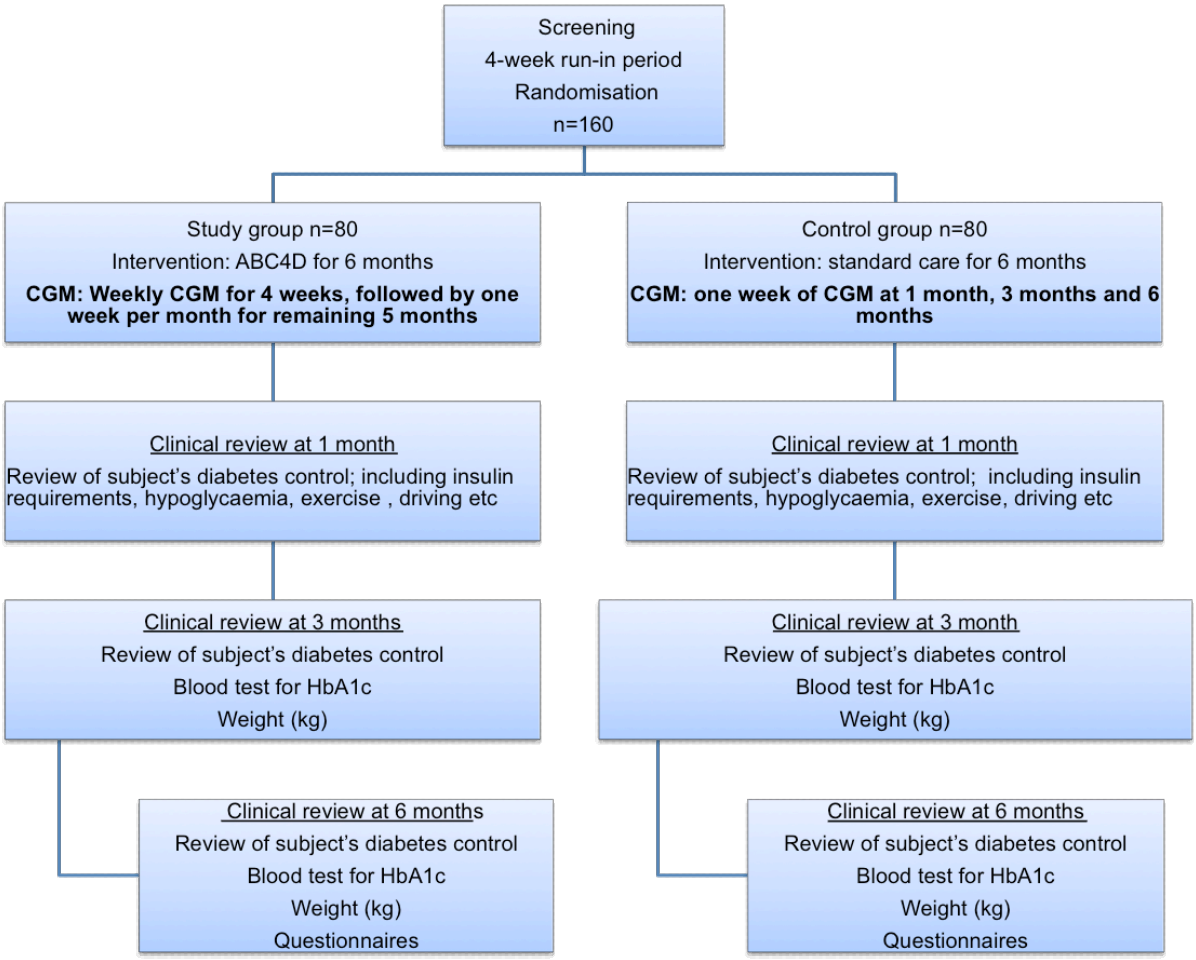
Missing, unused, and spurious data will be assessed on an individual basis and may be ignored, withdrawn or the visit may be removed from the analysis with appropriate justification adjudicated by the Principal Investigator.

Table: Overview of activities at each visit for subjects in the intervention group

Activity / Visit no	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Insertion of CGM sensor	x	x	x	x	x		x		x		x		x		x	
Removal of CGM sensor		x	x	x	x	x		x		x		x		x		x
Food diary	x															
CGM review with subject		x														
Initialise CBR algorithm and ABC4D start		x														
Upload and synchronise CGM data and data from ABC4D application			x	x	x	x	x	x		x		x		x		x
Update CBR algorithm with new cases			x	x	x	x		x		x		x		x		
Clinical examination	x															
Weight measurement	x									x						x
Venous blood test	x									x						x
Urine test	x															
Pregnancy test	x															
ECG	x															

Questionnaire/s	x															x
Follow-up clinical review						x				x						x

Phase 3 of ABC4D study: Overview of study



Phase 4

Objective: To demonstrate efficacy of the ABC4D with real-time CGM (RT-CGM) compared to standard care with RT-CGM

Standard care is defined as the bolus wizard within insulin pumps, bolus calculator in glucose meter or the ABC4D app as a standard bolus calculator (i.e no CBR adaptation).

Methodology Randomised open-label study

Primary outcome:
HbA1c at 6 months

Secondary outcomes:

HbA1c at 3 months
Post-prandial AUC at 4 hours and 6 hours
Post-prandial AUC (<3.9) at 4 hours and 6 hours
Episodes of hypoglycaemia within 4- and 6-hours post-prandially
% time in target glucose (3.9-10mmol/l)
% time in hypo- (<3.9mmol/l) and hyperglycaemia (>10mmol/l)
Glycaemic risk: LBGI and HBGI
Glycaemic variability: MAGE and CONGA-2
Change in weight (kg)
Number achieving target HbA1c (≤ 53 mmol/mol)
24-hours insulin dose requirements
PAID score questionnaire
DQOL questionnaire
DTSQ Questionnaire
Acceptability questionnaire (non-validated)

These are validated, published metrics.

***Timescale*:** Each subject will be in the study for 6 months. It is anticipated that it will take 15 months to complete the 4th phase.

Population: 142 subjects with T1DM, are required to demonstrate an HbA1c difference of 0.6% with α of 0.05 and 90% power (two-tailed). We aim to screen n=180 and randomise n=90 in each group. This power calculation is based on using a population mean HbA1c of 7.9% with a standard deviation of 1.1.

The first 25 participants will be randomised to either the ABC4D running in semi-automatic mode (where the revisions are done using a semi-automatic process-see page 23) or a standard bolus calculator. The remaining participants will be randomised to either the fully automated ABC4D (where revisions are fully automated) or a standard bolus calculator. Screening 180 participants will ensure that at least 142 participants are included to enable demonstration of a significant difference between the fully automated ABC4D system and a standard bolus calculator.

***Subject inclusion criteria*:**

- Adults ≥18 years of age
- Diagnosis of T1DM for > 1 year
- On MDI using a basal-bolus insulin regime or continuous subcutaneous insulin infusion (insulin pump)
- Structured education done
- HbA1c ≥ 48mmol/mol and ≤ 86mmol/mol
- No severe hypoglycaemia (defined as needing 3rd party assistance) in previous year

Subject exclusion criteria:

- Recurrent severe hypoglycaemia
- Pregnant or planning pregnancy

- Breastfeeding
- Enrolled in other clinical trials
- Have active malignancy or under investigation for malignancy
- Addison's Disease
- Gastroparesis
- Autonomic neuropathy
- Concomitant use of GLP-1 analogues, SLGT2 inhibitors and gliptins
- Visual impairment
- Reduced manual dexterity

Subject withdrawal criteria:

- Loss of capacity to give informed consent
- Cessation of MDI of insulin as usual care for T1DM
- Recurrent severe hypoglycaemia
- Terminal illness

Withdrawal will be immediate and subjects will be followed up in the appropriate out-patient diabetes clinic within 4 weeks of withdrawal

Recruitment

Recruiting will be undertaken in the diabetes clinics at Imperial College Healthcare NHS Trust, from registered research databases and from interested subjects who contact us. Participant information sheets will be given to potential subjects and, after a minimum of 48 hours and following any questions, informed consent will be taken.

Subjects who have already participated in phase 1 and/or 2 of the study can also be recruited for phase 4 and they will be re-screened and re-consented.

Visit 1: Screening

- Attend the clinical research unit
- Routine clinical examination
- ECG
- Non-fasting venous blood taken for HbA1c, creatinine, lipids.
- Urine for albumin/creatinine ratio
- Urine pregnancy test in female subjects of childbearing age
- CHO counting and hypoglycaemia education revision by a qualified health care professional.
- The basal insulin dose, insulin:carbohydrate ratio (ICR) and insulin sensitivity factor (ISF) will be reviewed and adjusted if needed.
- PAID score, DQOL and DTSQ questionnaire to be completed
- Real-time continuous glucose monitor (Dexcom) placed in the anterior abdominal wall according to manufacturer's instructions.
- Subjects will be shown how to insert the sensor themselves, interpret the CGM data in real time and to set the hypo- and hyperglycaemia threshold alarms. The alarm threshold will be set at 4mmol/l and 11mmol/l and subjects will be encouraged to keep it at those levels and not to reduce the hypoglycaemia threshold below 3.3mmol/L).
- Subjects to complete a 4-week run-in period using RT-CGM (Dexcom) to familiarize themselves with the RT-CGM and for optimization of treatment prior to study start
- Instructions to subjects to ensure:

- Capillary blood glucose measurements fasting, pre-meals and pre-bed.
- Calibration of the CGM every 12 hours and sensor change every 7 days as per manufacturer's instructions (a copy will be given to subjects)
- Food diaries and physical activity record to be kept for the 4-week run-in period

Randomisation

Subjects who fit the inclusion criteria will be randomized to either ABC4D (intervention group) or standard care (control group) in a 1:1 ratio. Both groups will be using RT-CGM.

Standard care is defined as the bolus wizard within insulin pumps, bolus calculator in glucose meter or the ABC4D app as a standard bolus calculator (without CBR adaptation).

Intervention group:

Intervention: ABC4D with RT-CGM for 6 months

Visit 2: CGM review and intervention study start

- Attend 4 weeks after visit 1
- Remove CGM, upload data to DiaSend/Dexcom Studio software (subject can do upload the data at home prior to attending the visit) and review data with subject.
- Adjust ICR, ISF and basal rates if deemed necessary based on CGM data.
- Initialize CBR algorithm case base with 3 standard cases (breakfast, lunch and dinner) using subjects existing ICR
- Switch on the ABC4D device
- Instructions to subjects to ensure:
  - Capillary blood glucose measurements fasting, pre-meals and pre-bed.
  - Accurate subject input of pre-meal capillary blood glucose, carbohydrate (CHO) amount (g), alcohol (none/<2units/>2units), pre- or post-meal exercise (none/moderate/intense), type of meal absorption (fast/medium/slow), illness (yes/no), stress (none/mild/severe), menstrual cycle and insulin given if CBR algorithm advice not taken
  - Calibration of the CGM every 12 hours and sensor change every 7 days as per manufacturer's instructions
  - No correction boluses for 2 hours post-meal unless clinically indicated (CBG >15mM or ketosis)
- A detailed ABC4D user guide will be given to the subject

Follow-up clinic visits at 1 month, 3 months and 6 months:

Visit 3

Review at 1 month:

- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.

Visit 4

Review at 3 months:

- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.
- Random venous blood taken for HbA1c
- Weight (kg)

Visit 5

Review at 6 months:

- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.
- Random venous blood taken for HbA1c
- Weight (kg)
- Questionnaires to be completed

ABC4D case base revision and adaptation

The ABC4D case base will be revised every two weeks throughout the study and this will be a semi-automatic process for the first 25 participants entered into the study if allocated to the intervention group. For the remaining 155 participants, if allocated to the intervention group, the revisions will be fully automated requiring minimal manual input. The adaptation summary will be approved and the case-base updated by the study team. This provides remote supervision and prevents any potential system faults despite safety measures. The subjects will not need to attend the clinical research unit for the ABC4D revisions.

Control group:

Intervention: Standard care for 6 months

Visit 2: CGM review and control study start

- Attend 4 weeks after visit 1
- Remove CGM, upload data to DiaSend/Dexcom Studio software (subject can do upload the data at home prior to attending the visit) and review data with subject.
- Adjust ICR, ISF and basal rates if deemed necessary based on CGM data.

Follow-up clinic visits at 1 month, 3 months and 6 months:

Visit 3

Review at 1 month:

- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.

Visit 4

Review at 3 months:

- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.
- Random venous blood taken for HbA1c
- Weight (kg)

Visit 5

Review at 6 months:

- Review of subject's diabetes control including insulin requirements, incidence of hypoglycaemia, exercise, driving etc.
- Random venous blood taken for HbA1c
- Weight (kg)
- PAID score questionnaire and acceptability questionnaire to be completed

Usual care will be maintained for diabetes throughout the study. No concomitant medical therapies are contra-indicated, except GLP-1 analogues, SLGT2 inhibitors and gliptins. Support will be offered to any participants who have concerns about their diabetes management.

Subjects in the intervention group using the ABC4D will have the opportunity to call a physician for medical support and an engineer for technical support 24 hours a day throughout the study.

Statistics This is a randomised study with an intervention group and a control group. Outcomes from the study are absolutes as described above.142 subjects with T1DM, are required to demonstrate an HbA1c difference of 0.6% with α of 0.05 and 90% power (two-tailed). We aim to screen n=160 and randomise n=80 in each group. This power calculation is based on using a population mean HbA1c of 7.9% with a standard deviation of 1.1.
The sample size is comparable to other technology transfer studies, is a realistic number for recruitment and provides robust clinical validation and safety date of a new technology.

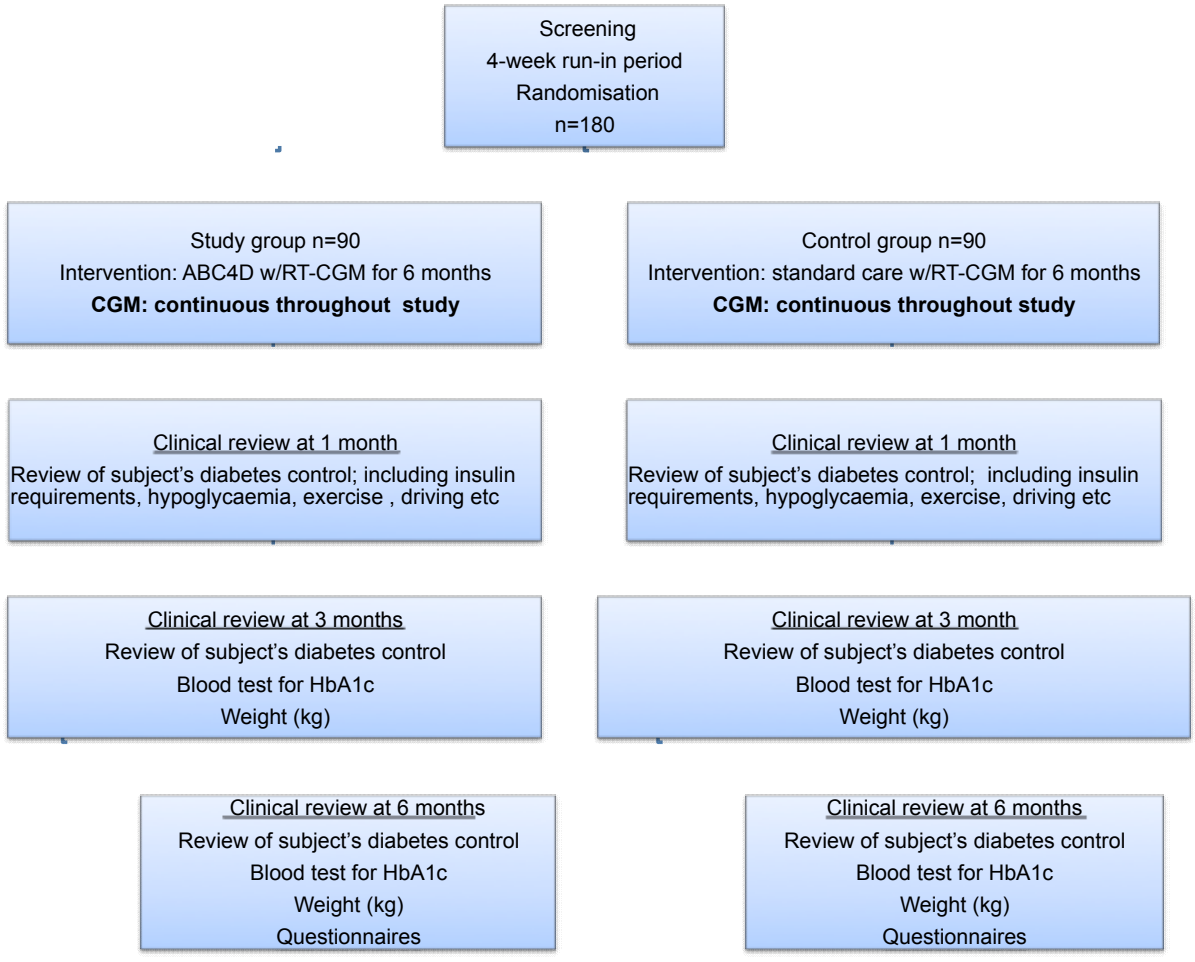
Missing, unused, and spurious data will be assessed on an individual basis and may be ignored, withdrawn or the visit may be removed from the analysis with appropriate justification adjudicated by the Principal Investigator.

Table: Overview of activities at each visit for subjects in the intervention group

Activity / Visit no	1	2	3	4	5	Additional information
Insertion of CGM sensor	x					Subjects will change the sensor every week at home throughout the study (24 weeks
Removal of CGM sensor						x
Food diary	x					
CGM review with subject		x				
Initialise CBR algorithm and ABC4D start		x				
Update CBR algorithm with new cases						This will be done automatically with remote supervision every 1 week throughout the study

Clinical examination	x					
Weight measurement	x			x	x	
Venous blood test	x			x	x	
Urine test	x					
Pregnancy test	x					
ECG	x					
Questionnaire/s	x					
Follow-up clinical review		x	x	x	x	

Phase 4 of ABC4D study: Overview of study



The following information applies to all four phases of the study:

Potential risks and benefits
The potential risks and burdens for research participants are as follows:

At the beginning of each phase of the study there is a venous blood test and in addition the 1st phase includes insertion of an intravenous cannula. These have the potential to cause discomfort. This will be minimised by experienced research personnel and appropriate use of equipment.

During the studies, subjects will have a subcutaneous CGM sensor inserted. Sensor insertion can be associated with some discomfort but the insertion devices are spring-loaded with introducers, making the process rapid and often painless. Any discomfort will be minimised by adhering to manufacturer's instructions.

During the time subjects are using the ABC4D there is a risk from the new technology. The ABC4D may suggest an insulin dose too high or too low potentially resulting in hypo- or hyperglycaemia. In the Phase 1 study subjects are closely monitored in a controlled supervised environment to ensure safety of the ABC4D. In addition, subjects will be given contact phone numbers to call a physician for medical support and an engineer for technical support 24 hours a day throughout phase 2 and 3 of the study.

Insulin will be administered subcutaneously by the subject as per their usual basal-bolus insulin regime. The subcutaneous route is the standard route of insulin administration in T1DM irrespective of whether they are on MDI or pump therapy.

It is acknowledged that the clinical schedule is demanding of subject's time and includes frequent visits to the clinical research unit. This inconvenience is necessary to adequately and safely validate the device. We will minimise the burden as much as possible by making every effort to schedule visits around subject's lifestyles, and by being flexible with attendances at the St Mary's, Charing Cross or Hammersmith campuses of Imperial College Healthcare NHS Trust.

Research participants will benefit from being in the study by having increased access to diabetes professionals and more frequent visits to hospital with an emphasis on improved glycaemic control. They will also have the opportunity to use continuous glucose monitoring and review the results with a diabetologist experienced with monitoring. The benefits to people with T1DM include the potential to carry forward technology to improve the risks of high glucose concentration leading to complications and distressing low glucose values.

Data During the course of the study visits some data will be stored on laptop computers, not connected to the Internet, for later statistical analysis. These data will be coded and non identifiable. Participant data will be stored in a locked filing cabinet in a secure room in Imperial College Healthcare NHS Trust. Only the research team will have access to the filing cabinet.
Electronic data will be stored by subject number only on NHS desktop computers which are in the same locked room. Only the research fellow and nurse will have access to the data.

Laptop computers may be used during the visits for portability and convenience. At the end of each visit the anonymised data will be transferred immediately to the secure NHS computers and will be deleted from the laptop. Access to NHS computers is only by members of NHS staff with appropriate login privileges.
All data will be stored in an anonymised form by using study numbers for identification of participants. The NHS code of confidentiality will be followed and all activity will meet the requirements of the data protection act.
Only members of the clinical research team and those responsible for direct care will have access to subjects' data during the study. The data generated by the study will be analysed by the research team including the engineering team from Imperial College. The analysis will be on anonymised data and will take place in Imperial College Healthcare NHS Trust and in Imperial College academic buildings, both in the Faculty of Medicine and in the Faculty of Engineering.
Fully anonymised glucose, insulin and carbohydrate data, along with the ABC4D parameters (including time, day, exercise, alcohol, menstrual cycle) may be shared with collaborators including Dexcom to support further development

For phase 3 and 4 of the study a data monitoring committee will be convened to assess the data collected throughout the study. This committee will comprise of the PI (Dr Oliver), Prof Johnston, Dr Reddy, a lay member, an independent diabetologist and an independent scientist and will meet twice a month.

Safety During intercurrent illness, subject visits will be postponed as insulin requirements will be altered. Adverse events will be reported to the REC, the sponsor and the Principal Investigator immediately. Full reports will be submitted through the Imperial College Healthcare Datix system. Subjects will be followed-up after one week following an adverse event and thereafter in the diabetes clinic or any other clinically indicated follow up.

Direct Access to Source Data/Documents The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

Regulatory Issues

Ethics Approval The Chief Investigator has obtained approval from the London-Chelsea Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Consent Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in

the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Confidentiality The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Indemnity Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Sponsor Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

Funding This study is being funded by the Biomedical Research Council.

Audits The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

Study Management The day-to-day management of the study will be co-ordinated byDr Nick Oliver. Weekly research meetings and monthly data reviews will be chaired by the chief investigator or other senior researcher. Annual reports to the funder and sponsor will be written and submitted. The management team will meet at the conclusion of each phase of the study to review data and ensure that no events have occurred requiring progression to the study to be halted. The management team will meet again prior to commencing the next phase to ensure appropriate action is taken to mitigate risk of further events. The management team includes a lay member with diabetes and a consultant diabetologist not involved with the study.

Publication Policy The study will be registered on the clinicaltrials.gov system and results will be disseminated by peer reviewed scientific journals, internal report, conference presentation and publication on websites. No identifiable personal data will be published. All anthropometry and personal clinical data will be expressed as mean/ median and spread of the population in the study. All participants will be informed of the results by letter at the conclusion of the study and details of any publications that arise from the study will be disseminated to participants.

References

1. Diabetes in the UK 2012: Key statistics on diabetes http://www.diabetes.org.uk/Documents/Reports/Diabetes-in-the-UK-2012.pdf

2. Pickup J. Insulin-pump therapy for Type 1 Diabetes Mellitus. N Engl J Med 2012; 366: 1616-24.

3. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008; 359: 1464-76

4. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Bode B, Beck RW, Xing D, Gilliam L et al. Sustained benefit of continuous glucose monitoring on A1C, glucose profiles, and hypoglycemia in adults with type 1 diabetes. Diabetes Care 2009; 32: 2047-9

5. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New Engl J Med 1993; 329: 977 – 986

6. Buckingham B, Wilson DM, Lecher T, Hanas R, Kaiserman K, Cameron F. Duration of nocturnal hypoglycemia before seizures. Diabetes Care 2008; 31: 2110-2112

7. Sovik O, Thordarson H. Dead-in-bed syndrome in young diabetic patients. Diabetes Care 1999; 22(Suppl 2): B40-42

8. CG15 Type 1 diabetes in children, young people and adults: NICE guideline. Online access: http://guidance.nice.org.uk/CG15/NICEGuidance

9. Howard Zisser, Lauren Robinson, Wendy Bevier, Eyal Dassau, Christian Ellingsen, Francis J Doyle, and Lois Jovanovic. Bolus calculator: a review of four ”smart” insulin pumps. Diabetes Technol Ther 2008, 10(6):441–444

10. Aamodt A and Plaza E. Case-based reasoning: foundational issues, methodological variations, and system approaches. AI Communications 1994, 7(1):39–59

11. Kovatchev BP, Breton M, Man DM, Cobelli C. In silico preclinical trials: a proof of concept in closed-loop control f type 1 diabetes. Diabetes Sci Tech 2009; 3: 44-55