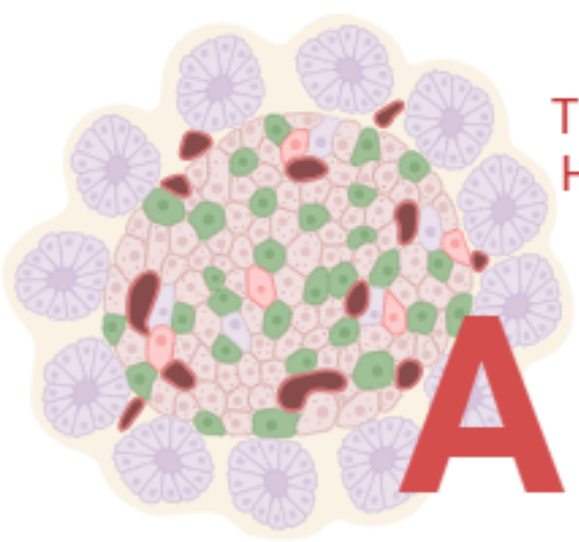


ANIRACETAM FOR THE PREVENTION OF HYPOGLYCAEMIA IN TYPE 1 DIABETES

APH1D

Participant Information Booklet

accord

Academic and Clinical Central Office for Research and Development

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

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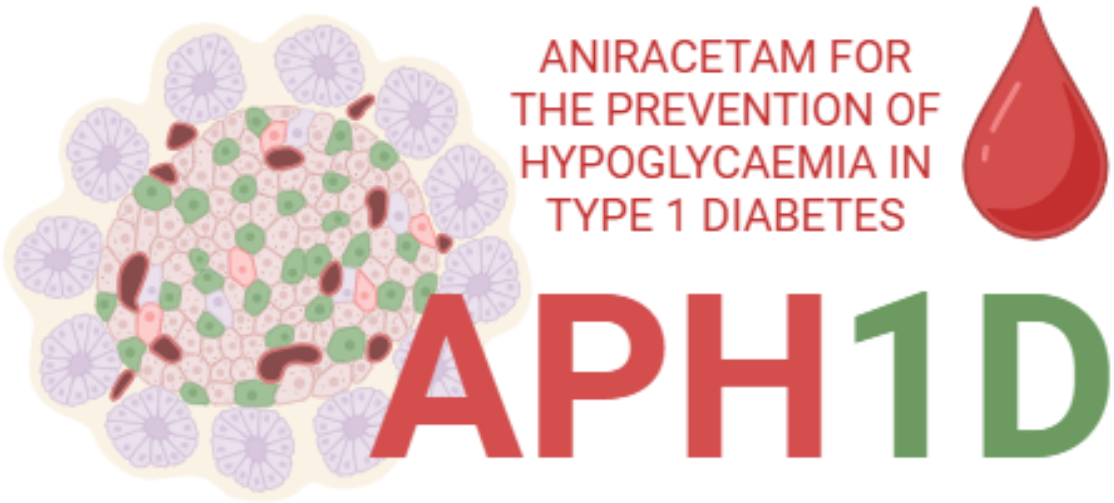
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Aniracetam for the Prevention of Hypoglycaemia in Type 1 Diabetes

Welcome to the APH1D Study!

This booklet is designed to help you navigate taking part in the APH1D study. It contains key information, dates and times, as well as how to contact the research team if you have any questions.



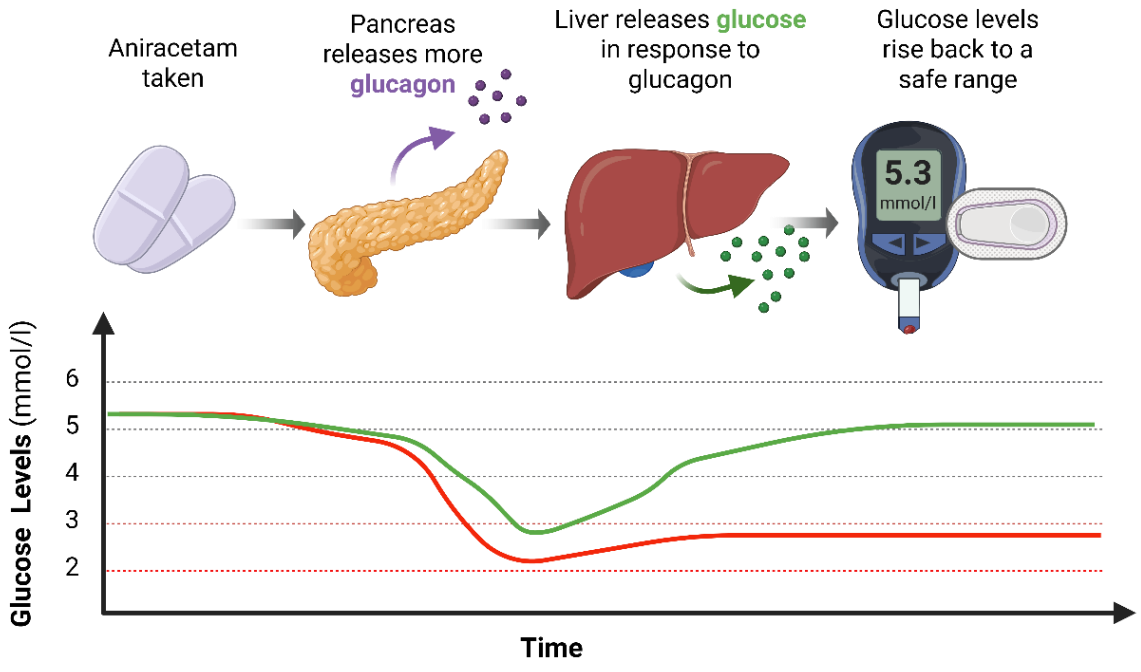
To help you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the information in this booklet carefully. Talk to others about the study if you wish. Contact us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

This is the first study of its kind in people with Type 1 Diabetes. We are going to test whether a drug supplement called Aniracetam can help prevent hypoglycaemia in Type 1 Diabetes and are recruiting adults with Type 1 Diabetes from Edinburgh and the surrounding areas to assist with this research.

Low blood sugar (hypoglycaemia) is a common problem for people with type 1 diabetes who use insulin. It can be dangerous, affect daily life, and is often hard to prevent. Current treatments (like taking quick acting sugar tablets or injectable glucagon) only work once a “hypo” has already started.

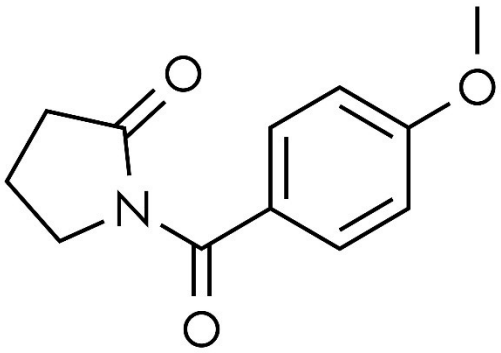
Hypoglycaemia is a big challenge and affects the quality of life for people who take insulin, their loved ones and also has high healthcare costs. We are trying to develop a new treatment that can stop people becoming hypoglycaemic in the first place, as shown below:



The red line shows what currently can happen when someone develops a low blood sugar. The green line shows how we think Aniracetam may work to prevent this from happening.

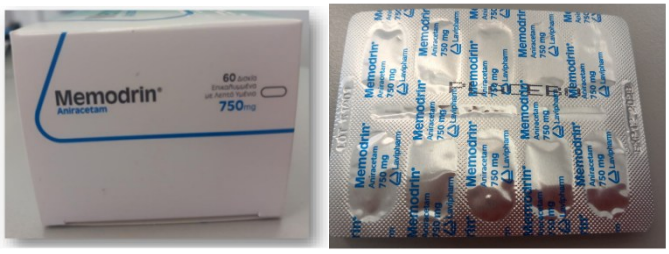
What is Aniracetam?

This research is an “exploratory physiological” study. This means that we are testing whether a supplement called **Aniracetam** (pictured below) can help the body cope better with low blood sugar.



Aniracetam is authorised for use in Europe under the brand name Memodrin™. The European Medicines Agency (EMA) have licensed it for use across Europe as a supplement to treat different types of dementia and similar diseases. It is not currently available in the UK but has an excellent safety record and has been a prescribed medication for over thirty years.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



No one has ever studied Aniracetam before in the field of diabetes. Aniracetam has an excellent safety record. You will only take it once during the study – at a standard dose of two 750 mg tablets (1500 mg).

Participation FAQs:

Why have I been invited?

If you were recruited from Diabetes clinic, you may have read our recruitment flyer as you or your diabetes doctor believes you may be eligible for the study. You may have previously indicated an interest in taking part in diabetes research studies and/or listed your details on the Diabetes Research Register.

Who can take part?

- ☐ You are between 21 and 65 years old
- ☐ You have had Type 1 Diabetes for at least 5 years
- ☐ Your blood tests show no detectable insulin production

Do I have to take part?

No. Taking part in the study is your choice. If you do take part, you can change your mind and stop at any time without giving a reason. This will not affect the care you receive, or your legal rights.

Who cannot take part?

You would not be able to take part in the study if any of the following apply:

- ☐ You have certain diabetes complications, such as proliferative retinopathy or maculopathy (serious eye disease) which require current treatment.
- ☐ You have had diabetic ketoacidosis (DKA) or an episode of severe hypoglycaemia needing help from someone else in the past six months
- ☐ Your glucose monitor shows too much time spent with low blood sugar in the two weeks before your first visit (we aim for 4% time spent below range or lower)
- ☐ You have heart disease, heart rhythm problems, previous stroke, epilepsy, seizures with low blood sugar, haemophilia, phenylketonuria, cystic fibrosis, or past pancreatic disease/surgery

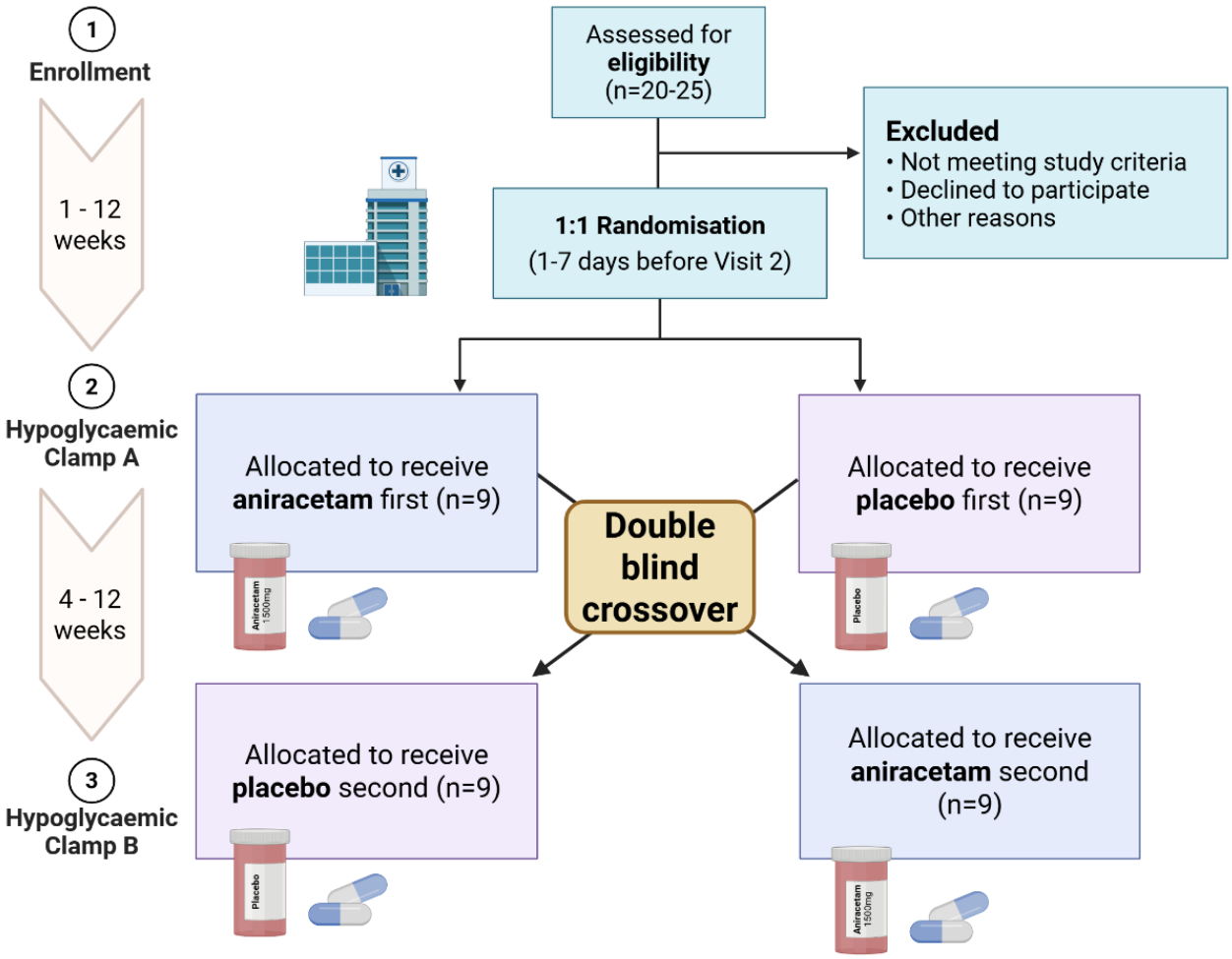
- ☐ You are pregnant, planning pregnancy, or unable to use reliable contraception in order to prevent becoming pregnant during the study
- ☐ You take other diabetes medicines (besides insulin) or certain other long-term medicines that affect blood sugar (e.g. SSRIs), and these cannot be paused safely
- ☐ You have untreated hypothyroidism
- ☐ You are unable to follow the study timetable, give informed consent, or speak English well enough for safe communication during the experimental procedure
- ☐ You plan to donate blood regularly around the study period – we ask that people do not donate blood for at least 12 weeks (if male) and 16 weeks (if female) before the two clamp experiments are completed.

It is possible that a study visit may need to be postponed. For example, in the event of illness or a medication change during the experimentation period. If a postponement is needed, the study team will coordinate with you.

If you are a woman and become pregnant during the study, please contact the study team immediately.

Study Visit Overview

The APH1D study involves **three** visits to the Clinical Research Facility at Edinburgh Royal Infirmary Hospital. Below is a picture of how the study is designed:



Visit 1 - Enrolment & Consent:

- ☐ Meet the team
- ☐ Ask questions
- ☐ If you wish to proceed, sign a consent form.

This visit then involves

- A full medical assessment
- Routine blood tests similar to those you would get in clinic
- An ECG
- A specialist test called an “Arginine Stimulation Test”

Visits 2 and 3 - Hypoglycaemic Clamp Experiments:

These experiments are explained in more detail later on in this booklet.

- ☐ Briefly, we use insulin and glucose delivered through a drip, to gently lower your blood sugar
- ☐ We can use this drip to then then keep your blood sugar fixed (or “clamped”) at a hypoglycaemia (low) level of 2.5 mmol/l for 1-1.5 hours.
- ☐ During hypoglycaemia, you are given two tablets to take which will either be aniracetam or placebo (neither you nor the investigators will know which).

The study doctor will also explain these experiments to you at Visit 1 and answer any questions that you have.

Visit 1: Enrolment and Consent (1-2 hours)

Purpose: To understand if you can take part in the rest of the study

Before the visit:

- Phone / text to arrange a morning visit (1-7 days ahead of time)
- Fast for 8 hours before the visit (you can take water during this time)
- Bring a list of your medications and insulin doses
- Make sure you have uploaded to Glooko (if using a pump) or Libreview / Clarity (if using insulin pens and a glucose sensor)
- Bring a morning urine sample if possible
- We may also ask you to adjust your basal/ background insulin

What will happen during the visit?

- Arrive for visit in the morning (8-11am) and meet the investigators
- Discuss your participation in the study, and if agree to continue, sign the consent form to participate in the study and allow our team to access your medical records
- Questions about your medical history & physical exam from the doctor
- Basic medical tests (blood pressure, weight), blood tests and urine test
- Eye test (if not done in the last year)
- Injection of arginine into a vein (a medication which stimulates your insulin) & 4 blood tests
- ECG (sticky patches attached to chest to test heart rhythm)

After the visit: A late breakfast of tea/toast. Home & follow up phone call from investigators 1-4 weeks later to confirm eligibility and next visit(s)

Visits 2 and 3: Hypoglycaemic Clamp Experiments (4-6 hours)

Purpose: To find out if Aniracetam increases hormone release during hypoglycaemia in people with type 1 diabetes

Before the visit:

- Phone call / text 1-7 days beforehand to confirm the visit
- No food or drinks (water only) from 11pm the night before
- No alcohol or exercise for 48 hours (2 days) before the visit
- No caffeine (tea, coffee, energy drinks, etc) for 12 hours (1/2 day) before the visit
- Avoid hypoglycaemia for longer than 20 minutes in the 48 hours (2 days) before the study

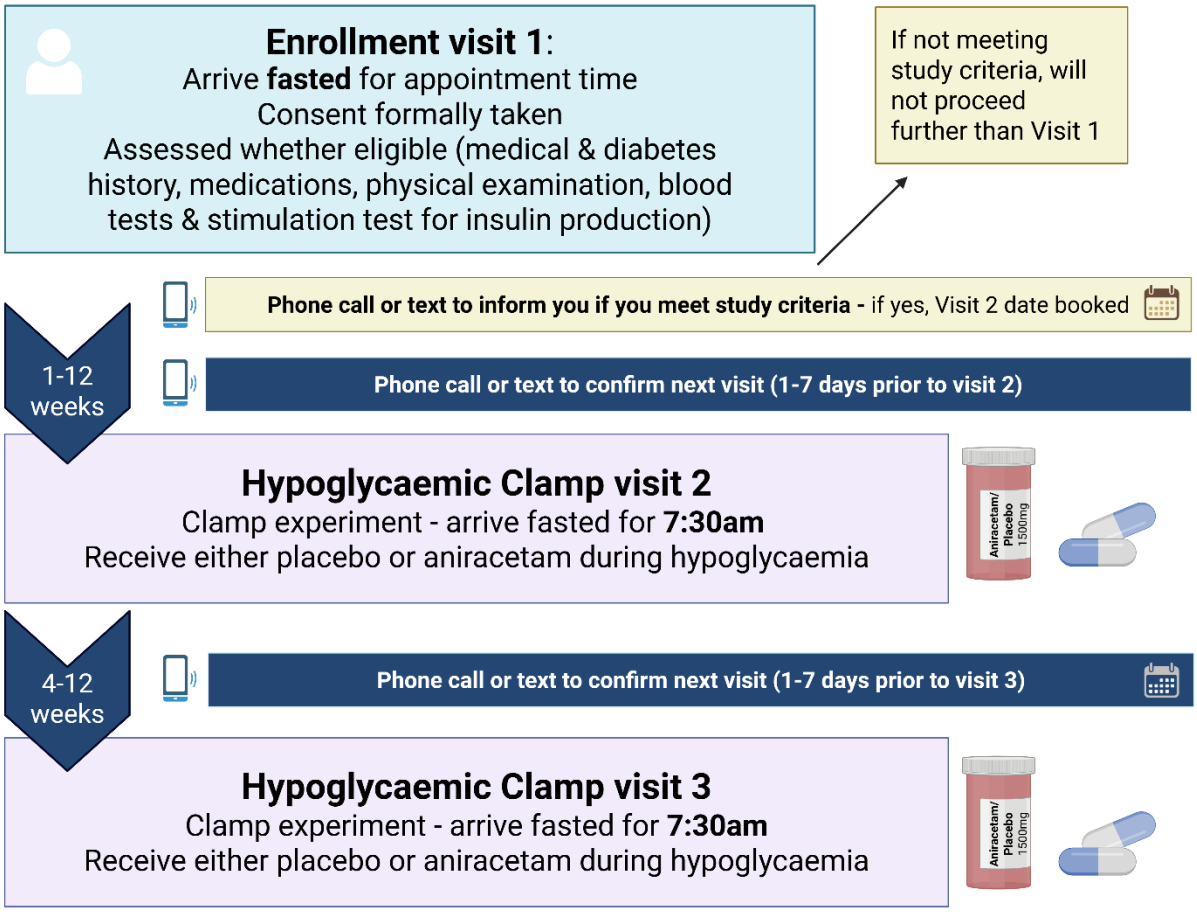
What will happen during the visit?

- Arrive for **7:30am**, have your height & weight taken & urine sample if needed
- A needle is used to place one cannula (small plastic tube) in each arm or hand and we will connect a drip to one and take blood samples from the other
- Complete a questionnaire rating any symptoms of hypoglycaemia at several points during the experiment
- An insulin / glucose drip is connected to one cannula and used to bring your blood sugar to 5 for 40 minutes and then 2.5 for 50 minutes.
- Blood tests and observations (blood pressure, heart rate) are taken every 10 minutes and your glucose level checked every 5 minutes during the experiment
- Halfway through, you will take two pills. This will be either aniracetam (the drug we are testing) or placebo (a pill which does nothing)
- We will then monitor your recovery to a normal blood sugar of 5.0

After visits 2 and 3: Once your glucose level reaches 5.0, you will be given lunch and advice on what to do with your insulin for the next 12-24 hours. You will be given a £100 shopping voucher after each clamp (£200 total over two clamp experiments) and goody bag of spares and hypoglycaemia correction. You should not drive, so if a relative cannot collect you, a taxi will be provided to take you home.

Schedule of Events

Below is an example of the Schedule of events you will be given for each visit and on the opposite page is a breakdown of what each visit to the research facility involves and how long each visit is expected to take.



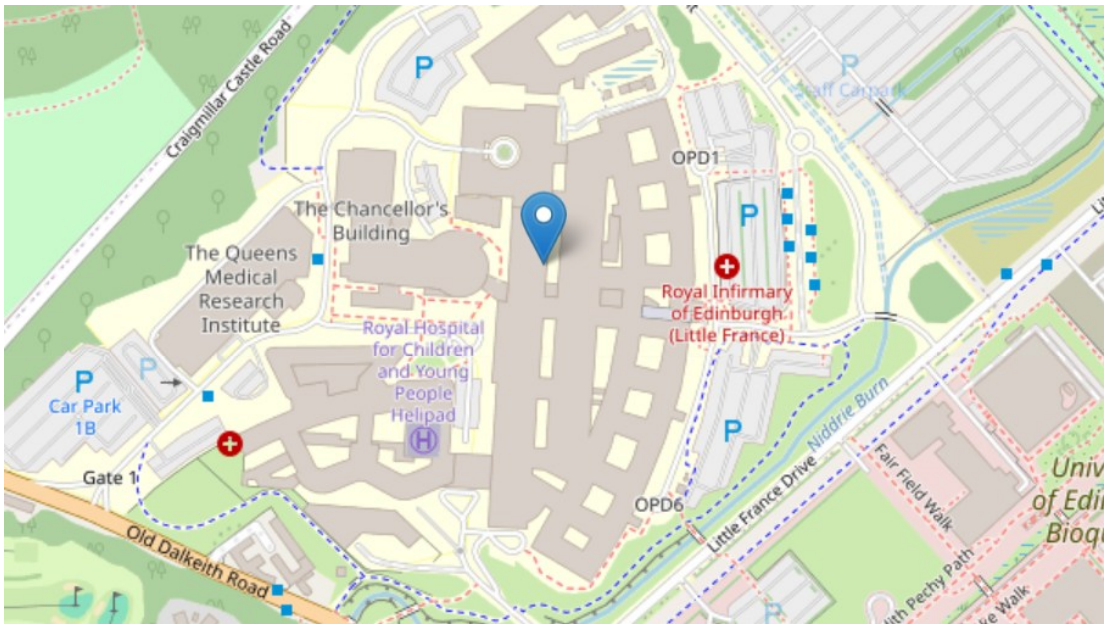
We will confirm with you via text and telephone at one week and 48-24 hours before each study visit is due.

We will also confirm with you the time of your taxi pickup to the Clinical Research Facility.

Location and Directions

All study visits will take place at the **CLINICAL RESEARCH FACILITY** (CRF) which is located on the ground floor of the Edinburgh Royal Infirmary. The CRF is situated in a corridor leading off from the main mall of the Royal Infirmary.

https://clinical-research-facility.ed.ac.uk/about-us/how-to-find-us/rie-clinical-research-facility



Arriving by Taxi | Entry by the West Entrance

Taxis will be pre-booked for you and should know drop you off at the **West Entrance** of the Royal Infirmary Edinburgh (diagonally opposite the Royal hospital for Sick Children building). Go in through the rotating doors and then the blue double doors on the right which lead towards the hospital main Mall. The corridor is just after the information desk on your left, and is signposted to the RIE Clinical Research Facility. The door to the CRF is the first door immediately on your right.

Arriving by Public Transport | Entry by the East (Main) Entrance

If arriving by bus, you will most likely disembark at the main bus terminal on the East side of the hospital. Go in through the Main Entrance and walk straight on past the central reception desk and the shops. After you pass the cash machines, the corridor is just before the information desk on your right, and is signposted to the RIE Clinical Research Facility. The door to the CRF is the first door immediately on your right.

CRF Facility Contact & Address Information:

Address: 51 Little France Crescent, Edinburgh, EH16 4SA
Telephone: **0131 242 7183** and email: info@edinburghcrf.ed.ac.uk

Visit 1 Overview

Visit 1 is your opportunity to meet the research team, ask questions, and if you wish to proceed, you will sign a consent form.

You will be given a unique study identifier so that all the data we collect will be anonymous. At this visit, you will undergo a full medical assessment including some blood tests and an ECG to ensure you are eligible to proceed with the other study visits. You will also undergo a special test called an Arginine Stimulation Test.

Visit 1 Preparation Checklist

- ☐ Arrive **fasted** – nothing but water after midnight the night before
- ☐ Bring a morning urine sample with you
- ☐ Bring a list of your usual medications, insulin doses and any over-the counter supplements or herbal medicines with you
- ☐ Bring your insulin pens with you if you are on insulin injections.
- ☐ Ensure you have uploaded to **Glooko** (pro-connect code is "**ukriofe**") if you are on an insulin pump. Note, some pumps automatically upload after the first time. Others, such as the Tandem T-Slim, require you to do a manual upload each time using a computer.
- ☐ Ensure you have uploaded to Libreview / Clarity if you are on insulin injections (**this includes linking your insulin smart-pens** to Libreview if you have Novopen 6 devices).

What Can I Expect During Visit 1?

Informed Consent: The doctor will go through this information booklet with you and answer any questions you may have. They will go through the consent form, which you should initial. Both you and the doctor will sign the consent form and you will be given a photocopy of the consent form to keep. This will take about 30-45 minutes.

Clinical assessment: The doctor will take a full medical history, including a special focus on your diabetes history. They will ask questions about your general health and take a note of your regular medications, any supplements you take, and any allergies you have. The doctor will also perform a full physical examination.



General measurements: General observations including height, weight, blood pressure, heart rate will be taken at this and at each subsequent study visit.

Urine samples: A urine sample is needed at Visit 1 for **everybody**. Women of childbearing age must complete a urinary pregnancy test at each visit.

Blood tests: Between 350 - 650 ml (under a pint) of blood will be needed across the ***whole*** study (500 ml is a similar amount to what is taken when someone gives blood for a transfusion). Bloods are taken several times from a small plastic tube (known as a cannula) during the Arginine Stimulation test at Visit 1. No more than 65ml of blood will be taken in total at this first visit.

ECG: An electrocardiogram, known as an ECG is a quick, painless tracing of the heart using stickers applied to the chest. The doctor will review your ECG to confirm it shows a healthy heart rhythm so that you can be included in the study.

Eye screening: Your diabetes eye screening for retinopathy will be updated at the end of visit 1 if it has not been performed within in the last 12-24 months – you will be escorted to the eye screener in outpatients department 2 to have this test updated.

What is an Arginine Stimulation Test (Visit 1)?

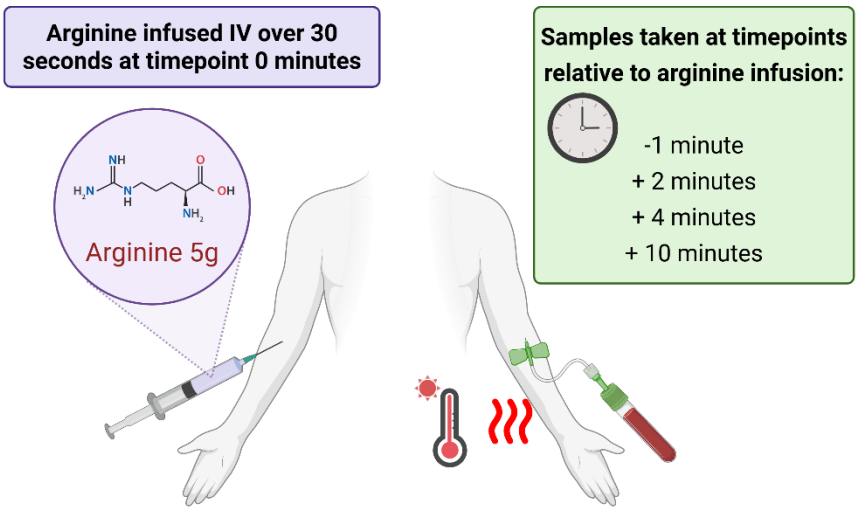
This test will be done **only** during Visit 1. For the test to give the correct result, it needs to be done when you have fasted for at least 8 hours, taking only water to keep hydrated beforehand. This test helps us work out whether your body is still able to make a tiny amount of insulin when it is properly stimulated by Arginine and is performed as a control for the later clamp experiments during Visits 2 and 3.

An Arginine Stimulation Test is performed by infusing a small volume of a natural substance, an amino acid called **Arginine,** through a little plastic tube called a cannula inserted into an arm or hand vein. This will make the pancreas release insulin along with some other hormones (if it is still able to).

From this first cannula, the study doctor will take your routine clinic bloods (checking your kidney function, thyroid function, liver function and HbA1c) and then flush the cannula with some saline solution. This cannula can then be used to give you the infusion of Arginine slowly over 30 seconds followed by another flush.

You may feel warm, flushed or tingly in your hands or face after the Arginine has been given. Occasionally, people feel light-headed or a bit sick, but this usually passes quickly after a minute or two.

Your other arm or hand will have a second cannula sited, and be placed under a heated blanket. The doctor will take blood samples from here at several time points to measure how your insulin levels change. A blood sample is taken just before the arginine is given, then at 2, 4 and 10 minutes afterwards as shown below:



The whole test usually takes about 30 minutes to complete. The samples for this test are stored for later analysis after you have completed all three study visits.

What happens after Visit 1?

At the end of Visit 1, you will be given a late breakfast of coffee/tea and toast and can bolus your mealtime insulin before this as you normally would.

You will be given a unique identifier (e.g. APH_XX) to use throughout the rest of the study and provisionally booked in for your Visit 2 (and possibly Visit 3) once your contact details are confirmed.

The doctor will discuss with you the preparation and any adjustments to your insulin delivery that you will need to perform before the next study visit

We will make sure you have our contact details (below) and you will be able to contact us any time during working hours if you have any questions.

You are advised to **contact us if you have any other appointments or contact with any doctors or nurses during the study period** (whether it is related to your diabetes or not).

A member of the study team will contact you (by email, text or telephone) within two weeks to confirm that you are eligible to proceed with the next study Visit.

We will also touch base with you at the following times before Visit 1:

- 1 week before
- 48 hours before
- The day before

This is to make sure everything is in place. However, **you do not need to wait for us to contact you. If something changes you can get in touch with us using the contact information below**.

If you have a doctors appointment, have been admitted to hospital, fall pregnant or if you have had severe hypoglycaemia, please call or text us to let us know. DO NOT quote your name or date of birth when emailing. Use your **unique study ID** (**e.g. APH_00X**) in all emails or texts.



Dr Victoria Tyndall

- vtyndal2@ed.ac.uk
- forbes_clinical@mlist.is.ed.ac.uk



Text (anytime) or call between hours 9am-4pm:
07345 732 303

Visits 2 and 3: Hypoglycaemia Clamp Experiments Overview

A **hypoglycaemic clamp experiment** is a safe, hospital-based test where we gently lower your blood sugar and keep it fixed ("clamped") at a desired low level of **2.5 mmol/l.**

These sorts of glucose levels can be experienced by people living with type 1 diabetes on insulin. We use insulin and glucose drips to do this, and take measurements of how your body reacts.

It is important to note that careful monitoring by experienced doctors and nurses is undertaken during the clamp experiment, and we do not anticipate any problems with this in a controlled research setting. Our CRF team and our clinical team have extensive experience performing these experiments.

You should prepare for an early start! Although the experiment will be finished by lunchtime, we would advise you not to plan anything for the remainder of the day.

When will Visits 2 and 3 happen?

You will need to arrive at the CRF at 07:30am sharp for both Visits 2 and 3 for the clamp experiments.

Visit 2 can happen any time after Visit 1. However, visits 2 and 3 should ideally take place 4-6 weeks apart, again in the Clinical Research Facility. This timeframe is flexible, so if, for example, you have holidays booked, we can work around them.

The timing is coordinated between you and a member of our study team. As you will be experiencing hypoglycaemia for a long time, it would **not be safe for you to drive** afterwards.

We will therefore organise a taxi to pick you up and drop you off before and after your visit (provided you live within Edinburgh and the Lothians). If you prefer, a friend or relative may drop you off and pick you up instead.

You can expect to be finished at around lunchtime, and we will provide you with lunch before you go home.

How do I prepare for the hypoglycaemic clamp experiments?

The body's response to hypoglycaemia (and therefore the results of this research) can be affected by food, drink (especially alcohol), exercise, caffeine and some medications.

This means that are certain restrictions that you will be asked to undertake before Visits 2 and 3 in order to ensure the experiments can be as accurate as possible.

Contact the study team on their number by text or call if you have any medication changes at any time. You should also contact us if you start to take any new medications, over the counter medications or supplements that you don't normally take, as this may mean that a clamp experiment study visit needs to be postponed.

Here are a couple of examples of when Visit 2 or 3 may need to be postponed:

- Some antibiotics can affect the body's response to hypoglycaemia
- Aspirin and drugs like it (salicylates) can also affect the body's response to hypoglycaemia

If you have a doctors appointment, have been admitted to hospital, fall pregnant or if you have had severe hypoglycaemia, please call or text us to let us know. DO NOT quote your name or date of birth when emailing. Use your **unique study ID** (**e.g. APH_00X**) in all emails or texts.



Dr Victoria Tyndall

- vtyndal2@ed.ac.uk
- forbes_clinical@mlist.is.ed.ac.uk



Text (anytime) or call between hours 9am-4pm:
07345 732 303

Checklist before Visits 2 and 3

- ☐ **Ensure Glooko / Libreview / Clarity are connected** and if needed, that you have performed an upload of your data to the appropriate platform
- ☐ **No alcohol for 48 hours (2 days)**
- ☐ **No moderate or high intensity exercise for 48 hours (2 days)** → This is anything which raises your heart rate and causes you to sweat for a long period of time, e.g. swimming, running, weight training, exercise classes, cross trainer. If you have a busy or active job, this would not count.
- ☐ **Avoid prolonged >20 minutes of hypoglycaemia in the 48 hours (2 days) before the study**. If this does happen, do not worry. You can contact the study team to let them know, and if needed we can postpone the study to a later date.
- ☐ **No caffeine, particularly coffee or caffeine containing energy drinks**, for 12 hours (i.e. from 7:30pm the day before the visit). Decaf options are fine.
- ☐ **Fast from 11pm the night before** → Do not eat or drink anything except water after 11pm

- ☐ You ***may*** be asked to adjust or avoid certain medicines ***provided*** **it is both reasonable and safe to do so**

- ☐ **You *may* be asked to adjust your background/basal insulin** or if you are on a closed loop pump system, to put your pump onto exercise mode or raise your personalised glucose target

1. **Ensure Glooko / Libreview / Clarity are uploaded and/or connected to the hospital system**

   Some closed loop systems require a manual upload to Glooko (Glooko pro-connect code: **ukriofe**)



2. **No alcohol for 48 hours (2 days)**



3. **No moderate or high intensity exercise for 48 hours (2 days)**

   This is anything which raises your heart rate and causes you to sweat for a long period of time e.g. swimming, running, weight training, exercise class.



4. **Avoid prolonged hypoglycaemia of <3.0 mmol/l in the 48 hours (2 days) before the study**

   If this does happen, do not worry. You can contact the study team to let them know, and if needed we can postpone the study visit to a later date



5. **No caffeine (especially coffee or caffeine containing energy drinks) for 12 hours before the study visit**

   Decaf options or tea are fine. This applies from 7:30pm the evening before the visit.



6. **Fast from 11pm the night before**

   Do not eat or drink anything except water after 11pm



7. **You may be asked to adjust or avoid certain medications, provided it is both reasonable and safe to do so**

   This will be agreed with you by the study doctor at visit 1



8. **You may be asked to adjust your insulin:**
   - **a reduction in basal insulin**
   - **an adjustment to pump settings (e.g. exercise mode, raising personalised glucose target)**

   This will be agreed with you by the study doctor at visit 1



What to do just before Visits 2 and 3

Participants are asked to arrive at **ERI CRF for 07:30am sharp**. You will have a taxi booked in advance to pick you up.

Preparation the night before/morning of:

- ☐ Ensure you have done an upload to Glooko / Clarity / Libreview if you have been asked to
- ☐ Insulin adjustment the night before/morning of
    - For those on a pump, this may be a change of settings (e.g. changing your glucose target or using the pump in exercise mode)
    - For those on insulin injections, this will likely be a reduction in your basal insulin (e.g. if you normally take 20 units of Tresiba before bed, you would be asked to reduce this to 16 units for a day or two before)
- ☐ Spare sensor(s)
- ☐ Spare insulin and consumables:
    - Mealtime insulin pens and needles if you are on injectable insulin
    - Enough spare parts for a full set change if you are on a pump (we will have some spares in the department, but we know from experience that it is safest for participants to bring their own in case there are unforeseen problems, such as an initial set change not working or if the kit, we can provide you with is slightly different)
- ☐ A urine sample if you are female and yet to go through menopause
- ☐ A list of any changes to your medications
- ☐ If you wish, you may bring your smartphone or tablet to watch during the experiment, or a book to read. If you plan to watch or listen to something, please bring headphones.

What happens in a clamp experiment?

Safety considerations

On arrival you will have observations taken and will run through a checklist with the doctor to make sure it is safe to proceed with the clamp and that you are still eligible for the study.



This will again include details of your glucose readings and insulin doses downloaded from Glooko / Libreview / Clarity, as well as questions about your general health since the last study visit.

Planning lunch after the experiment

Before getting started, the doctor will discuss with you what you will plan to have for your lunch. You will plan how you will bolus your lunchtime insulin as this may require a dose adjustment if you are on injectable insulin, or restarting your pump with certain settings adjusted at the end of the clamp.



You will **turn off any low glucose alarms**.

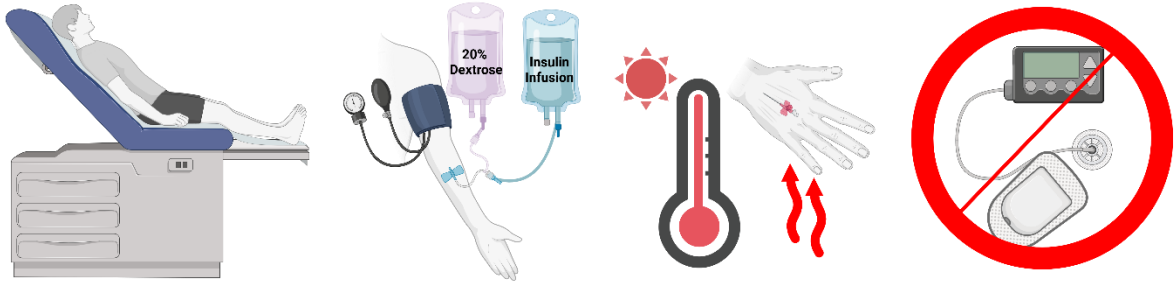
Once you are happy with the plan, if you are on an insulin pump, you will get ready to disconnect it / pause insulin delivery for the duration of the clamp.

Participant Setup

You will be set up comfortably on a hospital bed with the head of the bed raised. During the experiment there will always be at least 2 people in the room with you.

You will be connected up to an automatic blood pressure monitor, which will monitor your blood pressure and heart rate every 10 minutes.

Using needles, the doctor will place one small plastic tube (called a cannula) in each arm: one for the drip infusions into your arm and the other is for taking all blood samples from your hand (so that unless something goes wrong with the cannula, you only get jagged twice).



Your hand where the blood samples will be taken from will be kept under a heated blanket for the duration of the experiment.

Once this is all set up, an insulin infusion and glucose infusion will be started into one arm and the other will be placed inside a heated blanket – warming the blood before it is taken helps us to ensure the results are accurate.

You will be instructed to pause/disconnect your insulin pump if you have one.

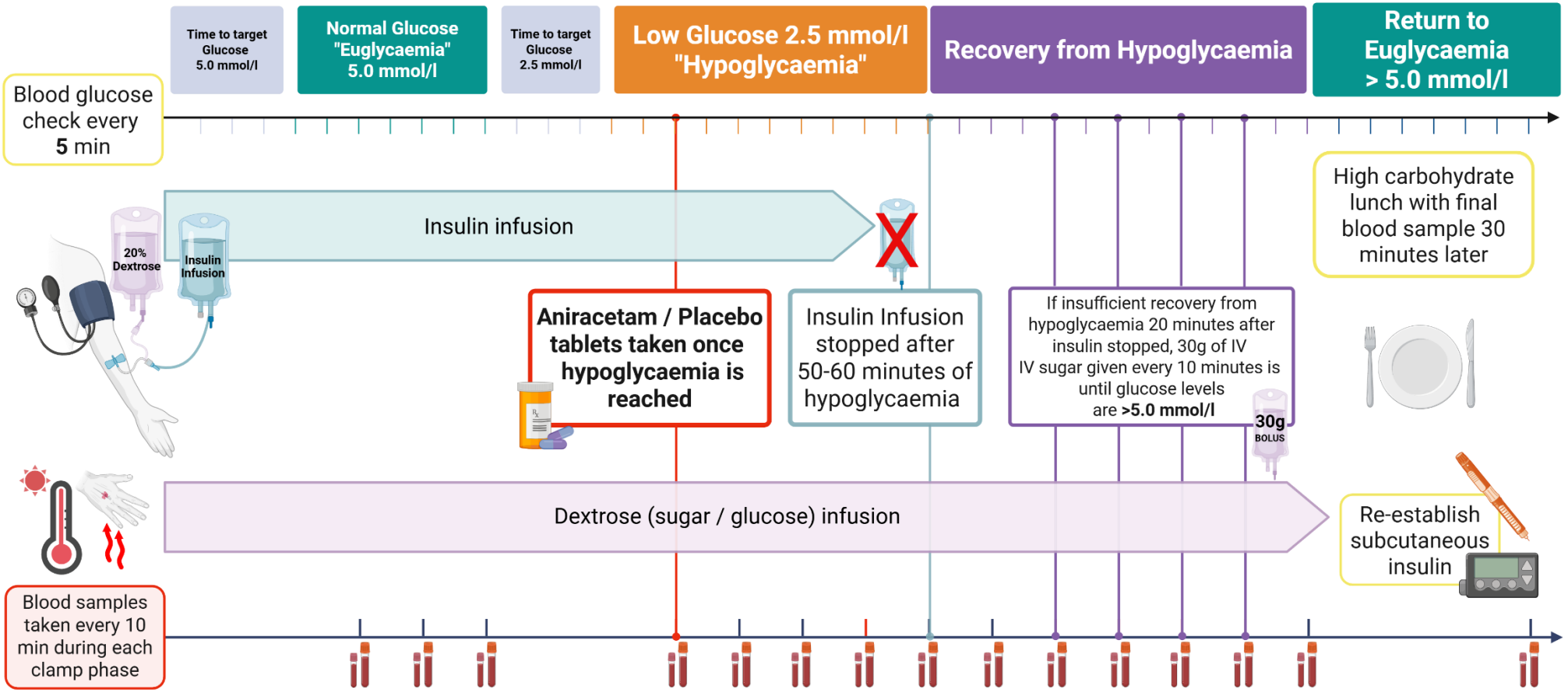
How does a clamp experiment work?

Your blood sugar will be slowly brought down in two steps, each lasting 40-50 minutes.

The doctor will monitor you closely and you can let them know if you need to stop at any time. You will be asked to score your symptoms of hypoglycaemia at several stages during the experiment.

During the clamp we will take a tiny blood sample (0.2 ml) to measure your sugar levels from your hand **every five minutes** to ensure it is at the desired level.

We will take approximately 7.5ml of blood during the hypoglycaemic period and recovery from the hypoglycaemic period **every ten minutes** in order to measure how your hormone levels respond.



The above diagram shows a timeline of how a hypoglycaemic clamp experiment is set up. It may look complicated, but the study doctor will explain how this diagram relates to the clamp experiment at Visit 1. An insulin infusion and glucose (dextrose) infusion are run alongside one another. The glucose infusion rate is adjusted down gradually and then kept low in order to "clamp" your blood sugar at a low level of 2.5. Every five minutes, a glucose check is performed at the bedside by taking a small blood sample from the cannula. During the experiment, additional blood tests are taken every 10 minutes as shown. Once you have had a low blood sugar for 40 minutes, the insulin infusion is stopped and your glucose level is allowed to rise. Once the glucose level reaches 5.0, that is the end of the experiment and you can restart insulin delivery by pen or pump in preparation for lunch. A final blood sample is taken 30 minutes after lunch. You may get your taxi home 45 minutes after lunch.

When do I take the study tablets?

About halfway through each clamp experiment you will be given two tablets to swallow with some water when your glucose level has been low for 10 minutes.

Our pharmacy team will have randomly allocated you to receive 1500 mg of aniracetam (the drug we are studying) at one visit and placebo (a drug which looks like the aniracetam but does nothing) at the other.

Neither you, nor the investigators will know which you have been given – this is called "**blinding**".

What does recovery from a clamp look like?

Accounting for preparation and recovery time, each clamp experiment takes about 4-5 hours.

After you have been hypoglycaemic for about 40 minutes, the insulin infusion will be stopped and your blood sugar will be brought back to normal. If this is taking over an hour (as shown on the big diagram on the previous page), you will be given regular boluses of 30g glucose every 10 minutes through the drip to bring your glucose levels up.

Once your glucose level has recovered **to 5.0 mmol/l** the experiment will be considered complete. We will still continue to monitor you during this time.

How do I bolus my lunchtime insulin after a clamp?

You will have discussed with the doctor ahead of time your choice of lunch which must contain at least 60g of carbohydrate



If you are on a pump, you will re-initiate it at the settings discussed with the doctor before the experiment began and turn your low-glucose alarms back on.

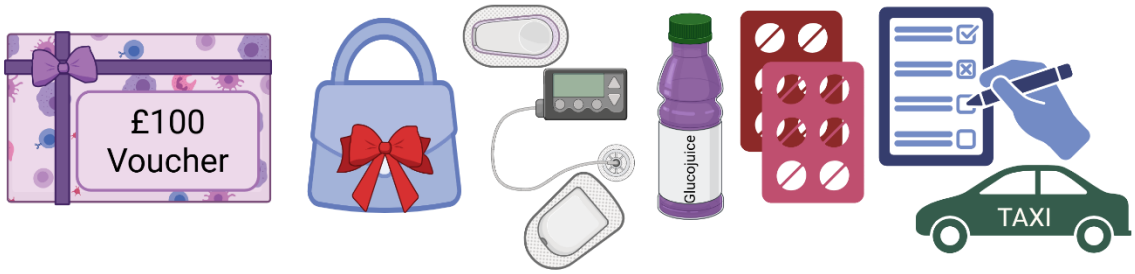
You will then bolus your mealtime insulin (either through the pump or using an injection) and let the doctor and nurses know how much you have taken. You will do this **15 minutes before eating lunch** in order to ensure that the glucose peak from your meal and the insulin peak from your bolus match up (this is to avoid any post-meal hypoglycaemia).

Going Home after a clamp

At the end of visit 2 and 3, you will receive a £100 shopping voucher for your time (**coming to £200 in vouchers total after two clamp experiments**).

We will also give you relevant sensor spares, insulin-giving sets (where possible) and extra hypoglycaemia treatments in a "goody bag" for you to take home.

If you live within Edinburgh and the Lothians, we can organise a taxi to take you home or if you prefer, a relative may collect you.



You will be advised by the study doctor how to adjust your insulin delivery over the next 12-24 hours

The study doctor will

- ☐ Remind you the following day to revert any adjustments you have made back to your usual diabetes management
- ☐ Remotely review your glucose readings 48 hours after a clamp to make sure things are okay
- ☐ Contact you if they have any concerns.

At 48 hours after your last study visit (Visit 3) you will receive a call, text or email from one of the study team to check in with you. They will then be able to confirm that you have completed participation in the study.

Risks and benefits of taking part in this research

What are the possible benefits of taking part?

You will have direct and regular contact with the study doctors and receive a comprehensive medical assessment from a doctor who specialises in diabetes. This gives you an extra opportunity to speak with a specialist about your health and diabetes care.

You will help us understand how to prevent low blood sugars in type 1 diabetes and be involved in cutting edge research. The research we are doing has the potential to improve care for many people in the future and prevent people who take insulin from coming to harm from hypoglycaemia.

What compensation is provided to me for taking part?

After study Visits 2 and 3 (the clamp experiments), each participant will receive:

- A £100 **Love2Shop** voucher – so **£200 total** over the whole study

- A **"goody bag"** containing:
  - A spare sensor
  - Hypo correction (glucotabs and glucojuice)
  - Spare consumables for your pump or insulin pens as needed

We will also provide **free taxi transport** to and from study visits as parking can be difficult and as Visits 2 and 3 involve hypoglycaemia, it would not be safe for you to drive.



What are the possible disadvantages of taking part?

At Visit 1, you may feel warm, flushed or tingly in your hands or face after the Arginine Stimulation Test. Sometimes people feel light-headed or a bit sick, but this usually passes quickly after a minute or two.

Rarely, we may find something on your tests that needs follow-up (this is called an **incidental finding**), but we will let you and your GP know if this happens to make sure nothing is missed.

You may feel unwell from hypoglycaemia during the clamp experiments in Visits 2 and 3. We will monitor your glucose level every 5 minutes and also monitor your heart rate, blood pressure and symptoms, closely. Our research team are very experienced at doing these experiments in people with diabetes.

We will stop the clamp experiment at any point if you are too unwell or if you wish to discontinue.

There are small risks of bruising or discomfort from blood tests and cannulas.

Are there any additional risks after I have been hypoglycaemic?

Following a clamp experiment, as you will have been in hypoglycaemia for over an hour, we know from previous experience that this can make some people **more likely than usual to experience hypoglycaemia later over the next 24 hours**.

To prevent this, you will have discussed with the doctor how to avoid hypoglycaemia for the next 24 hours, specifically with respect to how to dose your insulin and/or adjust your pump settings accordingly.

The study team will make sure you have had a high carbohydrate lunch and dosed your insulin appropriately for that lunch. We will ensure that your glucose levels are stable for at least 45 minutes before sending you home.

The "goody bag" you are given includes hypoglycaemia treatments and appropriate sensor and other spares to mitigate against further hypoglycaemia problems.



The doctor will perform a remote check of your glucose readings 2 days (48 hours) after each clamp experiment. They will call or text you if there are any concerns.

What if problems arise?

What if something goes wrong during or after a clamp?

We have robust procedures in place to report any and all problems which may occur during the study time period, regardless of whether or not they are related to you having diabetes or having attended a research study visit. We therefore encourage you to let us know if **anything** occurs with respect to your health (e.g. new appointments/referrals, a hospital admission, a change in medication, or you think you may have been unwell as the result of a study visit) while you are enrolled in this research project, using our direct contact information given later on in this booklet.

What if I have a problem?

If you have a problem, the appropriate person to contact is Professor Shareen Forbes. If you are harmed because of something the study team did wrong, you may be able to seek compensation against NHS Lothian. Normal NHS complaints procedures apply.

If something else happens which means you can no longer take part in the study, or need to delay an appointment, you can contact the study team to discuss and rearrange if necessary.

Is there a complaints procedure?

If you wish to make a complaint relating to the study, please contact **NHS Lothian Patient Experience Team:**

Waverley Court
4 East Market Street
Edinburgh, EH8 8BG
Telephone: **0131 536 3370**
Email: LOTH.Feedback@nhs.scot



What if I change my mind?

You can leave the study at any time without giving a reason. **This will not affect your medical care.** You can email the Forbes Group email, Dr Tyndall or Professor Forbes, or contact Dr Tyndall by text or telephone on the mobile number used in the study.

You can also request to have previous data collected about you removed and not used in our research.

How we use and store your information (GDPR)

Who is the Sponsor of the research?

The Academic and Clinical Central Office for Research and Development (ACCORD) is a joint research office between the University of Edinburgh and NHS Lothian, managing over 1,000 clinical research projects annually right here in the city.

Under ACCORD, the University of Edinburgh and NHS Lothian Health Board are the Co-Sponsors of the research study and are responsible for looking after your information. The University of Edinburgh and NHS Lothian process your personal data for scientific research in accordance with UK data protection legislation.

Will my information be kept confidential?

Yes. Your personal details will be kept secure and replaced with a study code whenever possible. Only authorised members of the research team and those responsible for oversight of the study will have access to information that could identify you. Your GP will be informed that you are taking part.

Authorised representatives of the Sponsor, regulatory authorities and NHS organisations may also review and inspect study records to ensure the research is being conducted correctly.

How will you use my information?

We will need to use information from your medical records for this research project. This will include:

- Name
- Date of Birth
- Ethnicity
- Contact details (address, phone number, email, next of kin contact)
- Medical history and medications history
- Blood & urine test results
- Retinopathy screening result
- Continuous glucose monitoring and insulin delivery data

We will only collect and use information that is necessary for the conduct of this research study. This information will also include your unique NHS (CHI) number. Our research doctors and nurses will use this information to do the research and to check your records to make sure that the research is being done properly.

This information is held securely on NHS computers and passed to the University of Edinburgh for administration/monitoring of the study. Non-clinical staff who do not need to know who you are will not be able to see your name or contact details.



If you consent to take part, we will anonymise/pseudonymise your data by giving you a unique participant identification number (PIN), which means that no one outside of our team will know who you are. If you give consent, this PIN only data will be stored securely, and may be transferred along with research samples (also PIN only), inside and outside the UK, as part of ongoing research we may share data collected in this study with other academic organisations.

You can withdraw your consent at any time.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. We will inform you, in writing, of study results when the study is complete, results have been analysed and the paper has been written.

International Transfers

We may share data about you obtained during the course of the study with researchers outside of the UK for research related purposes. This would be to our collaborators at other academic and healthcare institutions.



If this happens, we will only share the data that is needed. Where possible, we will also make sure you cannot be identified from the data that is shared. This may not be possible under certain circumstances e.g., if you have a rare illness, it may still be possible to identify you.

We will make sure your data is protected. Anyone who accesses your data outside the UK must follow our instructions so that your data has a similar level of protection as it does under UK law. We will make sure your data is safe outside the UK by only sharing either completely anonymous data, or data that has been pseudonymised using your unique participant study code.



- [Some of] the countries your data will be shared with have an adequacy decision in place. This means that we know their laws offer a similar level of protection to data protection laws in the UK.
- We use specific contracts approved for use in the UK which give personal data the same level of protection it has in the UK. For further details visit the Information Commissioner's Office (ICO) website.
- We do not allow those who access your data outside the UK to use it for anything other than what our written contract with them says.
- We need other organisations to have appropriate security measures to protect your data which are consistent with the data security and confidentiality obligations we have. This includes having appropriate measures to protect your data against accidental loss and unauthorised access, use, changes or sharing.
- We have procedures in place to deal with any suspected personal data breach. We will tell you and applicable regulators when there has been a breach of your personal data when we legally have to. For further details about UK breach reporting rules visit

What if new information becomes available during the study?

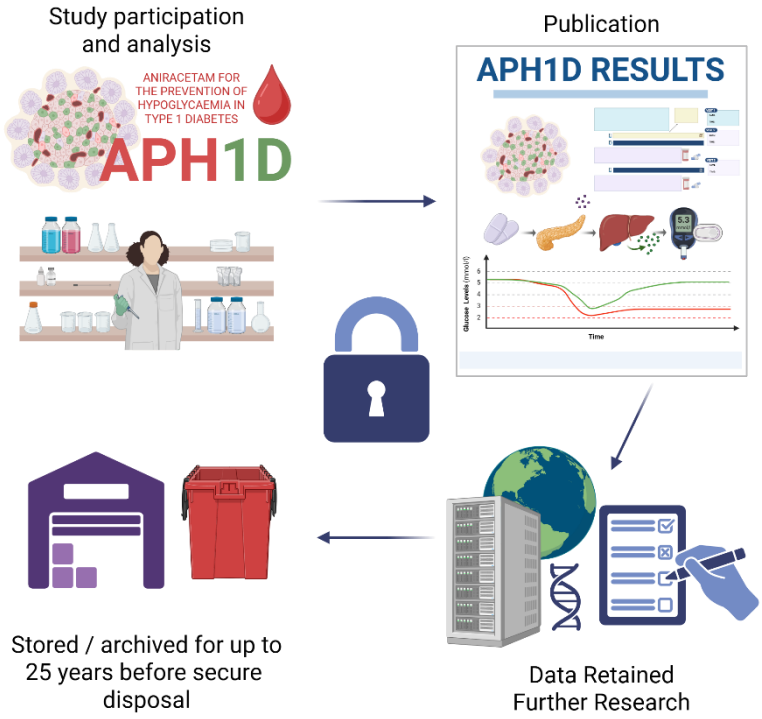
If new information becomes available during the course of the study that may affect your willingness to continue taking part, we will inform you as soon as possible and discuss with you whether you wish to continue.

How will we use information about you after the study ends?

Once the study is finished, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

We will keep your study data for a maximum of 25 years. The study data will then be fully anonymised and securely archived or destroyed.

If you agree to take part in this study, you will have the option to take part in future research, we will save and use your contact data from this study.



Non-identifiable data will be kept on a secure server for up to 25 years, after which point it will be archived at the university. Any physical paperwork (both with and without identifying information) will be stored securely in our research facility and archived when it is not longer immediately needed. Physical paperwork is also kept for up to 25 years and then disposed of via confidential waste in line with NHS Lothian and University policy.

Remaining blood samples will similarly be stored in the Queen's Medical Research Institute for a period up to 5 years and then disposed of in accordance with Human Tissue Authority's code of practice.

Participants should be aware that future related research using data and samples may take place in this facility or in other approved research facilities.

What are my choices about how my information is used if I withdraw from the study?

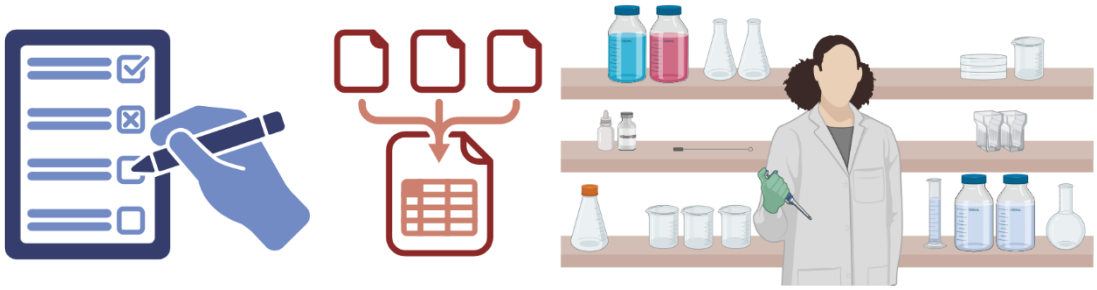
You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we have already collected.

The study doctor may withdraw you from the study if it becomes medically unsafe for you to continue, if the study is stopped by the Sponsor or regulators, or if you are unable to follow study requirements.

If you withdraw from the study, information already collected may still be retained and used to preserve the integrity of the research unless you specifically request otherwise and it is possible to do so.

You have the right to ask us to remove, change or delete data we hold about you for the purposes of the study. We might not always be able to do this if it means we cannot use your data to do the research. If so, we will tell you why we cannot do this.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.



If you agree to take part in this study, you will also have the option to allow our research team (within the sponsoring organisation) to securely store your contact details and agree to be contacted about other ethically approved research studies. You will only be contacted by a member of this research team to determine if you are interested in taking part in another research study.

Your verbal consent may then be sought to pass your contact details to another research team within the University of Edinburgh and/or NHS Lothian. Agreeing to be contacted **does not oblige you to participate** in further studies.

If you agree to take part in this study, you will have the option to allow the research team (within the sponsoring organisation) to securely store your contact details and agree to be contacted with a summary of the results of the study. You will only be contacted by a member of this research team with the results.

Where can I find out more information about how my data is used?

You can find out more about how we use your information in several ways:

- Information available at: www.hra.nhs.uk/patientdataandresearch
- By asking one of our study team (**See APH1D Study Contact Information**)
- By Sending an email to the Data Protection Officer (dpo@ed.ac.uk)

To ensure that the study is being run correctly, we will ask your consent for responsible representatives from the Sponsor and NHS Institution to access your medical records and data collected during the study, where it is relevant to you taking part in this research. The Sponsor is responsible for overall management of the study and providing insurance and indemnity.

Participants are covered by the University of Edinburgh and/or NHS Lothian insurance and indemnity arrangements applicable to this research:

Data protection contact information:

University of Edinburgh	**NHS Lothian**
Data Protection Officer Governance and Strategic Planning University of Edinburgh Old College Edinburgh EH8 9YL Tel: 0131 651 4114 dpo@ed.ac.uk	Data Protection Officer NHS Lothian Waverley Gate 2-4 Waterloo Place Edinburgh EH1 3EG Tel: 0131 465 5444 Lothian.DPO@nhs.net

Is the APH1D study registered anywhere?

APH1D is registered in the UK on the International Standard Randomised Controlled Trial Number (ISRCTN) Registry, under number **9590 1685**. You can find more information about ISRCTN at: https://www.isrctn.com/page/about .

What will happen to the results of the study?

The results of this study may contribute to the future development of treatments for hypoglycaemia and Type 1 Diabetes. You will not receive any financial benefit from any such development. The results will be published in a research paper. You will not be identifiable. A summary will be sent to you.

Who is organising and funding the study?

The study is sponsored by NHS Lothian and the University of Edinburgh, and funded by a grant from the Helmsley Charitable Trust.

https://helmsleytrust.org/our-focus-areas/type-1-diabetes/

Who has reviewed the study?

The study has been reviewed and approved by the following organisations:

- The MHRA
- Under ACCORD, the University of Edinburgh and NHS Lothian Health Board are the Co-Sponsors and have reviewed this study
- NHS Research Ethics Committee (REC) East of Scotland
- NHS Lothian management

Have people with Type 1 Diabetes helped shape this study?

This study booklet was designed with help from people living with Type 1 Diabetes.

People with Type 1 Diabetes have reviewed the study procedures, participant information materials and practical arrangements before the study opened. Their feedback helped us improve the wording used throughout this booklet, explain study procedures more clearly and make participation as straightforward as possible.

Many aspects of the booklet, including the detailed visit guides, preparation checklists and explanations of the clamp experiments, were developed in response to suggestions from people with lived experience of Type 1 Diabetes.

We are very grateful for their time, expertise and feedback. This research would not be possible without their contribution.

APH1D Study Contact Information

Research Lead: Dr Victoria Tyndall

Clinical Research Fellow and lead for APH1D

Email: vtyndal2@ed.ac.uk (Monday-Thursday)

Clinical Group Email: forbes_clinical@mlist.is.ed.ac.uk (Monday-Friday) – this email is checked by Dr Tyndall, Dr Baillie and other members of the Forbes clinical research group

Study Mobile: **07345 732 303**

The best time to contact our team is during working hours Monday to Thursday **09:30am – 4pm. Please do still contact us outside working hours (ideally by text) if you are a participant and have a time-sensitive issue/circumstances changed and you need to tell us asap**.

Times to get in touch with us urgently include:

- If you are admitted to hospital **or** have suffered severe hypoglycaemia
- If you are at the last minute unable to attend a study visit the next day
- If you are started on a new medication (e.g. antibiotics) and want to check whether this will affect your inclusion in the study
- If you are a woman and fall pregnant

You should quote "**APH1D**" and your **unique study identifier** (this will be given to you at Visit 1 when you enrol in the study and look like this: "**APH_00X**") in all texts and emails. One of the study team will respond to you as soon as they can.



Clinical Research Associate: Dr Nicola Baillie

Clinical Group Email: forbes_clinical@mlist.is.ed.ac.uk

Principal / Chief Investigator: Professor Shareen Forbes

Email: Shareen.Forbes@ed.ac.uk

Clinical Research Facility (CRF)

Email: info@edinburghcrf.ed.ac.uk
Reception Telephone: **0131 242 7183**

You can email or call the CRF if you run into a problem on your way to/from one of your study visits (e.g. if you have left a personal belonging in the CRF, or are running late or need to change a visit date/time).



Independent doctor: Dr Faye Baxter

If you would like to discuss this study with someone independent of this research who has done hypoglycaemia clamp experiments in the past, please contact Dr Faye Baxter by post or by email citing "APH1D question" in the subject title.

Dr Faye Baxter
Paediatric Endocrine Registrar
Royal Hospital of Sick Children
Little France, Edinburgh
Email: Faye.Baxter@nhs.scot

Appendix 1: Example Consent Form

Below is an example of the consent form you will be asked to sign at study Visit 1

Participant Study ID: APH_____ **Centre ID: 01_ERI_CRF**

Aniracetam for the prevention of Type 1 Diabetes (APH1D)

	Please INITIAL box (Do not tick)
1. I confirm that I have read and understand the participant information sheet (Version dated) for the above study. I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care and/or legal rights being affected.	☐
3. I give permission for the research team to access my medical records for the purposes of this research study	☐
4. I give permission for the research team to access my medical records for the purposes of other future ethically approved research.	☐
5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the Sponsor (University of Edinburgh and/or NHS Lothian), from regulatory authorities or from the NHS organisation, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data and/or medical records.	☐
6. I give permission for my personal information (including initials, name, date of birth, ethnicity, address, postcode, telephone number, email address, and consent form) to be retained on NHS servers / passed to the University of Edinburgh for administration of the study	☐
7. I agree to my non-identifiable data and blood samples being stored for use in future ethically approved research.	☐
8. I give permission for my Community Health Index (CHI) number/ to be collected and passed to the ERI Clinical Research Facility.	☐

9.	**I understand that data collected about me during the study may be converted to pseudonymised /anonymised data.**	☐
10.	**I give permission for investigators to contact me regarding this study and my participation in it.**	☐
11.	**I give permission for my General Practitioner to be informed of my participation in the study.**	☐
12.	**I agree to my contact details being stored securely so that I can be contacted for future research studies.**	☐
13.	**I agree to take part in the above study and agree to undergoing the procedures outlined in the information sheet.**	☐
14.	**I agree to receive feedback regarding my data or blood sample results if the need arises**	☐
15.	**I consent to the collection, processing, storage, secure transfer and reporting/ analysis of my healthcare data and research samples. I understand that pseudonymised/ anonymised data may be sent to other academic institutions outside of the UK / European Economic Area, where laws protecting my personal information may be different to my own country. I understand that this will only be done for purposes related to this study and other ethically approved academic research in line with GDPR and corresponding local data protection laws.**	☐

Name of Person Giving Consent	Date	Signature

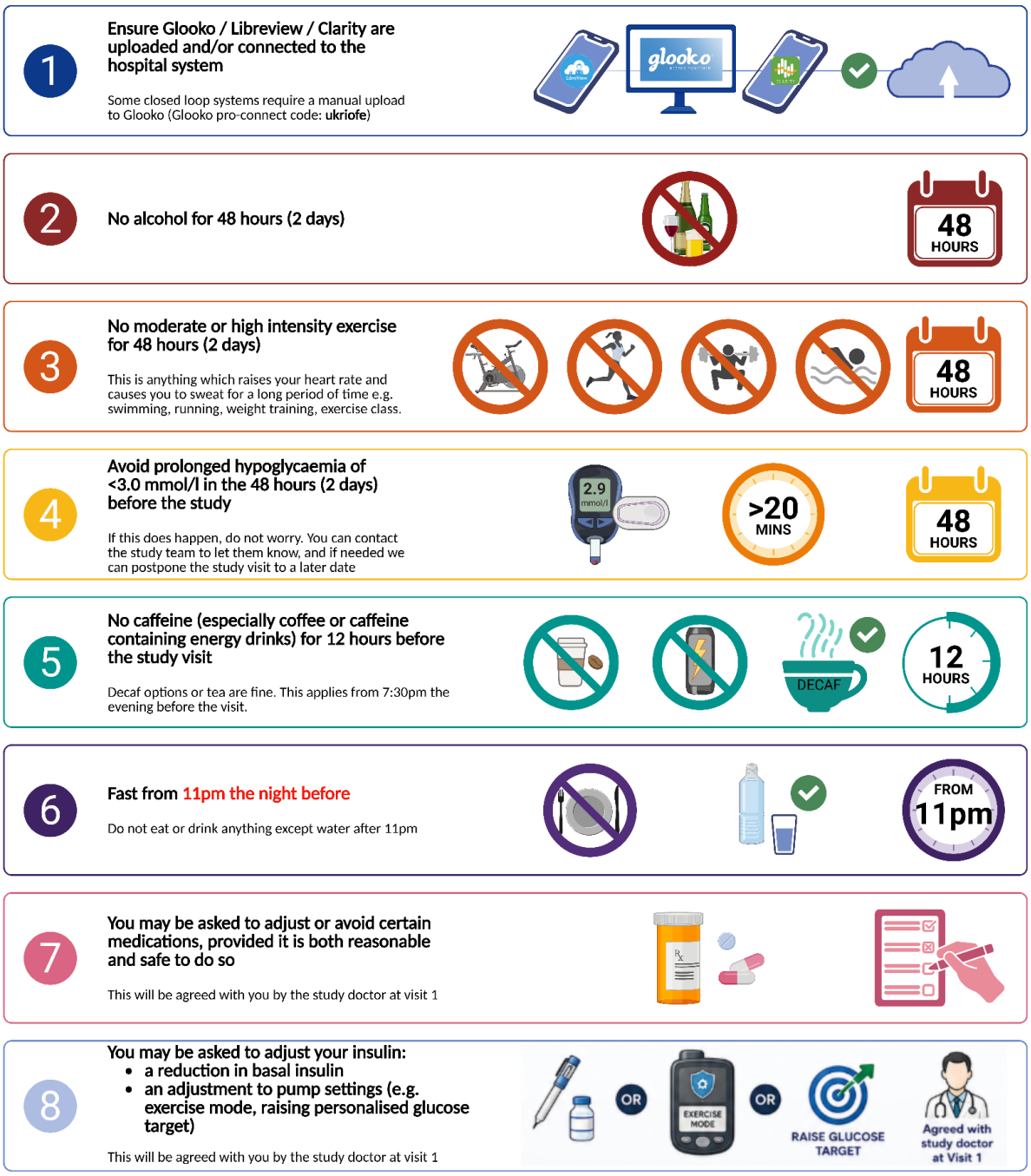
Name of Person Receiving Consent	Date	Signature

1x original – into Site File; 1x copy – to Participant; 1x copy – into medical record

Appendix 2: Visit 1 Preparation Checklist

- ☐ **Fasted** – nothing but water after midnight the night before
- ☐ Bring a morning urine sample in a collection pot
- ☐ Bring a list of usual medications
- ☐ List of usual insulin doses
- ☐ List of any over-the counter supplements or herbal medicines with you
- ☐ Bring your insulin pens with you if you are on insulin injections
- ☐ Pump patients: Ensure uploaded to **Glooko** (pro-connect code is "**ukriofe**")
    - Some pumps automatically upload after the first time. Others, such as the Tandem T-Slim, require you to do a manual upload each time using a computer.
- ☐ Insulin injection patients: Ensure uploaded to Libreview / Clarity if you are on insulin injections (**this includes linking insulin smart-pens** to Libreview if you have Novopen 6 devices).

Appendix 3: Hypoglycaemia Clamp Preparation Checklist



Bring with you:

- ☐ **Spare sensor(s)**
- ☐ **Spare insulin and consumables** (pens & needles or full kit for a set change)
- ☐ A list of any changes to your medications since the last visit
- ☐ A urine sample if you are female and yet to go through menopause

APH1D contact information at a glance:

It is important that we keep a record of the health of our participants during this research study. Please contact us **if any** of the following occur:

- You have an appointment with a healthcare professional that was not scheduled before you enrolled at Visit 1 (regardless of seriousness or whether or not it is related to your diabetes)
- You are admitted to hospital for **any** reason
- You have an episode of severe hypoglycaemia (requiring third party assistance to recover)
- You need to reschedule a study visit
- You are started on a new medication or plan to start a new medication
- You are unwell (regardless of whether related to your diabetes or not)

You should also feel free to contact us if you have any questions between study visits

You can call or text the study mobile number below. If you have a question, you can also email Dr Tyndall directly. If she is away, you can email the Forbes clinical group and another team member will get back to you. Quote your **unique study ID** (e.g. APH_00X) in all emails and texts.



Text (anytime) or call between hours 9am-4pm:
07345 732 303



Dr Victoria Tyndall
- **vtyndal2@ed.ac.uk**
- forbes_clinical@mlist.is.ed.ac.uk

Clinical Research Facility (CRF)

Email: info@edinburghcrf.ed.ac.uk
Reception Telephone: **0131 242 7183**

You can email or call the CRF if you run into a problem on your way to/from one of your study visits (e.g. if you have left a personal belonging in the CRF, are running late or a taxi didn't turn up).

Thank You!



Thank you for considering participation in the APH1D study.

Whether or not you decide to take part, we appreciate the time you have taken to read this booklet and learn about our research.