THE UNIVERSITY of EDINBURGH | usher institute | NHS Lothian | Bipolar Scotland | — A KETOGENIC DIET — FOR BIPOLAR DISORDER

MRC/CSO Social and Public Health Sciences Unit

UKRI Medical Research Council | CHIEF SCIENTIST OFFICE | University of Glasgow

PARTICPANT INFORMATION SHEET

A pilot study of the ketogenic diet in bipolar disorder

Bipolar disorder is a major lifelong condition which significantly impacts the lives of those who live with it. Our current understanding of the cause of bipolar and its treatment is limited, but there is some evidence that a ketogenic diet may be an effective treatment. With this research we aim to find out how easy it is for people with bipolar to follow this diet, and to take part in all the relevant assessments we need to do to help us understand its effects. This will help us develop a full clinical trial, which will answer this question more definitively.

We are inviting you to take part in a research study. Participation is voluntary and will last for 10 weeks, to include baseline and follow up assessments at the Royal Infirmary of Edinburgh over 3-4 appointments

To help you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take the time to read the following information 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 you wish to take part. You will have at least 3 days to do this, and you will not be expected to consent unless you have had time to read and consider this leaflet. Please note that we will follow ethical and legal practice and all your personal information will be treated in the strictest confidence.

What is the purpose of the study?
Bipolar disorder (BD) is a major lifelong mental health condition, which significantly impacts on the quality of life of those who live with it. Our current understanding of how it develops is poor, and as such treatments are not always effective. There is some evidence that the ketogenic diet (KD), which is low in carbohydrate and high in fat, may be an effective treatment for BD, and some people with BD already follow this diet. To date there has been no clinical trial of the KD in BD, which means we cannot draw any conclusions about whether it is an effective treatment.

This study will pilot the introduction of a KD for 8 weeks in people with BD. We aim to find out how easy it is to do this, the main challenges, and how to address these. Acceptability of the intervention and measurements taken before and after will be assessed, looking at how many participants remain on the diet, what adverse effects they experience, and what support they require in sticking to the diet. This will provide the information we need to design a future full clinical trial. A full clinical trial will be very important to help us understand the effects of the KD in people with BD, and whether it should be considered as a treatment option.

How will the study work?
Participants will adhere to a ketogenic diet alongside their usual psychiatric treatment for 8 weeks, followed by a 2-week period over which the diet is stopped (unless they chose to continue it). They will receive support from

a specialist dietitian and psychiatrist throughout. Different aspects of their health will be measured before, during and after being on the diet (specified below). This will help us understand how the diet might work.

Who can take part?
To be eligible to take part in the study you need to have a diagnosis of bipolar disorder (type 1 or 2). You must not have had any episodes of major depression, mania or hypomania in the preceding 3 months. You need to be aged between 18-70, and you must be able to read and understand English.

There are several factors or conditions which would exclude you from taking part in the study, including:

- Pregnancy or breastfeeding (or if you are planning to become pregnant within 3 months)
- Active substance misuse with alcohol or illicit drugs
- Following the ketogenic diet within the previous 2 months
- Currently following a vegan diet
- Admission to hospital within the past 3 months
- Current involvement in another research study
- Inability to complete the baseline assessments
- Liver or kidney disease
- Cardiovascular disease
- Severe hyperlipidaemia (high blood lipids)
- Type 1 diabetes

If you would like to discuss any of these criteria further, please contact us at ketostudy@ed.ac.uk.

Do I have to take part?
You do not have to take part or give a reason for not doing so. If you do decide to take part, you are still free to withdraw at any time and without giving a reason. You have been sent this information sheet either because you have already expressed an interest in the study, or because your clinical team have identified you as someone who may be eligible to take part.

What will happen to me if I take part?
You will be offered an initial online meeting (using the secure platform Near Me) or phone call to answer any questions you may have about the study, and to check you are eligible to take part. If you would still like to take part, we will ask you for some basic information (name, date of birth and address) to allow our Clinical Research Facility (CRF) to register you on NHS Lothian's clinical system (TRAK), and a time will be arranged for you to attend the Royal Infirmary of Edinburgh hospital CRF to sign a consent form and answer any further questions. If you would still like to go ahead, you will then complete the baseline assessments. The different aspects of involvement in the study are detailed below.

Timescale

Your participation in the study should last between 10 to 12 weeks.

Initial assessments (likely over 2 appointments)

Appointment 1 – Clinical Research Facility (CRF) at the Royal Infirmary of Edinburgh (RIE)

- You will be asked to complete a consent form if you are happy to proceed
- You will be asked to provide information about your medical and medication history
- You will be asked to complete a range of questionnaires, which will take around 1 hour. These will include questions about your mental health, how any reported mental health symptoms impact you, your education, employment and financial income and outgoings.
- You will have your blood pressure, height and weight measured
- You will be taught how to use all necessary devices and apps to take part in the study (detailed below in 'Intervention period'.

Appointment 2 – CRF *and* The Edinburgh Imaging Facility, RIE

- You will be asked to give a blood sample to be sent for analysis. Specialist markers which may change on the ketogenic diet will be measured, and will not be routinely fed back to you. Your liver function, kidney function, lipid levels, Hba1c (a measure of your average glucose level over the past 2-3 months) and CRP (a measure of inflammation) will also be measured. If any of these results are outside of the normal reference range, we will let your GP know. You may be required to fast prior to this sample, which would involve attending for an early appointment prior to having your breakfast.
- You will attend for an MRI brain scan (see section below for more information)

Intervention period (10 weeks continuous)

- The 10-week intervention period will consist of a 2-week ketogenic diet initiation period, 6-week ketogenic diet continuation period, and 2-week ketogenic diet cessation period. If you decide to continue the diet after the study has ended, you will not have to stop it after week 8 but would still like you to continue in the study for the full 10 weeks
- The ketogenic diet is low in carbohydrate and high in fat. A specialist dietitian from the ketogenic diet service will provide you with all the information you need to be able to start and follow this diet successfully. This will include how to prepare and manage a ketogenic diet by yourself, using recipe cards and meal planning, dietary booklets, and advice on common problems. You will have regular support over the first few days to problem solve and identify any adverse effects, and weekly support thereafter.
- You will continue usual medical treatment from your regular care teams, including mental health services if you are under their care
- You will be required to take small pinprick blood samples from the end of your finger to measure glucose and ketone levels once a day at home. You will be required to take these at the same time of day, and enter them into an app. This will allow us to monitor your adherence to the diet and the level of ketosis you achieve. We will explore any correlations of these measurements to your mood assessments.
- You will enter aspects of your mental state into an app on your phone at the same time each day setting a reminder, using a scale of 0-100 to assess your mood, energy, speed of thought, impulsivity, and anxiety
- You will be required to wear a wrist device called an actigraph, throughout the 10-week study period. This will measure your sleep and activity levels, and help us understand how these may relate to the diet.

Follow up assessments (weeks 6-10)

Appointment 1 (in weeks 6, 7, or 8) - (CRF) *and* The Edinburgh Imaging Facility at the (RIE)

- Your baseline blood tests will be repeated (see above)
- You will attend for a repeat brain scan (see above)
- You will be asked to repeat the baseline questionnaires (see above)
- You will have your blood pressure, height and weight repeated

Telephone interviews (week 11)

Some people will be asked to take part in audio recorded telephone interviews following completion of the 10-week study intervention period, to explore their experience of being in the study. With your consent we will approach you to see if you are willing to consider taking part in the interviews. If you are, we will send out a more detailed5 information sheet and a consent form.

Return of equipment (week 11) – CRF, RIE

After completion of the study we will ask you to attend to return your actigraph device and ketone/glucose monitoring device. This will allow us to download your data from the former.

What is an MRI and what is involved?

MRI uses the combination of a powerful magnet and radio waves to create high-quality images of the human body. MRI does not use X-rays or other types of ionising radiation. The MRI scan will include a technique called MRI spectroscopy, which detects the levels of certain chemicals in your brain. This will allow us to see if these correlate with circulating ketones in the blood, self reported mental state, or sleep and activity levels. This scan will not involve the use of any drugs or injections.

There are no known side effects from MRI and it is a safe procedure but we don't scan people who have certain kinds of medical implant, such as heart pacemakers and some metal clips, or who have metal fragments in their eyes, perhaps as a result of their job. However, many implants such as hip replacements are rarely a reason not to have a scan. We don't scan pregnant people for research purposes so you need to let us know if there is a chance you could be pregnant. You would not be eligible for this study if you were.

When you come for your scan, we'll ask you to put all your metal objects, such as keys, watches, coins and credit cards in a locker. Please don't wear any makeup, and be prepared to take out your contact lenses. The scan can take up to an hour. Please find a link to a video for more information about what to expect (https://www.ed.ac.uk/clinical-sciences/edinburgh-imaging/for-patients-study-participants/finding-our-scanners/my-scan-is-at-the-eif-rie/having-a-mr-scan-at-the-eif-rie). We can also email this link.

Research shows that for every 1,000 people who volunteer for an MRI brain scan, 50 will have a scan that shows an abnormality that needs to be looked into. Mostly, these investigations show that nothing more needs to be done, but some people may need immediate medical attention. A medical report of your scan will always be made, and in the unlikely event that we find an abnormality we will inform your GP.

Can I continue the ketogenic diet after the study has ended?
You will be free continue the ketogenic diet (KD) after the study has ended if you wish. You will be able to keep the menu plans and information you have been given. You will have had ongoing support during the 10-week study period, which should have allowed you to identify and manage any short-term initial side effects. If you continue the KD, we will provide you with dietitian support for a further 4 weeks, during which time you will still be able to contact the team. There are some possible longer-term side effects of the KD if you chose to continue following it. These can include kidney stones, and the dietitian will give you advice regarding this.

What are the possible disadvantages or risks associated with taking part?
You may find blood tests uncomfortable or distressing in the event of a needle phobia. A chaperone will be available if you would like one. You may find the brain scan claustrophobic. You will be able to watch a video about what will happen to help familiarise yourself with the process.

Following the ketogenic diet for 8 weeks may be intrusive and may impact on things such as being able to eat with family and friends or attend social events involving food. You may feel you have to deprive yourself of food you normally enjoy, and you may find it difficult to find dietary options that you like. To help with this, you will be provided with intensive support at the beginning of the diet. You will then have weekly contact with the dietitian and will be able to contact a dietitian or psychiatrist in the research team during working hours.

You may experience side effects from the ketogenic diet. When commencing the diet these may include fatigue, thirst, irritability, hunger, and constipation. Other possible side effects include, weight loss, leg cramps, menstrual irregularity (in women of childbearing age), nausea, and vomiting. We will provide you with advice about how to manage these symptoms, which are typically mild and can be managed with some dietary changes. As the Ketogenic diet is high fat it can increase blood levels of cholesterol and triglycerides. These will be monitored before and after commencing the diet. We can minimise this effect by using unsaturated fats where possible. High levels of cholesterol and triglycerides usually return to normal when the diet is stopped.

What are the benefits of taking part?
Potential benefits include learning more about your mental state over a period of 10 weeks, as you will be recording difference aspects of this daily into an app. You will also have the opportunity to better understand your sleep and activity pattern, as a summary of the data from your actigraph device will be sent to you. If you are overweight, a potential benefit is weight loss, a well- known effect of the ketogenic diet.

Will I receive any financial compensation?
You will be reimbursed for any travel expenses. You will need to buy the correct food to allow you to follow a ketogenic diet, which should be roughly equivalent to the costs of your regular food shopping.

What will happen to the results of the study?
The findings of this study will be written up and may be published in academic journals or presented at conferences, but individual names or identifying information will never be disclosed. We will produce fact sheets to communicate important research findings to study participants and the general public.

How will we use information about you?
We will follow ethical and legal practice and all your personal information will be treated in the strictest confidence. Some blood samples and your imaging scans will be visible on your medical records, which means anyone who accesses these may see the results. Only approved members of the research team will have access to the rest of your data. People who do not need to know who you are will not be able to see your name or contact details, and your data will be allocated a code number instead. It will be password protected and stored within a highly secure computer system in a secure building. Any written information will be stored similarly in locked premises. Please do not provide personal details when completing free text questions in the study questionnaires or during telephone interviews, to allow this data to remain anonymous.

We will need to use information from you and your medical records for this research project. This information will include your CHI number (your unique identification number within Lothian NHS), your name and contact details. We will also collect answers to the questionnaires you complete, and the results of your blood tests and brain scans. Additionally, we will collect data inputted by you into apps on your phone, and data that is collected on the wrist worn actigraph device. People will only use this information to do the research or to check your records to make sure that the research is being done properly.

NHS Lothian cannot guarantee the safety of your information on your own device when accessing the ketomojo and ilumivu apps. Data collected via the Ilumivu app will be processed in the USA, outside of GDPR compliant zone, but this app will not collect any personal identifiable data. The ketomojo app will collect your first name, second name, and email address, to allow you to register an account with them. Third parties will have access to general usage analytics such as metrics about what parts of the apps are used, but not to your data itself.

Once we have finished the study, we will keep some of the data so we can check the results, as it can take a long time to look in detail at every aspect of the study. All the information collected will be stored safely on a secure University of Edinburgh (UoE) or University of Glasgow (UoG) server, or within the secure NHS network. All personal data will be destroyed after 12 months, and once the study is complete only an anonymised master copy of the data will exist. We will review all data for destruction after 10 years.

This study is a collaboration between the UoE, UoG, and NHS Lothian. Therefore, some of your anonymised data will need to be securely transferred between the UoE and the UoG, via secure file sharing platforms. The UoG will need access to your personal data (name, telephone number, email address) if you agree to being contacted about taking part in interviews after the study has ended. This data would be sent in an encrypted format via a secure university file-sharing platform.

Sections of your medical notes and data collected during the study may be looked at by individuals from the co-sponsors (University of Edinburgh and NHS Lothian), or other regulatory authorities where it is relevant.

Your GP will be informed that you are participating in the study with your consent. If any of your blood tests are outside of the normal range, there are any unexpected findings on your brain scan, or if we are concerned about your safety, we will give this information to your GP.

What are your choices about how your information is used?
You can stop being part of the study at any time, without giving a reason, but we may keep information about you that we already have. To withdraw from the study, you will need to inform the researchers involved.

What if I become unable to consent?
If at any point in the study you lose the ability to give informed consent – for example, if you develop difficulty understanding, remembering or communicating information about taking part – you will no longer be able to

take part in the research assessment. However, we may still use data that was collected before you lost the ability to consent and may also access data from your medical records.

Where can you find out more about how your information is used?

- At www.hra.nhs.uk/information-about-patients/
- From our leaflet available from www.hra.nhs.uk/patientdataandresearch. If you do not have access to the internet, please speak to the research team and we can provide you with a printed copy of this leaflet.
- By asking one of the research team

Who is organising this research?

This pilot study is being organised by Professor Harry Campbell, Professor Daniel Smith and Dr Iain Campbell, who work for the University of Edinburgh. They will be working as part of a wider team, including researchers in imaging, blood analysis, behavioural sciences and health economics, and dietitians. Please be aware this research team is not part of the NHS and is separate to any clinical care you receive. The study is being funded by The Baszuki Brain Research Fund and is sponsored by the Academic and Clinical Central Office for Research and Development (ACCORD), who take responsibility for the provision of insurance and indemnity.

Who has reviewed the research?

This study received a favourable ethical opinion from the South East Scotland Research Ethics Committee 02.

What if there is a problem?

If you have any questions or concerns about the study, please contact the researchers using the details below.

How do I take part?

If you are interested in taking part in the study after reading this information sheet, please contact the research team at ketostudy@ed.ac.uk. We will then contact you to arrange an initial telephone appointment.

We may ask you to do the following prior to attending your first face to face appointment:

- Complete a food diary, recording everything you have had to eat and drink for 3 days and send this back to us
- Complete a pre-ketogenic diet and nutrition history and send this back to us
- Download the ilumivu app on your phone – we can help you if you have not been able
- Download the ketomojo app on your phone – we can help you if you have not been able

Thank you for reading this information sheet

If you have any queries about the study, please contact the study team:
Study email: ketostudy@ed.ac.uk **Study office telephone/answer machine**: 0131 5376531
Study website: www.bipolarketostudy.com
***Dr Nicole Needham**, Project Coordinator: nneedham@ed.ac.uk*
***Professor Harry Campbell**, Chief Investigator: harry.campbell@ed.ac.uk*

If you would like to speak to someone independent and not involved in the study, please contact:
Prof. Stephen Lawrie Professor of Psychiatry, Centre for Clinical Brain Science, The University of Edinburgh
Email: s.lawrie@ed.ac.uk **Tel**: 0131 537 6671

If you have a complaint, please contact:

The University of Edinburgh Research Governance Team
Email: resgov@accord.scot

NHS Patient Experience Team
2 – 4 Waterloo Place, Edinburgh, EH1 3EG
Email: feedback@nhslothian.scot.nhs.uk **Tel**: 0131 536 3370