



Participant Information Sheet

Evaluating Nutritional Ketosis Versus the NHS EatWell Guide for Bipolar Depression: Single Blind Randomised Controlled Trial (ENERGISE-BD)

1. You are invited to take part in a research study

Before you decide, it is important that you understand why this research is being carried out and what it would involve for you. Please take time to read this information carefully. You may also want to discuss it with others. Please get in touch with us if anything is not clear or if you would like more information.

If you decide to take part, we will ask you to sign a consent form. If you choose not to take part, this will not affect the care you receive from your doctors. You can decide to stop taking part in the study at any time without giving a reason.

2. Important things you need to know

Bipolar disorder is a mental health condition which causes repeated episodes of low and high mood. Many people with bipolar disorder also experience long-lasting symptoms of depression, which can significantly affect everyday life. The current understanding of how bipolar disorder develops remains unclear, and treatments for the depressive symptoms are not always effective and often have unwanted side effects. Some evidence suggests that changes in diet might help treat depressive symptoms in bipolar disorder, so we are doing this study to investigate this further.

This study will compare the impact of using nutritional ketosis (following a diet which is high in fat and very low in carbohydrates, so your body will switch to burning fat for energy) or the NHS EatWell guide (eating a variety of foods to achieve a healthy, balanced diet) for 12 weeks on depressive symptoms in people with bipolar disorder. Each participant will be randomly allocated to one of the two diets, giving them an equal chance of being assigned to either group. They will continue their usual treatment for bipolar disorder at the same time. We will study aspects of mental and physical health before, during and after the diets to see if either is an effective treatment for bipolar depression.



3. Why are we doing this study?

Many people with bipolar disorder experience symptoms of depression, and both mental health professionals and the bipolar community would like to have better treatments available to help. Current treatments for depression in people with bipolar disorder (such as antidepressants) are not always effective and can cause unwanted side effects, including weight gain and increased risk of abnormally high mood. Therefore, there is a clear need to develop and test new treatments for bipolar depression. Dietary changes have been used as an effective treatment in patients with epilepsy, and using different diets may be helpful for patients with mental health conditions such as bipolar disorder too.

We are doing this study to compare the impact of using nutritional ketosis (following a diet which is high in fat and very low in carbohydrates) or following the NHS EatWell guide (eating a variety of foods to achieve a healthy, balanced diet) for 12 weeks on depressive symptoms in people with bipolar disorder. We are also investigating whether these diets affect other aspects of physical and mental health, if they are easy-to-follow, and if they are a cost-effective treatment option for people with bipolar disorder which could be used within the NHS. This could have a positive impact on the lives of people living with bipolar depression.

We would like to recruit 206 people who have been diagnosed with bipolar disorder and who have significant symptoms of depression. Each participant will be randomly assigned to follow one of the two diets for 12 weeks, with support from a dietitian throughout the trial. Assessments will be carried out before the diet starts and after it ends. Participants will also be asked to check the levels of ketones and glucose in their blood each day at home, using finger-prick blood tests and a KetoMojo device. Some of the participants in the study who are based in Edinburgh (72 people; 36 who are following each of the two diets) will undergo a Magnetic Resonance Spectroscopy scan of the brain before starting the dietary intervention, at week 6 and after finishing the diet (at week 12), so we can look for any changes in the way the brain meets its energy demands.

4. Why am I being asked to take part?

You are invited to take part because you have been diagnosed with bipolar disorder and are experiencing significant symptoms of depression.

5. Do I have to take part in the study?

- No, it is up to you to decide whether or not to take part.
- If you take part, you are still free to withdraw at any time and without giving a reason.
- Deciding not to take part or withdrawing from the study will not affect the healthcare that you receive, or your legal rights.



6. What will happen if I take part?

You will first have a phone or video call to answer any questions you might have about the study, and to check whether you are eligible to take part. If you would like to take part, we will then arrange an in-person appointment at the Royal Infirmary of Edinburgh Clinical Research Facility to answer any more questions you might have, sign a consent form, and begin the study assessments. We will give you a copy of the signed consent form. The different parts of the study are detailed below.

Who can take part?

To be eligible to take part in the study, you need to be an adult (over 18 years old) with a diagnosis of bipolar disorder and be experiencing significant depressive symptoms.

If you have certain conditions, such as liver failure or type 1 diabetes, you will not be able to take part in this study. If you are currently experiencing abnormally high mood (mania) you will not be able to take part. You will not be able to take part if you don't have access to a smartphone – as you will check the levels of ketones and glucose in your blood each day at home using finger-prick blood tests and a KetoMojo device, and then record these in a smartphone app.

You may also not be able to take part if you have previously used a diet to promote nutritional ketosis (within the last 2 months) or are using certain weight-loss medications, as this could affect the accuracy of the study measurements.

We will check your eligibility to take part in the study during the initial appointment. If you would like to ask any questions about this, please contact us via email (ENERGISE-BD@ed.ac.uk) or phone (07393142772).

What will I have to do?

We will ask you to be in the study for 24 weeks (about 5 and ½ months) and to follow the diet plan for 12 weeks (about 3 months).

Screening assessment (estimated to last around one and a half hours):

- This appointment will be by phone or video call, depending on your preference
- We will answer any questions you might have, collect basic contact details, and carry out an initial assessment to see whether you may be eligible to take part in the study by asking questions about your physical and mental health (especially around your symptoms of bipolar disorder)

Week 0: Consent, baseline assessment and diet allocation (estimated to last around three and a half hours, or five hours if you are undergoing a scan of the brain):

- This will be a face-to-face appointment with a member of the research team, held at the Royal Infirmary of Edinburgh Clinical Research Facility
- For this appointment, we will ask that you do not eat or drink anything except water for at least eight hours beforehand
- We will confirm if you are eligible to take part in the study
- You will be asked to complete a consent form if you would like to take part in the study
- You will be asked to complete a series of questionnaires, which will ask you about your demographic information, mental health and physical health
- We will take a blood sample to assess different markers of physical health



- We will measure your height, weight and blood pressure
- We will take a urine test to check you are not pregnant (if relevant to you); this is to confirm whether you are eligible to take part in the study
- Some of the participants in the study who are based in Edinburgh will undergo a Magnetic Resonance Spectroscopy scan of the brain, and further details about this are described later in this leaflet. Please note that this may take place up to one week later if it is not possible to do it on the same day
- You will then be randomly assigned to follow either nutritional ketosis or the NHS EatWell guide for 12 weeks, whilst continuing your usual treatment for bipolar disorder
- A trained research dietitian will provide a dietary package containing all the information you need to start and follow your allocated diet, including recipes
- You will be shown how to check the levels of ketones and glucose in your blood each day at home, using finger-prick blood tests and a KetoMojo device – including how to download and use an app on your phone, how to use the device and how to record your results
- We will offer you two weeks of pre-prepared meals to make your transition onto your allocated diet easier

Dietary intervention period (lasting 12 weeks):

- You will receive support from the study dietitian, including weekly check-ins with the research dietitian throughout the 12-week diet plan (this can be by phone, video call or in-person appointments, depending on your preference)
- You will be asked to check the levels of ketones and glucose in your blood each day at home, using finger-prick blood tests and a KetoMojo device, and to submit these measurements via the smartphone application
- If you have trouble entering your measurements into the smartphone application, we will help you.

Week 6: Follow-up assessment (estimated to last around two hours) – only for participants who had a Magnetic Resonance Spectroscopy brain scan before starting the diet

- If you had a Magnetic Resonance Spectroscopy brain scan before starting the diet, you will receive the same scan after six weeks
- This will take place at the same time of day as your previous scan, and again, we will ask that you do not eat or drink anything except water for at least eight hours beforehand

Week 12: Follow-up assessments (estimated to last around one and a half hours, or three hours if you are undergoing a scan of the brain):

- This will be a face-to-face appointment with a member of the research team, held at the Royal Infirmary of Edinburgh Clinical Research Facility
- For this appointment, we will ask that you do not eat or drink anything except water for at least eight hours beforehand
- You will be asked to complete the same series of questionnaires which you completed before starting the diet
- We will take another blood sample to assess the same markers of physical health measured before you started the diet, to look for any changes
- We will measure your weight and blood pressure



- If you had a Magnetic Resonance Spectroscopy brain scan before starting the diet, you will receive the same scan again

Week 24: Follow-up assessments (estimated to last around one hour):

- You will receive a phone or video call to complete a series of questionnaires about your mental and physical health

What is nutritional ketosis?

- Nutritional ketosis involves following a diet which is high in fat and very low in carbohydrates, so your body will switch to burning fats as its primary source of energy.
- With support from the research dietitian, you will aim to consume around 60-75% of your calories from fat, 5-7% from carbohydrates and the remainder from protein.

What is the NHS EatWell Guide?

- The NHS EatWell Guide shows how to eat a healthy, balanced diet by including a variety of foods from the different food groups.
- With support from the research dietitian, you will aim to eat five portions of fruit and vegetables per day, consume around one-third of your calories from starchy foods (such as pasta or potatoes), have lean sources of protein (such as chicken, fish or beans), eat some sources of dairy (such as milk, cheese or yoghurts) or alternatives (such as soya products), eat some healthy fats (such as olive oil), and have smaller amounts of foods high in fat, salt and sugar (such as chocolate, biscuits and cakes) less often.

What is a Magnetic Resonance Spectroscopy brain scan, and what is involved?

This brain scan will happen inside a Magnetic Resonance Imaging (MRI) scanner at the Edinburgh Imaging Facility at the Royal Infirmary of Edinburgh. MRI scanning is a safe method that uses a strong magnet and radio waves to take pictures of the brain without using X-rays or other harmful radiation. A special type of MRI called Magnetic Resonance Spectroscopy will measure certain chemicals in your brain, allowing us to track any changes caused by the diet.

MRI scanning is a safe procedure with no known side effects. However, we do not scan people who have certain kinds of medical implants, like heart pacemakers or some metal clips, or who have metal fragments in their eyes. Many other implants, such as hip replacements, do not necessarily stop someone from having an MRI scan. We cannot scan pregnant people for research purposes, so please tell us if you might be pregnant, because you would not be able to take part in this study.

A minority of people find Magnetic Resonance Spectroscopy brain scans anxiety-provoking and may experience a fear of small spaces (claustrophobia) during the scans. The scanner makes loud tapping noises, so you will be provided with earplugs or headphones to block the sound. You will be given an emergency buzzer which can be used if you wish to stop the scan or come out of the scanner at any time.

When you come for your scan, you will need to put all personal items such as keys, watches, phones, and bank cards in a safe locker. Please do not wear makeup and be ready to take out contact lenses and piercings. The scan will take about one 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>).

Research shows that for every 1,000 people who volunteer for an MRI brain scan, about 50 will have an abnormality detected on the scan. Mostly, these investigations show that no further action is needed, but some people may require immediate medical attention. Your brain scan will be reviewed by a doctor trained in assessing scans (a radiologist), and we will inform you and your General Practitioner (GP) of any significant abnormalities.

Can I continue with my allocated diet after the study has ended?

After you complete the follow-up appointment after week 12 of the diet, the research dietitian will guide you on how to gradually stop your assigned diet if you wish. You will be provided with information about both diets should you wish to consider staying on your assigned diet or switching to the other diet.

What is random allocation to a study treatment?

- Random allocation to a study treatment means each person is placed into one of the treatment groups by chance, not by choice. This makes sure the groups are very similar at the start, so it is fair to compare the effects of the treatments.
- You have an equal chance of being in either group (50:50 chance). This means you have the same chance of being allocated to follow the nutritional ketosis intervention or the NHS EatWell guide.
- The researchers do not choose which of these two dietary interventions you receive; a computer system decides for you.
- The only intended difference between the two groups is the treatment itself; both groups will continue to receive their standard care for bipolar disorder in addition to the study treatment.
- You will be informed about which study group you are in.
- We will write to your General Practitioner (GP) (and if applicable, your psychiatrist) to let them know that you are taking part in the study.

Process evaluation

We are also carrying out a process evaluation as part of this trial. The aim is to understand how the trial is delivered, how patients and healthcare professionals experience it, and whether any improvements can be made for future studies.

You do not have to take part in this evaluation. However, taking part would help us improve how the trial is run and you will be compensated for your time.

If you choose to take part, you may be invited to a short interview (in person, online, or by phone) at different points during the trial. If you agree to share your contact details with the process evaluation team, they will provide more information about what taking part involves.

7. What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part?



There are no guaranteed benefits to taking part in this study. However, potential benefits may include:

- Learning more about your mental health and mood over the time you spend in the study, and how they relate to changes in your diet.
- Education and advice on a dietary intervention from a qualified dietitian.
- The results from this study may help us to improve treatments for people with bipolar depression in the future, and your participation could make a meaningful impact on this important area of research.

What are the possible disadvantages of taking part?

You may find the study time-consuming, as it will last 24 weeks and require you to attend between 3 or 4 face-to-face appointments, depending on whether or not you are one of the participants who will undergo brain scans (Magnetic Resonance Spectroscopy). You will also receive additional input from a dietitian.

Appointments will include questionnaires which may take some time and ask sensitive questions about your personal and mental health history. If any questions upset you, you should talk to the research team for support and advice on getting more help if needed.

Changing your diet can be challenging, especially if you are making significant changes in comparison to your ordinary diet. This will vary between participants. Following either the NHS EatWell guide or nutritional ketosis requires planning of meals and shopping for food, which may be more difficult when you are depressed. Both dietary interventions may be more expensive than your ordinary diet.

Nutritional ketosis may cause side effects including stomach upset, nausea, vomiting, changes in bowel habits (particularly constipation), hunger, thirst, headaches, tiredness, irritability, weight loss, low blood sugar (hypoglycaemia), high levels of fat in the blood (hyperlipidaemia), high levels of ketones in the blood, leg cramps, or irregular periods in women. As nutritional ketosis involves eating a high proportion of fat, it may increase levels of fat in the blood (cholesterol and triglycerides). These levels will be monitored before and after the dietary intervention. High levels of fat in the blood (cholesterol and triglycerides) usually return to normal when the diet is weaned.

Changing your diet to follow the NHS EatWell guide may cause side effects such as stomach upset, bloating or changes in bowel habits (including constipation or looser bowel movements).

In line with recommendations, we will advise you to drink enough fluids to stay well hydrated and take a multivitamin and mineral supplement that meets the recommended daily allowances. If you choose to continue either of the diets beyond the 12-week study period, we recommend continuing the multivitamin.

The dietitians will have a manual detailing what to do in specific situations, and you will be encouraged to contact the dietitian if you have any concerns. You will also have the contact details of a psychiatrist on the research team, who will be available during normal working hours to answer any questions you may have.

Blood tests, including daily finger-prick blood tests, may be uncomfortable or upsetting especially if you are afraid of needles. They may cause small bruises.

There is a small chance that blood tests or brain scans might find unexpected abnormalities. If there are significant abnormalities, we will inform you and your General Practitioner (GP).



If serious, unexpected problems happen because of the dietary interventions, the research team may stop the study early to keep participants safe.

8. Will I be reimbursed for taking part in the study?

- We will reimburse all enrolled study participants for reasonable travel, food and drink, and accommodation expenses incurred for all in-person study visits.
- In recognition of participants' time, participants will receive three payments of £50 over the course of the study: after the baseline appointment, after the 12-week follow-up appointment, and after the 24-week follow-up appointment.
- In addition, participants who undergo brain scans (Magnetic Resonance Spectroscopy) will receive £30 for each scanning visit. This includes the additional study visit at week 6.

9. Samples and genetic tests

What samples will I be asked to donate?

A trained professional will collect blood samples from your arm (approximately 15 millilitres or 3 teaspoons per appointment), which will allow us to look at different markers in your blood before and after the 12-week dietary intervention.

What will happen to the samples I give?

Samples will be analysed in the appropriate local NHS laboratory department and destroyed as per standard laboratory procedure. They will only be accessed by authorised personnel in the laboratory department.

If you agree, a sample of the blood will also be frozen and stored for future use in other ethically approved studies for up to ten years. All samples will be securely destroyed after this period.

Will genetic tests be performed?

No, genetic tests will not be performed.

10. More information about the study

Who is organising and funding the study?

The University of Edinburgh and the NHS Lothian Health Board have joint overall responsibility for this study and are the sponsors of this research. The Wellcome Trust are the funder of this study. Professor Rebecca Reynolds is the Chief Investigator in charge of the study.



Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee. A favourable ethical opinion has been obtained **from East Midlands - Leicester South Research Ethics Committee**. All participants are covered by the University of Edinburgh's insurance policy, which is checked before the study starts. Local NHS approval has also been given. When designing this study, we have taken into account patients' opinions on what is involved in the study. A group with lived experience of bipolar disorder have reviewed and commented on this participant information leaflet.

Is there anything I need to do or avoid?

- You will need to attend the clinic and Magnetic Resonance Spectroscopy brain scan visits after an overnight fast of at least 8 hours (no food or drinks to be consumed except water) and having avoided alcohol and recreational drugs for the previous 24 hours.
- You should continue with your regular treatment/medication (if any) throughout the duration of the trial.
- You will be asked to change your diet over a 12-week period with support from a research dietitian.
- If you are pregnant or planning to become pregnant, it is not suitable for you to take part, as we don't know the impact of these diets in pregnancy. If you were to become pregnant (or your partner becomes pregnant with your baby), you should let the study team know, as we will want to follow up with you until the end of the pregnancy.

What will happen to the results of the study?

When the study is finished, we will offer all participants a summary of the study results, whatever the results show, if you would like to receive them. It is your choice whether or not you receive the results. The summary will be written in clear, easy-to-understand language and sent to you using the contact details you have given us. We will also publish the same summary on the study website so that it is available to all participants and anyone else who is interested. We will let you know when the results are expected to be available and will share them as soon as we can. If you need the results in a different format or have any communication needs, please let us know and we will do our best to provide them in a way that is accessible to you. Patients and members of the public will help us make sure the results are clear, relevant and easy to understand. This study will be written up for publication in scientific journals and presented at conferences. The findings of the study will be shared, but individual names or identifying information will never be disclosed.

Your identity and any personal details will be kept confidential. No named information about you will be published in any report of this study.

What if new information becomes available during the study?

If new information becomes available which might influence whether you should continue to take part in the study, we will contact you by email or post.

What if there are any problems?

If you have a concern about any part of this study or wish to complain, please refer to the contact details at the end of this leaflet to identify the appropriate person to contact.



In the unlikely event that something goes wrong and you are harmed by taking part due to someone's negligence, you may be able to take legal action for compensation against your local NHS trust. You may have to pay your legal costs.

The normal NHS complaints mechanism is also available to you, if appropriate.

What will happen if I don't want to continue the study?

If you would like to withdraw from the study, please contact the study team via email:

ENERGISE-BD@ed.ac.uk

- You are free to withdraw from the study at any time without giving a reason, but data already collected up to the point of withdrawal will still be used, as this is important for maintaining the integrity of the research.
- If you wish to stop your allocated dietary intervention, you will be offered the option to continue with follow-up measures.

If you lose the ability to understand information and use it to make decisions about your ongoing participation in the study (lose capacity), you will be withdrawn from the study, but data already collected will still be used.

11. What will happen to information collected about me during the study?

Please read the GDPR Information Leaflet for detailed information about how your data will be collected and handled.

12. Contacts for further information

Contact the central study team with questions or about participating:



Email: **ENERGISE-BD@ed.ac.uk**

Telephone: **07393 142772**

Website: www.medicine-vet-medicine.ed.ac.uk/energise-bd

You can obtain independent advice about this study by contacting:



Name: **Professor Charlotte Hanlon**

Job title: **Chair of Global Mental Health**

Address: **Division of Psychiatry, Institute for Neuroscience and Cardiovascular Research, University of Edinburgh**



Email: chanlon@ed.ac.uk

Telephone: 0131 650 1000

The contact for complaints in your NHS region is:

Edinburgh:

Name: NHS Lothian Patient Experience Team

Address: Mainpoint, 102 Westport, Edinburgh, EH3 9DN

Telephone: 0131 536 3370 (open Monday to Friday, 9 am to 2 pm)

Email: loth.feedback@nhs.scot

Thank you for taking the time to read this information sheet and for thinking about taking part in this study.



Participant ID:

Centre ID (if applicable):

CONSENT FORM

Evaluating Nutritional Ketosis versus NHS Eat Well Guidelines for Bipolar Depression: Single Blind Phase III Randomised Controlled Trial (ENERGISE-BD)

			Please initial box
I confirm that I have read and understand the Participant Information Sheet for the above study.			
	*Date (DD/MM/YYYY)	*Version Number	
Participant Information Sheet			☐
<i>*complete during the consent process</i>			
1. 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 understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the Sponsors (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.			☐
5. 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 / Edinburgh Clinical Trials Unit for administration of the study.			☐
6. I give permission for my personal details (name, address, phone and email) to be shared with university approved suppliers for the purpose of providing a two-week supply of the allocated diet.			☐
7. I understand my data will be transferred from the KetoMojo app and stored on a secure computer server in Europe managed by MyMojoHealth.			☐
8. I agree to my General Practitioner and psychiatrist (if applicable) being informed of my participation in the study and being contacted by the research team if it's relevant to my medical care.			☐



	Please initial box	
9. I understand that data collected about me during the study may be anonymised and used for future ethically approved studies.	☐	
10. I agree for my contact details to be accessed by the Process Evaluation team, and for them to contact me with further details of the process evaluation.	Yes ☐	No ☐
11. I agree to be contacted about ethically approved research studies for which I may be suitable. I understand that agreeing to be contacted does not oblige me to participate in any further studies.	Yes ☐	No ☐
12. I agree to provide a sample of blood which will be frozen and stored for future use in other ethically approved studies.	Yes ☐	No ☐
13. I agree to be contacted with a summary of results of the study.	Yes ☐	No ☐
14. I agree to be contacted up to 5 years after completion of the study, to assess for longer-term outcomes of the study, if this is possible for the research team to do so.	Yes ☐	No ☐
15. <u>FOR EDINBURGH-BASED PARTICIPANTS ONLY:</u> I give permission to the research team to perform Magnetic Resonance Spectroscopy brain scans as part of this study, and to access the results. I understand that I am not being scanned at the request of my medical doctor for any specific medical condition. I am aware that my scans will be viewed by a doctor in medical imaging who will provide an imaging report. I agree to my clinical care team, including my general practitioner, being informed of any unexpected findings on my brain scan report. I am aware that unexpected findings occur in some study participants.	Yes ☐	No ☐
16. I agree to take part in the ENERGISE-BD study.	☐	

Name of Person Giving Consent	Date	Signature
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