Participant Information Sheet – MixLi study

Study title: Lithium orotate: a potential accessible supplement for people experiencing depression

IRAS ID: **329291** REC ID: **24/LO/0620** Chief Investigator: **Dr Rebecca Strawbridge**

We would like to invite you to take part in a research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it would involve. Please take as much time as you need to read the following information carefully (at least 24 hours). Talk to others about the study if you wish and please contact the study researchers for any explanations, more information, or questions you may have. Take time to decide whether or not you agree to take part.

Information about the study is provided in two parts:

- Part 1 tells you the purpose of this study and what will happen if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

PART 1

1. What is the purpose of the MixLi study?

The main aim of our study is to find out whether we can test a natural supplement to see if it can help people who are having treatment for depression . The supplement is called lithium orotate. This is already available to buy in health food outlets and online, and people have been using it this way for a long time. We know that it is safe to take, but it has not been rigorously tested in research studies for its potential benefits. This is detailed more in part 2 of this sheet.

2. Why have I been invited?

The study is looking for people who are aged between 18-65, who are having treatment for depression but are still experiencing symptoms. People who have a very disabling illness or for whom lithium is not suitable for (for example due to other medications taken) will unfortunately not be able to take part, but we will make sure of this with you beforehand.

3. Do I have to take part?

No, this is completely voluntary - it is up to you to decide whether to take part. If you do, we will go through the study information, you will be given this sheet to keep and be asked to sign a consent form. You will be free to stop taking part at any time and you don't need to give a reason. A decision to not be in the study at any time will not affect any aspect of your usual care. If you agree, we may also contact you to ask for feedback or invite you to take part in other studies we are doing. This is optional and will not affect your taking part in the MixLi study.

4. What will happen if I take part?

If you decide to take part in the study, first we will ask you questions about yourself and your past experiences. This should take about 25 minutes over the phone or on video-call (via "Microsoft Teams") – whichever you prefer. If the research team finds you to be eligible to take part, then we will make an appointment to begin the study.

Taking part involves the following visits, which would be to Denmark Hill (South London, close to the train station). There is some flexibility in the times below, so we will always try to arrange days that are convenient for you.

1) The first visit will include a blood test, some 'thinking skills' exercises, as well as questionnaires about your life and mood. This usually takes 1 hour, and we can take as many breaks as you wish.
2) After this, you will be given the lithium supplement with information all about it to take home. You will be asked to start taking up to four of the lithium supplement capsules per day, starting the day after the study visit.
3) After two weeks, we will ask you to come back for another blood test and to repeat the questionnaires and thinking skill exercises, which takes around 45 minutes to complete.
4) The above visit will be repeated *six* weeks later (8 weeks after first visit).
5) The above visit will be repeated *eight* weeks later (16 weeks after first visit)
6) The final visit will be 6 months after the first visit. We ask you to repeat the same exercises above as well as a few final questions (around 1 hour), which will let us find out if any changes have taken place while you were taking the lithium supplement.

In summary, the study includes five visits to the research site, over a six-month period during which you are asked to take the lithium supplement, if you are happy to.

Each appointment includes:

- *Blood test:* this is very quick and similar to most blood tests you would have in usual care.
- *Thinking skills exercises:* These are exercises measuring things like memory, concentration, planning and reasoning. They take about 15 minutes.
- *Questionnaires:* With the researcher, questionnaires are about things like illness experiences, daily life functioning, quality of life, mood, sleep quality, and difficulties with thinking skills.

If you agree, we will also send you a daily message or help you set yourself a daily alarm, to remind you to take the lithium supplement.
The main parts to the study can be seen in the flow diagram on the next page.

5. What is a lithium supplement?

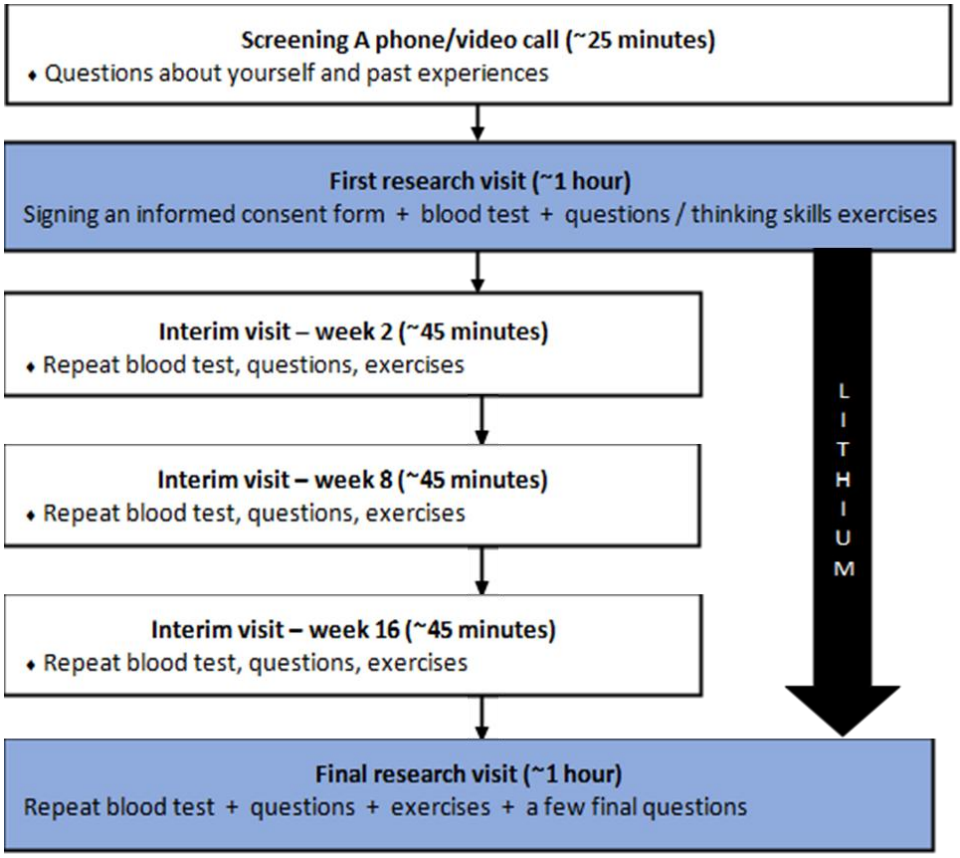
Lithium is a natural mineral salt – a bit like sodium – and is present in very small quantities in most rocks. As a result, there are tiny amounts of lithium in mineral water (usually less than 1 milligram per litre). In some areas of the world, these are naturally higher than others. There is some evidence that dementia and suicide rates are lower in these areas with higher lithium in drinking water. When used as a medication, people take doses of lithium usually between 300-1500mg per day (these forms actually contain 56-281mg of lithium itself).

Supplements of lithium in low doses are available to buy because these are judged to be safe, in doses between 5-20mg of lithium per capsule. We would like to study people taking lithium in these doses, which appear a) safe, b) potentially beneficial and c) are available already for people to take over the counter as a nutritional supplement.

We suggest people take 4 x 5mg capsules per day (adding up to 20mg) every day. If at any time, for any reason, people feel that the dose they are taking is too much, they can reduce this. They can also stop taking it anytime they wish. The bottle states "take one veggie capsule per day with food and water". There are many other lithium supplements available to buy over the counter which are 20mg (containing exactly the same amount of lithium and orotate), which are safe. The reason we provide 5mg capsules instead of 20mg is that you then have more flexibility about how much you take. The other difference between this study and the bottle is the statement advising not to take this product if you are "taking any prescription medications, especially antidepressants or MAOIs [monoamine oxidase inhibitors]." Although there are some medications which would mean you could not take part in this study, there is strong evidence of no safety problems taking both antidepressants and lithium supplements. We will provide more information about lithium and the supplement and you can review this before you decide to take part. We will also chat with you about any medications that you are taking before taking part, to make sure that it is safe to take them with the lithium supplement.

The study team will be available to talk through any questions, concerns, difficulties or curiosities that people who are taking part might have. They will be available 9am-5pm on weekdays and will always aim to call people back within 2 hours.

Study process:



6. What reimbursement will I receive for taking part?

For each of the 5 visits, you will be given £24, to thank you for giving your valuable time to the study. We can also cover travel expenses up to £10 per visit, and will consider additional travel expenses if you require more. The total amount will usually be paid in one instalment after your last visit, although if you are in need of earlier

payment, please speak with the research team about this. You will be reimbursed for all study assessments you attended, even if you choose to stop taking part before study end.

7. How will you use information about me?

In this research study we will use information from you. We will only use information that we need for the research study. We will let very few people know your name or contact details, and only if they really need it for this study. Your data will have a unique code number instead. Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules. At the end of the study, we will save some of the data in case we need to check it and, if you consent to that, for future research. We will make sure no-one can work out who you are from the reports we write. Part B tells you more about this.

8. What are the possible benefits of taking part?

Lithium is known to help people with bipolar disorder and depression improve their mood, as well as other parts of everyday living. There is some evidence that lithium can also help people with dementia, people who are suicidal, and people with some viruses. Although we are using lower doses, as a supplement, compared to most previous research, we hope that you might find benefits to your mood and/or thinking skills and possibly other areas of life. Whether you experience benefits or not, findings from this study may help people in the future, as supplementary lithium is being tested to see if it is helpful for people experiencing a range of mood and brain conditions. Your taking part is valuable for helping us understand lithium and in identifying possible strategies to help people with brain-related difficulties. If you would like to know about the study's findings overall, we will send you this information.

9. What are possible disadvantages or risks of taking part?

The evidence shows that supplementary lithium is safe and very acceptable for people with different conditions. Supplementary lithium has been available to buy and been taken by many people for decades, and there have not been concerns raised in scientific literature. Secondly, we have reviewed all published evidence of studies using low doses of lithium (mostly still higher doses than in this study, and all 17 studies reported the lithium to be safe. In many of these studies, people were also taking antidepressants). Though there are potential risks to kidney and thyroid function, there is no evidence of this occurring from taking supplementary lithium, and is generally associated with taking much higher doses of lithium over an extended period of time. Just in case, we are not recruiting anyone for MixLi who has any known issues with their thyroid (if untreated) or kidneys.

As such, we do not expect any significant risks or negative effects associated with taking part in the study. If you feel any distress during a visit, or are experiencing any negative effects from the lithium or the study, please let the research team know. We would like to reassure you that we are monitoring people's wellbeing while they are taking part in the study, and this is the main reason why we ask people to come in for blood tests and checks quite often. If we do find anything to be worried about, we will let you know and 1) ask you to stop taking the lithium if it is indicated, 2) tell your GP or named healthcare professional.

We hope that the visits will not cause difficulties. Sometimes when doing 'thinking skills' exercises, people can feel frustrated or worried that they are not performing well, and sometimes focusing on any difficulties can temporarily affect mood. Sometimes filling in questionnaires about mood can also temporarily affect mood. For this reason, we highlight that we are only asking for information where it is needed to answer relevant questions in the study, we offer people as many breaks during visits, and try to assist and minimise difficulties in any way that we are able to. Therefore, please do let the study researcher know if you are experiencing any

distress at any other time during the visits. We also ask this if you find any of the tests or questionnaires stressful at a later time.

10. What if there is a problem?

In the first instance, the research team will do what they can to support you and resolve any problems. However, any complaints about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. You can find detailed information in Part 2.

11. What happens when the research study stops?

When the study stops, you can receive a summary of changes in things we have measured during your participation in the study. We could also send a summary to your healthcare professional. Later, if you would like to know, we will keep in touch to let you know the results of the study with a brief newsletter.

12. Will my taking part in the study be kept confidential?

Yes. We will follow ethical and regulatory guidelines. Information about your participation in this study will be anonymous and handled in confidence. The details are included in Part 2.

Contact Details: If you would like more information, or to discuss the study with a member of the research team, please contact us on lithium@kcl.ac.uk or 07570 661382.

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are thinking about participating, please continue to read the information in Part 2 before deciding.

PART 2

13. Can you tell me more about the study, and the reasons for doing it?

We know that lithium (in doses usually above 100mg) is an effective medication for people with depression and bipolar disorders, and there is also evidence that it can effectively treat suicidal thoughts and behaviours, and also symptoms of dementia. We know that lithium is generally safe in these medication doses, but there are risks of problems with the kidney and thyroid amongst others. In doses between 0.3 – 100mg, lithium has shown benefits to mood and cognition (thinking skills) without safety concerns.

We believe that it is very important to identify things that may help which are both safe and accessible to high numbers of people and that can be taken for a long time if felt to be beneficial. A downside of lithium as a medication is that it often has side effects in high doses, but this has not been evidenced in its form as a supplement. Some people prefer natural substances that they can purchase and manage themselves, but some natural supplements are not effective because bodily systems do not fully absorb the ingredient into its circulation, and some supplements have not been subjected to high quality evidence. We are researching a supplement that can be accessed easily, is suggested by current evidence to be potentially helpful and that can be subject to rigorous scientific evidence to show if it is safe and effective.

14. What if relevant new information becomes available?

Sometimes during the course of a research study, new information becomes available about the therapy or the illness being studied, that is relevant to the project or participants. Although unlikely, if this happens, a study researcher will tell you about it and discuss whether you want to continue in the study. If you decide to

continue in the study, you may be asked to sign an updated consent form. If the study is stopped for any other reason, you will be told why and will have opportunities to talk this through with a researcher.

15. What will happen if I don't want to carry on with the study?

The decision about whether to take part is entirely yours. You can decide not to take part and you are free to stop at any time, without having to give a reason, and this will not affect your care in any way. If you decide to stop, we will keep the data we have already collected from you, but you will not have to take part further in the study. We will also securely destroy any blood samples you have given us. The same will apply if for any reason you are no longer able to make an informed decision about continuing to take part, for example if your health worsens.

16. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The lead researcher is Dr Rebecca Strawbridge; becci.strawbridge@kcl.ac.uk. If you remain unhappy and wish to complain formally, you can do this through the South London and Maudsley NHS Foundation Trust (SLaM) Patient Advice and Liaison Service (PALS) on 0800 731 2864, pals@slam.nhs.uk. In the event that something does go wrong, and you are harmed during the research, you may have grounds for legal action for compensation against King's College London (KCL) and/or SLaM NHS Foundation Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. If you have any medical concerns that cannot wait until you can talk to a member of our team, you should get help from your GP using the information in this sheet to tell them about the study. At the beginning of the study, we will ask you to give us the contact details of a healthcare professional that you can see regularly. This will usually be a GP, care coordinator, or keyworker. We will tell them that you are taking part in the study. If we are concerned about you during the study, such as if you become significantly more depressed, or express thoughts of harming yourself or others, it is possible that we will contact your named healthcare professional. We will make an effort to ask for your approval before doing this.

17. What kind of data will be collected about me?

We will record the following type of data about you:

- Name and initials
- Contact details (telephone number/email address/postal address). Telephone number and email address are so we can be in contact with you throughout the study. Postal address (if you agree) is so that we can send you the lithium supplement when needed. If you do not agree to sharing your postal address, you would need to come in between other visits and collect the supplement. Each of these will be destroyed at the end of the study. The only thing we would keep is your email address and/or telephone number and this is only if you consent for us to contact you again in the future.
- Demographics, clinical/medical history, current medications and health.
- Results of exercises/questionnaires/other assessments you undertake at study visits (about your thinking skills, daily life functioning, quality of life, mood, health and difficulties with thinking skills).
- Markers from blood tests, including levels of lithium and other proteins.

18. Will my taking part in this study be kept confidential?

Other than informing your named healthcare professional, your participation in the study will be kept confidential. In addition, if you are in significant distress or if there are significant concerns about your or

someone else's safety while taking part, the research team may deem it necessary to inform your named healthcare professional or the relevant authorities.

All information collected about you during the study will be strictly confidential: at the beginning, you will be given a unique number that will be used to identify all information we keep about you. Information that can directly identify you (e.g., your name, contact details) will be kept in a separate password-protected document, so that it is not possible to identify any data stored about you. Only researchers involved in the study will have access to this data, although they will keep your named healthcare professional informed if there are concerns during the study, and the researcher can write a brief report after the study, to be sent to them, if you wish. All data will be collected directly from you - we will not access any medical records or ask for information from your healthcare professional(s). After the end of the study, non-directly identifiable data collected from you will be looked at by authorised members of the research team (e.g., statisticians). They have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research team. The data will be stored for 10 years and then disposed of securely. The procedures for handling, processing, storage and destruction of their data are compliant with the Data Protection Act 2018.

19. How will you use information about me?

We will need to use information from you for this research project (mentioned in section 16 above). All information will be collected as part of study visits and members of the research team will not access your medical records. The information will include your name and contact details. People will use this information to conduct the research or to check your study records to make sure that the research is being done properly. People outside of the research team who do not need to know who you are will not be able to see your name or contact details. Your data will have a unique code number instead. We will keep all information about you safe and secure. Specifically, information will be held securely on paper and electronically. Your data will be stored on a password protected computer, on secure university servers, and written in research notes which are stored securely in locked filing cabinets. 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.

For blood samples, the tubes will be labelled with your unique study ID code and not with any personal information. All samples will be collected at King's College London / South London & Maudsley NHS Foundation Trust, and they will then be kept secure in a freezer within a locked room at the laboratory where the analysis takes place. Biological samples you give will only be used for the purposes of the study outlined here and then discarded securely. Following analysis, if there are any concerns about the results from your sample, we will notify your named healthcare professional for further review. After samples are analysed, they will be securely destroyed.

Most information about you will first be recorded on paper during study visits. It will be stored in lockable, fire-proof filing cabinets. These documents will later be scored by study researchers and then uploaded to a secure database provided by King's College London and held on their secure servers. This database will not contain any information that can directly identify you (e.g., your name, contact details).

20. What are my choices about how my information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. If you agree to take part in this study, you will have the option to take part in future research using your (anonymous) data saved from this

study. We ask you for your permission to use information that you provided for future research, but you can 'opt out' of this and still take part in the study.

21. Where can I find more about how my information is used?

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

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.kcl.ac.uk/research/support/research-ethics/kings-college-london-statement-on-use-of-personal-data-in-research (KCL) or https://www.slam.nhs.uk/about-us/privacy-and-gdpr (SLaM)
- by asking a member of the research team
- by sending an email to info-compliance@kcl.ac.uk (KCL) or dataprotectionoffice@slam.nhs.uk (SLaM)

22. How long are you going to retain the information collected from me?

We will only keep identifiable information about you (name, contact details) and the data you provided for as long as reasonably necessary to fulfil the purposes we collected it for the current study. However, with your permission, we will a) keep your details in a secure password-protected electronic file for researchers to invite you to take part in future studies, and b) store your anonymous data for use in future studies and share this data with other researchers, inside or outside the UK, working in collaborative projects with the Lead Investigator (Dr Rebecca Strawbridge). This permission is optional and does not affect your study participation in any way. When the study is completed or if it is stopped for any reason, we will hold your data for 10 years. When the data is destroyed, this will be done securely.

23. What will happen to the results of the research study?

When complete, the study's results will be written and published in international scientific journals and presented at conferences (including scientific and public meetings). We will also share our results on social media and other websites. We will also produce a newsletter summarising the findings of the study which we will send to you, if you wish. You will not be identified in any report or publication.

24. Who is organising and funding the research?

The study is organised by the Centre for Affective Disorders at King's College London. The lead sponsor of the study is King's College London jointly with South London and Maudsley NHS Foundation Trust. The study is funded by a charity called the Psychiatry Research Trust.

25. Who has reviewed the study?

This study has been reviewed by scientists as part of a Psychiatry Research Trust funding application process (as well as similarly, previously, as part of another funding application process). The Health Research Authority and a Research Ethics Committee have also reviewed and approved the study: a favourable ethical opinion for conduct in the NHS was given by the London - Westminster Research Ethics Committee on 4th October 2024 (reference 24/LO/0620).

26. Further information and contact details

You are encouraged to ask any questions before joining this study. If you have any questions about this study or require further information, please speak with a study researcher or the Lead Investigator. If you are still unsure as to whether you would like to participate you may wish to discuss this with your GP, another healthcare professional or people close to you. If you have any concerns, please contact the team (details above). If you would like to know more about how your information is used, you can:

- visit https://www.hra.nhs.uk/information-about-patients/

- ask the study researcher you have been in contact with

Study email address: lithium@kcl.ac.uk
Lead Investigator email address: becci.strawbridge@kcl.ac.uk
Postal address: PO74 Centre for Affective Disorders, IoPPN, King's College London, SE5 8AZ.

Thank you for taking the time to read this information & thinking about taking part in the study! Please feel free to keep a copy of this information sheet. You will also be given a copy of the consent form if you decide to sign it.