PROTOCOL FULL TITLE

Lithium orotate: a potential accessible supplement for people experiencing depression with mixed features.

MixLi

Study Identifiers

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1. Study Synopsis

TITLE OF STUDY:	Lithium orotate: a potential accessible supplement for people experiencing depression with mixed features.
Protocol Short Title/ Acronym:	MixLi
Study Phase If Not Mentioned In Title:	Feasibility open label study
Sponsor Name:	King's College London & South London and Maudsley NHS Foundation Trust
Chief Investigator:	Dr Rebecca Strawbridge

Medical Condition or Disease Under Investigation:	Episode of major depression with mixed features
Purpose Of Clinical Study:	To establish initial feasibility of studying a commercially available supplement (lithium orotate; LiOr) for its potential mood effects in people with depression including mixed features (DMF).
Primary Objective:	This is a feasibility study comprising the preliminary work required, prior to formal (initially feasibility) trials examining commercially available LiOr supplementation for people with DMF. A single arm open label study in volunteers with DMF will explore four co-primary objectives: 1. The potential to examine bioavailability of LiOr, assessing lithium levels in serum. 2. The acceptability of 20mg daily LiOr over 6 months (assessed by self-report adherence and discontinuation rates) to inform a future study design. 3. Description of positive and/or negative effects of 20mg daily LiOr over 6 months (assessed via participant-report) to inform a future study design. 4. The feasibility of the protocol including intervention delivery and assessment visits (including assessments mentioned above, plus putative primary (depressive and (hypo)manic symptoms) and key secondary outcomes (functioning, cognition) as well as assessment of potential confounders. Overall feasibility will be assessed via missing data and study withdrawal rates.
Secondary Objective(s):	Exploratory analysis of change in measures over time to inform a future definitive study design: 1. Biological measures: (1) key candidate blood-based biomarkers, namely neuroprotective growth factors (BDNF, VEGF) and inflammatory cytokines (IL-6, TNFα, IL-1b, IL-8, CRP). 2. Symptom measures (mood symptoms, both depressive and (hypo)manic). 3. Functional measures (psychosocial functioning and cognition).
Study Design:	The study is a single site, unblinded single arm open label study of LiOr for people with DMF.
Endpoints:	Throughout the protocol, week 0 refers to the baseline assessments; all other references to “week” timepoints anchor from week 0. Week 0: Baseline assessment, pre-intervention Week 2, 4, 8, 16: Intermediary follow-up assessments Week 26: Final follow-up assessment
Sample Size:	40 individuals.

Summary Of Eligibility Criteria:	Aged between 18-65 at study entry. Meet DSM-5 criteria for a current depressive episode and exceed thresholds indicating presence of mixed features. Undergoing antidepressant treatment (stable intervention/dose unchanged for >6 weeks). No diagnosis of bipolar disorder received. No other severely impairing health condition. No contraindications to lithium treatment (including currently taking lithium). No significant suicidality.
Intervention (Description, frequency, details of delivery):	Open label lithium orotate supplement as available commercially, 20mg once per day. Participants will be instructed to begin taking the supplement the day after the baseline assessment for a period of up to six months. If participants prefer to move to a lower dose, they can titrate down to 15mg, 10mg or 5mg. Intervention is self-managed, but participants are provided with information about the supplement and have access to the research team to answer any questions or provide further information. Participants who discontinue will remain in the study, although will not be required to attend intermediary follow-up visits, which collect information related to the intervention. We will ask them to attend the final endpoint visit, however.
Comparator Intervention:	n/a
Maximum Duration Of Treatment Of A Participant:	6 months / 26 weeks (i.e., from baseline up until the final follow-up assessment). Participants are permitted to discontinue the supplement at any time they wish.
Version And Date Of Final Protocol:	[to be completed]
Version And Date Of Protocol Amendments:	n/a as yet

2. Revision History

Document ID – (Document Title) revision X.Y	Description of changes from previous revision	Effective Date

3. Glossary of terms

ACEI: Angiotensin-Converting Enzyme Inhibitors
AE: adverse event
AHY: Prof Allan Young
ANOVA: Analysis of variance
AR: adverse reaction
ARB: Angiotensin receptor blockers
ASRM: Altman Self-Rating Mania Scale
BD: bipolar disorder
BDNF: brain-derived neurotrophic growth factor
CI: chief investigator
CRF: clinical research facility
CRP: c-reactive protein
DMF: depression with mixed features
EQ5D: Euroqol health-related quality of life measure
FAST: Functional assessment short test
GAD7: Generalised anxiety disorder 7-item questionnaire
GCP: good clinical practice
HCL: hypomanic checklist
HTA: human tissue act
IME: important medical event
ID: identification code
IDS: Inventory of depressive symptoms
IQR: Inter-quartile range
IRAS: integrated research application system
ISRCTN: international Standard Randomised Controlled Trial Number
ISS: internal states scale
KCL: King's College London
LiOr: lithium orotate supplement
LiSERS: Lithium Side Effects Rating Scale
M3VAS: Maudsley 3-item visual analogue scale
MixLi: the lithium supplement study for depression with mixed features
MDD: Major depressive disorder
NHS: national health service (UK)
NIHR: national institute for health research
NSAID: non-steroidal anti-inflammatory drugs
PI: principal investigator
PIS: participant information sheet
PPI: patient and public involvement
REC: research ethics committee
RCT: randomised controlled trial
RS: Dr Rebecca Strawbridge
SAE: serious adverse event
SAP: statistical analysis plan

SAR: serious adverse reaction
SD: standard deviation
SLaM: South London & Maudsley NHS Trust
SOP: standard operating procedure
SSC: study steering committee
SUSAR: suspected unexpected serious adverse reaction
TEMPS: Temperament Evaluation in Memphis, Pisa and San diego
THINC-IT: THINC-it cognitive screening tool
TRQ: tablets routine questionnaire
UAR: unexpected adverse reaction
UK: United Kingdom
VEGF: vascular endothelial growth factor
YMRS: Young mania rating scale

4. Protocol Contents

5. Background & Rationale

Lack of access to best-practice treatment is extremely common both in unipolar1 and bipolar2,3 affective disorders. Undertreatment is especially an issue for people experiencing depression with mixed features (DMF),4

where criteria for a depressive episode are met alongside concurrent symptoms of mania (e.g., activation, increased thought and speech rate).4 DMF is common5 and highly burdensome, not only with regard to a scant evidence base for effective treatments4 but also associations with bipolar disorder (progression to diagnosis or risk thereof)6, suicidality7 and psychosocial (including cognitive) disability.8 Moreover, DMF is under-detected in healthcare services and patients are routinely treated with standard antidepressant medications.4 These medications confer risk in DMF for worsening the manic symptom severity.4 Concomitant treatment with an antidepressant and a mood stabiliser could improve outcomes4,6, but this treatment strategy is rarely used in those without a full bipolar diagnosis.1,9

The gold standard mood stabiliser is lithium, usually prescribed in carbonate or citrate form.3 Despite its effectiveness against both symptoms of depression and (hypo)mania, including bipolar DMF,10 lithium is under-used not least because the prescribed forms require regular blood monitoring to ensure patient safety.3 Thus, despite its putative effectiveness for people with DMF without a bipolar diagnosis, lithium is not routinely available for this population.

Our recent systematic review indicates effectiveness of lithium at 'sub-therapeutic' doses to patients with depression, mania and cognitive impairment (from 17 studies assessing intervention with lithium as low as 0.3mg elemental lithium.11 This is in contrast to 'therapeutic' doses, which average ~600-800mg lithium carbonate (containing >112mg ionic lithium).

This is pertinent because these low doses are also evidenced to be safe, and a low-dose form of lithium (lithium orotate; LiOR) is available to purchase cheaply (without a prescription) as a supplement (up to 20mg ionic lithium) with our early work indicating that even lower doses (5 mg) result in detectable brain levels of lithium.12 If evidenced to be effective, LiOR could therefore be an accessible treatment option. My PPI work suggests it may also be desirable for patients, being a 'natural' substance. Despite evidence of safety11,12 LiOr has not been subject to clinical trials.11 This project seeks to determine whether commercially available LiOr has viability as an accessible adjunctive intervention for people with DMF.

6. Study Objectives and Design

6.1. Study Objectives

This research aims to elucidate LiOr's plausibility, at a known safe dose, over an extended period in a preliminary study. This is a feasibility study comprising the preliminary work required prior to formal trials examining commercially available LiOr supplementation for DMF. No specific hypotheses are therefore proposed. In this open label study, people who constitute a target population for LiOR will be invited to take commercially available LiOr for up to six months to establish its plausibility as a putative intervention for trials. The specific objectives are to investigate up to six months of open-label 20mg daily LiOr to identify its within-subjects effects on the following as co-primary outcomes:

1. The potential to examine bioavailability of LiOr (i.e. whether lithium is present at detectable levels in the serum using a standard laboratory lithium test), assessing lithium levels in serum.

2. The acceptability of 20mg daily LiOr over 6 months (assessed by self-report adherence and discontinuation rates) to inform a future study design.

3. Description of any positive and/or negative experiences of 20mg daily LiOr over 6 months (assessed via participant-report) to inform a future study design.

4. The feasibility of the protocol including intervention delivery and assessment visits (including assessments mentioned above, plus putative primary (mood) and secondary (functioning, cognition) outcome measures and assessment of potential confounders). Overall feasibility will be assessed via missing data and study withdrawal rates.

An exploratory analysis of change will be undertaken as secondary objectives for measures over time to inform a future definitive study design:

1. LiOR's biological effects, through assessment of key candidate blood-based biomarkers, namely neuroprotective growth factors (BDNF, VEGF) and inflammatory cytokines (IL-6, TNFa, IL-1b, IL-8, CRP) between week 0 and week 26.

2. LiOr's effects on mood, through assessing changes in mood ratings between week 0 and week 26.

3. LiOr's effects on cognition and functioning, through assessing changes in cognitive and psychosocial function between week 0 and week 26.

These aims will be met via within-subjects comparisons for each timepoint relative to baseline (weeks 2, 4, 8, 16, 26).

6.2. Study Design

A single site, one arm unblinded open label study investigating the effects of LiOr supplementation (20mg, once per day) for up to six months. We will recruit 40 people for this feasibility study.

6.3. Study Flowchart

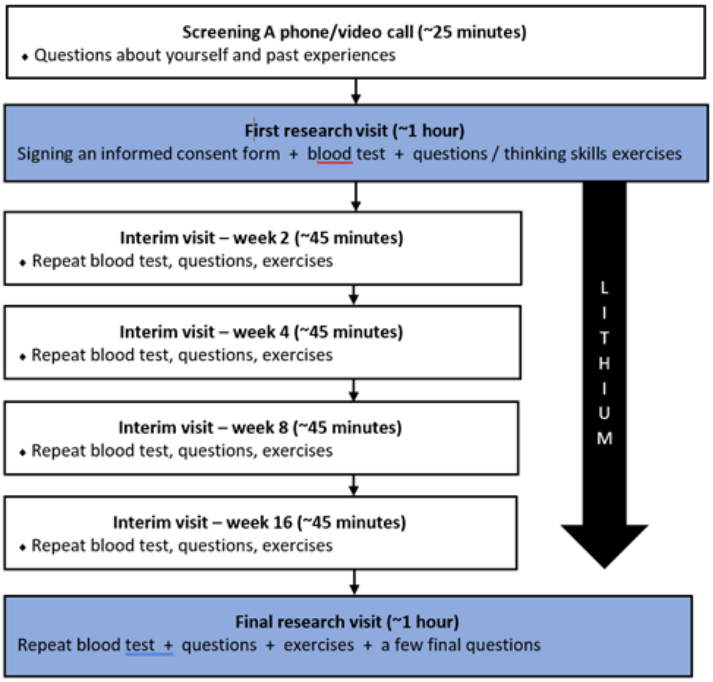

Table 1: Summary of study procedures and measures.

Procedures/Measures	Screening	Baseline (W0)	Intermediary (W2, 4, 8, 16)	Follow-up (W26)
Eligibility assessment [questions, MINI suicide, bipolar, & MDD[13],	X			
Informed consent		X		
LiOr provision		X	X	
Patient information	X			
Sociodemographic		X		X
Illness history [questions, HCL[15], TEMPS[16*]]		X		
Service use and health-related quality of life (EQ5D)[17]		X		X
Cognitive battery (THINC-IT[18])		X	X	X

Procedures/Measures	Screening	Baseline (W0)	Intermediary (W2, 4, 8, 16)	Follow-up (W26)
Mood self- (ASRM[28]/ M3VAS[19] / GAD7[20] / ISS[14]) & investigator-report (IDS[21] / YMRS[22])		X	X	X
Functioning [FAST[23]]		X		X
Blood test	X	X	X	X
Subjective experiences (LiSERS[24])			X	X
Adherence (TRQ[25])			X	X

7. Study Intervention

7.1. Therapy/Intervention Details

This section relates to the lithium orotate (LiOR) supplementation (N=40). The study will not interfere with usual care in any way, although the study team will inform participants' named healthcare professionals (GPs or secondary care clinician if under outpatient care) of their participation which includes LiOR supplementation. LiOr is available in 5mg, 10mg or 20mg doses. As our previous research has shown that individuals frequently take 20mg LiOR once per day of their own accord, without need for titration, we encourage participants to start from this dose. We do not permit a higher dose, as there is no evidence to date of commercial LiOR supplementation at these doses. We will permit a lower dose, if participants desire: as capsules are 5mg each, participants can select to take fewer capsules daily and we will collect this information. We will measure the rates and duration of doses taken. We will support participants if they have questions. Participants will receive bottles/pots as can be purchased, which contain 60 x 5mg capsules (which covers up to 20mg per day for 15 days). Between weeks 0 - 2, and 2 – 4, one supply can be provided at the earlier time until the upcoming visit. Subsequently, or if visits are not conducted within 15 days (i.e., participants would otherwise have depleted supply), the next supply of LiOR will be delivered via special delivery Royal Mail with receipt confirmed. This will be undertaken on the basis of checking with participants regularly the quantity of LiOR they have remaining to ensure a continual supply. At the 26-week assessment, participants will be asked to return any remaining LiOR. The lithium orotate purchased is manufactured by Swanson www.swanson.co.uk. Dr David Cousins' team at Newcastle University have examined the quantity and consistency (both within and between batches) determining these to be accurate and stable. Swanson have provided King's Clinical Trial Unit with quality documents (including demonstration of quality, purity and potency at the point of release of the product onto the market, and over-time). These were reviewed by the CTU's pharmacist who has confirmed appropriateness for progressing in the study with these. The supplement will be purchased directly from the supplier and stored in locked cupboards, in a locked office at King's College London, that only the research team will have access to. These will be a cool, dry place as per manufacturer instructions and we will ensure that the product expiry date outlives the date to participants' next supply date. Records will be kept of distribution to participants as per above. The products will not be unsealed or altered in any way before distribution to participants.

7.2. Intervention timeline

The intervention will begin at the start of Week 1, the day after baseline assessment. The intervention will continue for 6 months, until the final assessment at week 26, or as long as participants are willing to continue with the intervention during this time.

7.3. Intervention adherence

Adherence will be examined via completion of the participant-reported, validated Tablets Routine Questionnaire.[25] A TRQ score equating to 80% adherence is a conservative threshold for dichotomous adherence definition. (see Section 10 for more details).

7.4. Concomitant treatments (usual care)

All participants will continue receiving TAU including all concomitant interventions and service use. We will monitor and record these. In addition to monitoring at each assessment, participants are asked to inform the team immediately of any new intervention they have been prescribed and/or are considering initiating, to ensure these have no potential contraindications with the study supplement.

8. Research environment

The study will take place in one location. The Clinical Research Facility (CRF) at King's College Hospital will be used for all study procedures (blood tests, interviews and questionnaires), but the screening assessment will be conducted via telephone/videocall. The CRF is a purpose-built facility to support clinical trials and provides ideal infrastructure for studies of this nature (biological testing and processing facilities, quiet, private rooms with appropriate space for testing materials).

9. Selection and Withdrawal of Participants

9.1. Inclusion Criteria

Participants will be:

1) Aged between 18-65 at study entry.

2) Meet DSM-5 criteria for a current depressive episode (MINI[13]) and exceed thresholds indicating presence of mixed features (Internal States Scale; ISS[14]).

3) Undergoing stable pharmacological treatment for depression (intervention/dose unchanged for >6 weeks).

4) Willing to try a commercially available lithium supplement.

5) Willing to attend planned study visits.

9.2. Exclusion Criteria

People meeting any of the following criteria will be excluded:

1) Clinical diagnosis of bipolar disorder.

2) Other health condition that is severely impairing (as per self-report).

3) Known contraindication to lithium treatment. This includes currently taking lithium. These are derived from those applicable to medically prescribed forms of lithium. Although these are not established contraindications to microdoses of lithium, we are including them to fully ensure no ill effects to our study participants. These include:

- Known allergy to lithium or its excipients
- Known cardiac disease or cardiac insufficiency
- Known renal impairment
- Known untreated thyroid dysfunction
- Breast-feeding or pregnant
- Known hyponatraemia or frequent dehydration
- Addison's disease

- Brugada syndrome or family history of Brugada syndrome
- Psoriasis
- Upcoming use of, unable or unwilling to abstain from using any of the following medications during the upcoming 6 months:

  - non-steroidal anti-inflammatory drugs (NSAID) or cyclo-oxygenase-2inhibitors i.e., aceclofenac, acemetacin, celecoxib, dexibuprofen, dexketoprofen, diclofenac, diflunisal, etodolac, etoricoxib, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, lumiracoxib, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid, ketorolac, metronidazole.

  - angiotensin-converting enzyme inhibitors (ACEI) i.e., captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril.

  - Angiotensin receptor blockers (ARBs) i.e., azilsartan, candesartan, irbesartan, losartan, Olmesartan, telmisartan, valsartan.

  - diuretics i.e., Bendroflumethiazide, chlortalidone, cyclopenthiazide, indapamide, metolazone, xipamide, bumetanide, furosemide, torasemide.

It is worth noting that several other medications can interact with lithium e.g., steroids or reduced lithium levels from e.g., empagliflozin, aminophylline, theophylline. However, these are not included in guidelines as contraindicatory for high-dose lithium and are not included in exclusion criteria.

4) Unable to communicate fluently in English (defined as ability to read and understand the participant information sheet plus ability to communicate with the researcher throughout screening assessment);

5) Suicide risk (assessed using the MINI[13])

6) Unable to travel to one of the research sites on a regular basis over 6 months;

7) Unable to provide informed consent to participate, for any other reason.

8) Participation in another research study which could potentially influence engagement or outcomes in the present study e.g., presents contraindications with LiOR, examination of another pharmacological or psychological intervention for affective symptoms.

Individuals of any sex/gender can take part. Informed consent to participate will be obtained before inclusion into the study.

9.3. Selection of Participants

There will be 4 routes for participant selection:

1. Existing database of people interested in research participation, who have consented to be contacted by researchers within the Centre for Affective Disorders team (KCL).
2. Community offline and online advertisements: posters in the public domain, online advertising via research portals (e.g., NIHR BRC, MQ), social media posting, advertising campaigns on various platforms, such as Gumtree, to publicise the study to interested potential participants.
3. Primary care services i.e. GP mailouts to local patients as coordinated by CRN Portfolio teams (to be confirmed).
4. Network of clinicians and services who/which provide care to people with affective disorders within South London & Maudsley NHS Trust.

After potentially eligible individuals are identified through any of these routes, they will be provided with information about the study and a full screening for eligibility will take place subject to verbal consent; for details, see Section 10).

9.4. Randomisation Procedure / Code Break

n/a

9.5. Blinding Procedures

As an initial feasibility study, there is no blinding included: participants will be made aware of all information regarding the intervention. Researchers undertaking assessments and liaising with participants, as well as the study clinicians and researchers undertaking statistical analyses, will all be aware that this is a single-arm open label study and that no attempts are required to mask whether a participant is currently taking the intervention or whether they have discontinued.

9.6. Withdrawal of Participants

We will highlight to all participants that they are free to withdraw from the study at any time, without prejudice or consequences for either their clinical care, or involvement in any other research studies. Similarly, therapy can be discontinued at any point, if a participant withdraws from the study or if a participant decides they no longer wish to continue the intervention. Researchers will also be available throughout the study course to answer further questions about withdrawal. The investigator also has the right to withdraw patients from the therapy and/or study, for any reason e.g., if a participant loses the capacity to consent to the study, they will be withdrawn. This will be assessed by researchers during every contact with participants (e.g., phone calls, study appointments).

Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Importantly, LiOr discontinuation does not constitute as a withdrawal from the study. Thus, should a patient withdraw from the intervention only, efforts will be made to continue to obtain follow-up data, with the permission of the patient; participants who wish to withdraw from LiOR will be asked to confirm whether they are still willing to provide the study data already provided for research.

9.7. Expected Duration of Study

The total study duration for a given participant will be 26 weeks. Week 0 will comprise the baseline assessment and LiOR initiation will occur as soon as feasible after this. Intermediary assessments will be conducted at week 2, week 4, week 8 and week 16, followed by the final follow-up assessment and discontinuation of LiOR at week 26. The beginning of the study overall will be Week 0 (baseline assessment) of the 1st participant, estimated October 2024, and the end of the study will be one month after the last week of the 40th participant's follow-up assessment, estimated to be in August 2025, to allow for sample analysis.

10. Study Procedures

10.1. By Visit

The summary table in section 6.3 describes the procedures at each 'visit' (or measurement timepoint) which are also described below. We refer to each timepoint by its week number (W), (except for the first screening, which is not assigned a 'W' timepoint).

Once identified through different recruitment sources, potential participants will be first contacted regarding the study by a researcher who will send them a copy of the Participant Information Sheet (PIS; via email, post or in person). The researcher will encourage potential participants to spend as much time as they need asking questions about the study (via email or phone call) and consider whether they wish to participate or not.

As a minimum, study information will be provided to potential participants at least 24 hours prior to screening. After reading the PIS and having any questions answered, if the participant is happy to take part in the study, an appointment for screening will be arranged.

An alternative option to above is that participants will be provided with a link to a Qualtrics pre-screening questionnaire. The first page seen, if participants choose to follow this link, is the PIS. If participants confirm that they have read this, they are invited to either give preliminary consent to undertake the initial screening questionnaire, or contact the study team to discuss further (as in above route). If they select to complete the initial

screening questionnaire, this comprises questions which can be used to quickly exclude ineligible participants (e.g., age, health status, medication status) and the ISS to indicate whether they may be experiencing depression with mixed features. If participants are not indicated to be ineligible from this questionnaire, they can select for the study team to be contacted with their results and to establish further contact and potentially progress to full screening.

Screening session

Usually conducted over the phone by a trained researcher, or if potential participants are willing, by videocall (i.e., King's College London MS Teams) study information will be discussed and verbal consent for screening obtained. Verbal consent for screening will be recorded in a secure, password-protected spreadsheet for all potential participants. If the potential participant is willing, screening will provide an initial determination of eligibility. Specifically, eligibility will be assessed via screening procedures as follows:

- Open questions for self-report:
  - Eligible age range.
  - Willingness to try a commercially available lithium supplement.
  - Clinical health diagnoses (including bipolar disorder).
  - Severity of any diagnoses [participants are excluded if admitted to hospital within the past 6 months, have a planned admission in the upcoming 6 months, or attend outpatient/secondary services for an illness other than an affective disorder at least once per month].
  - Current treatments undergone for depression [name(s) of current medication, initiation / withdrawal and historical dose changes].
  - Ineligibility for lithium [as above; taking lithium, known cardiac disease or insufficiency, renal impairment, untreated thyroid dysfunction, breastfeeding, pregnancy, hyponatraemia, dehydration, regular use of NSAID, ACEI or diuretics, psoriasis, Addison's disease, Brugada syndrome or family history of Brugada.]
  - Ability to travel to one of the research sites on a regular basis over 6 months.
- MINI interview, MDD module, to establish current depressive episode and suicide module to establish non-significant suicide risk.
- (if not completed within Qualtrics within the last week), Internal States Scale [ISS] to establish presence of mixed features within current depressive episode.
- Ability to communicate fluently in English: researcher-defined, via ability to communicate during discussions about understanding of participant information and prior questions.
- Ability to provide informed consent to participate: researcher-defined, via communications and understanding of the procedures being consented to.

If inclusion criteria are met following this, the W0 assessment will be scheduled.

All assessments are expected to take place in the morning, as (post-LiOR initiation), blood samples are taken in the morning, at least 12 hours after the last LiOR dose, to avoid acute effects of lithium intake.

W0: Baseline Assessment

Before the assessment begins, written informed consent will be completed by the participant. The following measures will then be administered.

Blood test

- 2 x tube serum for the detection of lithium levels, using a standardized validated assay, with a lower limit of detection of 0.1mmol/L[26] and candidate inflammatory markers and growth factor proteins.[27]

Sociodemographic/illness-history/service use questions

- Date of birth, gender, ethnicity, height, weight, education level (highest level of education), employment status, substance use (e.g., smoking, alcohol), stressful life events within the past 12 months [baseline only]
- Current health symptoms [week 0 and 26]
- Current pharmacological or other medical treatments (type, dose, frequency of use, duration of use) [all timepoints]
- Previous use of lithium [baseline only]
- Use of healthcare and related services [week 0 and 26]
- Psychiatric comorbidities (questions) [week 0 and 26]
- Bipolar risk measures (questions; MINI bipolar section[13], HCL[15], TEMPS[16]) [week 0 and 26]

Cognitive measures

- Digital THINC-IT battery[18] including validated tests of processing speed and attention, memory, executive function and subjective cognitive functioning [Spotter (Choice Reaction Time), Symbol Check (1-back test), Trails (Trails Making Test B), and Codebreaker (Digit Symbol Substitution Test), Perceived Deficit Questionnaire, 5-item) [all timepoints].

Wellbeing measures

- Low mood: The Maudsley 3-item visual analogue scale (M3VAS)[21] and investigator-rated Inventory of Depressive Symptoms (IDS)[21] [all timepoints]
- Anxiety: The Generalised Anxiety Disorder 7-item scale (GAD7)[22] [all timepoints]
- Elevated mood: The internal states scale (ISS)[14] and investigator rated Young Mania Rating Scale (YMRS)[22] [all timepoints]
- Functional/wellbeing measures [EQ5D[17][week 0 and 26], FAST[23][all timepoints]]

Participants will, at the end of the assessment, be provided with one pot containing 60 LiOR capsules (for weeks 0 to 2). They will also be provided with an information sheet regarding LiOr, and instructed to begin taking the supplement the next day and once each day thereafter.

The researcher will offer two aids to help participants remember to take the supplement: participants can choose to receive a daily text message from the team to remind them to take their daily LiOR, or they can (along with the researcher if desired) set themselves an alarm/reminder for themselves.

The researcher will subsequently send a letter of notification regarding the study (and information about LiOR) to the participants' named Healthcare Professional.

W2: Intermediary assessment:

- Blood test (repeat from baseline)
- Cognitive test (repeat from baseline)
- Wellbeing measures (repeat from baseline)
- Adherence: Tablets Routine Questionnaire (TRQ)[25] [all remaining timepoints]
- Subjective effects of LiOR: Lithium Side Effects Rating Scale (LiSERS)[26] modified to bolster both positive and negative effects of lithium [all remaining timepoints]

W4: Intermediary assessment: repeat of W2

W8: Intermediary assessment: repeat of W2/4

W16: Intermediary assessment: repeat of W2/4/8

W26: Follow-up assessment: All outcome measures listed at W0 and intermediary assessments are repeated, with the exception of some sociodemographic information gathered at baseline only (specified above).

Additionally, participants will be asked for feedback regarding study conduct and their experiences (including satisfaction regarding amount/detail of information received, clarity of information, extent of support during the study, logistics, suggestions for improvements to their experience) and they will be asked whether they would consider continuing or restarting lithium supplementation in the future (self-management, outside of research).

10.2. Laboratory Tests

Collection of blood samples will be identical between intermediary assessments (2 x serum tube). Blood samples will be collected by a trained clinical nurse following local SOPs. Collection and processing will be conducted according to the Clinical Research Facility at King's College Hospital SOPs. Samples will be immediately processed and transferred to Synnovis' local laboratories as per collaboration agreements in accordance with Human Tissue Act procedures. 2 serum samples will be analysed for lithium levels and biomarkers on a regular basis (within one week of transfer) according to standard lithium laboratory procedures. Sample tubes will not contain any identifiable information and could be linked with participant data only by using the collection pack label, unique to each study participant and corresponding to their participant ID. After samples have been analysed, any surplus biological material will be disposed of in accordance with the Human Tissue Act 2004 Code of Practice.

11. Assessment of Safety

11.1. Assessment of Therapy Safety

Safety is not an outcome of this study, as the supplement has been evidenced to be safe (having been available and used without supervision, in the community, for decades). However, the welfare of our participants is paramount, and we will closely monitor information obtained from participants to ensure their safety. Specifically, this includes monitoring of lithium levels and wellbeing measures (as soon as each information are available to the research team). Monitoring and proposed actions comprise:

a. If any abnormalities are noted from clinical blood tests, participants and their GPs will be informed within one working day by study researchers. NB these are likely to be incidental, not associated with the intervention, given evidence to date of safety.

b. If any lithium levels exceed 0.6mmol/L, the dosing regime will be lowered from 20mg to 10mg as maximum dose as soon as practicable. This would be highly unexpected, given that the typical dose of lithium carbonate required to achieve therapeutic levels (0.6-0.8mmol/L) is 600-800 (approximately 6-8 times the elemental equivalent in LiOR 20mg).

c. If >50% participants (at any point in time) report a desire to reduce from 20mg, the dosing regimen will be lowered from 20mg to 10mg as soon as practicable.

d. If any wellbeing concerns arise in general, participants will be contacted within one working day by a study researcher for a wellbeing discussion and to provide support (i.e., study-related actions, signposting e.g., to support or healthcare services).

11.2. Specification, Timing and Recording of Safety Parameters

The study researcher will be responsible for checking with the participant verbally that there are no current negative effects and will record any injuries, notable events or other phenomena that might be of concern. These will be treated as any adverse event in any trial (see section 11.3). Any concerns will be communicated to the Lead Investigator (RS) and the medical expert (AHY).

11.3. Procedures for Recording and Reporting Adverse Events

Any adverse events will be recorded by a researcher at each visit asking participants if they have had any troubles and record these systematically. Even though LiOR is not a medicinal product, the standard definitions provided by The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 with regards to adverse events will be used, as follows:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom an intervention has been administered including occurrences which are not necessarily caused by or related to that intervention.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an intervention which is related to the intervention administration to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the intervention in question.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: results in death; is life-threatening; required hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; consists of a congenital anomaly or birth defect.

Important Medical Events (IME): Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require an intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Any AEs (excepting those specified in this protocol as not requiring reporting; see below section 11.4) that occur throughout the duration of the study will be recorded in the participant case report form. Investigators will assess whether the AE may be related to study participation and will also assess the severity of the event. Documented AEs reported after a participant signs the consent form will be included in the primary study report.

All AEs classified as ARs and UARs will be recorded and immediately addressed with the Chief Investigator (certainly no later than 24 hours), as well as be considered in Steering Group Meetings. All SAEs and SARs will be reported immediately (certainly no later than 24 hours) by the Chief Investigator to the Sponsor and the R&D office using a SAE report form. In accordance with the Health Research Authority procedures, only SUSARs will be reported by the Chief Investigator to the Research Ethics Committee for review (sent within seven days of the reaction for fatal or life-threatening events and 15 days of the reaction for not fatal or life-threatening events).

Although we do not anticipate any SARs or SUSARs, participants presenting any such reactions will be withdrawn from LiOR and, if not already done by the participant, these reactions will be brought to the attention of their named healthcare professional. Non-serious ARs may also warrant a referral back to the named healthcare professional, but withdrawal from the study will depend on risk assessment, circumstances and participant's wishes.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, will be followed until: the event resolves, the event stabilises, the event returns to baseline (if a baseline value is available), the event can be attributed to agents other than the study participation or to factors unrelated to the study, when it becomes unlikely that any additional information can be obtained. All follow-up information for SAEs that have not resolved by the end of the study or by the time of participant withdrawal will be reported to the Sponsor.

11.4. Adverse events that do not require reporting

No SAEs are expected in this study. Therefore, any SAEs will be reported as will ARs, UARs, SARs or SUSARs or IMEs. AEs that do not meet the above criteria but require intervention (e.g., safety concerns communicated to healthcare professional or incidence of acute episode requiring changes to treatment regime) will be reported. Other AEs do not require reporting (e.g., mild distress disclosed by participants where no further action is required or unrelated to the study/LiOR).

11.5. Stopping Rules

Other than plans noted above, no stopping rules are planned for the study. The study may be prematurely discontinued by the Sponsor or Lead Investigator based on new safety information arising during the conduct of the study, in the case of AEs associated with the intervention, or for other reasons given by the Research Ethics Committee. The study may also be prematurely discontinued due to lack of recruitment or high attrition from the

study, as advised by the Study Steering Committee (SSC). If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Research Ethics Committee will be informed within 15 days of the early termination of the study. Participants may discontinue treatment at any time they choose or as recommended by study researchers (section 9.6).

12. Statistics

This protocol will be published to ensure transparency of study analyses and outcome reporting following the study.

12.1. Sample Size

As an initial feasibility study, a sample size calculation is not warranted. However, a sample of 40 participants permits estimation of a 50% dropout rate to within a 95% confidence interval of +/-15%.[Research Design Service. NIHR. Available at: https://www.rds-london.nihr.ac.uk/resources/justify-sample-size-for-a-feasibility-study/]. The existence of six repeated measures and focus on within-subjects change/variability will help boost power to observe effects without aiming to determine statistical significance of effects with any precision.

12.2. Analysis

Intention-to-treat analyses will be undertaken. In a few cases, a sensitivity analysis will be carried out, excluding non-adherent participants (these are specified below, where this applies).

Final analyses will be conducted after data collection has been completed and data cleaned. However, it is worth noting that an interim analysis is planned in May 2025 for all primary analyses below. This is for the purpose of initial pilot data to be included in funding applications being submitted for a feasibility study. No changes to the protocol or any procedures will be made based on this.

Variables will be summarised using descriptive statistics (i.e., mean and standard deviation [SD] or median and interquartile range [IQR] or frequencies and proportions, as appropriate).

Analyses pertaining to each outcome are listed below:

1. LiOR bioavailability as assessed by lithium levels in serum. This will be analysed descriptively, as above. Intra- and inter- participant variation will be calculated. Overall changes over time may be assessed using a repeated-measures ANOVA (including only adherent participants taking a stable dose) to inform a potential future trial design.

2. LiOR acceptability as assessed by adherence rates (TRQ) and discontinuation. Rates of adherence (< 20% missed) will be assessed descriptively for each timepoint, and extent of adherence will also be described as a continuous (total TRQ score) measure. Rates of discontinuation (participant-report) will be described. Continuous adherence scores (for participants not discontinuing LiOR) over time will be tentatively compared using a repeated-measures ANOVA to inform a potential future trial design.

3. Subjective experiences of LiOR: negative experiences will be described via continuous LiSERS score measure, and positive experiences will be reported as participant-reported rates (yes/no to those listed). LiSERS scores over time (adherent participants only) will be compared using a repeated-measures ANOVA (possibly including dose as a between-subjects factor, pending dose variation within and between participants) to inform a potential future trial design.

4. Protocol feasibility as assessed by the rates (assessed descriptively) of attrition from the study, and of visits missed, and specific data for the putative primary outcomes i.e., mood measures.

There are three secondary outcomes, analysed as exploratory indications of change to inform a future definitive study design:

1. LiOR's biological effects, through assessment of key candidate blood-based biomarkers, namely neuroprotective growth factors (BDNF, VEGF) and inflammatory cytokines (IL-6, TNFa, IL-1b, IL-8, CRP) throughout the study. This will be examined using a repeated-measures ANOVA according to the intention-to-treat principle, with a sensitivity analysis to examine only adherent participants.

2. LiOr's effects on mood, through assessing changes in mood ratings (M3VAS, ISS, IDS, YMRS) throughout the study. These will be examined using a repeated-measures ANOVA according to the intention-to-treat principle, with a sensitivity analysis to examine only adherent participants.

3. LiOr's effects on cognition and psychosocial function, through assessing changes in THINC-IT and FAST scores respectively, throughout the study. These will be examined using a repeated-measures ANOVA according to the intention-to-treat principle, with a sensitivity analysis to examine only adherent participants.

Ancillary exploratory analyses will examine other wellbeing outcomes (e.g., EQ5D), service use, and a potential impact of bipolar features on outcomes during the study. Additional exploratory analyses using the data collected may be conducted.

13. Study Steering Committee

The Study Steering Committee (SSC) will be comprised of the Lead Investigator (Dr Rebecca Strawbridge), any other study researchers, the medical expert (Prof Allan Young) and the lithium expert (Dr David Cousins), as well as one individual with current/past lived experience of a mood disorder. The SSC will meet every 3 months at key times of the study (just before recruitment, early stages of recruitment, end of project) and 6 months at other times. The SSC will aim to provide oversight of the project, ensuring that it is conducted to a rigorous standard in line with Good Clinical Practice guidelines and other best practice conduct and reporting standards. These include pre-registration of this protocol, comprehensive and transparent reporting, and study progress and participant welfare.

14. Data Monitoring

LiOR is known to be safe and the study does not replace any usual clinical treatment or responsibility for participants. Therefore, this is considered a small feasibility, low risk study. The purpose is not to assess safety or efficacy as outcomes and therefore a formal independent Data Monitoring and Ethics Committee (DMEC) is not considered to be warranted (Ellenberg, Fleming and DeMets, 2003).

15. Direct Access to Source Data and Documents

The study investigators will permit study-related monitoring, audits, and REC review by providing the Sponsor and REC direct access to source data and other documents (e.g., case report forms, test reports, etc.) when required.

16. Ethics & Regulatory Approvals

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Mental Capacity Act 2005. This protocol and related documents will be submitted for review to a local Research Ethics Committee (REC) [to be confirmed] in May 2024. The Chief Investigator will submit a final report at conclusion of the study to the funder, the REC and the Sponsor.

17. Quality Assurance

Monitoring of this study will ensure compliance with Good Clinical Practice and scientific integrity will be managed by the study team and overseen from the SSC. Our procedures ensure that study researchers are trained and supported in conducting assessments, liaising and informing participants, and handling data. The Lead Investigator maintains overall study responsibilities, working closely with other members of the team to ensure the study is conducted according to the protocol, best practice SOPs and GCP. During the planning of the project, the proposal was reviewed by experienced academics, statisticians, and clinicians. The proposal was also reviewed by people affected by cognitive concerns and/or lived experience of caring for individuals with dementia, who were consulted using various approaches. The full proposal was formally peer reviewed via the funding application process (to the King's Prize Fellowship committee and Psychiatry Research Trust Early Career Award), where the project was judged of good quality and strong design, as well as being considered worthwhile in terms of future implications regarding benefits to patients and the NHS.

18. Data Handling

The Lead Investigator will act as custodian for the study data. Patient data will be anonymised as far as possible (see below for detail). All study data will be stored in line with the Data Protection Act and archived in line with Sponsor requirements. The electronic database will be stored as an Excel file, hosted securely on a dedicated server within KCL, with database access strictly restricted through user-specific passwords to the authorised research team members, with passwords not to be shared and ensuring that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested from the Lead Investigator. Database and other study document access will be revoked for any staff members leaving the project. This database will only store pseudonymized data, not including any direct identifiers (e.g., names, dates of birth, email / telephone / residential addresses, etc.). The data will not contain most indirect identifiable information including Indirect identifiers are variables that may be used together or in conjunction with other information to identify individual participants. Examples include: area of residence, any organisations affiliated with participants, previous academic or occupational institutions, occupational titles, dates of any other life events, income, etc.).

19. Data Management

The source data for the study will be collected on paper CRFs. Participants' data will be stored using a coded identifier, e.g. MxLi001, MxLi002 and paper forms of participant data will be stored securely within the recruiting site in locked filing cabinets (in offices locked while empty). This source data will then be entered by recruiting site staff, typically within 14 days of data collection by authorised staff onto the study databases (see above). Participant initials and month/year of birth will be entered on the database, however identifiable information such as NHS number, email addresses, participant names and addresses and full postcodes will not be entered. No

data will be entered onto the EDC system unless a participant has signed a consent form to participate in the study.

The study team will undertake appropriate reviews of the entered data where appropriate for the purpose of data cleaning and will request amendments as required. Following checks of data correctness and completeness, all data can be formally locked for analysis.

We will adhere to NHS confidentiality practices, and to the Research Governance Framework in monitoring and managing the research. Dr Strawbridge will undertake overall responsibility for management of the project.

20. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. We intend to publish the study protocol before the end of the first year of recruitment. A primary publication will include all primary and secondary outcomes as per the protocol.

21. Insurance / Indemnity

Indemnity and insurance are provided through KCL/SlaM schemes.

22. Financial Aspects

This project is funded by the Psychiatry Research Trust (award holder Dr R Strawbridge). The views expressed in this publication are those of the authors and not necessarily those of the funder or the Department of Health and Social Care.

23. Signatures

Dr Rebecca Strawbridge _____

Chief Investigator TBC

24. References

1. Strawbridge R, McCrone P, Ulrichsen A, Zahn R, Eberhard J, Wasserman D, Brambilla P, Schiena G, Hegerl U, Balazs J, De Almeida JC. Care pathways for people with major depressive disorder: A European Brain Council Value of Treatment study. European Psychiatry. 2022 Jan;65(1):e36.

2. BipolarUK. The findings of the bipolar commission. [Internet]. 2022 [cited 2023 July 10] Available from: https://www.bipolaruk.org/bipolar-commission-findings

3. Post RM. The New News about Lithium: An Underutilized Treatment in the United States. Neuropsychopharmacology. 2018;43(5):1174–1179. doi:10.1038/npp.2017.238

4. McElroy SL, Guerdjikova AI, Romo-Nava F. Diagnosing and treating major depressive episodes that lie along the mood disorders spectrum: focus on depression with mixed features. CNS spectrums. 2021 Apr;26(2):133-9.

5. Grover S, Adarsh H. A comparative study of prevalence of mixed features in patients with unipolar and bipolar depression. Asian Journal of Psychiatry. 2023 Mar 1;81:103439.
6. Targum SD, Nierenberg A. The complexity of “mixed” depression: a common clinical presentation. Innovations in Clinical Neuroscience. 2011 Jun 1;8(6):38.
7. Akiskal HS, Benazzi F. Psychopathologic correlates of suicidal ideation in major depressive outpatients: is it all due to unrecognized (bipolar) depressive mixed states?. Psychopathology. 2005 Oct 6;38(5):273-80.
8. Perugi G, Angst J, Azorin JM, Bowden CL, Mosolov S, Reis J, Vieta E, Young AH, BRIDGE-II-Mix Study Group. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. The Journal of clinical psychiatry. 2015 Mar 25;76(3):12074.
9. Day E, Shah R, Taylor RW, Marwood L, Nortey K, Harvey J, McAllister-Williams RH, Geddes JR, Barrera A, Young AH, Cleare AJ. A retrospective examination of care pathways in individuals with treatment-resistant depression. BJPsych Open. 2021 May;7(3):e101.
10. Ulrichsen A, Hampsey E, Taylor RH, Gadelrab R, Strawbridge R, Young AH. Comparing measurements of lithium treatment efficacy in people with bipolar disorder: systematic review and meta-analysis. BJPsych Open. 2023 May;9(3):e98.
11. Strawbridge R, Kerr-Gaffney J, Bessa G, Loschi G, Freitas HL, Pires H, Cousins DA, Juruena MF, Young AH. Identifying the neuropsychiatric health effects of low-dose lithium interventions: A systematic review. Neuroscience & Biobehavioral Reviews. 2022 Nov 24:104975.
12. Neal MA, Strawbridge R, Wing VC, Cousins DA, Thelwall PE. Under review. Human brain 7Li-MRI following low-dose lithium dietary supplementation in healthy participants.
13. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiat. 1998;59:22–33.
14. Bauer M, et al. Independent assessment of manic and depressive symptoms by selfrating. scale characteristics and implications for the study of mania. Arch Gen Psychiatry 1991; 48:807-12.
15. Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, Skeppar P, Vieta E, Scott J. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. Journal of affective disorders. 2005 Oct 1;88(2):217-33.
16. Akiskal HS, Mendlowicz MV, Jean-Louis G, Rapaport MH, Kelsoe JR, Gillin JC, Smith TL. TEMPS-A: validation of a short version of a self-rated instrument designed to measure variations in temperament. Journal of affective disorders. 2005 Mar 1;85(1-2):45-52.
17. Fryback DG, Hanmer J. The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective. Evidence from the EuroQol BIOMED Research Program.
18. Harrison JE et al. Stability, reliability, and validity of the THINC-it screening tool for cognitive impairment in depression: A psychometric exploration in healthy volunteers. Int J Meth Psychiatr Res. 2018 Sep;27(3):e1736.
19. Moulton CD [Strawbridge R] et al. The Maudsley 3-item Visual Analogue Scale (M3VAS): Validation of a scale measuring core symptoms of depression. J Affect Disord. 2021;282:280–3.
20. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine. 2006 May 22;166(10):1092-7.
21. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The inventory of depressive symptomatology (IDS): psychometric properties. Psychological medicine. 1996 May;26(3):477-86.
22. Young R, Biggs J, Ziegler V, Meyer D. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiat. 1978;133:429–35.
23. Rosa AR, Sánchez-Moreno J, Martínez-Aran A, Salamero M, Torrent C, Reinares M, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin Pract Epidemiol Ment Health CP EMH. 2007 Jun 7;3:5.
24. Haddad P, Wieck A, Yarrow M, Denham P. The Lithium Side Effects Rating Scale (LISERS); development of a self-rating instrument. European Neuropsychopharmacology. 1999(9):231-2.
25. Adams J, Scott J. Predicting medication adherence in severe mental disorders. Acta Psychiatr Scand. 2000;101(2):119-124.
26. Synnovis’. Personal communication.
27. Strawbridge R et al. Peripheral inflammatory effects of medications recommended for treatment-resistant depression: A systematic review. Applied Neuroscience. 2022.
28. Altman EG, Hedeker D, Peterson JL, Davis JM. The Altman Self-Rating Mania Scale. Biol Psychiatry. 1997 Nov 15;42(10):948-55.