CEQUEL

Comparative Evaluation of

QUEtiapine-Lamotrigine combination

versus quetiapine monotherapy,

(and folic acid versus placebo)

in people with bipolar depression:

a 2x2 factorial randomised trial

Comparative Evaluation of QUEtiapine-Lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in people with bipolar depression.

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Approved by: Professor John Geddes _____ 15/05/2013
Name *Signature* *Date*

Comparative Evaluation of QUEtiapine-Lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in people with bipolar depression.

Investigator Agreement

I have read this protocol and agree to abide by all provisions set forth therein.
I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

Principal Investigator (Print Name)	Investigator Signature	Date
John Geddes		17th May 2013
Co-Investigator (Print Name)	Investigator Signature	Date
Co-Investigator (Print Name)	Investigator Signature	Date

Confidentiality Statement
This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust and members of the Research Ethics Committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Professor Geddes.

A copy of this agreement will be obtained for each trial site and filed in Trial Master File in the CEQUEL Office in Oxford.

Page

1. Background and Rationale

1.1. Bipolar depression

Bipolar disorder is a mental disorder characterised by episodes of elevated or irritable mood (manic or hypomanic episodes) and episodes of low mood, loss of energy and sadness (depressive episodes). Much of the personal and economic burden of the illness is caused by depressive symptoms (Judd, 2002; Judd, 2003) but there is little randomised evidence to inform treatment. Furthermore, bipolar disorder is associated with increased mortality attributable largely to suicide which most commonly occurs during depressive episodes.

1.2. The need for more effective, safer treatments for bipolar depression

In contemporary clinical practice, bipolar depression is often treated with the same medicines as major depressive disorder (also called unipolar depression). In unipolar depression there is strong evidence that antidepressants alleviate symptoms in the short-term and that continued therapy decreases the risk of relapse. In bipolar disorder, by contrast, treatment with antidepressant drugs is complicated by the risk of switching to manic states, the potential for further mood destabilisation and even some doubt about short-term efficacy. These concerns are reflected in the National Institute of Health and Clinical Excellence guidelines on treatment of bipolar depression (NICE, 2006) which recommend that treatment with selective serotonin reuptake inhibitors (SSRIs) should only be used with an antimanic agent and should be discontinued when a patient is in remission from depressive symptoms or symptoms have been significantly less severe for 8 weeks. Furthermore, the guideline recommends that SSRIs should be avoided for patients who have rapid cycling disorder, a recent hypomanic episode or recent functionally impairing, rapid mood fluctuations – which includes a substantial proportion of patients with bipolar disorder. These recommendations indicate considerable uncertainty surrounding treatment of bipolar depression both in the short- and medium-term and the trend away from using antidepressant medicines. At the same time there is an urgent need to identify effective treatments for bipolar depression which:

- provide safe, tolerable and rapid reduction of depressive symptoms
- avoid induction of manic symptoms in the short- term
- maintain continued remission from depressive symptoms and freedom from manic symptoms.

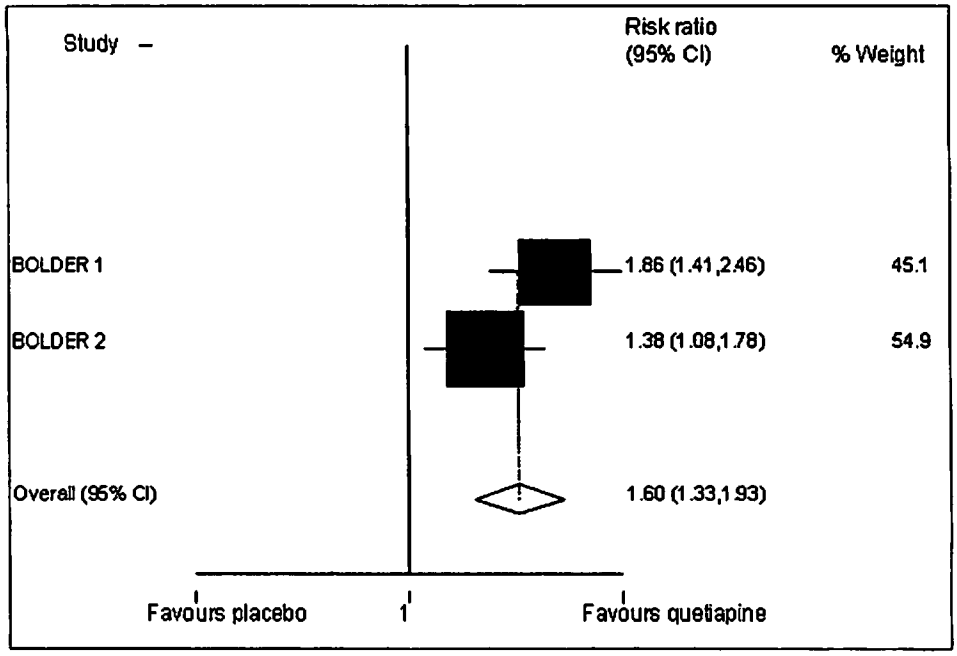
1.3. Other available treatment for bipolar depression

1.3.1. Quetiapine: One of the first-line treatments recommended in the NICE guidelines for acute episodes of bipolar depression is quetiapine (Seroquel®, Astra-Zeneca), an atypical antipsychotic agent. In October 2006 the US Food and Drug Administration (FDA) licensed quetiapine (at a dose of 300mg/day) for treatment of bipolar depression and the European Medicines Evaluation Agency (EMEA) granted a license in November 2010.

There are two short-term RCTs of quetiapine in bipolar depression: BOLDER 1 and 2 which had essentially identical designs (Calabrese, 2005; Thase, 2006). In these RCTs, approximately 52% of participants allocated to quetiapine (300mg/day or 600mg/day) had achieved remission by 8 weeks compared to approximately 32% of those allocated to placebo (combined N=978, pooled relative risk [RR] 1.60, 95% CI 1.33 to 1.93 – see Figure 1). There was no evidence that quetiapine increased the risk of manic switching (the rates of hypo(mania) were 2.2% for participants on quetiapine 600 mg/day, 3.9% for those on quetiapine 300 mg/day and 3.9% for those on placebo). A number of adverse events were more frequent on quetiapine than placebo including dry mouth (~40%), sedation (~30%), somnolence (~20%) and dizziness (~20%). The rate of discontinuation of allocated treatment ranged from

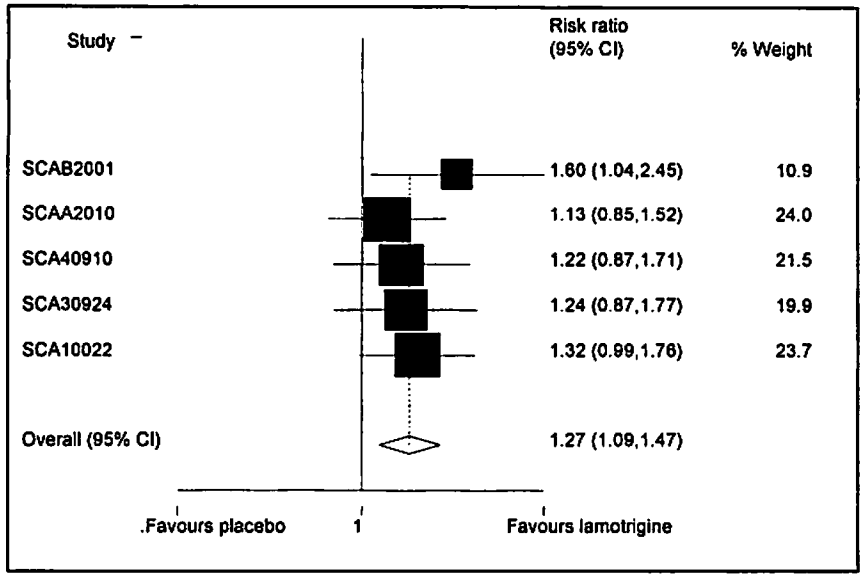
33% of participants to 46% participants with most withdrawals in the first week post-randomisation. Overall, the trials suggest that quetiapine provides rapid relief of acute depression but with a high incidence of sedation and study withdrawal indicating the need for alternative treatments, especially in the medium-and long-term.

Figure 1: Quetiapine versus placebo – remission by 8 weeks (defined as MADRS ≤ 12)



1.3.2. Lamotrigine: Lamotrigine (*Lamictal®*, Glaxo-Smith-Kline) is an anticonvulsant which is licensed in the USA and many European countries for the long-term treatment of bipolar disorder and is also often used in the treatment of bipolar depressive episodes. It is well tolerated in the long-term by the majority of patients but can cause skin rashes in up to 10% of patients and, rarely, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. The risk of skin reactions can be reduced by slow dose escalation but this also delays achieving a therapeutic dose and, hence, therapeutic response. A systematic review found five GSK-sponsored trials comparing lamotrigine with placebo in acute phase bipolar depression – only one has been fully published (Geddes, 2006). In an individual patient-level data meta-analysis, patients treated with lamotrigine were more likely to remit (pooled RR 1.21 95% CI 1.03 to 1.42, Heterogeneity chi-squared=5.86 (df=4) p=0.210, Test of RR=1: z=2.30 p=0.021) than those treated with placebo. No adverse events occurred on lamotrigine more frequently than placebo. A recent independent Dutch trial, LAMLIT, found that lamotrigine add-on therapy to lithium was more effective than lithium plus placebo (RR for response 1.61 95% CI 1.05 to 2.53) (van der Loos, 2006). The failure of the individual GSK-sponsored trials to show a drug-placebo difference may reflect under powering due to an overestimation of the likely treatment effect, baseline inflation of depression scores to meet eligibility criteria or be a consequence of the need to build up the dose slowly for safety reasons. Whatever the reason, it has prevented registration of the drug for acute bipolar depression. However, the pooled analysis shows a significant, if modest, treatment effect indicating the potential of lamotrigine for treatment of bipolar depression is worth exploring (see Figure 2).

Figure 2: Lamotrigine versus placebo – remission by 8 weeks (defined as MADRS<12)



1.3.3. Quetiapine/lamotrigine combination: These apparent costs and benefits of quetiapine and lamotrigine raise the possibility that, in combination, they could provide both rapid relief of acute symptoms and longer-term mood stability because:

- in the acute phase the use of quetiapine to reduce depressive symptoms might make the slow introduction of lamotrigine more acceptable
- as the dose of lamotrigine increases, the efficacy of the combination is likely to exceed that of quetiapine alone
- if quetiapine is not tolerated in the longer-term, it can be withdrawn to leave lamotrigine monotherapy at a therapeutic dose.

It is also possible that increased adherence will lead to a functional synergy with combination therapy i.e. greater efficacy than the combined additive benefits of quetiapine and lamotrigine.

1.3.4. Adjunctive therapy with folic acid: Folic acid and folate are forms of the water-soluble vitamin B9. Low plasma and red cell folate are thought to be associated with clinical depressive disorders and treatment with folic acid has been shown to improve the therapeutic effect of fluoxetine in depressed patients (Coppen, 2000). Furthermore, case control studies have shown a high incidence of serum and red blood cell folate deficiency in psychiatric patients and lower folate levels have been linked to a poorer response to antidepressant treatment (Fava, 1997). It is possible therefore that addition of folic acid to other treatments for depression may lead to more rapid reduction in depressive symptoms and a lower risk of relapse.

1.3.5. Genetic studies: Folic acid is required for DNA synthesis and metabolism of amino acids including homocysteine. A growing number of epidemiological studies suggest links between low folate status, increased homocysteine and depressive symptomatology in the general population (Tiemeier, 2002; Bjelland, 2003; Morris, 2003). There are genetic variations in at least three genes which affect the extent to which folic acid lowers homocysteine levels, or the absorption of dietary folate, and these would therefore be predicted to affect the antidepressant effect of adjunctive folic acid:

i) 5,10-Methylenetetrahydrofolate reductase (MTHFR) is involved in the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate which is the main circulating form of folate. The MTHFR C677T single nucleotide polymorphism (SNP) has three genotypes arising from a C/T transition i.e. CC, CT and TT. 677TT homozygotes have only have 30% of enzyme activity and consequently have lower levels of folate (and higher levels of homocysteine) than non-677TT-homozygotes (Refsum, 2006a).

ii) There is also some evidence for a potential interaction between the catechol-o-methyltransferase (COMT) enzyme genotype and response to treatment with folic acid. The COMT gene has a functional SNP (Val158Met) which alters enzyme activity and Val158 homozygotes have been found to have significantly higher levels of homocysteine than Met158 carriers, The COMT effect was independent of, and additive with, the MTHFR 677TT effect (Tunbridge et al. in press).

iii) Folate hydrolase 1 (FOLH1) facilitates the transfer of dietary folate into the body. Its activity is modulated by a functional variant in its sequence (T484C): the 484T variant has higher activity than the 484C form. Accordingly, the effects of folate supplementation on homocysteine levels and depressive symptoms may be more pronounced in 484TT homozygotes, compared with 484C carriers (Roffman et al 2013).

CEQUEL will investigate the hypothesis that there will be an interaction between folic acid treatment and genotype at these loci. We predict a greater reduction in homocysteine levels – and also depressive symptoms - in 677TT and Val158 homozygotes. In addition, we hypothesise that the impact of folate on biochemical measures (and depressive symptoms) will be more pronounced in FOLH1 484TT homozygotes.

1.3.6. B12 status: There is growing evidence of interactions between vitamin B12 status and folate status, with adverse effects of high folate in those with low B12 status. We will also look at baseline B12 status in relation to outcome measures by analysis of total cobalamin and holotranscobalamin [Refsum, 2006b].

1.4. Summary

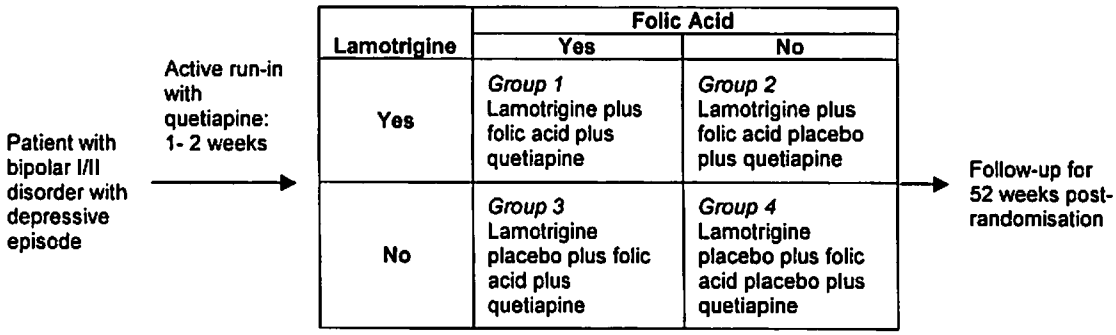
There is uncertainty about optimum short- and medium-term treatment for bipolar depression. The combination of lamotrigine plus quetiapine potentially offers enhanced treatment for patients by maximising the benefits of both drugs without inducing mood instability. In addition to this, folic acid is a promising adjunctive therapy for depression. The greater biological homogeneity of bipolar depression would actually make a separate trial of folic acid therapy in bipolar depression worthwhile: however, the proposed trial provides an excellent opportunity to conduct a 2 x 2 factorial design efficiently investigating both the beneficial effects of adding lamotrigine to quetiapine *and* the effects of adding folic acid. The availability of a relevant and measurable function-related metabolite (homocysteine) and good

candidate genes for effect modification will make possible a powerful investigation of the neurobiology of the regulation of mood by folic acid.

2. Research Questions

CEQUEL will investigate the effects of adding lamotrigine to quetiapine and the effects of adding folic acid to treatments for bipolar depression. It employs a 2 x 2 factorial (see Figure 3).

Figure 3: Randomisation to lamotrigine vs placebo and to folic acid vs placebo



2.1. Principal research questions

1. Does combination therapy with quetiapine plus lamotrigine (Groups 1 & 2) lead to greater improvement in depressive symptoms over 12 weeks than quetiapine monotherapy plus lamotrigine placebo (Groups 3 & 4) in patients with bipolar depressive disorder?
2. Does adjunctive treatment with folic acid (Groups 1 & 3) lead to greater reduction in depressive symptoms by 12 weeks than folic acid placebo (Groups 2 & 4) in patients with bipolar depressive disorder?

2.2. Secondary research questions

1. Does combination therapy with quetiapine plus lamotrigine produce superior outcomes to quetiapine monotherapy plus lamotrigine placebo at 12 months?
2. Does adjunctive folic acid produce superior outcomes to folic acid placebo at 12 months?
3. Are there important differences in the relative efficacy, safety and tolerability of quetiapine plus lamotrigine versus quetiapine monotherapy plus lamotrigine placebo between patients with bipolar I disorder and patients with bipolar II disorder and between patients with different levels of baseline severity of depression?
4. Are there important differences in the relative efficacy, safety and tolerability of folic acid and placebo between subgroups of patients defined by genotype (MTHFR C677T, COMT Val158Met and FOLH1 T484C)?
5. Does the baseline homocysteine, folate or vitamin B12 status influence response to folic acid?
6. What are the incremental cost, effects and cost-effectiveness of quetiapine plus lamotrigine combination therapy versus quetiapine monotherapy?
7. What are the incremental costs, effects and cost-effectiveness of folic acid versus placebo?

3. Trial Design

CEQUEL is a multicentre, double-blind, randomised, placebo-controlled, parallel group, 2 x 2 factorial clinical trial (see Figure 3) which will include economic, biochemical and genetic analyses. The trial is investigating short-term remission from depressive symptoms and longer-term maintenance of remission and prevention of depressive or manic relapse.

3.1. Outcome measures

3.1.1. Primary outcome measure: The primary outcome measure is improvement in depressive symptoms at 12 weeks from the date of randomisation using the Quick Inventory of Depressive Symptomatology, self-report version [QIDS-SR_{16}].

3.1.2. Secondary outcome measures:

1. The proportion of participants who both achieve remission by 12 weeks following randomisation (defined as a score of ≤5 on QIDS-SR_{16}) and remain free from symptomatic relapse by 52 weeks. Depressive relapse is defined as a QIDS-SR_{16} score ≥10 on two consecutive weekly ratings and manic relapse as an Altman Self-Rating Mania Scale (ASRM) score of ≥ 10 on a single weekly rating.
2. Proportion of time over 12 months when participants were free from manic symptoms (ASRM ≤5).
3. Proportion of time over 12 months when participants were free from depressive symptoms (QIDS-SR_{16} ≤5).
4. New intervention (admission or drug treatment) for manic episode by 52 weeks.
5. New intervention (admission or drug treatment) for depressive episode by 52 weeks.
6. Death (all cause and cause-specific including suicide).
7. Deliberate self-harm.
8. Quality of life – rated using the EuroQol EQ-5D.
9. Unexpected adverse events.
10. Withdrawal from quetiapine or lamotrigine due to adverse effects.
11. Use of health and social care service resources.
12. Social costs/benefits.

3.2. Details of the trial design

The trial is designed to integrate with rather than replace the normal clinical care of participants. For most participants the investigator will be their consultant psychiatrist (or a member of his/her team). Where this is the case, the investigator retains overall responsibility for the clinical care of the participant and should always act in the participant's best interests. This includes ensuring that the clinical investigations recommended by the NICE guidelines on bipolar disorder for initiating and continuing trial treatments are carried out (NICE, 2006). The investigator should assess adherence to treatment and monitor levels of trial drugs according to normal practice and should undertake any other investigations that are clinically indicated. Where the investigator is not a member of the participant's clinical team, the consultant retains overall responsibility for the care of the participant and the investigator should liaise with him/her to agree on the activities to be undertaken by the investigator.

Participants will be people with bipolar I disorder or bipolar II disorder who require new pharmacological treatment for an acute depressive episode (see Eligibility Criteria sections 4.1 and 4.2). All participants will initially enter a 7 to 14 day active run-in phase during which they will receive open-label quetiapine monotherapy. The run-in phase will provide immediate treatment to patients with moderate/severe bipolar depression. It will also ensure that only people with depressive episodes of sufficient duration for longer-term and combination treatment to be appropriate are entered into the randomised phase. This stepwise initiation of drugs is consistent with

routine clinical practice and will improve the efficiency of the trial by avoiding early withdrawal from the randomised phase of participants who cannot tolerate quetiapine and/or do not adhere to trial procedures.

At the end of the run-in phase, participants who can tolerate quetiapine, are adhering to trial procedures and remain moderately/severely depressed will be randomised to the addition of lamotrigine or matched placebo, and separately to folic acid or matched placebo[1]. Allocated treatments will be continued for 12 months unless there are clinical reasons to discontinue or consent is withdrawn.

The trial will investigate both short-term (relief from depressive symptoms) and medium/longer-term outcomes (including safety, freedom from depressive and manic symptoms, and tolerability). The randomised phase lasts for one year during which time, participants will be asked to provide weekly self-reports of mood symptoms via short message service (SMS), webform or on paper.

3.2.1. Informed consent to participate in the trial: Before any trial specific procedures are performed, the patient must personally sign and date the Informed Consent Form (see section 12.3) using the latest Research Ethics Committee (REC) approved version of the form.

Eligible patients who are currently depressed will be given as long as they would like to decide whether or not to participate in the trial. However, there will often be a clinical need to initiate treatment for depression as soon as possible and therefore immediate entry into the run-in phase will be permitted and, for patients who are already taking quetiapine, immediate entry into the randomised phase. Patients entering the run-in phase will have a minimum of 7 days on open-label standard treatment (i.e. quetiapine) and those entering the randomised phase will have at least 24 hours between consenting to take part and beginning trial treatment.

3.2.2. Patients who might become eligible for the trial: The chronic and cycling nature of bipolar disorder means that many patients under the care of trial investigators will experience an acute depressive episode during the recruitment period of the trial. Patients considered by the investigator to be at risk of a depressive episode will, at the investigator's discretion, be informed about the trial, given a Participant Information Sheet and offered the opportunity to express their views on participation. In the event of a depressive episode, patients who have already expressed an interest in the trial will be invited to take part (see section 3.2.1). This process closely resembles routine clinical care where treatment options for future acute episodes may be discussed with patients when they are well to reduce the burden of making treatment decisions when acutely unwell.

3.2.3. Randomisation: A randomisation visit should take place between 7 and 14 days after trial entry. If the dose of quetiapine has not been established within 14 days or an appointment cannot be made, the investigator should contact the CEQUEL office to request an extension. The randomisation visit will include checks that the participant is willing to enter the randomised phase and meets the eligibility criteria including uncertainty about optimum treatment.

A centralised randomisation service will be used. Investigators with internet access in their clinic room will access the service via the web. Investigators without internet

[1] If randomisation to folic acid/placebo is not feasible or appropriate, randomisation will be to lamotrigine/placebo only.

access will fax a randomisation form (together with a trial prescription form) to the CEQUEL Office. A member of the CEQUEL team will then perform the randomisation using the centralised system. Each participant will be randomised to either lamotrigine or lamotrigine placebo and also to either folic acid or folic acid placebo[1].

A non-deterministic minimisation algorithm will be used to produce treatment groups balanced for important prognostic factors. Trial sites will be arranged into geographical regions. The first 60 patients will be allocated randomly without minimisation to avoid predictability. Subsequently, the minimisation algorithm will be applied with an allocation ratio that is not fully deterministic: there will be an 80% bias in favour of allocations that minimise the imbalance.

The randomisation algorithm will minimise for 16 variables related to prognosis at baseline:

- bipolar I or bipolar II (based on DSM-IV criteria)
- baseline severity of depression (QIDS-SR_{16}) – 4 categories: mild ≤10, moderate 11-15, severe 16-20 and very severe ≥ 21
- age – classified as ≤ 30, 31-40, 41-50 and > 50
- gender
- dose of quetiapine (150mg/day; >150 to < 300mg; 300mg/day; >300mg/day)
- concurrent medicines: the algorithm will minimise on each of 7 treatments - lithium, valproate, other mood stabiliser, olanzapine, other atypical antipsychotic, conventional antipsychotic and antidepressant
- pre-screening treatment with quetiapine
- pre- screening treatment with lamotrigine
- number of mood episodes in the past year (< 4 or ≥ 4)
- trial region

Once randomisation has taken place the trial management program will generate a letter to the participant confirming that randomisation has taken place. The letter, prescription form and a list of pack numbers (see section 6.7.1.) will be sent to the trial pharmacy. At the pharmacy the appropriate packs of medicines will be dispensed and sent to the participant (or other agreed recipient) together with the letter. All participants will continue to be prescribed open-label quetiapine according to routine practice.

3.2.4. Minimisation of Bias: The centralised randomisation system guarantees complete allocation concealment and prevents subversion of randomisation.

Double-blind investigational treatments will minimise performance and ascertainment biases. Use of placebo to conceal treatments should be effective because neither lamotrigine nor folic aid cause easily recognisable adverse reaction and both are generally well-tolerated.

Multiple methods of minimising loss to follow-up, including telephone follow-up, will be employed to avoid attrition bias. The main statistical analysis will be carried out on the basis of intention-to-treat i.e. after randomisation, data for each participant will be analysed according to the treatment they were allocated irrespective of what treatment they actually received. This removes any elements of subjectivity in deciding whom to include in the analysis (and thus the risk of selection bias).

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[1] If randomisation to folic acid/placebo is not feasible or appropriate, randomisation will be to lamotrigine/placebo only.

4. Selection of Trial Participants

4.1. Inclusion and exclusion criteria for entry to the active run-in phase

Patients must satisfy all the following criteria to be eligible for the run-in phase:

4.1.1. Inclusion criteria:

1. primary diagnosis of bipolar disorder type I or II (based on DSM-IV criteria for a hypomanic or manic episode)
2. consent to participate in the trial
3. aged 16 or over
4. current depressive episode requiring new pharmacological treatment (either as add-on therapy or as a change of treatment)

4.1.2. Exclusion criteria:

1. definite indications or contraindications to lamotrigine, quetiapine or folic acid* (Including pregnancy and planned pregnancy)
2. new course of a specific psychosocial intervention[1] started in the past 4 weeks
3. first appointment for a specific psychosocial intervention[1] booked within the next 14 weeks
4. In the opinion of the investigator, currently experiencing manic or mixed episode.
5. primary diagnosis of schizophrenia

Plus, for women of child-bearing potential

6. currently breast feeding or not using adequate contraception.

* Participants who have active cancer, a diagnosed pre-malignant condition, a strong family history of cancer or are unwilling to stop taking folic acid supplements can, where clinically appropriate, be randomised to the lamotrigine/placebo arm (see section 3.2.3.)

[1] Defined as Cognitive Behaviour Therapy (CBT), Group Psychoeducation, Family-focused Therapy and Interpersonal and Social Rhythm Therapy (IPSRT)

4.2. Additional inclusion criteria for entry to the randomised phase
Patients must satisfy the eligibility criteria above plus all the following criteria to be eligible for entry to the randomised phase:

1. able to tolerate quetiapine at a dose of at least 150mg/day
2. uncertainty whether quetiapine plus lamotrigine would be more effective than quetiapine monotherapy
3. acceptable adherence to quetiapine (>90%) and self-report satisfactory
4. willing to accept random allocation of treatments
5. In the opinion of the investigator, not currently experiencing manic or mixed episode.

5. Trial Procedures
Investigators will record data onto web-based forms or paper forms and send the data to the CEQUEL office either electronically or by fax. The trial office will then instruct the trial pharmacy to post the allocated medicines to the address nominated by the participant (see sections 6.7.3. and 6.7.4.)

5.1. Entry to the run-in phase
Patients will be informed about the trial and provided with a copy of the Participant Information Sheet by their psychiatrist (or, at the request of the psychiatrist and with the patient's permission, by a member of the CEQUEL team) during a routine appointment. They will be given the opportunity to ask questions and as much time as they require to decide about participation. For patients who are willing to take part, informed consent will be obtained by their psychiatrist or, with his/her agreement, by a trial investigator.

5.1.1. Pre-treatment checks: Investigators will be prompted to arrange the investigations recommended by the NICE guidelines on bipolar disorder (NICE, 2006) when initiating treatment with quetiapine.

5.1.2. Data to be collected on entry to run-in phase:
Demographics and contact details:

- participant name (title, given name and family name), date of birth, gender, ethnicity
- participant address, mobile phone number, other daytime telephone number, email address
- GP name, surgery address

Clinical information:

- check eligibility for run-in phase (see section 4.1.)
- diagnosis – bipolar I disorder or bipolar II disorder (based on DSM-IV criteria for a hypomanic or manic episode)
- current use of vitamin supplements containing folic acid

Blood test:
A blood sample will be taken to check:

- baseline folate and B12 (cobalamin and holotranscobalamin) and homocysteine levels*
- single nucleotide polymorphisms MTHFR C677T; COMT Val158Met; FOLH1 T484C

* See section 7.4. for procedures to be followed if a participant is found to be B12 deficient.

At the end of the appointment, quetiapine will be prescribed according to local practice and data forms will be submitted to the CEQUEL Office electronically or by fax.

Self-reporting by SMS, webform or hardcopy will be requested after the appointment
- QIDS-SR_{16}
- ASRMS
- Quality of Life Questionnaire

5.2. Entry to the randomised phase
Following successful completion of the run-in phase participants will be invited to attend a randomisation appointment:

5.2.1. Initiation and monitoring: Investigators will be prompted to follow guidelines on initiation and monitoring for lamotrigine and folic acid including providing information to women on the use of oral contraceptives whilst taking lamotrigine as outlined in the Summary of Product Characteristics.

5.2.2. Data to be collected at the randomisation visit:
Clinical Information
- check eligibility for randomised phase (see section 4.2.)
- dose of quetiapine to be continued
- comorbid substance abuse, anxiety disorder, eating disorder or psychotic symptoms# (according to DSM-IV criteria)
- previous treatment for this episode
- psychotropic medicines taken in the 30 days prior to screening
- psychotropic medicines to be continued in trial
- DSH history

Note: patients who have a primary diagnosis of schizophrenia are not eligible for CEQUEL

Participant completed in clinic
- QIDS-SR_{16} *
- ASRM
- Quality of Life Questionnaire

* to be scored by investigator during appointment to check eligibility

Drug supply
- Address for medicines to be sent to (if different from home address)

Randomisation will be arranged with full allocation concealment via the electronic Case Report Form (CRF). Investigators who do not have internet access will fax the randomisation forms to the CEQUEL Office where random allocation will be arranged (see section 3.2.3.).

At the end of the appointment, quetiapine will be prescribed according to local practice, Lamotrigine/placebo and folic acid/placebo will be prescribed using electronic or paper trial prescription forms which will be submitted to the CEQUEL Office together with the data forms electronically or by fax.

5.3. Follow-up visit 1 (12 weeks)
The first follow-up visit should be scheduled for 12 weeks post-randomisation (+/- 14 days).

5.3.1. Data to be collected at follow-up visit 1:
Clinical Information
- details of any changes to dose of quetiapine
- dose of lamotrigine/placebo established post-randomisation
- details of any subsequent changes to dose of lamotrigine
- adherence to lamotrigine/placebo and folic acid/placebo and quetiapine
- details of any admissions to hospital
- details of any new treatments for emergent manic or depressive symptoms
- details of any new SAEs or non-serious AEs that are subject to routine reporting (see section 8.2.3.)
- DSH.

Blood test:
A blood sample will be taken to check:
- folate, B12 (cobalamin and holotranscobalamin) and homocysteine levels.

5.4. Follow-up form (22 weeks)
The investigator will be asked to provide follow-up data and to confirm doses of allocated treatment 22 weeks after randomisation. Provided that routine follow-up is continuing, there will be no need for the participant to be present when these forms are completed.

5.4.1. Data to be requested at 22 weeks:
Clinical Information
- details of any changes to dose of quetiapine
- details of any changes to dose of lamotrigine
- adherence to lamotrigine/placebo and folic acid/placebo and quetiapine
- details of any admissions to hospital
- details of any new treatments for emergent manic or depressive symptoms
- details of any new SAEs or non-serious AEs that are subject to routine reporting (see section 8.2.3.)
- DSH

5.5. Follow-up Visit 2 (52 weeks)
The second follow-up visit should be scheduled for 52 weeks post-randomisation (+/- 2 weeks).

5.5.1. Data to be collected at follow-up visit 2:
Clinical Information
- details of any changes to dose of quetiapine
- details of any changes to dose of lamotrigine
- adherence to lamotrigine/placebo and folic acid/placebo and quetiapine
- details of any admissions to hospital
- details of any new treatments for emergent manic or depressive symptoms
- details of any new SAEs or non-serious AEs that are subject to routine reporting (see section 8.2.3.)
- DSH

5.6. Participant reported outcomes
Participants will be asked to complete the QIDS-SR_{16} and the ASRM rating scales by SMS (or webform or hardcopy) once a week for the duration of the randomised phase (see section 5.7. for procedures). In addition to this, participants will be asked, once a month, to complete the EuroQol scale and report contact with health and

social care professionals and initiation of new treatment for mood symptoms. If either contact or new treatment is reported, a member of the CEQUEL team will phone or email the participant to collect further information.

5.7. SMS (or webform) self-reporting of mood by participants

Participants will be given credit-card sized version of the QIDS-SR_{16} and the ASRM and EuroQol (EQ-5D) rating scales. For each scale an SMS prompt will be sent to participants' mobile phones when the rating is due. The SMS responses will consist of a single letter to identify the scale followed by a series of numbers corresponding to participants' ratings of the individual items on the scale.
Replies received by the administering computer system will be automatically checked for transcription errors (i.e. too many or too few digits or numbers that are not valid for the scale). If any errors are detected, the system will notify the participant, via an SMS message, and ask him/her to re-send his/her answers.

If a reply is not received, the administering computer system will generate daily prompts for two days unless or until a reply is received.

Participants who do not have access to a mobile phone or who do not want to complete ratings by SMS will be able to complete ratings by webform with weekly prompts as for SMS ratings. Participants unwilling/unable to use SMS or webform will be provided with paper copies of the two scales and freepost envelopes in which to return them to the CEQUEL office.

5.8. Emergency procedures for unmasking treatment allocation

Investigators and participants will be provided with the telephone number for an on-call member of the trial team. This number will operate 24 hours a day 7 days a week and can be used to request unblinding of one or both treatment allocations in the event of a medical emergency. Procedures will be put in place to verify the identity of the participant and caller and the decision on whether to reveal the allocation will be based on a set of criteria for judging clinical need.

5.9. Unblinding at the end of the trial

Premature disclosure of allocation risks introducing bias and invalidating the trial results. Masking of treatment allocation will therefore be maintained during the course of the trial unless an adverse event arises that clinically requires disclosure. If a participant formally (in writing to the CEQUEL office) requests disclosure of their treatment allocation, this will be made available to them alone after they have left the trial or at 12 months post-randomisation (whichever is the longer).

5.10. Post-trial follow-up

Following completion of the randomised phase or withdrawal from trial follow-up, participants will be contacted by telephone between 7 and 10 days after final contact to update the status of any continuing adverse events and to record any new events. Further follow-up by visit or telephone call will be arranged as required.

5.11. Duration of trial
The active run-in phase will last for 7 to 14 days and the randomised phase for 52 weeks.

5.12. Definition of the end of trial
The end of the trial will be the date of the last visit of the last participant.

5.13. Discontinuation criteria and procedures
In accordance with the current revision of the Declaration of Helsinki (amended October 2000, with additional footnotes added 2002 and 2004), a participant has the right to stop trial treatment and to withdraw from the trial at any time and for any reason, without prejudice to his or her future medical care by the physician or at the institution, and is not obliged to give his or her reasons for doing so.

The investigator may withdraw a participant from trial treatment at any time in the interests of the participant's health and well-being or for administrative reasons. The date and reason for termination of treatment will be recorded. Trial follow-up (including weekly self-reports of mood) will continue after treatment has been withdrawn unless the participant withdraws consent.

If a participant withdraws from the active run-in phase or withdraws from follow-up during the randomised phase, the date and reason for withdrawal will be recorded in the CRF.

6. Trial Treatments

6.1. Provision of trial treatments
Investigators will be responsible for arranging the supply of quetiapine and for using trial prescription forms to prescribe both lamotrigine/placebo and folic acid/placebo according to the dose regimens outlined in sections 6.2 to 6.4. (Recommended rescue medicines are recorded in section 6.5.2.)

Participants will be advised to contact the investigator to report any unexpected occurrence or effect that they think might be related to quetiapine, lamotrigine or folic acid.

6.2. Standard treatment – quetiapine
At the start of the active run-in phase, all participants will be prescribed oral quetiapine once daily as standard first-line treatment for bipolar depression (NICE, 2006). This will be prescribed by the investigator or the participant's GP according to local practice. Investigators will be encouraged to request that 25mg tablets be dispensed until the dose is established to allow rapid changes of dose.

The recommended titration schedule to a target dose of 300mg is shown in Table 1 but a lower starting dose and/or slower titration may be used. If the participant is not able to tolerate 300mg/day, the maximum tolerated dose should be prescribed. Quetiapine may be given twice daily if this is considered to be clinically appropriate. Participants who are not able to tolerate at least 150 mg/day are not eligible for randomisation.

The dose of quetiapine should not be altered within 3 days of randomisation to ensure that the tolerability of the proposed dose has been established.

Prescription of quetiapine at the dose established during the run-in phase should continue throughout the randomised phase unless there are clinical reasons to stop or the participant withdraws consent. Changes to the dose of quetiapine post-randomisation will be considered to be protocol non-compliant. When this does occur the reason for the change will be recorded.

Table 1: Recommended titration schedule for quetiapine

	Days 1 & 2	Days 3 & 4	Day 5	Days 7 to 52
Daily dose	50mg	100mg	200mg	300mg →

6.3. Lamotrigine (or matching placebo according to allocation)
The recommended dose of lamotrigine will vary according to whether participants are on concurrent valproate and, for women, combined oral contraceptives – see Table 2 for recommended and minimum doses and sections 6.3.1. to 6.3.3 for titration schedules.

Table 2 Recommended doses (and minimum doses)

Concurrent valproate	Concurrent combined oral contraceptives	Recommended (minimum) dose (mg/day)	Section
No	No	200 (100)	6.3.1.
Yes	No	100 (50)	6.3.2.
Yes	Yes	100 (50)	6.3.2.
No	Yes	400 (200)	6.3.3.

The investigator will explain the dosing schedule to the participant and the pharmacy will provide a chart showing the daily dose of lamotrigine/placebo for each week during the period when the lamotrigine dose is being titrated.

6.3.1. Titration schedule for participants not taking valproate or combined oral contraceptives: The initial dose of lamotrigine (or placebo) following randomisation will be 25mg/day increasing to 200mg/day after 6 weeks. For participants who cannot tolerate the 200mg/day, the highest dose that can be tolerated should be prescribed with a minimum recommended dose of 100mg/day.

Table 3: Titration schedule for lamotrigine for participants not on valproate or combined oral contraceptives

Target dose	Weeks 1 & 2	Weeks 3 & 4	Weeks 5 & 6	Weeks 7 to 52
200mg/day	25mg	50mg	100mg	200mg →

6.3.2. Titration schedule for participants also taking valproate (regardless of whether they are also taking combined oral contraceptives): The initial does of lamotrigine or placebo will be 25mg every other day increasing to 100mg after 6 weeks. For participants who cannot tolerate the 100mg/day, the highest dose that can be tolerated should be prescribed with a minimum recommended dose of 50mg/day.

Table 4: Titration schedule for lamotrigine for participants also taking valproate (+/- combined oral contraceptives)

Target dose	Weeks 1 & 2	Weeks 3 & 4	Weeks 5 & 6	Weeks 7 – 52
100mg/day	25mg every other day	25mg	50mg	100mg→

6.3.3. Titration schedule for women also taking combined oral contraceptives but not valproate: The initial dose of lamotrigine or placebo will be 25mg/day increasing to 400mg/day after 7 weeks If this is not tolerated (including during pill-free weeks) the dose can be reduced to 200mg.

Table 5: Titration schedule for lamotrigine for women also taking combined oral contraceptives but not valproate .

Target dose	Weeks 1 - 2	Weeks 3 - 4	Week 5	Week 6	Weeks 7	Week 8
400mg/day	25mg	50mg	100mg	200mg	300mg	400mg →

Note: Women should be advised to tell the investigator if they stop oral contraceptives so that the doses of lamotrigine can be adjusted.

6.4. Folic acid (or matching placebo according to allocation)
The dose (to be taken orally) will be 500μg/day as a single daily dose for the full 52 weeks of the randomised phase.

6.4.1. B12 deficiency: The results of the blood sample taken during the run-in phase should be available to the co-ordinating centre within 8 weeks of the participant starting treatment with folic acid. If the results indicate B12 deficiency the investigator will be informed immediately so that B12 supplements can be given. The blinding will not be broken unless it is clinically mandatory to do so (see section 5.8).

6.5. Concurrent medication
6.5.1. Pre-trial medicines: There are no restrictions on concurrent medication on entry to the run-in phase.

6.5.2. Folic acid: Folic acid (prescribed and over-the-counter preparations) should also be stopped (unless there are reasons why the participant should not be randomised to folate/placebo [see section 4.1.2.]).
6.5.3. Carbamazepine: Carbamazepine (which decreases the serum level of lamotrigine) should be stopped during the run-in phase or replaced by oxcarbazepine.

6.5.4. Other psychotropic medicines: Investigators will be encouraged to consider withdrawing any other treatments for mood symptoms that participants were taking prior to entry to the run-in phase but these drugs can be continued where clinically indicated. Drugs that are not withdrawn should be continued at the same dose for the duration of the trial unless there is a clinical need for change. All concurrent psychotropic medicines should be recorded on the baseline assessment form and any subsequent changes reported.

6.5.5. Rescue medication: Investigators will be asked to avoid altering the dose of quetiapine during the first 12 weeks of the randomised phase. Emergent psychotic symptoms should be treated with an alternative antipsychotic (e.g. risperidone) and agitation should be treated with short courses of benzodiazepines.

6.5.6. Additional treatment for depressive symptoms: Investigators will be asked not to prescribe any additional treatment for depressive symptoms during the first 12 weeks of the randomised phase. After 12 weeks, new treatment for depressive symptoms can be initiated as clinically appropriate if response to allocated treatment is considered to be inadequate or if new symptoms emerge.

6.6. Supply of trial treatments

6.6.1. Lamotrigine and matching placebo: Lamotrigine and matching placebo will be donated by/purchased from GSK according to the contract agreed by GSK and the University of Oxford.

6.6.2. Folic acid and matching placebo: Folic acid and matching placebo will be donated by Recip.

6.7. Packaging, labelling and accountability of trial treatments

All tablets will be packaged by a clinical trial supplies packaging company and delivered to the Oxfordshire and Buckinghamshire Mental Health Partnership NHS Trust Pharmacy. All movements of trial medicines between manufacturer, packaging company and pharmacy will be documented. Qualified Person (QP) release will be provided by the packaging company.

6.7.1. Packaging: The clinical trials packaging company will be provided with 6 lists of pack numbers – one for each tablet size of active lamotrigine (i.e. 25mg and 100mg), one for the same tablet sizes of lamotrigine placebo, one for active folic acid (500μg tablets) and one for matching folic acid placebo tablets. The numbers will be generated by the CEQUEL computer programmers and stored directly in a restricted-access database table. When a participant enters the randomised phase, the computer program will generate a list of numbers which correspond to the appropriate allocation and planned lamotrigine/placebo dose for the first packs of trial medicines to be sent. The numbers for subsequent packs of medication will be generated as required in the same way.

6.7.2. Prescription of lamotrigine: The first prescription for lamotrigine/placebo will cover medication for up to 6 months. The medication will be sent out in quantities that cover four or eight week periods. The first pack will be sent after randomisation. The second pack will be sent 2 weeks later. This will establish a 2-week overlap between packs. Thereafter packs will be sent at 4-week intervals for the first 12 weeks and then at 8-week intervals for the remainder of the six-month period.

Twenty-two weeks (5 months) after randomisation, the investigator will be asked to complete a new prescription form for lamotrigine/placebo for weeks 27 to 52 to ensure continuity of treatment. This medication will be sent out in 8-week packs.

If the dose of lamotrigine is altered at any time and the new dose is protocol compliant, the investigator will be required to complete a new prescription form which will supersede all previous forms for the remainder of the six-month period. The investigator will be asked to specify whether the change should be effected immediately or when the next pack is sent. If the new dose is not protocol compliant the supply of trial medicines will be stopped and the investigator will be asked to arrange for treatments to be supplied locally.

6.7.3. Prescription of folic acid: The first prescription for folic acid/placebo will cover medication for 6 months. The medication will be sent to the participant after randomisation. The investigator will be asked to complete a second prescription after 22 weeks (5 months) of treatment and a second pack containing enough folic acid for 6 months will be sent out after 24 weeks (5 ½ months).

6.7.4. Dispensing trial medicines: A Service Level Agreement will be set up between the Department of Psychiatry CEQUEL Office and the Oxfordshire and Buckinghamshire Mental Health NHS Trust Pharmacy to cover dispensing of medicines, re-ordering of stock, checking of expiry dates etc.

The list of pack numbers assigned to a participant for a new supply of medicines (see section 6.7.1.) will be sent to the trial pharmacy by encrypted email together with a passworded letter to the participant. The pharmacy will print a copy of the letter, dispense the treatments and mail them to the participant at their home address, or other address agreed with the participant, investigator and proposed recipient. Packages of medication will usually be sent by Royal Mail Recorded Delivery to facilitate tracking of packages. When this is not appropriate, first class mail or courier services will be used. Participants will be required to acknowledge receipt of each package before a subsequent package is sent. If receipt is not confirmed and the participant cannot be contacted, authorisation to send the next package will be sought from the investigator. When required, participants will be provided with Freepost labels to return any unwanted trial medicines to the trial pharmacy.

The pack labels will contain all the information required by law and will be agreed with the Medicines and Healthcare products Regulatory Agency.

7. Blood Tests

7.1. Timing of blood samples

Participants will be asked to give a blood sample (approximately 10ml.) at the screening appointment and again at the 12-week follow-up appointment.

7.2. Obtaining blood samples

Investigators will be provided with blood collection tubes that can be used to collect samples for homocysteine assay and serum tests. Investigators will also be provided with packaging so that the samples can be mailed to the CEQUEL office. At the screening appointment the investigator should either take the blood samples or arrange for the samples to be taken before randomisation.

7.3. Storage and analysis of blood samples

On receipt at the CEQUEL office, samples will be taken to the Department of Neurosciences where they will be centrifuged. The serum will be sent to the Department of Physiology Anatomy and Genetics where the biochemical tests will be performed. The test results will be available within 2 months of receipt of the sample. The remainder of the samples will be retained in Neurosciences for genotyping.

7.4. B12 deficiency

In the unlikely event that a participant is found to be B12 deficient (defined as serum level below 150pmol/L), the investigator will be informed and advised about the need for the participant to be prescribed B12 supplementation. No other blood test results will be reported to investigators.

8. Assessment of Safety

(See Appendix 2: Classification of adverse events)

8.1. Definitions

8.1.1. Adverse Event (AE): Any untoward medical occurrence in a trial participant administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment (the trial medication).

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the trial medication, whether or not considered related to the trial medication.

8.1.2. Adverse Reaction (AR): All untoward and unintended responses to a medicinal product related to any dose. Response is taken to mean that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.1.3. Serious or Severe Adverse Events: To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.1.4. Serious Adverse Event or Serious Adverse Reaction: A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (see note below)
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether an adverse event is serious in other situations.

8.1.5. Suspected Unexpected Serious Adverse Reactions (SUSARs): A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or pack insert/summary of product characteristics for an approved product).

8.1.6. Assessment of causality: All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

8.2. Serious Adverse Event Reporting Procedures

8.2.1. Reporting by investigator: All SAEs, except those SARs that do not require immediate reporting (see 8.2.3.), must be reported to the Chief Investigator (CI) within one working day of discovery or notification of the event. All SAE information must be recorded on an SAE form and emailed/faxed to the CI. Additional information received for an event (follow-up or corrections to the original event data) need to be detailed on a new SAE form and sent/faxed to the sponsor.

In addition to SAE reporting, investigators should report to the CI any non-serious adverse reactions that they consider to be unexpected or for which they consider the severity or duration to be greater than that indicated in the Summary of Product Characteristics (SmPC). Adverse events that lead to withdrawal from the run-in phase or termination of any of the trial treatments during the randomised phase should also be reported.

Investigators are not required to report other non-serious adverse events.

8.2.2. Reporting by the Chief Investigator: The CI will:

- report all SUSARs to the Competent Authorities (MHRA in the UK) and the REC concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days
- report all SAEs (including SUSARs) to the participant's NHS Trust and to the IDMEC
- inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, the CI will:

- submit once a year throughout the clinical trial or on request a safety report to the Competent Authority (MHRA in the UK), the main REC and participating NHS Trusts and send a copy to the University of Oxford Clinical Trials Research Governance Team.
- provide data on all reported AEs to the IDMEC as required.

8.2.3. *Expected Serious Adverse Reactions:* Immediate reporting of Suspected Serious Adverse Reactions that are listed in the SmPC for the appropriate trial treatment(s) will not be required provided that the severity and seriousness are consistent with the information given in the SmPC.

8.2.4. Other expected Serious Adverse Events
Immediate reporting of the details of hospital admission to treat mood episodes will not be required.

8.3. Reporting Procedures for all Adverse Events
All SAEs whether observed by the investigator or reported by the participant and whether attributed to trial medication or not, will be reported in the CRF. SAEs considered by the investigator or the CI to be related to the trial medication will be followed until resolution or until the event is considered stable. The following attributes must be assigned by the investigator: description, date of onset and resolution date, severity[1], assessment of relatedness to trial medication, other suspect drug or device and action taken. The investigator may be asked to provide follow-up information.

It will be left to the investigator's clinical judgment whether or not an SAE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE.

All SAEs that are related to trial medicines or trial procedures and either result in a participant's withdrawal from the trial or are present at the end of the trial should be followed up until symptoms cease or the condition becomes stable.

All deaths occurring on trial must be reported to the CI. These include deaths within 30 days of the final dose of trial medication and deaths up to the last formal follow-up observational period, whichever is longer. For all deaths, available autopsy reports and relevant medical reports will be requested for reporting to the relevant authorities.

Any pregnancy occurring during the trial and the outcome of the pregnancy should be reported to the Chief Investigator.

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[1] The severity of events will be assessed on the following scale:
1 = mild, 2 = moderate, 3 = severe.

9. Statistics

9.1. Analyses

The principal comparisons (outlined in section 2.1) will be performed on an intention-to-treat basis. The results from the trial will be presented as comparative summary statistics with 95% confidence intervals. Continuous outcomes: To address the principal research questions (see section 2.1), an analysis at the margins will be conducted (McAlister, 2003). Depending on the distribution of the continuous outcome measures, if appropriate, a mixed effect model will be used to analyse QIDS-SR_{16} collected over 12 months. Treatment-time interaction will be included in the model to assess the treatment effect at 12 weeks. The model will adjust for baseline value and stratification/minimisation covariates, plus other variables that are considered to be of prognostic importance. We will formally assess the distribution of the continuous outcome for evidence of departure from normality. If necessary, data will either be transformed or analysed using a non-parametric equivalent. Binary outcome (proportion achieving remission): Multiple logistic regression will be adopted to analyse binary outcomes. The model will test for an intervention effect after adjustment for the other intervention, stratification/minimisation variables and known prognostic factors. Secondary analyses will include multiple logistic regression to explore the possible gene-treatment interaction on remission rates.

9.2. Number of participants

The primary outcome is the level of depressive symptoms, measured using the QIDS-SR_{16}. For comparisons of treatment groups at the margins as detailed in section 2.1, a minimum total sample size of 236 randomised participants (59 per arm) is required to detect a clinically important treatment effect on this outcome. This assumes a 20% loss to follow-up. Sample size has been calculated for the principal comparison for the primary outcome measure, the effect of lamotrigine on the primary outcome. A power of 90%, a 5% level of statistical significance, use of two-sided statistical tests throughout and an equal allocation to each arm have been assumed.

9.2.1. Main effect of lamotrigine on primary outcome: An absolute difference of 2 points on the QIDS score between Quetiapine+Placebo and Quetiapine+Lamotrigine is considered to be clinically important. From previous data, it has been estimated that the standard deviation of the QIDS in this population is 5.4. In order to detect this standardised difference of 0.37, a total of 186 randomised patients are required. This assumes a repeated measures analysis with 3 time points and a correlation between time points of 0.4. Allowing for a 20% loss to follow-up this increases to 236.

9.2.2. Main effect of folic acid on primary outcome: There is currently no QIDS-SR_{16} data available to assess the effect of folic acid. However, a total sample size of 186 gives the following power for a given effect size:

Effect size	Power
0.2	42%
0.25	60%
0.3	75%
0.35	87%

9.2.3. Gene-treatment interaction (MTHFR C677T), (COMT Val158Met) and (FOLH1 T484C): There are currently no QIDS-SR_{16} data available in the effect of treatment by genes. Therefore, we will conduct an exploratory analysis of the possible interactions between the genes MTHFR C677T, COMT Val158Met or FOLH1 T484C and response to treatment with folic acid.

9.3. Criteria for the termination of the trial

Prior to the start of recruitment, the dataset that will be required by the Independent Data Monitoring and Ethics Committee (IDMEC) (Chair - Professor Thomas Barnes) for interim analyses will be agreed. Stopping rules will also be agreed which specify the point at which interim results will be judged to be sufficiently conclusive for it to be appropriate for the IDMEC to recommend to the Trial Steering Committee (Chair - Professor Shôn Lewis) that they consider early termination of the trial.

10. Direct Access to Source Data/Documents

The investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents to authorised auditors and monitors.

11. Quality Control and Quality Assurance Procedures

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The trial will be conducted in accordance with procedures identified in the protocol. Standard Operating Procedures (SOPs) will be used at all clinical and laboratory sites. Regular monitoring will be performed according to ICH-GCP. Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. When requested, the investigator site will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12. Ethics and Good Clinical Practice

12.1. Declaration of Helsinki

The Investigator will ensure that the trial is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

12.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that the trial is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

12.3. Informed Consent

Participant information sheets and consent forms will be provided so that patients can find out more about the trial before deciding whether or not to participate. The information will also be presented verbally by the investigator (or, at the investigator's request and with the patient's permission, by a member of the CEQUEL team). The information will include an explanation of the exact nature of the trial; the requirements of the protocol; any known adverse effects of trial medicines and any known risks involved in taking part. It will be clearly stated that the patient is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The patient will be allowed as much time as they want to consider the information, and the opportunity to question the investigator, their GP or other independent parties to decide whether to participate in the trial. Written Informed Consent will then be obtained by means of patient dated signature and signature of the Principal Investigator or named Co-Investigator. The informed consent will include permission for the CEQUEL office to notify the patient's GP about the trial and the allocated treatment. A copy of the signed Informed Consent will be given to the patient. The original signed form will be retained at the trial site.

12.4. Research Ethics Committee

A copy of the protocol, proposed informed consent form, other written patient information and any proposed advertising material will be submitted to a REC for written approval.

The Investigator will submit and, where necessary, obtain approval from the REC for all subsequent protocol amendments and changes to the informed consent document.

12.5. Patient confidentiality

The CEQUEL Office will need to be informed of participants' names and addresses in order to arrange for allocated treatments to be mailed to them. The Participant Information Sheet will inform patients of this and the number of staff with access to identifiable information will be kept to the minimum required to ensure smooth running of the trial.

Wherever possible forms containing clinical data will be contain only the participant's initials and a participant ID number assigned after entry to the run-in phase. All documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act 1998

13. Data Handling and Record Keeping

Electronic trial data will be stored on a secure database server with restricted access. All identifiable information will be encrypted in the database so that, in the unlikely event of a security breach, it would not be a straightforward matter to obtain participant details from the database. The database will be backed up daily in encrypted form and offsite copies will be made at regular intervals. Paper forms will be kept in a locked filing cabinet in the CEQUEL office. (The office is locked when empty.)

14. Financing and Insurance

14.1. Funding
CEQUEL is funded by the NIHR Efficacy and Mechanism Evaluation programme. The funding is held by the trial sponsor, the University of Oxford.

14.2. Non-negligent harm
Indemnity and/or compensation for harm arising specifically from an accidental injury, and occurring as a consequence of the research participant's participation in the trial for which the University is the research sponsor will be covered by the University of Oxford.

14.3. Negligent Harm
Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the University is legally liable as the research sponsor will be covered by the University of Oxford. The NHS will owe a duty of care to those undergoing clinical treatment, with Trust Indemnity available through the NHS Litigation Authority Scheme.

15. Publication Policy
The primary report will be submitted to a high impact medical journal and will be attributed to the CEQUEL Investigators and Collaborators. The names of all investigators who enter a participant into the randomised phase and of members of the trial management team will be listed at the end of the primary publication. The results will be further disseminated via systematic reviews, guidelines and evidence syntheses. Health economic analyses and results will be reported to field conferences and journals.

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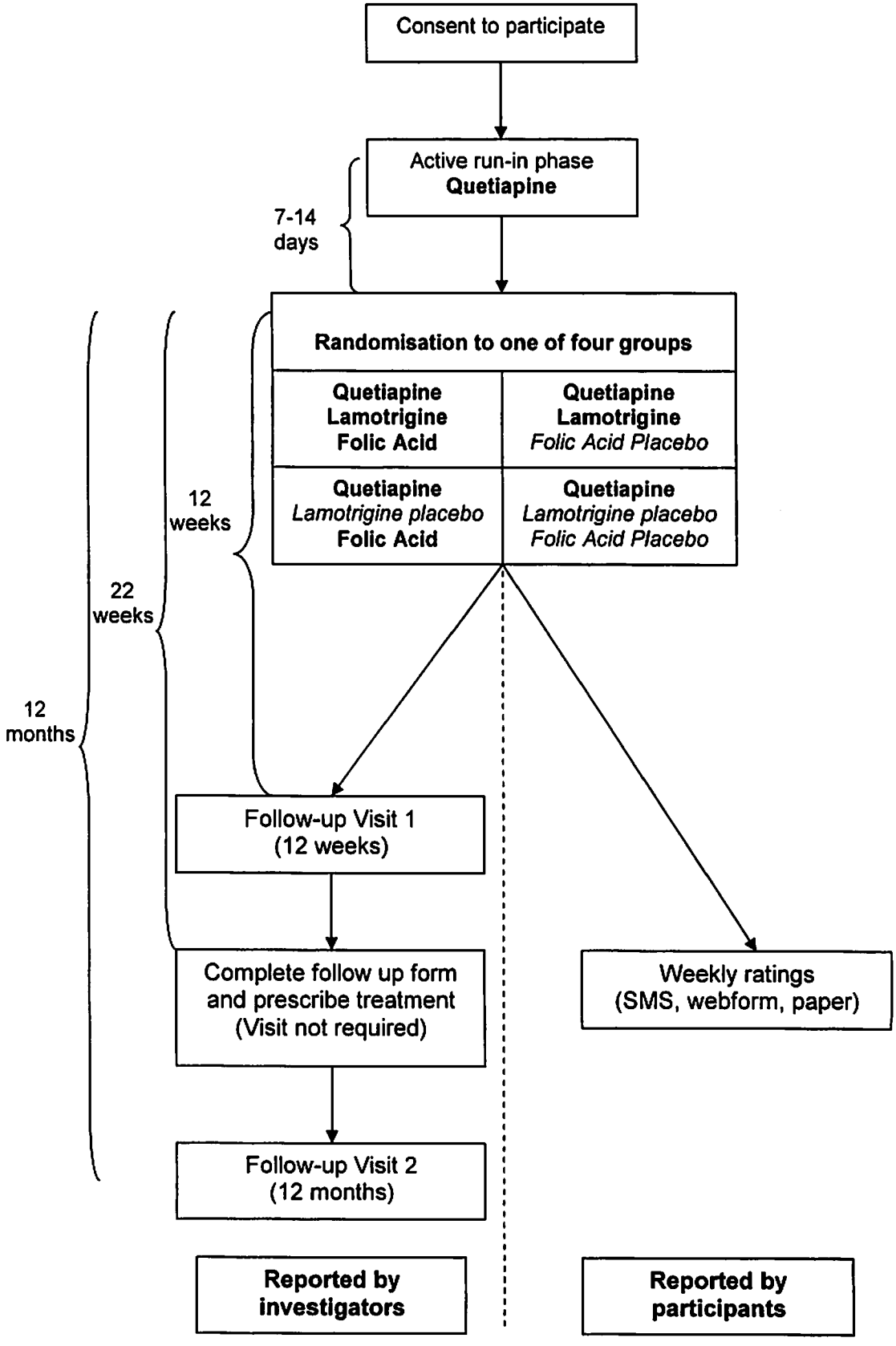
Appendix 1: Flow chart showing stages of the trial



Appendix 2: Classification of adverse events

A. Assessment of whether an adverse event is SERIOUS		
	YES	NO
1. Has the participant died?		
2. Was the participant at risk of death because of the AE?		
3. Did the AE lead to admission or extension of admission to hospital?		
4. Has the AE resulted in persistent or significant disability/incapacity?		
5. Was the AE an important medical event that may jeopardise the participant (or an unborn child) and may require medical or surgical intervention to prevent one of the outcomes listed above?		
** If YES to ANY of the questions above, the event is SERIOUS **		

B. Assessment of whether an event is a SUSPECTED ADVERSE REACTION		
	YES	NO
Is a causal relationship between a trial medicine and the adverse event at least a possibility? i.e. a relationship cannot be ruled out.		
** If YES, the event should be classed as a SUSPECTED ADVERSE REACTION **		

C. Assessment of EXPECTEDNESS (Suspected Serious Adverse Reactions only)		
	YES	NO
Is the nature of the adverse reaction consistent with the Summary of Product Characteristics or other relevant product information?		
** If NO, the event should be classed as an UNEXPECTED REACTION **		