NIHR HTA Programme

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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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LAMOTRIGINE AND BORDERLINE PERSONALITY DISORDER:
INVESTIGATING LONG TERM EFFECTIVENESS

PROTOCOL

Funder's reference number:	National Institute of for Health Research Health Technology Assessment Programme (HTA): 10/103/01
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Confidentiality Statement

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For general queries, supply of trial documentation, and collection of data, please contact the Trial Coordinating Office.

Clinical queries should be directed to the local Principal Investigator [PI], who will direct the query to the appropriate person.

Lamotrigine And Borderline Personality Disorder: Investigating Long Term Effectiveness [LABILE]

A multi-centre, two-arm, parallel group, double blind, placebo-controlled, randomised trial with a 12, 24 and 52-week follow-up assessment *to establish the clinical and cost effectiveness of lamotrigine for people with Borderline Personality Disorder.*

Principal Investigator Agreement

Recruitment

1. To keep a list of all consented patients, randomised patients and withdrawals; and to notify the Trial Coordinating Office of these when requested.
2. Ensure the rights of individual participants are protected and that they receive appropriate medical care whilst participating in the study.
3. Inform appropriate health or social care professionals if their patient is a participant of the study in accordance with the Research Governance Framework.
4. To ensure that the data collected and reported are accurate, complete and procedures adhere to the Data Protection Act.

Pharmacovigilance

5. To record all Adverse Events/Reactions according to Sponsor's Standard Operating Procedure.
6. To report expected Serious Adverse Reactions to Sponsor via the Trial Coordinating Office, using the provided form, as regularly as dictated by the protocol.
7. To report all Suspected Unexpected Serious Adverse Reactions immediately to Sponsor via the Trial Coordinating Office, using the provided form, according to Sponsor's Standard Operating Procedure.
8. To report all follow-up information on Suspected Unexpected Serious Adverse Reactions and unresolved Serious Adverse Events/Reactions.
9. To provide information to the Chief Investigator to enable him to write the annual Development Safety Update Report (DSUR) for submission to Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC) and to send to Sponsor.

Delegation of responsibilities

10. To record and update the names of all significant personnel involved in the trial on a Site Delegation Log. (Trial Coordinating Office to provide form).
11. To ensure responsibilities of all significant personnel involved in the trial are documented on a Site Delegation Log and stored in the Investigator Site File.
12. To document protocol training and maintain a record of the qualifications and experience of all significant personnel involved in the trial.

Record keeping
13. To maintain an Investigator Site File. 14. To keep a numerical list of all amendments (substantial and non-substantial) in real time. 15. To ensure that the most up-to-date approved version of all study documents are used at all times.
Site Visits
16. To be available for on-site monitoring visits as dictated by the Protocol, and in accordance with the requirements of the Sponsor. 17. To be available for audit by the Sponsor or local Trust, or inspection by the regulatory body, where required. 18. To communicate and work with the Chief Investigator and Trial Coordinating Office to ensure appropriate close-out. 19. To ensure that there is local provision for archiving site study documents at close-out.
Other
20. To report immediately any Protocol violations or breaches of Good Clinical Practice (GCP) using the form provided by the Trial Coordinating Office. 21. To conduct the study according to ICH GCP and in line with the Research Governance Framework for Health & Social Care.

SIGN OFF:			
Principal Investigator	Signature	Print Name	Date:
Co- Investigator (If Applicable)	Signature	Print Name	Date:

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

1. STUDY BACKGROUND

Borderline Personality Disorder (BPD) is a severe mental disorder that is characterised by affective instability, recurrent suicidal behaviour and poor interpersonal functioning[1]. It is estimated that between 0.5 and 2% of people have BPD[2], and that the lifetime prevalence of the condition is as high as 6%[3]. Far higher levels of BPD are found among people in contact with mental health services, particularly inpatient mental health units, where as many as a fifth of people have this diagnosis[4].

People with BPD are more likely to experience other mental health problems such as anxiety, depression and substance misuse problems. One in ten people who attend emergency medical services following deliberate self-harm meet diagnostic criteria of BPD[5]. It is estimated that the rate of completed suicide among people with BPD is 50 times that in the general population[6]. People with this condition have poor social functioning, are socially isolated, and are usually unemployed or on long-term sick leave[7]. Physical health is also often poor and people with BPD have increased levels of mortality due to cardiovascular disease and other physical health problems[8].

1.1 Treatment of Borderline Personality Disorder

Concerns have been expressed about the quality of services for people with BPD[9]. Many people with this diagnosis report dissatisfaction with the treatment they receive[10,11], and mental health practitioners often find it difficult to work with people with this condition[12].

While psychological treatments such as Dialectical Behaviour Therapy and Mentalisation Based Therapy have been shown to improve the mental health of people with BPD[13], most people with this disorder do not have access to specialist psychological services. Among those that do, many do not engage with psychological services, and as many as half of those who do engage drop out before it has been completed[14]. People with the most severe problems are less likely to engage in psychological treatment than those with milder forms of the disorder[15].

No drug treatments are licensed for people with BPD, but despite this people with this condition are usually prescribed large amounts of psychotropic medication[16]. Antidepressants are widely used despite evidence that they do not improve people's mental health or social functioning[17]. Evidence from clinical trials of antipsychotic medications is equivocal. While some studies have shown reductions in symptoms of anger and hostility, sustained improvements in symptoms of BPD have not been found[9].

1.2 Mood Stabilizers in the treatment of BPD

Affective instability and higher than expected levels of comorbidity with bipolar disorder among people with BPD has led to considerable interest in the role that mood stabilisers might play in improving the mental health of people with this condition. Research into the effects of established mood stabilisers among people with BPD such as lithium and carbamazepine has been limited due to their toxicity in overdose – a not infrequent occurrence among people with this disorder. However small-scale placebo-controlled trials of four anticonvulsants (carbamazepine, valproate, topiramate and lamotrigine) have shown promising results[17]. The use of placebos in randomised trials of treatments for people with BPD may be particularly important because people with this disorder are highly sensitive to

feelings of rejection and abandonment when expectations about possible treatments are raised and then not delivered[18].

Of the four anticonvulsants that have been tested among people with BPD three (carbamazepine, valproate and lamotrigine) have been shown to also work as mood stabilisers in people with bipolar affective disorder. Of these drugs, valproate and lamotrigine appear to be safer in overdose than carbamazepine[19]. Another concern about the use of anticonvulsants in people with BPD is the increased incidence of birth defects among children born to women taking these drugs[20]. Most people with BPD who are in contact with mental health services are women of child bearing age. Many women with BPD report impulsive behaviour including unplanned and unprotected sex. Data from women taking anticonvulsants for epilepsy have shown that levels of major congenital malformations are more common among people taking valproate than among those taking other drugs[21]. Concerns have also been raised about long-term cognitive impairment among children born to women taking valproate[22].

Evidence on the effects of lamotrigine for people with BPD comes from three open-label studies and two placebo controlled trials. In open-label studies, judgements made by unmasked clinicians suggested that people taking lamotrigine had improved mental health and global functioning over follow-up periods that ranged from 3 to 12 months. The two randomised controlled trials of lamotrigine for people with BPD both report positive findings. The first involved 24 women recruited mainly from advertisements placed in primary care practices. In comparison with those taking placebo, those taking up to 200mg of lamotrigine were found to have lower levels of anger eight weeks later[23]. The second trial recruited 28 men and women through websites, television, and radio advertisements. Those randomised to receive up to 225mg of lamotrigine were subsequently found to have lower levels of affective instability and impulsiveness (assessed using the Zanarini Rating Scale for BPD), 12 weeks later[24]. These studies have a number of important limitations including their focus on short-term outcomes, small sample size and the absence of an economic evaluation. Furthermore, people who took part in these two studies may not have had the degree of severity of the disorder that is seen among people who are treated by the National Health Service (NHS).

Lamotrigine is associated with a range of side effects which include cutaneous reactions such as Stevens-Johnson syndrome. The incidence of this problem is higher among people taking valproate. It is reduced by gradual dose escalation. However, serious events are rare, and the drug is widely used in the United Kingdom (UK) for the treatment of people with bipolar disorder, so psychiatrists are familiar with its dose titration requirements and the need for vigilance for severe cutaneous adverse reactions.

2. STUDY OBJECTIVES

The main objectives of the study are as follows:

i. To test whether adding lamotrigine to usual care for adults with BPD improves mental health over a 52 week period, in comparison to a placebo control.

ii. To examine whether the addition of lamotrigine to usual care for adults with BPD improves social functioning and quality of life, reduces the incidence of suicidal

behaviour, and lowers the amount of antipsychotic and other psychotropic medication that people are prescribed, in comparison to a placebo control.

iii. To compare the incidence of side effects among those prescribed lamotrigine in addition to usual care for adults with BPD, in comparison to a placebo control.

iv. To examine the cost, cost-utility and cost-effectiveness of adding lamotrigine to usual care for adults with BPD, in comparison to a placebo control.

3. STUDY DESIGN

The study to be undertaken will be a multi-centre, two-arm, parallel group, double-blind, placebo-controlled, randomised trial with a 12, 24 and 52-week follow-up assessment. 252 eligible patients will be randomised 1:1 to receive lamotrigine or placebo.

4. OUTCOME MEASURES

4.1 Primary Outcome

The primary outcome measure is symptoms of BPD measured at 52 weeks using the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD)[25]. The ZAN-BPD is a widely used measure of symptoms and behavioural problems experienced by people with BPD. It includes measures of anger, impulsivity and affective instability. The ZAN-BPD has been used in previous studies of pharmacological and psychological treatments for people with BPD and is sensitive to change[24, 26, 27].

4.2 Secondary Outcomes

- Total score on the ZAN-BPD at baseline, 12 and 24 weeks;

- Depression: depressive symptoms will be assessed using the 21-item Beck Depression Inventory[28] at baseline, 12, 24 and 52 weeks. The Beck Depression Inventory has been widely used as a self-complete questionnaire, providing a valid assessment of the severity of depressive symptoms and can be completed in less than 10 minutes[29].

- Self-harm: incidence and severity of suicidal behaviour will be assessed using the Acts of Deliberate Self-Harm Inventory[30] at baseline, 12, 24 and 52 weeks. This structured interview collects detailed information about the number and severity of episodes of self-harm and has been used successfully in other trials of treatments for people with BPD[31].

- Social functioning: social functioning will be assessed using the Social Functioning Questionnaire at baseline, 12, 24 and 52 weeks. The questionnaire is an eight-item self-report scale that asks people about problems across a range of settings that people with personality disorder often experience[32].

- Health-related quality of life: health related quality of life will be assessed using the Euro-QOL-5D (EQ-5D)[33] at baseline, 12, 24 and 52 weeks. The EQ-5D provides a brief and reliable measure of health-related quality of life which is responsive to change in people with BPD[34].

- Side effect scale: possible side effects of lamotrigine will be assessed using a proforma designed to cover the possible effects listed in the British National Formulary (BNF) entry for lamotrigine[35], at baseline, 12, 24, and 52 weeks.

- Service use: resource use will be collected using a modified version of the Adult Service Use Schedule[37, 38] at baseline, 12, 24 and 52 weeks. This questionnaire collects detailed data on use of all hospital and community health and social care services including medication.

- Medication adherence: to assess medication adherence at 12, 24 and 52 weeks the Morisky Scale shall be utilized.

- ~~Body weight: body weight will be measured at baseline, 24 and 52 weeks.~~

5. STUDY ENROLLMENT AND WITHDRAWL

5.1 Inclusion Criteria

- Age 18 or over.

- Fulfilling DSM-IV diagnostic criteria for BPD.

- Competent and willing to provide written, informed consent.

5.2 Exclusion Criteria

- Currently fulfilling criteria for Bipolar affective disorder (type I & II)[36], or psychotic disorder (schizophrenia, schizoaffective disorder, or mood disorder with psychotic features).

- At present receiving a mood stabiliser(s) (e.g lithium, carbamazepine, or valproate)*.

- Known medical history of liver or kidney impairment.

- Cognitive or language difficulties that would preclude subjects providing informed consent or compromise participation in study procedures.

- Any woman who is pregnant or planning a pregnancy, and any woman of child bearing potential unless using adequate contraception. This will be established using structured questioning at screening and follow-up, and documented in the case report form.

- *Participants will be required to discontinue any mood stabiliser(s) (e.g. lithium, carbamazepine, or valproate) for at least four weeks before entry into the study.

Study researchers will discuss with the potential participant whether they are involved in any other study during the initial discussion, and should the service user have been involved in other Clinical Trial Investigational Medicinal Products (CTIMPs), then the guidance from the Association of the British Pharmaceutical Industry (ABPI) will be followed, and study researchers will ensure at least a 4-month gap has elapsed before participation in the LABILE study is broached.

5.3 Assessment of covariates for eligibility

- Diagnosis of BPD will be determined using the Structured Clinical Interview for Axis II Personality Disorders (SCID-II)[37]. The SCID-II provides a reliable assessment of BPD[38], has a shorter administration time than other semi-structured interviews used to assess BPD, and can be completed within one hour. Data from the SCID-II together with information on social functioning from the Social Functioning Questionnaire will used to establish severity of BPD[39].

- To assess whether potential participants have bipolar affective disorder (type I & II) the Structured Clinical Interview for Axis I Disorders (SCID-I) [40] will be used.

- Hypomanic symptoms will be assessed using the 32-item Hypomanic Checklist[41], a relatively short screening questionnaire that can distinguish those with bipolar disorder from those with unipolar depression[41].

- To assess the use of alcohol and other drugs at baseline, the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[42] will be used. This short questionnaire provides a reliable and valid screening test for problem substance use[43].

5.4 Randomisation

Randomisation will be undertaken by the Nottingham Clinical Trials Unit. Equal numbers of participants will be randomised to each arm of the trial using a web based randomisation system. Stratification will occur by study centre, severity of personality disorder (simple or complex PD according to criteria developed by Tyrer and Johnson[39]), and extent of bipolarity (using a score of more or less than 14 on the hypomania checklist[41]).

After consenting to participation and completing screening assessments, patients who are found to be eligible will be randomly allocated to the intervention or comparator arm of the trial by the automated randomisation service. This will generate a unique participant identification number for that participant, which will be used on the Case Report Forms (CRFs). Blinding of investigators, researchers, clinicians and patients will be maintained until all data entry and processing are complete and the database has been locked. All patients, carers, and study personnel will be blinded to treatment assignment. The study statistician will also be blind to trial arm allocation and will monitor recruitment rates on a monthly basis.

5.5 Unblinding

Premature disclosure of allocation runs the risk of introducing bias and invalidating the trial results. Masking of treatment allocation will therefore be maintained during the course of the trial unless the following occur:

- A serious adverse event arises that clinically requires disclosure.
- Overdose of the trial drug.
- The participant becomes pregnant.
- There is a clinical need to start the participant on medication which has a risk of interaction.

5.5.1 Emergency unblinding

In anticipation of an emergency, investigators, clinicians and participants will be provided with the telephone number for a 24-hour emergency unblinding service at the Medical Toxicology and Information Services, with medical support. This system will allow a medical request for unblinding in the event of a medical emergency to be responded to 24 hours a day, 7 days a week. Procedures will be put in place to verify the identity of the participant and caller, and the decision on whether to reveal the study medication allocation will be based on a set of criteria for judging clinical need. All requests for unblinding are recorded.

5.5.2. Unblinding at the end of the follow-up period

52 weeks after a participant is randomised into the study, regardless of whether they withdraw from the study early or complete the participation period in full, a letter will be sent to the referring psychiatrist informing them of the participant's trial arm allocation. Where a participant has completed the participation period in full, this will allow the psychiatrist time to make arrangements for the participant to continue on lamotrigine if appropriate and desired. Upon completion of their 52-week follow-up assessment, the participant will be advised to contact their psychiatrist to discuss their trial arm allocation if he/she wishes to know whether they were taking the active or placebo medication. However, if any participant expresses a desire to know their trial arm allocation, and does not wish to discuss this with their psychiatrist, an option for them to discuss this with an unblinded member of the research team will be made available.

5.6 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. A trial participant shall be withdrawn from the study if he or she experiences a rash that is clinically judged as being associated with lamotrigine. The date and reason for termination of treatment will be recorded. Trial follow-up will continue after treatment has been withdrawn, unless the participant withdraws consent.

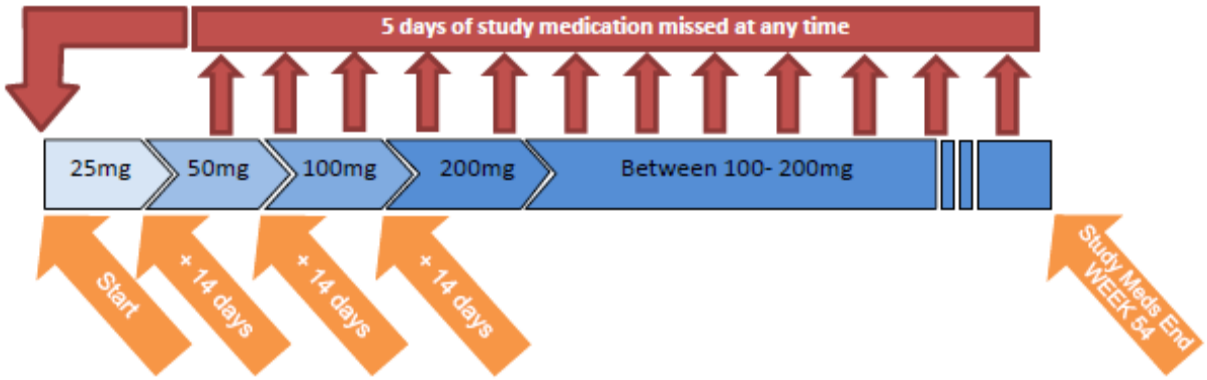
6 TREATMENTS

6.1 Treatment arms

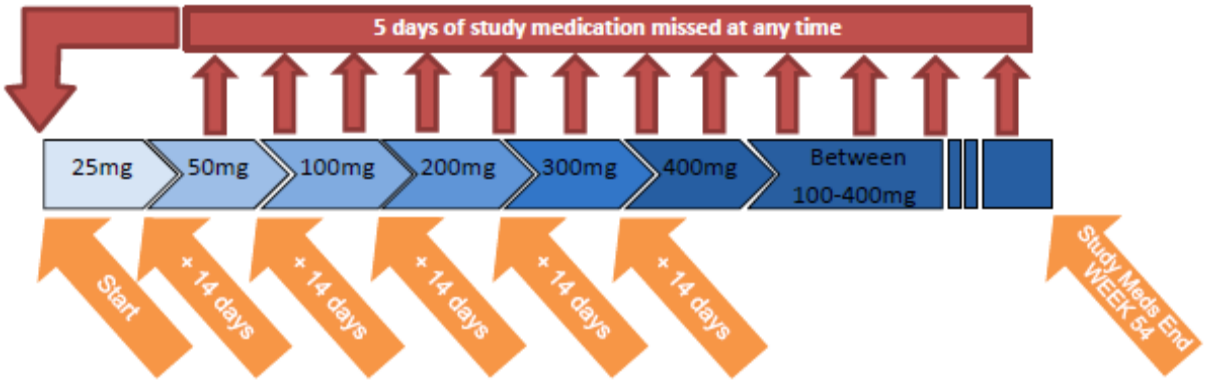
Treatment dose will be titrated according to the established British National Formulary (BNF) protocol for prescribing lamotrigine (http://bnf.org/bnf/bnf/61/9832.htm), but with the titration occurring at standardized 14-day intervals. The dose will be altered if participants are also

taking the combined oral contraceptive pill, which affects the metabolism of lamotrigine. For those not taking the combined oral contraceptive pill, the starting dose will be 25mg per day. Depending on the response and tolerance it will be increased to 50mg after two weeks, 100mg after four weeks and 200mg thereafter (see example (a) below). If there are problems with tolerability at 200mg, the clinician can reduce the dose back to 100mg/day. For those who are taking the combined oral contraceptive pill the starting dose will be 25mg per day. This will be increased to 50mg after two weeks, 100mg after four weeks, 200mg after six weeks, 300mg after eight weeks, and 400mg after ten weeks (see example (b) below). If there are problems with tolerability at 400mg, the clinician can reduce the dose back to 200 or 100 mg/day. Where a participant misses five or more consecutive days of the medication at any time during their participation, they will be advised to contact the study team so that dose titration can be restarted. The dosing schedule is diagrammatically shown below:

(a) dosing for people not taking the combined oral contraceptive pill



(b) dosing for people taking the combined oral contraceptive pill



The encapsulation of lamotrigine tablets, stability testing and packaging will be undertaken by St Mary's Pharmaceutical Unit**.** Trial medication will be issued to patients fortnightly to cover the dose titration period, and subsequent four-weekly packs issued once the maintenance dose is reached. This will ensure that non-adherence and subsequent study withdrawal are dealt with promptly, and that large supplies of medication cannot be accumulated by patients who may be at risk of overdosing. Supplies will be issued by the relevant hospital pharmacy services. The lamotrigine and placebo capsules will be kept in a suitable temperature controlled environment at each site.

6.2 Co-prescription and interaction with other drugs

It would be unethical to restrict the therapeutic options of the clinical team, therefore no restrictions will be imposed on the use of other treatments, except that those who remain in the trial will not be prescribed lamotrigine (aside from trial medication) or another mood stabiliser(s) (e.g. lithium, carbamazepine, or valproate). Our approach will therefore be primarily to record the use of all other medication, documenting details of dosage, and ensure the follow-up of all randomised participants, irrespective of the medication they subsequently receive.

6.3 Dispensing and accountability

Once randomisation has taken place, a LABILE study prescription form containing the patient's details (including their participant identification number) will be signed by the site Principal Investigator or other psychiatrist to whom the task is delegated, and sent to the study site pharmacy. Each pharmacy will have a master list containing randomisation codes and treatment arm allocations, and upon receiving the study prescription form, will select the appropriate pack of trial medication, blind and dispense it ready for collection. Pharmacy staff will retain the original prescription and complete the medication accountability form. Both will be stored in a Pharmacy Site File specific to the study.

Once dispensed, study participants may collect their trial medication from the pharmacy in person. Alternatively the site Principal Investigator may delegate this task to a researcher or suitable healthcare professional (e.g. care co-ordinator) who will collect the medication and give it to the participant.

Where the participant is an in-patient, the study medication will be delivered to their ward, with the prior consent of the Ward Manager. Where a participant is an in-patient, arrangements will be made for the study medication to be given by ward staff in the same way as other prescribed medication would be in this setting and it written up on the participant's drug chart.

6.4 Trial Medication Bottle Returns

Participants will be asked to return the study medication bottles including any study medication that they have not taken at the time of receiving their follow-on supply in order to prevent any excessive stock-piling of trial medication by the participant.

Where the participant is collecting the follow-on study medication themselves, the person dispensing in pharmacy will ask for the returns. In cases where the participant does not visit the pharmacy or see the researcher between assessments, the empty bottles will be collected by the researcher when meeting with the participant to carry out the assessments at 12-weeks, 24-weeks, and 52-weeks. These will therefore be returned to the pharmacy by the researcher.

6.5 Temperature Monitoring

Temperature will be monitored in the clinical trials area of all site pharmacies. Once the study medication is dispensed and leaves pharmacy, however, the temperature will not be monitored. This applies whether the study medication is passed to a participant, a delegated individual involved in the trial who is delivering the study medication to the participant, or a ward on which the participant is an in-patient.

7 STUDY SCHEDULE

7.1 Referral & Consent

A patient who may be eligible for the LABILE study will be initially approached regarding the study by any healthcare professional who is involved in their care providing that the consultant psychiatrist for the team has agreed in principle to patients under their care taking part in the study.

If a psychiatrist or other healthcare professional has a patient under their care who they believe meets the eligibility criteria (section 5.1 and 5.2) for the LABILE study, they should introduce the patient to the study at an appropriate time by briefly describing it, and providing an Information Sheet. The Information Sheet will include an explanation of the exact nature of the trial, the requirements of the protocol, any known adverse effects of the trial medicine, 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 must provide verbal agreement to discuss their eligibility and possible enrolment into the trial with a member of the research team before any further study process can take place. If a patient does not give verbal agreement to discuss their eligibility and possible enrolment to the trial, no further aspect of the screening process will be carried out at that time. However, where a patient later decides that they are willing to be considered for entry into the trial, previous refusal does not preclude this.

Where verbal agreement is given, the patient shall be assigned a screening number and contacted by the research team to discuss consent.

The patient will be allowed no less than 24 hours from receiving the Information Sheet to consider the information, and the opportunity to question the investigator, their GP or other independent parties regarding participation in the trial. Written informed consent will then be obtained and will include permission for the LABILE research team to notify the patient's GP and consultant (who may be the referring psychiatrist) about the enrolment of their patient into the trial. Additionally, the patient will be asked whether a family member or friend can be contacted solely for the purpose of helping the research team to get in contact with the participant, if the research team are not able to get in contact with the participant directly. A separate written informed consent will be required for this. The patient will not be excluded from the study if he/she does not give consent for the research team to contact family members or friends. A copy of the signed Informed Consent form(s) will be given to the patient and their consultant. The original signed form(s) will be retained at the trial site.

A patient that has been previously assessed and found not to fulfil all the eligibility criteria may be considered for later entry into the study if it is likely that they now fulfil the eligibility criteria.

7.2 Screening & Baseline

If consent is given and documented, a Screening Assessment Case Report Form (CRF) will be completed with the participant, where possible completing the assessments at the same

visit that consent is taken. When the screening assessment is complete, and if the participant fulfils the eligibility criteria, completion of the Baseline Assessment CRF may be commenced immediately, or a follow-up meeting for this purpose can be arranged, depending on the participant's tolerance.

Once eligibility is confirmed, the researcher will use the randomisation system to obtain participant identification number for the participant. Following randomisation, the participant's GP and consultant will be informed of their enrolment into the trial.

7.3 Follow-up

The 12, 24 and 52 week assessments (see Table 1) will be scheduled to coincide with the supplying of the participant's study medication.

Table 1: Study Assessment Schedule. [1] ZAN-BPD and Social Functioning Scale scores for baseline shall be derived from the Screening Assessment CRFs.

Assessments	Screening	Baseline	12 Week FUP	24 Week FUP	52 Week FUP
SCID-II	X	-	-	-	-
SCID-I	X	-	-	-	-
Hypomanic Checklist	X	-	-	-	-
ASSIST	X	-	-	-	-
Morisky Scale	-	-	X	X	X
ZAN-BPD	X[1]	-	X	X	X
Beck Depression Inventory	-	X	X	X	X
Acts of Deliberate Self Harm Inventory	-	X	X	X	X
Social Functioning Questionnaire	X[1]	-	X	X	X
EQ-5D	-	X	X	X	X
Side Effect Scale	-	X	X	X	X
Modified Adult Service User Schedule	-	X	X	X	X
~~Weight~~	~~-~~	~~X~~	~~-~~	~~X~~	~~X~~

Prior to the writing of each new study prescription and at multiple time point at the maintenance dose, the psychiatrist or researcher will contact the participant to elicit details of any adverse events, and to ascertain whether they wish to continue with the trial.

7.4 Follow-up procedure once a participant is no longer taking the study medication

Once a participant ceases to take the study medication, whether this is due to them reaching the end of the participation period, withdrawal or other reason, a Study Completion/Termination Form shall be completed by the researcher.

7-10 days later, the participant will be contacted by the researcher to update the status of any continuing adverse events and to record any new events. This will also provide an opportunity for the participant to ask any questions that they may wish to. This communication will be documented on a Post-Completion Follow-up form.

Where the participant is continuing to experience an adverse event(s), further monitoring will be performed even when they are no longer being prescribed the study medication. Further follow-up by visit or telephone call will be arranged as required.

7.5 Participant Financial Remuneration

All participants will be offered a £20 honoraria following completion of the 52-week follow-up interview. In addition, any travel costs that the patient may incur in the process travelling to and from study visits will be reimbursed.

8 PHARMACOVIGILANCE

8.1 Definitions

- **Adverse Event (AE):** any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

- **Adverse Reaction (AR):** all untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

- **Unexpected Adverse Reaction:** an AR, 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 summary of product characteristics (SmPC) for an authorised product). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.

- **Serious Adverse Event (SAE)** or **Serious Adverse Reaction:** any untoward medical occurrence or effect that at any dose:

    - Results in death;
    - Is life-threatening – *refers to an event in which the subject 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;*
    - Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
    - Results in persistent or significant disability or incapacity;
    - Is a congenital anomaly or birth defect.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in

death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

- **Suspected Unexpected Serious Adverse Reaction (SUSAR):** any suspected adverse reaction related to an IMP that is both unexpected and serious.

8.2 Causality

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the IMP being used in this study. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below:

Relationship	Description
Unrelated	There is no evidence of any causal relationship.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

If any doubt about the causality exists the local investigator should inform the trial co-ordinating office who will notify the Chief Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view

8.2 Reporting Procedures

The Principal Investigators at each recruitment site and the Chief Investigator will conduct safety monitoring of the trial according to the written standard operating procedures (SOPs) for pharmacovigilance agreed by the Imperial College AHSC Joint Research Office.

All adverse events (AEs), whether attributed to trial medication or not, occurring from the date of consent will be recorded on an Adverse Event Record Sheet. Depending on the nature of the event the reporting procedures below should be followed.

- **Non serious AR/AEs**

All such toxicities, whether expected or not, should be recorded in the toxicity section of the relevant case report form and sent to the trial coordinating office within one month of the form being due.

- **Serious AR/AEs**
  Fatal or life threatening SAEs and SUSARs should be reported on the day that the local site is aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

- **SAEs**
  An SAE form should be completed and faxed to the study coordination centre for all SAEs within 24 hours. However, relapse and death due to "condition", and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

- **SUSARs**
  In the case of suspected unexpected serious adverse reactions, the staff at the site should:

  Complete the SAE case report form & send it immediately (within 24 hours, preferably by fax), signed and dated to the trial co-ordinating office together with relevant treatment forms and anonymised copies of all relevant investigations.

  Or

  Contact the study coordination centre by phone and then send the completed SAE form to the trial co-ordinating office within the following 24 hours as above.

  The trial co-ordinating office will notify the MHRA, REC and the Sponsor of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

Any questions concerning adverse event reporting should be directed to the trial co-ordinating office in the first instance. A flowchart is provided (see appendix 1) to aid in the reporting procedures.

All clinicians referring patients to the LABILE study will be provided with a list of expected adverse effects associated with the study drug (see appendix 2). They will be asked to report all AEs, whether expected or not, to the local Principal Investigator for documentation and onward reporting.

The Principal Investigator's will be responsible for deciding whether or not an AE necessitates the participant's removal from treatment. Study medication will be discontinued immediately if rash or signs of hypersensitivity syndrome develop. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable AE.

8.3 Reporting of Pregnancy

Should a participant become pregnant, or aid in the conception of a child whilst taking part in the study, the pregnancy and resulting child will be followed up for a period of no less than 18 months to verify whether a congenital anomaly or birth defect is present. This process will be documented on a Pregnancy Reporting Form to the Trial Coordinating Office and the pregnancy report to the MHRA and Research Ethics Committee by the Chief Investigator. For pregnancy outcome, the local research team or Coordinating Centre will monitor the outcome, as appropriate. A participant who is pregnant will be withdrawn from the study and the study medication discontinued.

9 MONITORING

9.1 Routine Monitoring

JRCO Monitor will ensure that all documents are in place in the Trial Master File prior to the study starting and a JRCO Study Start Approval form must be issued before the study can commence. Monitoring must adhere to JRCO minimum standards. A JRCO monitoring plan outlining these minimum requirements will be calculated by means of a JRCO risk assessment. Copies of the monitoring reports must be sent to the Sponsor.

Day-to day monitoring will be carried out by the Trial Co-ordinating Office remotely via the online database system. This will include checking that:

- The data collected are consistent with protocol.
- CRFs are being completed by authorised staff.
- No key data are missing.
- The data appear to be valid.

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor, the Study Coordinating Office, and other regulatory bodies to ensure adherence to GCP. The Independent Data Monitoring and Ethics Committee (IDMEC) will also have a monitoring and audit role.

9.2 Site Initiation Visit and On-site Monitoring

9.2.1 Site Initiation Visit

Following confirmation from the sponsor that the lead site may commence patient recruitment, other sites will be opened by a Site Initiation Visit. During the Site Initiation Visit:

- Training will be provided on the study protocol and study standard operating procedures.

- Guidance on CRF completion and the electronic data management system will be given.

- The Investigator Site File will be checked to ensure that all necessary documents are held and correctly stored.

- Training will be provided on how to maintain the Investigator Site File.

- The Site Pharmacy will be checked to ensure that the resources in place are adequate and in line with study standard operating procedures.

- The Pharmacy Site File will be checked to ensure that all necessary documents are held and correctly stored.

- There will be an opportunity to discuss any aspect of the trial running at the site and have any queries answered.

Following the site initiation visit an “Open to Recruitment” letter will then be sent to the site, confirming that the site may begin enrolling participants into the study.

9.2.2 On-site Monitoring

Further to the Site Initiation Visit, every participating site will receive at least one further monitoring visit during the course of the study. The purpose of the visit will be:

- To provide on-going training, review understanding of the protocol and trial procedures.

- To assess whether the Investigator Site File is up-to-date and documents are being Maintained, in accordance with ICH-GCP and study SOPs.

- To check that pharmacy resources remain adequate.

- To assess whether data collected are consistent with the study protocol.

- To ensure that no key data are missing.

- To perform source data verification.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size

The sample size calculation for the study is based on the primary hypotheses: that, for people with borderline personality disorder who are in contact with mental health services, the addition of lamotrigine to their usual treatment will reduce symptoms of their disorder,

according to the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD). The ZAN-BPD has been used to examine the clinical effectiveness of a range of psychological and pharmacological treatments for people with borderline personality disorder. In a trial of problem solving therapy compared to treatment as usual, Blum and colleagues[26] found improvements in mental health and reduced use of emergency medical services among those who were randomised to problem solving therapy. This was associated with a difference of 3.6 (SD = 6.9) in total ZAN-BPD score.

The ZAN-BPD rating scale was also used to examine the clinical effectiveness of lamotrigine for people with borderline personality disorder in a randomised trial conducted by Reich and colleagues[24]. In this small trial (N = 28), a non-statistically significant difference in total score on the ZAN-BPD was found at 12 weeks of 5.6 (SD = 6.75). Seventeen (61%) of people in the trial completed all 12 weeks of the study and levels of adherence to trial medications in those that completed the study were judged to be high.

It is anticipated that levels of adherence to trial medications may be lower than in the study by Reich and colleagues[24], and the study has been powered on the basis of a clinically significant difference in ZAN-BPD score of 3.0 (SD = 6.75).

Two hundred and fourteen participants (107 receiving lamotrigine and 107 receiving placebo) would need to be randomised to have 90% power to detect a minimal clinically relevant difference of 3.0 (SD = 6.75) in total score on the ZAN-BPD at 52 weeks, using a 0.05 level of statistical significance. To take account of 15% loss to follow-up at 52 weeks sample size has been increased to 252.

10.2 Statistical Analysis

The planned analysis will be by intention to treat. Descriptive analysis will be performed to examine the distribution of each outcome of each group at baseline, at the end of intervention and the end of follow-up and differences in baseline variables between the two comparison groups. Generalised linear models (GLM) shall be utilized to compare and test changes of the primary and secondary outcomes from the baseline to 52 weeks between the intervention and control group. The GLM will allow analysis of different types of outcomes in different types of models, i.e. linear model for mean difference of outcomes with Normal or approximately Normal distribution, Logistic model for difference in proportions and Poisson model for difference in incident rates. Corresponding statistical tests and confidence intervals for the group difference will be obtained from the chosen model for a specific outcome. Any differences in baseline variables between patient groups will be adjusted in the GLM models when comparing the difference in outcome measures.

Before carrying out GLM model analysis, sensitivity analyses shall be performed to examine data missing mechanism to decide whether imputation approaches are necessary.

Given the nature of repeated measures of some outcomes at baseline, 12, 24 and 52 weeks, multilevel GLM shall be considered for the comparison of changes over time between the two groups adjusting for any differences in baseline data of patients and among centres. Simultaneous analyses of sub scales (i.e. anger, impulsivity and affective instability) will be performed using multilevel multivariate models.

10.3 Health Economics Analysis

The economic evaluation will take the NHS/Personal Social Services perspective preferred by the National Institute for Health and Clinical Excellence[44] and shown to be the key cost sectors in previous research among people with borderline personality disorder[45]. Data on the use of health and social services will be collected using a modified version of the Adult Service Use Schedule adapted for use in this population on the basis of previous research in this area[46, 47]. The cost of lamotrigine will be calculated using the generic cost listed in the BNF and the cost of the time with the dispensing clinician using national UK unit costs. National UK unit costs will be applied to medication, hospital contacts and community health and social services[48, 49].

Differences in mean costs will be analysed using standard parametric t-tests with the validity of results confirmed using bias-corrected, nonparametric bootstrapping (repeat re-sampling)[50]. Despite the skewed nature of cost data, this approach is recommended to enable inferences to be made about the arithmetic mean[51]. Cost-effectiveness will be assessed through the calculation of incremental cost-effectiveness ratios[52] and will be explored in terms of cost-utility using quality adjusted life years derived from the EQ-5D and cost-effectiveness using the ZAN-PD. Uncertainty around the cost and effectiveness estimates will be represented by cost-effectiveness acceptability curves[53]. All analyses of cost will be adjusted for baseline stratification variables and any other covariates found to differ between patient groups at baseline

11 ETHICS AND GOOD CLINICAL PRACTICE

11.1. 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).

11.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that the trial is conducted in full conformity with relevant regulations and with the Medicines for Human Use (Clinical Trials) Regulation 2004 transposed into law from the EU Clinical Trials Directive 2001/20/EC, the EU Good Clinical Practice Directive 2005 and all current and future acts and requirements pertaining to its conduct. A Clinical Trial Authorisation (CTA) application will be made to the MHRA.

11.3. Research Ethics Committee (REC)

A copy of the protocol and other written information to be provided to participants and relatives such as the informed consent form and information sheet 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 other written information.

The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The trial co-ordinating office will require a copy of the Trust R&D approval letter before accepting participants into the study.

Unless an urgent safety measure, amendments to the protocol must be approved by the Sponsor prior to being submitted to ethics. Upon receiving ethical approval, an amendment must also receive further Trust approval before being implemented at site. In the case of an urgent safety measure, the sponsor should be informed as soon as possible after the event.

11.4. Patient Confidentiality

Each study participant will be assigned a unique participant identification number at the start of the assessment process. This number will be written on all clinical assessment forms/datasheets and databases used to record data on study participants. A hard copy of a record sheet linking patient identity, contact details and participant identification number for all participants will be kept at each site. It will be placed in the Investigator Site File, in a locked filling cabinet, separate from the paper CRFs and other documents relating to a participant, which will be anonymised.

Recorded data will be entered onto an electronic data management system, designed by Nottingham Clinical Trials Unit, that will use the participant identification number rather than the patient's name or other information that could identify them.

12 REGULATORY ISSUES:

12.1. CTA

This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA. Reference: [insert reference no here].

12.2 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

12.3. Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

13 PROJECT MILESTONE

A 42-month study: 3 months preparation (drug supplies, packaging and delivery; research governance, appoint trial manager, assessor training, etc.); 24 months recruitment, 12 months for follow-up assessments, 3 months for completion of data entry and analysis.

14 TRIAL OVERSIGHT COMMITTEES

14.1 Trial Management Group (TMG)

The TMG will be set-up prior to the start of the study, and will include those individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, statistician, trial manager, health economist, research assistant, and data manager. In addition, a representative Principal Investigator, and expert by experience will be included in the management group. The role of the group will be to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action

to safeguard participants and the quality of the trial itself. The TMG shall consider and act on the recommendations of the Trial Steering Committee (TSC), Independent Data Monitoring and Ethics Committee (IDMEC), the MHRA, and the REC

14.2 Trial Steering Group (TSC)

The TSC will be set-up prior to the start of the study, and comprise study applicants, a representative of the HTA, and representatives of service users and providers. Service user input will be organised through the North London MHRN Hub Service User Group.

14.3 Independent Data Monitoring and Ethics Committee (IDMEC)

An IDMEC will also be established to monitor (1) recruitment of study participants, (2) ethical issues of consent, (3) quality of data (including missing data), (4) the incidence of adverse events, and (5) any other factors that might compromise the progress and satisfactory completion of the trial. This will also have an independent chairman, and include an independent statistician.

14.4 Criteria for the termination of the trial

Prior to the start of recruitment, the dataset that will be required by the IDMEC 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 TSC that they consider early termination of the trial.

15 SERVICE USER INVOLVEMENT

The North London MHRN hub user group will assist with the design of the Information Sheet and Informed Consent forms, advise on the methods to use for providing feedback on the study to participants, and contribute to the production of the final project report. Members of the user group will also contribute to the process of communicating study findings, such as helping to generate a user-friendly sheet summarising findings for study participants, and preparing a summary of study findings suitable for publication in a service user journal.

16 DATA HANDLING AND RECORD KEEPING

All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).The database will be backed up daily in encrypted form and offsite copies will be made at regular intervals.

All activities are conducted in accordance with the Data Protection Act and Imperials Data Protection Policy. The data will archived securely and then safely destroyed after 10 years.

17 FINANCING AND INSURANCE

17.1. Funding

LABILE is funded by the NIHR Health Technology Assessment programme. The funding is held by the trial sponsor, Imperial College London.

17.2. 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 Imperial College London.

17.3. 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 Imperial College London. The NHS will owe a duty of care to those undergoing clinical treatment, with Trust Indemnity available through the NHS Litigation Authority Scheme.

18 PUBLICATION POLICY

The primary report will be submitted to a high impact medical journal and will be attributed to the LABILE Investigators and Collaborators. The names of all investigators who enter a participant and 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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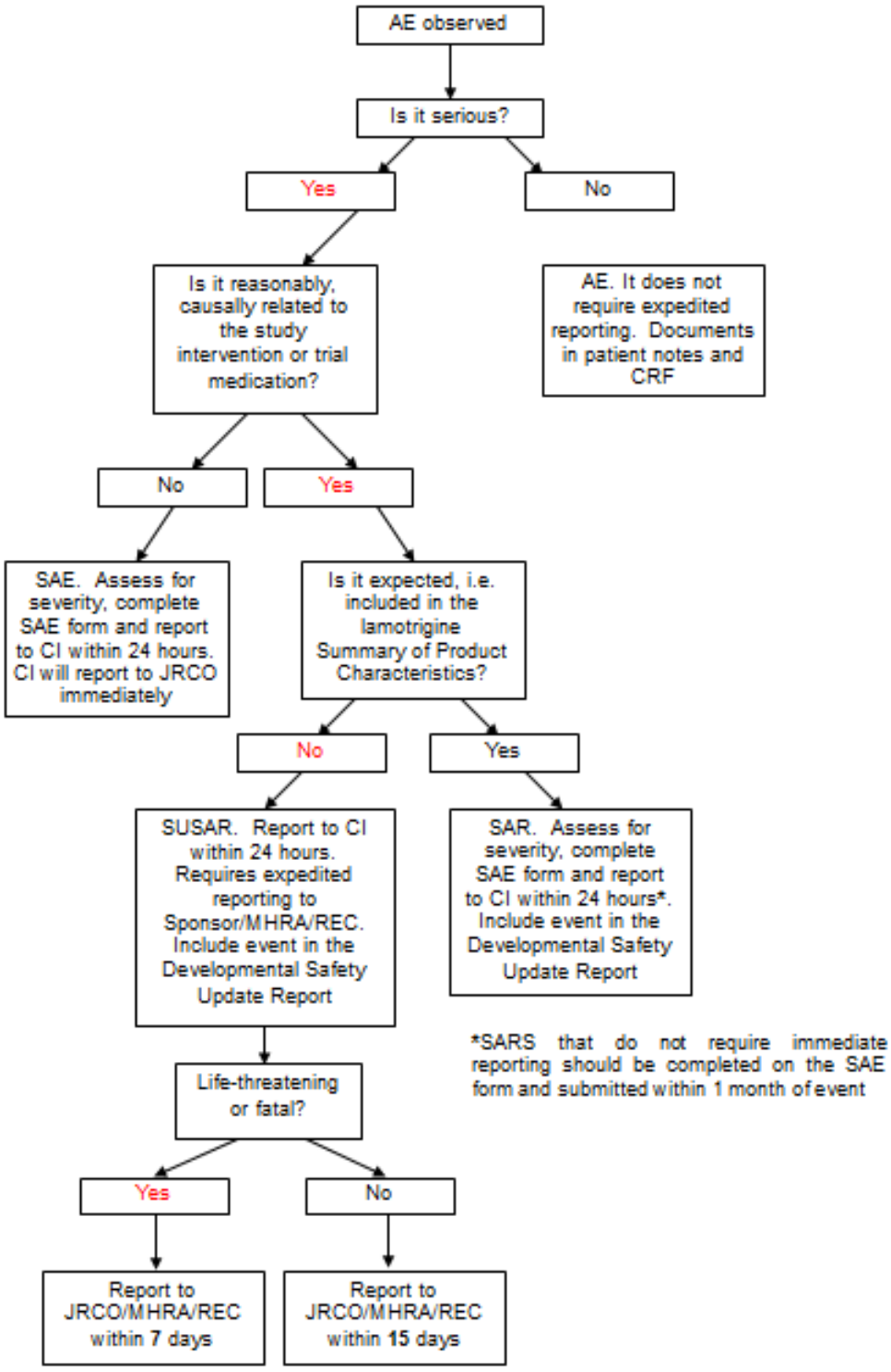
APPENDIX 1: ADVERSE EVENT REPORTING FLOW-CHART



Contact Details for Reporting SAEs and SUSARs:
Fax: 0207 386 1216
Please send SAE forms to: LABILE Trial Coordinating Office
Tel: 0207 386 1220 (Mon to Fri 09.00 – 17.00)

APPENDIX 2: SIDE EFFECTS OF LAMOTRIGINE

Extract from the Lamictal tablets SmPC (GSK): Summary of Product Characteristics last updated on the eMC: 16th August 2011

The undesirable effects have been divided into epilepsy and bipolar specific sections based on the data currently available. However, both sections should be consulted when considering the overall safety profile of lamotrigine

Adverse reactions identified from monotherapy clinical trials (identified by a dagger †) and during other clinical experience are listed in the table below by their incidence in clinical trials.

The following convention has been utilised for the classification of undesirable effects:- Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Epilepsy

System Organ Class	**Adverse Event**	**Frequency**
Blood and lymphatic system disorders	Haematological abnormalities including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis	Very rare
	Lymphadenopathy	Not known
Immune System Disorders	Hypersensitivity syndrome (including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation, multi organ failure).[1]	Very Rare
Psychiatric Disorders	Aggression, irritability	Common
	Confusion, hallucinations, tics	Very rare
Psychiatric Disorders	Headache†	Very Common
	Somnolence, dizziness, tremor, insomnia	Common
	Ataxia	Uncommon
	Nystagmus	Rare
	Agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency	Very Rare
		Not Known

	Aseptic meningitis	
Eye disorders	Diplopia†, blurred vision† Conjunctivitis	Uncommon Rare
Gastrointestinal disorders	Nausea†, vomiting†, diarrhoea†	Common
Hepatobiliary disorders	Hepatic failure, hepatic dysfunction, increased liver function tests	Very rare
Skin and subcutaneous tissue disorders	Skin rash[2] Stevens–Johnson Syndrome[2] Toxic epidermal necrolysis[2]	Very common Rare Very rare
Musculoskeletal and connective tissue disorders	Lupus-like reactions	Very rare
General disorders and administration site conditions	Tiredness	Common

Bipolar Disorder.

System Organ Class	**Adverse Event**	**Frequency**
Nervous system disorders	Headache Agitation, somnolence, dizziness	Very common Common
Gastrointestinal disorders	Dry mouth	Common
Skin and subcutaneous tissue disorders	Skin rash Stevens–Johnson Syndrome	Very common Rare
Musculoskeletal and connective tissue disorders	Arthralgia	Common
General disorders and administration site conditions	Pain, back pain.	Common

For more information: http://www.medicines.org.uk/emc/medicine/4228/SPC/lamictal/