PROTOCOL FULL TITLE:

# A randomised pragmatic trial comparing the clinical and cost effectiveness of lithium and quetiapine augmentation in treatment resistant depression (HTA Project: 14/222/02)

### Protocol Short Title/Acronym:

**LQD – L**ithium versus **Q**uetiapine in **D**epression

## Trial Identifiers:

EudraCT Number - 2016-001637-27
IRAS Number - 201898
REC Number - 16/EE/0318
ISRCTN registry - ISRCTN16387615, http://www.isrctn.com/ISRCTN16387615

## Co-Sponsors:

Name: King's College London, and South London and Maudsley NHS Foundation Trust
Contact: Helen Critchley, King's Health Partners Clinical Trials Office
Address: F16 Guy's Tower, Guy's Hospital, Great Maze Pond, London, SE1 9RT
Telephone: 02071885732
Fax: 02071888330
Email: helen.critchley@kcl.ac.uk

## Chief Investigator:

Name: Professor Anthony Cleare
Address: King's College London, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), 103 Denmark Hill, PO74, London SE5 8AF and the South London and Maudsley NHS Foundation Trust (SLaM)
Telephone: 02078485130
Fax: 02078480783
Email: anthony.cleare@kcl.ac.uk

## Name and address of Co-Investigators, Statistician, Laboratories etc.:

Name: Professor Allan Young, Principal Investigator (SLaM)
Address: IoPPN, King's College London
Telephone: 02078485895
Email: allan.young@kcl.ac.uk

Name: Dr. Hamish McAllister-Williams, Principal Investigator (Northumberland, Tyne and Wear NHS Foundation Trust)
Address: Institute of Neuroscience, Newcastle University
Telephone: 01912081370
Fax: 01912081387
Email: hamish.mcallister-williams@ncl.ac.uk

Name: Professor John Richard Geddes, Principal Investigator (Oxfordshire Health NHS Foundation Trust)
Address: Department of Psychiatry, University of Oxford
Telephone: 01865226451
Fax: 01865204198
Email: john.geddes@psych.ox.ac.uk

Name: Dr Rajesh Nair, Principal Investigator (Tees, Esk and Wear Valleys NHS Foundation Trust)
Address: West Park Hospital, Darlington, County Durham, DL22TS
Telephone:01325552002
Email:rajesh.nair1@nhs.net

Name: Professor Andrea Cipriani, Collaborator (Oxfordshire Health NHS Foundation Trust)
Address: Department of Psychiatry, University of Oxford
Telephone: 01865226393
Fax: 01865204198
Email: andrea.cipriani@psych.ox.ac.uk

Name: Ms Lindsey Marwood, Collaborator
Address: IoPPN, King's College London
Telephone: 02078485305
Email: lindsey.marwood@kcl.ac.uk

Name: Dr Kimberley Goldsmith, Senior Statistician
Address: IoPPN, King's College London
Telephone: 02078480059
Fax: 02078480281
Email: kimberley.goldsmith@kcl.ac.uk

Name: Ms Rachel Holland, Statistician
Address: IoPPN, King's College London
Telephone: 02078480309
Fax: 02078480281
Email: rachel.holland@kcl.ac.uk

Name: Dr. Renee Romeo, Health Economist
Address: King's Health Economics, IoPPN, King's College London
Telephone: 02078485082
Email: renee.romeo@kcl.ac.uk

# 1 Study Synopsis

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|---|---|
| Title of clinical trial | A randomised pragmatic trial comparing the clinical and cost effectiveness of lithium and quetiapine augmentation in treatment resistant depression (HTA Project: 14/222/02) |
| Protocol Short Title/Acronym | **LQD – L**ithium versus **Q**uetiapine in **D**epression |
| Trial Phase if not mentioned in title | IV |
| Sponsor name | King's College London, and South London and Maudsley NHS Foundation Trust |
| Chief Investigator | Professor Anthony Cleare |
| EudraCT number | 2016-001637-27 |
| IRAS number | 201898 |
| REC number | 16/EE/0318 |
| Medical condition or disease under investigation | Major Depressive Disorder (MDD) |
| Purpose of clinical trial | The aim of this research study is to determine if it is more clinically and cost-effective to decide to prescribe lithium or quetiapine augmentation for patients with treatment resistant depression. |
| Primary objective | The primary aim of this research study is to determine if it is more clinically effective to decide to prescribe lithium or quetiapine augmentation therapy for patients with treatment resistant depression followed up over one year. It is hypothesised that quetiapine will be superior in terms of time to all-cause treatment discontinuation and average symptom burden over 12 months. |
| Secondary objective (s) | The main other outcomes include assessment of economic costs, quality of life, social functioning, and adherence between the two trial arms. |
| Trial Design | 12 month, multi-centre, randomised, pragmatic, parallel group trial of the clinical and cost-effectiveness of the decision to prescribe lithium or quetiapine add-on treatment to antidepressant medication. This is a superiority design whereby we hypothesise that quetiapine will be superior to lithium in terms of time to treatment discontinuation and average symptom burden over 12 months. |

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| Endpoints | The primary endpoints are: 1) longitudinal depressive symptom severity (determined using the self-rated Quick Inventory of Depressive Symptomatology, QIDS-SR) rated weekly over 52 weeks; and 2) time to all-cause treatment discontinuation i.e. the time at which patients stop taking the medication (this will be monitored over the 12 month follow-up and determined via weekly monitoring using the True Colours system and at 8, 26, and 52 week study visits).<br><br>Secondary endpoints include assessments collecting study outcomes at baseline, 8, 26, and 52 weeks along with weekly monitoring via the True Colours system. Weekly monitoring includes (in addition to the primary outcome measure of depression symptom severity (QIDS-SR); social functioning (Work and Social Adjustment Scale, WSAS); and medication status measured for longitudinal analysis between the two treatment arms over 52 weeks. Economic costs associated with the treatment arms over 12 months (Client Service Receipt Inventory, CSRI) will also be determined. See Section 8.1.2 for a full list of outcomes. |
| Sample Size | 276 patients with MDD |
| Summary of eligibility criteria | **Inclusion criteria:**<br>1. Under the care of a GP and/or adult mental health services<br>2. Current episode of depression meeting DSM-5 criteria for major depressive disorder (MDD) – single or recurrent episode<br>3. 17-item HAM-D score ≥ 14 – this cut-off reflects a pragmatic minimum severity of depression as also chosen in comparable studies such as STAR*D (Rush et al 2006, Trivedi et al 2006)<br>4. Any gender and aged 18 years or over<br>5. Meet criteria for treatment resistant depression (Fekadu et al., 2009a; Cleare et al., 2015): current episode has not responded to at least two antidepressants given for at least 6 weeks at minimum therapeutic dose defined as fluoxetine ≥20mg/day, paroxetine ≥20mg/day, sertraline ≥50mg/day, citalopram ≥20mg/day, escitalopram ≥10mg/day, venlafaxine ≥75mg/day, duloxetine ≥60 mg/day, mirtazapine ≥30mg/day, tricyclic antidepressant ≥125mg/day, and dosage as guided by the national Maudsley Prescribing Guidelines or BNF for any other antidepressant. Please note, relapse whilst on an antidepressant also counts as a failed treatment trial<br>6. Current antidepressant treatment has remained unchanged for ≥6 weeks<br>7. Provision of written, informed consent |

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| | **Exclusion criteria:**<br>1. Diagnosis of bipolar disorder (defined as meeting DSM-5 criteria bipolar 1 or bipolar 2) on the MINI 7.0 (as recommended treatments are different for bipolar depression)<br>2. Diagnosis of current psychosis (as recommended treatments are different for current psychosis – antidepressants plus antipsychotics is the first-line treatment recommendation (NICE, 2009; Cleare et al., 2015)<br>3. Use of lithium or quetiapine during current episode<br>4. Ongoing use of another atypical antipsychotic (discontinuation will be required before study entry i.e. any time prior to randomisation)<br>5. Known contraindication to use of either lithium or quetiapine: known hypersensitivity of lithium or quetiapine or any of their excipients; severe renal insufficiency / impairment; untreated hypothyroidism; severe cardiac disease / insufficiency; low sodium levels e.g. dehydrated patients or those on low sodium diets; Addison's disease; Brugada syndrome or family history of Brugada syndrome; the rare hereditary inborn errors of metabolism galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption, concomitant administration of cytochrome P450 3A4 inhibitors; or previously diagnosed QT prolongation.<br>6. We will not recruit any individual who is currently participating in a clinical trial of an investigational medical product (CTIMP).<br>7. Insufficient degree of comprehension or attention to be able to engage in trial procedures.<br>8. We will exclude women who are pregnant, actively trying for pregnancy, or currently breastfeeding. This will be based on verbal report of the subject. Otherwise the management will be as appropriate according to standard clinical practice within the context of a pragmatic, open trial, for example adequate contraceptive precautions decided on the clinical judgement of the prescriber. |
| IMP, dosage and route of administration | Quetiapine, added on to the current antidepressant, taken orally once daily before bedtime. The dose will be decided by prescribing clinicians according to their clinical judgement for each patient. The recommended dosing, according to the BNF, is dose titration of 50 mg on days 1 and 2 and 150 mg on day 3, aiming for a dose of 300 mg/day by week 2 if tolerated. Thereafter, dosing in the range 150-300 mg/day according to tolerance. In elderly patients (>65 years old), 50 mg/day on Days 1-3, increasing |

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| | to 100 mg/day on Day 4, 150 mg/day on Day 8 and 300 mg/day not before Day 22 of treatment if required. |
| Active comparator product(s) | Lithium, added on to the current antidepressant. The dose will be decided by prescribing clinicians according to their clinical judgement for each patient. The recommended dosing, according to the BNF, is taken orally at night and flexible dose adjustment aiming for an optimal therapeutic plasma level of 0.6-1.0 mmol/l. |
| Maximum duration of treatment of a Subject | Initial prescribing of the IMPs will be conducted by a trial clinician. Thereafter treatment may be continued as per standard care with prescribing and monitoring conducted as appropriate in secondary and primary care. Patients will be monitored for 12 months in the study but treatment may be discontinued at any point in the 12 month follow-up or continued for longer outside of the study under the decision of the patient's treating clinician. We will still aim to follow up all patients over 12 months in order to obtain a full intention to treat analysis of the 12 month impact of the initial decision to prescribe either lithium or quetiapine. |
| Version and date of protocol amendments | Version 2.0 dated 26.09.2016<br>Version 1.0 dated 04.07.2016 |

# 2 Glossary of Terms

**Augmentation**: augmentation treatment in the management of depression involves the addition of a second drug to an existing antidepressant therapy, with the aim of improving clinical response. This strategy is often used when depression is treatment-resistant, insufficiently responsive to treatment, or to accelerate treatment response.

**Case Record Form (CRF):** a printed, optical or electronic (eCRF) document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

**DSM-5**: Diagnostic and Statistical Manual for Mental Disorders, Version 5.

**K(CTU)**: King's College, Clinical Trials Unit
**Summary of Product Characteristics (SmPC):** product details for drugs with a Marketing Authorisation.

**Treatment resistant depression (TRD):** describes cases of major depressive disorder that do not adequately respond to at least two courses of antidepressant given in therapeutic doses and for an adequate duration, defined in the Maudsley Prescribing Guidelines (Taylor et al., 2015) in the current depressive episode.

## Contents

# 3 Background & Rationale

Depression is a highly prevalent and disabling illness and requires effective treatment to reduce symptoms and improve quality of life (Kessler et al., 2003; Ustun, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). Clinical guidelines recommend the use of antidepressant medication for the treatment of moderate to severe MDD (Cleare et al., 2015). However around 30-50% (Cleare et al., 2015) of patients fail to obtain an optimal outcome to both first and second line treatments, commonly described as treatment resistant depression (TRD) (Rush et al., 2006; Trivedi et al., 2006). This is therefore a common problem and an important issue for the NHS. TRD is associated with a generally poorer prognosis, higher mortality and higher healthcare utilisation costs (Fekadu, Wooderson, Markopoulo, et al., 2009). Many patients with depression are undertreated (Fernandez et al., 2007), and adequate treatment of TRD can improve the prognosis (Wooderson et al., 2014) highlighting the importance of appropriately treating this condition.

Treatment options for patients with TRD include the options of increasing the dose of antidepressant the patient is on, switching antidepressant or augmenting with a second agent (Cleare et al., 2015). Increasing doses may be associated with increased efficacy for some antidepressants (Thase, Shelton, & Khan, 2006; Wade, Crawford, & Yellowlees, 2011) but not for many (Adli, Baethge, Heinz, Langlitz, & Bauer, 2005). Switching to an alternative antidepressant is recommended in cases where a patient has either made no response or is not tolerating their current drug (Cleare et al., 2015). However, remission rates to third or fourth line antidepressant treatments are in the order of just 10-15% (Rush et al., 2006). For patients with TRD where there is a partial response to the antidepressant they are on, augmentation is recommended (Cleare et al., 2015).

The efficacy of combinations of multiple antidepressants has been brought into question by the largest RCT examining this showing antidepressant monotherapy to be as effective as antidepressant combinations (Rush et al., 2011). However, lithium and atypical (second generation) antipsychotics could update augmentation and this is supported by meta-analyses (Bauer, Adli, Ricken, Severus, & Pilhatsch, 2014; Nelson & Papakostas, 2009). Recent guidance from NICE and the British Association for Psychopharmacology (Cleare et al., 2015) have emphasised that add-on alternative treatments are a standard treatment pathway for TRD, and that first line options include lithium and the newer atypical antipsychotics, including quetiapine, aripiprazole, olanzapine and risperidone. There have been very few studies that have compared these treatment approaches (lithium and the newer atypical antipsychotics) head-to-head (Cleare et al., 2015). The largest and best study to date compared lithium and quetiapine XR over 6 weeks only, finding quetiapine to be non-inferior to lithium (Bauer, Dell'Osso, et al., 2013). However, there was no long-term follow up which is imperative in such a chronic illness.

A systematic review of prospective studies of TRD outcome showed that TRD is frequently a chronic condition, and that up to 80% of those with a history of TRD relapse within the 12 months after responding to treatment (Fekadu, Wooderson, Markopoulo, et al., 2009). Follow up data has demonstrated the fluctuating nature of symptoms after a response to acute phase treatment (Vergunst et al., 2013). Clinical practice guidelines dictate that those responding to an acute trial of medication continue the effective medication for continuation treatment for at least 9-12 months (Cleare et al., 2015). Therefore, a 12-month trial duration, with frequent assessment of symptoms, is imperative for such a condition.

This study aims to address this requirement and gap in the literature by studying which of these two most commonly used add-on strategies for TRD, lithium and quetiapine, is more clinically effective over the course of a year. This recognition that TRD is a longitudinal condition in which patients experience mood fluctuations is a specific strength of the study. We will allow for this in our choice of primary outcome - a longitudinal measure of weekly depression symptom monitoring over the course of a year (via the self-rated quick inventory of depressive symptoms (QIDS-SR) using the True Colours system (www.truecolours.nhs.uk) as successfully used in similar studies (Geddes et al., 2016). Future patients will benefit from the results of the study by knowing which (if any) treatment is more likely to improve their condition over a longer duration of time rather than a standard short term and/or cross sectional measure.

The NHS will also benefit through cost effectiveness analysis, which will take into account the very different monitoring requirements for these patients, most obviously the need to take blood levels of lithium periodically. Essentially, the results would help shape a modified treatment pathway in which either one of these approaches will become a preferential first line intervention over the other, or one in which there is known equivalence and factors other than clinical or cost effectiveness will determine the appropriate treatment choice.

We have chosen to compare the effectiveness of these two medications specifically due to the following reasons. Lithium was recommended as the first-choice add-on treatment for treating patients with TRD at the World Federation of Societies of Biological Psychiatry Task Force (Bauer, Pfennig, et al., 2013) and is a first line treatment option recommended by NICE and by the recent BAP guidelines for treating depression (Cleare et al 2015). Quetiapine (extended-release) XR is the only atypical antipsychotic currently granted a marketing licence for use as add-on treatment for TRD in the UK and is supported by NICE. It has good evidence of efficacy versus placebo. NICE also supports the use of other atypical antipsychotics – quetiapine (immediate release), aripiprazole, risperidone and olanzapine – as add-on treatments in TRD, and there is some evidential support for their use, especially aripiprazole (Cleare et al., 2015). Such off-label prescribing is often appropriately undertaken in the treatment of TRD, but we also note that recent GMC guidance has left some uncertainty as to whether it is appropriate to use an off-label treatment where an appropriate licenced alternative exists (Cohen, 2015). NICE (2010) explicitly states that GMC guidance on off-label prescribing should be followed if using an atypical antipsychotic for TRD. We would also stress that there is as yet no reason to assume that it is a class effect of atypical antipsychotics with them all having the same mode of action when used for treating TRD, given that the relevant mechanism(s) underlying their effect remains unknown. Further, there are no good head-to-head comparative studies to suggest any one atypical antipsychotic is more effective than another. Thus, neither mechanism of action nor efficacy points to the preferential use of any one atypical antipsychotic. Finally, only quetiapine has been studied under trial conditions in a head-to-head comparison with lithium (Bauer, Dell'Osso, et al., 2013), so that we can be confident that there is at least comparable short-term efficacy of the two treatments (lithium and quetiapine) in study conditions. For all of these reasons, we think the most appropriate choice for a trial at the present time is to compare lithium versus quetiapine augmentation.

The trial will recruit patients who have TRD, defined as having had an inadequate response to two or more therapeutic trials of antidepressant medication (Cleare et al., 2015; Fekadu, Wooderson, Donaldson, et al., 2009), as it is at this point that the use of add-on treatment will usually be considered, and in which there is equipoise as to which treatment is superior. There was some evidence from the short-term study by Bauer and colleagues that quetiapine will be superior to lithium. It is clinically important to determine if one of these treatments, with proven efficacy, is superior to the other. We therefore proposed a superiority design and hypothesise that the decision to prescribe quetiapine will be superior to lithium in terms of time to all-cause treatment discontinuation and average symptom burden over 12 months.

We will recruit participants from secondary care, though to optimise recruitment we will also recruit suitable participants from primary care and directly from advertising in the community. The trial intervention will initially be prescribed by trial clinicians. Where participants have an existing secondary care clinician, we will invite them to join the study team as trial clinicians. After this initial prescription, the decision of potential continuation of prescribing of these medications will be undertaken as per standard NHS practice with input from primary care or existing secondary care clinicians as appropriate. The design will be a direct head-to-head comparison. We will use a 1:1 randomisation of lithium versus quetiapine stratified by geographical recruiting region (London, Oxfordshire, or North East England), baseline depression severity (determined via score on the Hamilton Depression Rating Scale, HAM-D) and TRD severity (determined by the number of failed antidepressant courses in the patient's current depressive episode) with the block size randomly varying. After randomisation, treatment will be undertaken open-label and pragmatically with trial clinicians initially prescribing the trial medications.

We propose a pragmatic trial that reflects real world UK clinical practice, in which add-on treatment for TRD is prescribed via secondary care trial clinicians initially leading to a decision point regarding

continuation of the treatment and/or the addition of other treatments, depending on response. Therefore, we have designed the trial with the protocol recommendations outlined in this document (Section 9.1) with the initial prescribing of the medications conducted by a trial clinician followed by a fully flexible continuation phase for up to 52 weeks post-randomisation as per standard care. Please note, these medications may be continued for longer than the 12-month follow up period of the trial. Trial clinicians should use their clinical judgement as to whether they think it is appropriate to prescribe the trial medication to each participant. In those that commence therapy, it is expected that a significant proportion of patients will not benefit from treatment, and will not continue treatment for the full 12 month follow up duration of the trial. Because of these expected high rates of discontinuation, and in order to capture what may be important differences between treatments, all-cause discontinuation from those who are prescribed the originally randomised medication will form a second component of the primary outcome. We will continue to follow up all patients in order to obtain a full intention to treat (ITT) analysis of 12 month impact clinically and economically of the initial treatment decision to prescribe either quetiapine or lithium.

Lithium and quetiapine are recommended first line interventions for TRD and therefore meet best pracrice guidelines. We will ensure that necessary safety checks are adhered to pre-treatment initiation. Thereafter, prescribing clinicians are provided with an outline of best practice guidelines, reminding them of, and acting as a reference for, the recommendations of standard of care as described in the medications' SmPCs. Therefore, the study poses little risk for the participating patients – they are getting the care currently recommended as first line treatment options by NICE and the British Association for Psychopharmacology. There are side effects associated with both treatments but the pre-prescribing essential safety tests and initial prescribing of the trial medications will be carried out by trial clinicians followed by an ongoing continuation phase as per standard NHS practice. Additionally, the patient will be made aware of the potential side effects associated with the medication before deciding to proceed. When a potentially eligible participant has a secondary mental health clinician, we will invite the clinician to join the study as a trial clinician. Side effects will be monitored regularly and judgments made regarding whether it is in the best interest for the patient to continue taking the add-on treatment. In the short-term study by Bauer, Dell'Osso, et al. (2013), comparing the effectiveness of quetiapine versus lithium, they reported no serious adverse events relating to these medications in a similar patient group.

# 4 Trial Objectives and Design

## 4.1 Trial Objectives

### 4.1.1 Primary endpoints

There are two primary endpoints: 1) longitudinal depressive symptom severity (determined using the self-rated Quick Inventory of Depressive Symptomatology, QIDS-SR) rated weekly over 52 weeks; and 2) time to all-cause treatment discontinuation i.e. the time at which patients stop taking the medication (this will be determined via weekly monitoring using the True Colours system and at 8, 26, and 52 week study visits).

### 4.1.2 Secondary endpoints

Assessments collecting study outcomes will also take place at baseline, 8, 26, and 52 weeks along with weekly monitoring via the True Colours system. Weekly monitoring (in addition to the primary endpoint of weekly depression symptom severity measurement (QIDS-SR)) includes social functioning (Work and Social Adjustment Scale, WSAS); and medication status. Economic costs associated with the treatment

arms over 12 months (Client Service Receipt Inventory, CSRI) will also be determined. See Section 8.1.2 for a full list of outcomes.

## 4.2 Trial Design

A 12 month parallel group, multi-centre, patient randomised, pragmatic, open label trial of the clinical and cost-effectiveness of the decision to prescribe lithium versus quetiapine add-on treatment to antidepressant medication. There will be two parallel groups: 1) Quetiapine add-on to existing antidepressant medication; and 2) Lithium add-on to existing antidepressant medication. 276 patients will be randomised 1:1 at baseline to the decision to prescribe either lithium or quetiapine, and treatment will then be undertaken by clinicians on a real-world basis. Initial prescribing of the trial medications will be conducted by trial clinicians. Decisions as to whether to continue treatment will continue as per standard care thereafter. All patients, regardless of their treatment status, will be followed up in the trial for one year. This is a superiority design whereby we hypothesise that quetiapine will be superior to lithium in terms of time to treatment discontinuation and average symptom burden (QID-SR) over 12 months.

Given that the treating clinicians, patients and trial researchers will not be blind to treatment, we will obtain data for the following clinician-rated assessments using a blind assessor at follow up visits in the following order: 1) Montgomery-Åsberg Depression Rating Scale (MÅDRS), and 2) Clinical Global Impressions scale (CGI). This will be conducted either face-to-face or over the phone by trained trial investigators. The blind assessor will not have access to any other data concerning the patient or be involved in any other trial procedures for that patient. They must remain blinded with respect to the study treatment the patient has been randomised to. The blinded assessor will remind the participant not to mention their treatment to them.

## 4.3 Trial Flowchart

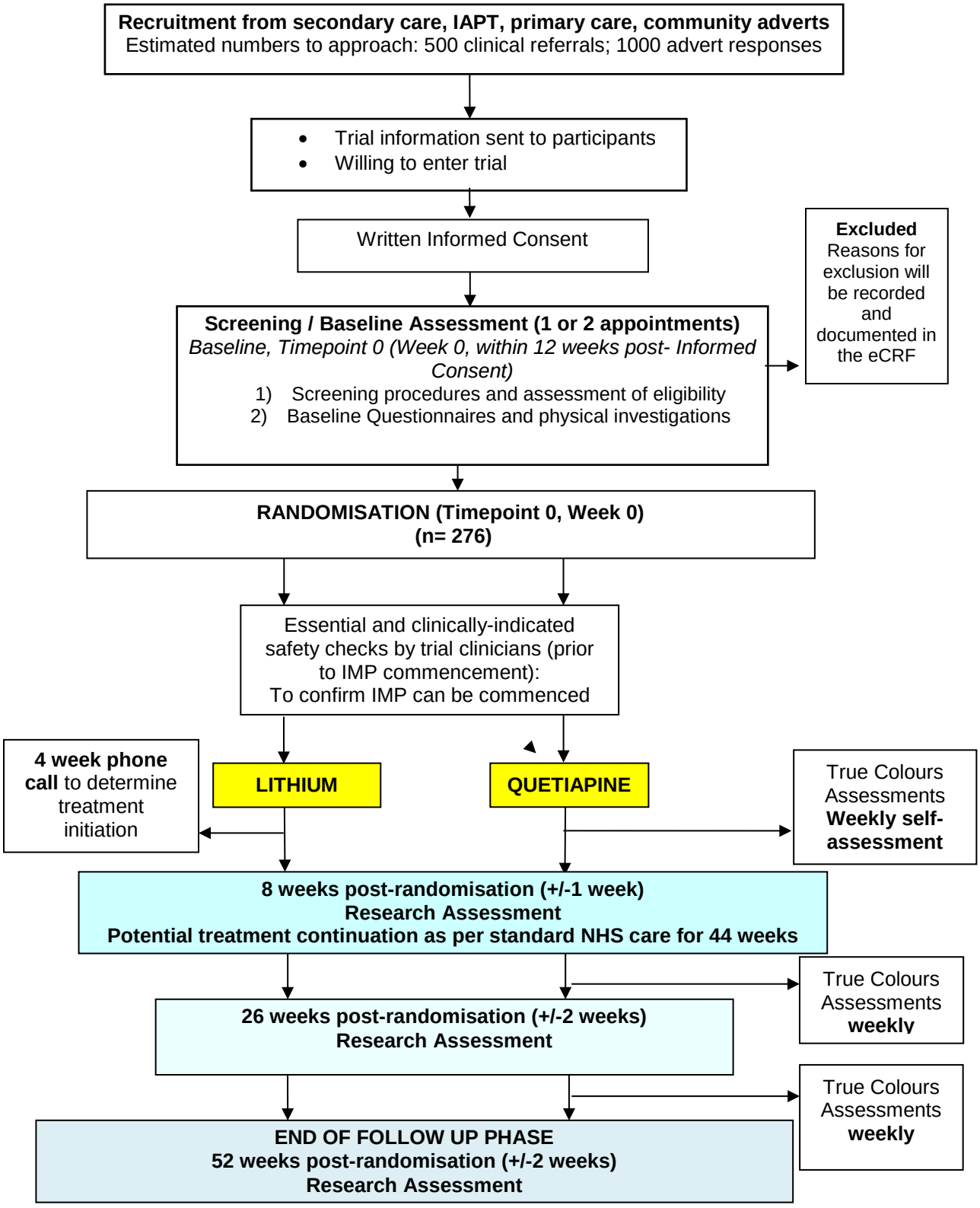

**Table 1: Summary of Measures**

| Measure | Screening /Baseline | Week of assessment (post-randomisation) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline study visit – week 0, within max. 12 weeks post consent | Weekly Monitoring 1-7 | 4 (+-1) week | Visit, week 8(+/-1) | Weekly monitoring 9-25 | Visit, week 26(+/-2) | Weekly monitoring 27-51 | Visit, week 52(+/-2) |
| Clinician/Researcher visit | X | | | X | | X | | X |
| Written Informed Consent | X | | | | | | | |
| MINI to confirm MDD and other Axis 1 disorders | X | | | | | | | |
| Sociodemographic/Psychiatric/Medical History including the MSM, MTI | X | | | | | | | |
| Eligibility assessment | X | | | | | | | |
| Concomitant medication / therapy | X | | | X | | X | | X |
| **Randomisation** | X | | | | | | | |
| HAM-D-17 | X | | | | | | | |
| Employment status | X | | | X | | X | | X |
| QIDS-SR | X | X | | X | X | X | X | X |
| IDS-C | X | | | X | | | | |
| MÅDRS | X | | | X | | X | | X |
| Altman Mania Scale | X | | | X | | X | | X |
| Maudsley-VAS-current | X | | | X | | X | | X |
| Maudsley-VAS-change | | | | X | | X | | X |
| CGI-S | X | | | | | | | |
| CGI | | | | X | | X | | X |
| WSAS | X | X | | X | X | X | X | X |
| SAPAS | X | | | X | | X | | X |
| EQ-5D | X | | | X | | X | | X |
| CSRI modified for TRD | X | | | X | | X | | X |
| HCL-16 | X | | | | | | | |
| GAD-7 | X | | | X | | X | | X |
| DSCT | X | | | X | | X | | X |
| PRISE | | | | X | | X | | X |
| FIBSER | | | | X | | X | | X |
| Optional research blood lithium / quetiapine levels | | | | X | | | | X |
| Optional research fasting blood tests (FBC, U&Es, LFTS, TFT, glucose, lipids, calcium (and Bioresource blood – genetic and inflammatory markers /hair/saliva collection – optional) | X | | | X | | | | X |
| Qualitative Interview on patient experience of using True Colours system (optional, subset of patients) | | | | X | | /X | | /X |
| THINC-it (subset of patients) | X | | | X | | X | | X |
| Phone call to determine treatment initiation | | | x | | | | | |
| Physical examination: height, weight, waist | X | | | X | | X | | X |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| circumference, BP, pulse | | | | | | | | |
| Medication status | | X | | X | X | X | X | X |
| MARS-5 (antidepressant) | X | | | | | | | |
| MARS-5 (lithium/quetiapine) | | | | X | | X | | X |
| Adverse Event Monitoring | | X | | | | | | |
| TSQM | | | | X | | X | | X |
| IMP safety checks – ECGs (if clinically indicated), pre-lithium work up blood tests and baseline blood tests for quetiapine (recommended but not essential) and blood monitoring and dosing of IMP | | | X | | | | | |
| Treatment commencement | | | X | | | | | |
| Standard care dosing and blood monitoring post-initial prescription) – data collected from medical records in standard care phase if available | | X | | | | | | |
| Treatment discontinuation | | X | | | | | | |
| Withdrawal | | X | | | | | | |

MSM, Maudsley Staging Method; MTI, Maudsley Treatment Inventory version 1.12; MINI, Mini International Neuropsychiatric Interview (MINI) Version 7.0 for DSM-5; HAM-D-17, Hamilton Depression Rating Scale – 17 item; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self Rated; IDS-C, Inventory of Depressive Symptomatology-Clinician Rated; MÅDRS, Montgomery-Åsberg Depression Rating Scale; Maudsley-VAS-current, Maudsley Visual Analogue Scale – Current depression severity; Maudsley-VAS-change, Maudsley Visual Analogue Scale – change in depression severity; CGI-S, Clinical Global Impression Severity scale; CGI, Clinical Global Impression rating scales; WSAS, Work and Social Adjustment scale; SAPAS, Standard Assessment of Personality – Abbreviated Scale; EQ-5D, EuroQol-5D health index; CSRI, Client Service Receipt Inventory; HCL-16, 16 item Hypomanic Checklist; GAD-7, Generalised Anxiety Disorder Questionnaire; DSCT, Digit Symbol Coding Test; PRISE, Patient Rated Inventory of Side Effects; FIBSER, Frequency, Intensity, and Burden of Side Effects scale; THINC-it tool for Cognitive Dysfunction in Major Depressive Disorder; FBC, Full blood count; U&Es, Urea, electrolytes and creatinine; LFTS, Liver function tests; TFT, Thyroid function tests; ECG, electrocardiogram; MARS-5, 5-item Medication Adherence Report Scale; TSQM, Treatment Satisfaction Questionnaire for Medication.

# 5 Trial Medication

## 5.1 Investigational Medicinal Product

This is a randomised trial of the decision to prescribe one of two existing add-on treatments for treatment resistant depression (lithium and quetiapine), which are recommended as first line add-on treatments by NICE and other bodies (Cleare et al., 2015) for the indication they will be prescribed in the study, and in which there is currently clinical equipoise. Treatment will be undertaken open-label and as pragmatically as possible by clinicians and in-line with the protocol pre-first prescription by trial clinicians who will instigate treatment. After first prescription, the treatment may be continued with primary care input and in collaboration with secondary care (trial or non-trial clinicians) as per usual NHS practice (treatment as per standard clinical practice). We will also provide patients with treatment booklets detailing how best they should take the study medication, what care they should expect and details of precautions and who to contact if they experience adverse effects.

## 5.2 Dosing Regimen

As this study is a pragmatic trial, we do not define a dosing regimen. Clinicians will be provided with the following recommendations which are in line with current best practice guidelines. Failure to follow these recommendations will not constitute a protocol deviation.

In both arms, the guidance will be to trial at least 6 weeks of active treatment within the 8-week post-randomisation period (allowing up to 2 weeks for necessary clinical and investigation work ups after randomisation but before starting treatment), and to keep the dose of existing antidepressant treatment unchanged and at or above minimal therapeutic dosage during that time. This is in line with published treatment guidelines i.e. The Maudsley Prescribing Guidelines and British National Formulary, BNF (BNF, 2015; Taylor, Paton, & Kapur, 2015). The recommended guidance for the two treatment arms will be as follows:

*Lithium arm:* lithium carbonate, added on to the current antidepressant. Lithium citrate is an acceptable alternative for those who cannot take tablets as it is available in liquid form. Standard BNF dose titration is detailed below for reference: the dose should be adjusted to achieve serum-lithium concentration of 0.4-1.0mmol/litre 12 hours after a dose on days 4-7 of treatment, then every week until dosage has remained constant for 4 weeks aiming for an optimal therapeutic plasma level of 0.6-1.0 mmol/l (Bauer, Pfennig, et al., 2013; Taylor et al., 2015). Blood monitoring should be performed as per Maudsley Prescribing Guidelines (national).

*Quetiapine arm:* quetiapine fumarate (XR or IR) added on to the current antidepressant, taken once daily before bedtime. Dose titrated upwards using a standard BNF dose titration protocol of 50 mg on days 1 and 2 and 150 mg on day 3, aiming for a dose of 300 mg/day by week 2 if tolerated. Thereafter, flexible dosing will follow in the range 150-300 mg/day according to tolerance (as per Bauer et al 2013). In elderly patients (>65 years old), the dose titration protocol will be modified according to the SmPC and best practice as follows: 50 mg/day on Days 1-3, increasing to 100 mg/day on Day 4, 150 mg/day on Day 8 and 300 mg/day not before Day 22 of treatment if required.

Dosing regimens may need to be altered in the case of concomitant administration of drugs that interact with either quetiapine or lithium (see Section 5.7). In these cases, doses will be adjusted according to the medications SmPC or according to best practice guidelines.

Add-on therapies for TRD are rarely, if ever, commenced in primary care and NICE recommendation is that these therapies are commenced in secondary care. Therefore, the interventions will be instigated in secondary care by trial clinicians with an ongoing decision regarding whether to continue treatment thereafter as per standard clinical practice thereafter.

It is expected that a significant proportion of patients will not benefit from an acute phase treatment (6 to 8 weeks), and will discontinue study medication before the 12 month follow up. Because of these expected high rates of study medication discontinuation, and in order to capture what may be important differences between treatments, all-cause discontinuation from the originally randomised medication will form a second component of the primary outcome. We will continue to follow up all of these patients in order to obtain a full intention to treat (ITT) analysis of 12 month impact clinically and economically of the initial treatment decision.

Treatment needs to be discontinued if a participant no longer wishes to continue the intervention, or in the event of a serious drug reaction. It is recommended that quetiapine and lithium are discontinued gradually to reduce discontinuation effects. Following treatment commencement, the monitoring, dosing and safety checks will be conducted as per standard NHS practice and by a trial clinician during the initiation of treatment.

The following dosing regimens are in line with current guidelines in the BNF and Maudsley Prescribing Guidelines and are provided as recommendations for clinicians only and the decision to prescribe

outside of these guidelines will not constitute a protocol deviation. Prescribing and monitoring visits between the patient and their trial clinician will not count as study visits but we will collect data on the frequency of these clinical visits and monitoring outcomes e.g. lithium serum levels, lithium and quetiapine prescribed doses, date of first prescription, monitoring blood test frequency and results, and ECG results. This data will be collected from the patient's medical records and recorded in the study's eCRF.

The following definitions are to inform us of the treatment a patient receives during the trial. They should not influence the practice of clinicians during the trial. Clinicians must treat trial patient's according to their clinical judgement and not be influenced by trial outcomes.

Treatment commencement will be defined as the date the patient is first prescribed the medication they are randomised to. Treatment initiation will be defined as the date the participant begins taking the medication. Time to treatment commencement will be calculated as the number of days post-randomisation before treatment is commenced (I.e. the patient begins taking the medications). In patients who do not commence or receive a prescription for the treatment they are randomised to, the reasons for this will be recorded in the eCRF under options which cover the following reasons: blood test / ECG / other contraindication discovered post-randomisation; patient fears over side effects; patient concerns over lifestyle requirements/changes; clinician safety concerns; clinician concerns over suicidality; remission/response of depressive episode; participant wishes to withdraw from the study; participant/clinician preference for a different therapy instead; or other. It will also be determined if and when the patient began an alternative therapy for their depression, what this was, and whether this treatment was pharmacological or psychological (this will be recorded in the concomitant medication/therapy forms). These patients will **not** be withdrawn from the study in order to capture data for our intention to treat (ITT) analyses.

A minimum adequate acute treatment trial, for purposes of analyses, at 8 week follow up visit will be defined as:

- Lithium serum levels between 0.4-1.0 mmol/L (as per BNF recommendations) at 8 weeks (+-10 days). However, due to uncertainty surrounding optimal lithium serum levels in TRD, we will also conduct analyses using levels between 0.6-1.2mmol/L as per Bauer et al. (2013) and with additional exploratory cut-offs.
- Quetiapine prescribed at ≥150mg/d (data gained from medical records) for at least 4 weeks at 8 week study visit (determined via True Colours).

Time to all-cause treatment discontinuation will be defined as, in patients who are randomised, the difference in days between treatment commencement (i.e. prescription) and the medication discontinuation date. Discontinuation data will be gathered when a participant indicates on True Colours that they have 'Stopped taking' the treatment. The participant will be asked each week: "Which medication are you currently taking?': Quetiapine; Lithium; orNot taken either at all in the past week. If a patient reports they have not taken the trial medication for 2 consecutive weeks (after previously taking the medication), the patient will be contacted to see if they have discontinued the medication. If the patient reports discontinuing treatment, the date and their reason for discontinuing the treatment will be determined. This will be recorded in the eCRF with the following options: due to side effects; clinical worsening; poor adherence; remission/response; death; inadequate clinical response; patient forgot (consistently for 2 or more weeks); patient dissatisfaction with medication; other medical reasons; or other. We will also determine whether discontinuation was conducted in discussion with the clinician or done unilaterally by the patient. Also, whether the medication dose was tapered at discontinuation. Where possible we will also supplement this self-report data with information from the patient's medical records and via discussion with the prescribing clinician.

## 5.3 IMP Risks

IMP safety assessments are detailed in section 9.1.

The risks of this study are limited as we are comparing the efficacy of the decision to prescribe two drugs that are currently licenced and widely used for the indication that they are prescribed in this trial. In addition, patients will be undergoing treatment initially prescribed to them by trial secondary care clinicians who will oversee their care and are free to make the clinical judgement to prescribe or terminate the patient's treatment at any time (the trial will not control length of treatment). Thereafter ongoing treatment will be as per standard NHS practice.

The Reference Documents will be the Summary of Product Characteristics (SmPC) for lithium (any brand e.g. Priadel (lithium carbonate) 200mg and 400mg prolonged release tablets or liquid form (lithium citrate)) and quetiapine (any brand e.g. Seroquel XR 50mg, 150mg, 200mg, 300mg, 400mg prolonged-release tablets) as prescribed as an add-on treatment to individuals with TRD. Treating clinicians and the study team will refer to the current SmPC of the actual medication taken as all brands are allowed. Patients with contraindications or safety concerns will be excluded.

We do not list a specific SmPC here i.e. for a specific brand but rather generally state the IMP risks for the active substances as treating clinicians will be free to prescribe the brand they would generally use. Main side effects and contraindications are listed in brief below:

**Lithium:**

**Contraindications**

- Hypersensitivity to lithium or to any of the excipients
- Cardiac disease
- Cardiac insufficiency
- Severe renal impairment
- Untreated hypothyroidism
- Breast-feeding
- Patients with low body sodium levels, including for example dehydrated patients or those on low sodium diets
- Addison's disease
- Brugada syndrome or family history of Brugada syndrome

**Undesirable effects**

Side effects are usually related to serum lithium concentration and are less common in patients with plasma lithium concentrations below 1.0 mmol/l. The adverse reactions usually subside with a temporary reduction or discontinuation of lithium treatment. Mild gastrointestinal effects such as nausea, a general discomfort and vertigo, may occur initially, but frequently disappear after the first few days of lithium administration. Fine hand tremors, polyuria and mild thirst may persist. Other potential side effects include:

- *Blood and lymphatic system disorders:* Leucocytosis.

- *Endocrine disorders:* Long-term adverse effects may include thyroid function disturbances such as euthyroid goitre and/or hypothyroidism and thyrotoxicosis. Lithium-induced hypothyroidism may be managed successfully with concurrent thyroxine. Hypercalcaemia, hypermagnesaemia and hyperparathyroidism have been reported.

- *Metabolism and nutrition disorders:* Weight increase, hyperglycaemia.

- *Psychiatric disorders:* Confusion, delirium

- *Nervous system disorders:* Ataxia, hyperactive deep tendon reflexes, slurred speech, dizziness, stupor, coma, myasthenia gravis, giddiness, dazed feeling, memory impairment. Tremor, especially fine hand tremors, dysarthria, myoclonus, benign intracranial hypertension, Vertigo, impaired consciousness, abnormal reflexes, convulsions, extrapyramidal disorders, encephalopathy, cerebellar syndrome (usually reversible), nystagmus. These symptoms may result in fall. Peripheral neuropathy may occur on long-term treatment and is usually reversible at cessation of lithium.

- *Cardiac disorders:* Cardiac arrhythmia, mainly bradycardia, sinus node dysfunction, peripheral circulatory collapse, hypotension, ECG changes such as reversible flattening or inversion of T-waves and QT prolongation, AV block, cardiomyopathy.

- *Gastrointestinal disorders:* Abdominal discomfort, taste disorder, nausea, vomiting, diarrhoea, gastritis, salivary hypersecretion, dry mouth, anorexia.

- *Skin and subcutaneous tissue disorders:* Folliculitis, pruritus, papular skin disorders, acne or acneform eruptions, aggravation or occurrence of psoriasis, allergic rashes, alopecia, cutaneous ulcers.

- *Musculoskeletal and connective tissue disorders:* Muscle weakness, rhabdomyolysis

- *Renal and urinary disorders:* Polydipsia and/or polyuria and nephrogenic diabetes insipidus, histological renal changes with interstitial fibrosis after long term treatment have been reported. This is usually reversible on lithium withdrawal. Long-term treatment with lithium may result in permanent changes in kidney histology, and impairment of renal function. High serum concentrations of lithium including episodes of acute lithium toxicity may aggravate these changes. *Rare cases* of nephrotic syndrome have been reported. Frequency unknown: Microcysts, oncocytoma and collecting duct renal carcinoma (in long-term therapy).

- *General disorders and administration site conditions:* Peripheral oedema. Urticaria and angioedema, attributed to some excipients such as acacia powder (or Arabic gum).

- *Reproductive:* Sexual dysfunction.

- *Senses:* Dysgeusia, blurred vision, scotomata.

**Overdose**
Lithium toxicity can also occur in chronic accumulation for the following reasons: Acute or chronic overdosage; dehydration e.g. due to intercurrent illness, deteriorating renal function, drug interactions, most commonly involving a thiazide diuretic or a non-steroidal anti-inflammatory drug (NSAID).

Symptoms of lithium intoxication include:
- *Mild:* Nausea, diarrhoea, blurred vision, polyuria, light headedness, fine resting tremor, muscular weakness and drowsiness.
- *Moderate:* Increasing confusion, blackouts, fasciculation and increased deep tendon reflexes, myoclonic twitches and jerks, choreoathetoid movements, urinary or faecal incontinence, increasing restlessness followed by stupor. Hypernatraemia.
- *Severe:* Coma, convulsions, cerebellar signs, cardiac dysrhythmias including sinoatrial block, sinus and junctional bradycardia and first degree heart block. Hypotension or rarely hypertension, circulatory collapse and renal failure.
- *Others:*
  *Gastrointestinal disorders*: increasing anorexia and vomiting.
  *Nervous system disorders*: Encephalopathy, cerebellar syndrome with symptoms such as muscle weakness, lack of coordination, drowsiness or lethargy, giddiness, ataxia, nystagmus, coarse tremor. Tinnitus, dysarthria, twitching, myoclonus, extrapyramidal disorders.
  *ECG changes* (flat or inverted T waves, QT prolongation), AV block, dehydration and electrolyte disturbances.
  At blood levels above 2-3 mmol/l, there may be a large output of dilute urine and renal insufficiency, with increasing confusion, convulsions, coma and death.

**Quetiapine:**

**Contraindications**

- Hypersensitivity to quetiapine or to any of the excipients
- Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin or nefazodone

**Undesirable effects**
The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine (≥10%) are somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

Common side effects (≥1/100, <1/10) include: leucopenia, decreased neutrophil count, eosophil increase, hyperprolactinaemia, decreases in total $T_4$, decreases in free $T_4$, decreases in total $T_3$, increases in TSH, increased appetite, blood glucose increased to hyperglycaemic levels, abnormal dreams and nightmares, suicidal ideation and suicidal behaviour, dysarthria, tachycardia, palpitations, blurred vision, orthostatic hypotension, constipation, dyspepsia, vomiting, dyspnoea, elevations in serum alanine aminotransferase (ALT), elevations in gamma-GT levels, mild asthenia, peripheral oedema, irritability, and pyrexia

Uncommon ((≥1/1000, <1/100) side effects include: neutropenia, thrombocytopenia, anaemia, platelet count decrease, hypersensitivity (including allergic skin reactions), decreases in free $T_3$, hypothyroidism, hyponatraemia, diabetes mellitus, exacerbation of pre-existing diabetes, seizure, restless legs syndrome, tardive dyskinesia, syncope, QT prolongation, bradycardia, rhinitis, elevations in serum aspartate aminotransferase (AST), urinary retention, and sexual dysfunction.

Rare (≥1/10,000, <1/1000) side effects include: agranulocytosis, metabolic syndrome, somnambulism and related reactions such as sleep talking and sleep related eating disorder, venous thromboembolism, pancreatitis, intestinal obstruction/Ileus, jaundice, hepatitis, priapism, galactorrhoea, breast swelling, menstrual disorder, neuroleptic malignant syndrome, hypothermia, and elevations in blood creatine phosphokinase.

Very rare (<1/10,000) / not known side effects include: anaphylactic reaction, inappropriate antidiuretic hormone secretion, Angioedema, Stevens-Johnson syndrome, rhabdomyolysis, Toxic Epidermal Necrolysis, and Erythema Multiforme.

**Overdose**
In general, reported signs and symptoms were those resulting from an exaggeration of the active substance's known pharmacological effects, i.e., drowsiness and sedation, tachycardia, hypotension and anti-cholinergic effects. Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

## 5.4 Drug Accountability

This is not required as the IMPs are being prescribed as per standard NHS protocols. No study specific labelling of the IMPs will be required since it is a Type A trial and the study drug will be used from commercial stock and according to its SmPC.

We will give the patient advice on best practice for drug returns in the treatment manual we will provide them with.

## 5.5 Storage of IMP

Not applicable – patients will be prescribed the medication following standard-care, local Pharmacy protocols. Patients will be instructed to store the medication as directed on the label from the local Pharmacy. As detailed in the IMPs SmPCs, quetiapine does not require any special storage conditions. Lithium is required to be stored below 25°C and in the original package in order to protect from moisture.

## 5.6 Subject Compliance

Adherence will be measured at follow up visits (weeks 8, 26, and 52 in participants still taking the medication) using the Medication Adherence Report Scale (MARS-5). Optional research visit plasma drug levels for both lithium and quetiapine will also be taken at the 8 and 52 week follow-up visits (as applicable) to investigate any plasma level/treatment response relationship as an ancillary outcome. See Section 5.2 for definitions of adequate treatment and treatment discontinuation.

## 5.7 Concomitant Medication

Concomitant medication and psychotherapy will be permitted in this study (in line with the SmPC, see Section 5.3) so as not to compromise the pragmatic nature of the study. A complete listing of all concomitant medication and psychotherapy received during the trial period, including new medications and changes to doses, will be recorded in the relevant eCRF (at each visit) and this will form a tertiary outcome measure. Trial clinicians will receive the below guidance when administering quetiapine or lithium with the concomitant medications outlined below which is in accordance with the Maudsley Prescribing Guidelines.

**Clinically relevant drug interactions with quetiapine:**

Drugs which are potent CYP3A4 inhibitors (such as azole antifungals and macrolide antibiotics), can significantly increase plasma concentrations of quetiapine and are contraindicated for quetiapine. As such, concomitant administration of cytochrome P450 3A4 inhibitors is contraindicated in quetiapine and listed as an exclusion criteria for subjects in line with the medications SmPC (see Section 6.2).

The following medications have clinically relevant interactions with quetiapine. The following advice is given, as per Maudsley Prescribing Guidelines to trial clinicians prescribing quetiapine:

- Use with caution in combination with other centrally acting drugs (including alcohol)
- Co-administration of carbamazepine and phenytoin increase the clearance of quetiapine
- Caution should be used if quetiapine is being administered concomitantly with medicinal products known to increase QTc interval

**Clinically relevant drug interactions with lithium:**

Trial clinicians are advised that more frequent monitoring is required in patients taking the following medications (as per Maudsley Prescribing Guidelines). Additional tests should be undertaken in the first month after the interacting drug is initiated, discontinued, or the dose is changed:

| Drug Group | Magnitude of effect | Timescale of Effect | Additional information |
|---|---|---|---|
| **ACE inhibitors** | Unpredictable. Up to four-fold increase in Li | Develops over several weeks | Seven-fold increased risk of hospitalisation for lithium toxicity in the elderly. Angiotensin II receptor |

| | | | |
|---|---|---|---|
| | | | antagonists may be associated with similar risks. |
| **Thiazide diuretics** | Unpredictable. Up to four-fold increase in Li | Usually apparent in first 10 days | Loop diuretics are safer.<br>Any effect will be apparent in the first month. |
| **NSAIDS** (inc. COX-2 selective inhibitors) and ACEIs (inc. Angiotensin II Antagonists) | Unpredictable, from 10% to four-fold increases in Li | Variable, few days to several months | NSAIDs are widely used on a P basis (advised they are to be prescribed regularly not prn).<br>Beware: Can be bought without a prescription. Paracetamol and aspirin are safe alternatives. |

# 6 Selection and Withdrawal of Subjects

We have designed this study as a pragmatic trial of effectiveness in routine clinical practice. We wish to minimise exclusions from the study in order to maximise the generalisability of the findings to routine clinical care. Psychiatric comorbidity is a common feature of TRD. This will be recorded, but will not lead to patients being excluded (other than the exceptions listed below) as this would reduce generalisability of the findings. Additionally, we will not exclude those who are actively undergoing psychological therapy as it is standard practice to combine such treatments in those with TRD (NICE 2009, Cleare et al 2015). Reasons for exclusion of patients that have been consented will be recorded at the person level and stored in the eCRF.

## 6.1 Inclusion Criteria

1. Under the care of a GP and/or adult mental health services
2. Current episode of depression meeting DSM-5 criteria for major depressive disorder (MDD) – single or recurrent episode
3. 17-item HAM-D score ≥ 14 – this cut-off reflects a pragmatic minimum severity of depression as also chosen in comparable studies such as STAR*D (Rush et al 2006, Trivedi et al 2006)
4. Any gender and aged 18 years or over
5. Meet criteria for treatment resistant depression (Fekadu et al., 2009a; Cleare et al., 2015): current episode has not responded to at least two antidepressants given for at least 6 weeks at minimum therapeutic dose defined as fluoxetine ≥20mg/day, paroxetine ≥20mg/day, sertraline ≥50mg/day, citalopram ≥20mg/day, escitalopram ≥10mg/day, venlafaxine ≥75mg/day, duloxetine ≥60 mg/day, mirtazapine ≥30mg/day, tricyclic antidepressant ≥125mg/day, and dosage as guided by the national Maudsley Prescribing Guidelines or BNF for any other antidepressant. Please note, relapse whilst on an antidepressant also counts as a failed treatment trial
6. Current antidepressant treatment has remained unchanged for ≥6 weeks
7. Provision of written, informed consent

## 6.2 Exclusion Criteria

1. Diagnosis of bipolar disorder (defined as meeting DSM-5 criteria for bipolar 1 or bipolar 2) on the MINI 7.0 (as recommended treatments are different for bipolar depression)
2. Diagnosis of current psychosis (as recommended treatments are different for current psychosis – antidepressants plus antipsychotics is the first-line treatment recommendation (NiCE, 2009; Cleare et al., 2015)
3. Use of lithium or quetiapine during current episode
4. Ongoing use of another atypical antipsychotic (discontinuation will be required before study entry

i.e. any time prior to randomisation)

5. Known contraindication to use of either lithium or quetiapine: known hypersensitivity of lithium or quetiapine or any of their excipients; severe renal insufficiency / impairment; untreated hypothyroidism; severe cardiac disease / insufficiency; low sodium levels e.g. dehydrated patients or those on low sodium diets; Addison's disease; Brugada syndrome or family history of Brugada syndrome; the rare hereditary inborn errors of metabolism galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption; concomitant administration of cytochrome P450 3A4 inhibitors; or previously diagnosed QT prolongation.
6. We will not recruit any individual who is currently participating in a clinical trial of an investigational medical product (CTIMP).
7. Insufficient degree of comprehension or attention to be able to engage in trial procedures.
8. We will exclude women who are pregnant, actively trying for pregnancy, or currently breastfeeding. This will be based on verbal report of the subject. Otherwise the management will be as appropriate according to standard clinical practice within the context of a pragmatic, open trial, for example adequate contraceptive precautions decided on the clinical judgement of the prescriber.

## 6.3 Selection of Participants

Participants will be drawn from across secondary care adult mental health services and their interface (e.g. Improving Access to Psychological Therapies (IAPT) services), with hubs at the following five NHS trusts: South London & Maudsley NHS Foundation Trust (SLaM); Oxfordshire Health NHS Foundation Trust; Northumberland, Tyne and Wear NHS Foundation Trust; Tees, Esk and Wear Valley NHS Foundation Trust; and the Cumbria Partnership NHS Foundation Trust. We will seek adoption by the appropriate National Institute for Health Research Clinical Research Networks (NIHR CRNs) to further aid recruitment. There is a need for such multi-centre approach in order to recruit the numbers necessary to deliver the outcomes specified.

In addition, we will use direct online advertisement via Facebook, Google and/or classified adverts such as Gumtree, and via primary care participant identification centres, to identify potential participants. We have used this strategy to recruit a difficult population of drug-free patients with depression for an fMRI study, and a population of patients about to undergo cognitive behavioural therapy for depression for another fMRI study (Wise et al., 2016). Both studies have been able to recruit 2-3 patients per month using part of one researcher's time for telephone and face-to-face screening.

We have selected five Trusts with expertise in TRD to participate in the study. Each Trust serves a large and diverse population with a high prevalence of depression and with established local links for research and trials between the study PIs and local clinicians. Any patients entering the trial from outside of the trusts will be allocated to a trial clinician for initial prescription. Thereafter the trial clinician can continue with the patient's care or transfer their care to non-trial secondary or primary care clinician as appropriate. This also applies to patients with existing secondary care clinicians who become trial investigators. Trial clinicians will only prescribe the medication the patient has been randomised to if they believe it is clinically appropriate.

**London: South London & Maudsley NHS Foundation Trust**

1. The Trust covers four London boroughs: Southwark, Lambeth, Lewisham and Croydon with a total catchment population of approximately 1.1 million. The local communities have very high levels of mental health needs.
2. The Trust has recently reconfigured and depressed patients in secondary care are now treated by one of 8 community Mood Anxiety & Personality teams. In addition, there is a tertiary-level Affective Disorder Service focussing on treatment resistant affective disorders run by Professors Cleare and Young.

3. Our Local IAPT services see approximately 15,000 patients per annum for treatment of predominantly anxiety and depression. We have an established infrastructure for recruiting patients undergoing IAPT treatments, the PROMPT study (Grant et al., 2014) in which Professor Cleare is Principle Investigator. Approximately 50% of patients do not respond to IAPT treatment, and 50% are on medication; thus, we estimate that several hundred potential TRD patients could be identified from this source.
4. Identification of participants will also be conducted through Consent for Contact (C4C). C4C is a SLaM initiative which allows approved researchers access to a computerised retrieval system (CRIS, developed through the BRC, with ethics approvals) to rapidly screen case notes of service users who have agreed that researchers can access their contact details and limited clinical information and invite them to participate in research projects.

**Oxfordshire: Oxfordshire Health NHS Foundation Trust**

1. The population served by the Trust is approximately 1 million for both Oxfordshire and Buckinghamshire.
2. Oxford Health NHS Foundation Trust provides specialist mental health services to people of all ages in Oxfordshire and Buckinghamshire, forensic mental health services across the Thames Valley, services for children and adolescents in Wiltshire, Bath and North East Somerset as well as specialist eating disorder services for adults in Wiltshire. It also provides community health services to people in Oxfordshire. Staff work closely with GP practices, community pharmacies, children's centres, school charities, universities, voluntary groups and county council services to make sure patients get 'joined up' care. NHS healthcare services are provided either in community hospitals or from within local communities to support people near or in their homes.
3. For adult mental health, Oxford Health NHS Foundation Trust service delivery is based on a ‘functional’ model. Community based care delivery is split into an assessment pathway (Assessment Teams) and a treatment pathway (Treatment Teams). In addition, further separate teams deliver in-patient services. For severely ill patients, like patients with treatment resistant depression, the bulk of outpatient care is provided by ‘care coordinators’, these are experienced mental health nurses or social workers. Patients are likely to be seen routinely twice a month by care coordinators and in the order of every three months by their consultant psychiatrist (more if clinical need requires). Medication changes may be made by the consultant remotely through close collaboration with the care coordinator who reviews the patient.

**North East England: Northumberland, Tyne and Wear NHS Foundation Trust (NTW); Tees, Esk and Wear Valleys NHS Foundation Trust; and Cumbria Partnership NHS Foundation Trust**

1. NTW covers a population of 1.4 million people across the North East of England from Sunderland in the South to Berwick in the North.
2. In addition to secondary care services, NTW also hosts the “Regional Affective Disorders Service” which is commissioned to provide tertiary advice regarding the management of patients with treatment refractory mood disorders not just over the NTW catchment area, but also across that of the Tees, Esk and Wear Valleys NHS Foundation Trust (TEWV) and the Cumbria Partnership NHS Foundation Trust, with a combined population of around 3.5 million
3. Dr. McAllister-Williams was the local Principle Investigator for “the ADD study” that successfully recruited 165 patients with similar inclusion/exclusion criteria to the current study into a randomised trial of metyrapone versus placebo augmentation of antidepressants (McAllister-Williams et al., 2013). Over 60% of the patients were recruited from NTW and TEWV utilising the involvement of the North East Hub of what was then the MHRA.

We will recruit patients with TRD, defined as an inadequate response to at least two courses of antidepressant medication given in therapeutic dose and duration (Fekadu et al 2009a, Cleare et al 2015). Consultation with primary care colleagues has suggested that it is very unusual for secondary care referral to be made until two antidepressants have been tried (unless there are other indications such as risk issues). It is at this point that the use of add-on treatment will usually be considered, and in which there is equipoise as to which add-on treatment is superior.

## 6.4 Randomisation Procedure / Code Break

### 6.4.1 Randomisation

Randomisation service will be provided by the King's Clinical Trials Unit (KCTU). Randomisation will use the web-based service hosted at the King's Clinical Trials Unit (KCTU) in accordance with a standard operating procedure and held on a secure server. Each participant will be assigned a unique study patient identification number (PIN) by the InferMed MACRO system once they have given informed consent and entered the study. Once informed consent has been signed and eligibility confirmed, the trained trial staff will access the KCTU randomisation system on the same day to randomise the patient at the individual level (trial time point 0). Each participant will be randomised 1:1 to lithium or quetiapine augmentation. Randomisation will be stratified by geographical region (London, Oxfordshire, or North East England), depression severity (based on baseline HAMD-17 score: moderate: 14-18, severe: 19-22; or very severe range: 23 or more) and TRD severity (failure of two or failure of three or more antidepressant treatments in the current episode) with the block size randomly varying. Randomisation will not be blinded.

### 6.4.2 Emergency Code Break

Not applicable due to the un-blinded nature of the randomisation.

## 6.5 Withdrawal of Subjects

We will highlight to all participants that they have the right to withdraw from the study at any time for any reason without prejudice or consequences for either their clinical care, or involvement in any other research studies. Researchers and therapists will be available throughout the study to answer any questions the participants have about withdrawal.

It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable as withdrawals will not be replaced; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to document the reason for withdrawal as thoroughly as possible.

*Treatment discontinuation does not constitute as a withdrawal of the patient from the trial:*

Participants who wish to withdraw from the treatment they are randomised to will be asked to confirm whether they are still willing to provide the following, as time to treatment discontinuation forms part of the primary outcome:

- trial specific data at all future visits, regardless of whether they discontinue treatment
- data collected as per routine clinical practice at all future clinical visits during their participation in the trial

The investigator has the right to discontinue patients from the study drug in the event of identified contraindications, inter-current illness, pregnancy, adverse drug reactions, adverse events, SUSAR's, protocol violations, administrative causes, or for other reasons.

## 6.6 Expected Duration of Trial

The duration of the study will be from the first patient visit to the last patient's 12 month follow up visit. Recruitment is intended to take 32 months. The trial duration for each patient will be 12 months, with day

0 as the baseline assessment and also when randomisation will take place. The end of the trial will be defined as the date when the data have been fully cleaned and the trial database is locked. An end of trial declaration will be made to Medicines and Healthcare Products Regulatory Agency (MHRA) and the approving REC.

# 7 Trial Procedures

## 7.1 By Visit

Please see Table 1. for details of the procedures carried out at each visit. Additional details of each participant visit are described below:

Patients will be first contacted regarding the study by a researcher who will send the potential participant a copy of the Participant Information Sheet, consent forms and medication booklets (via email or post). The research worker will encourage potential participants to spend as much time as they need asking questions about the study (via email or phone call) and considering whether they wish to participate or not. Where information regarding a participants suitability for the trial is not available via medical records, participants will be asked REC approved questions during the phone call with the study researcher to confirm they are within the target patient population (before confirmation via medical records).

If the participant is happy to take part in the study (after reading the participant information sheet and consent form) a screening/baseline study appointment will then be arranged.

The participant's GP and, if the participant is currently under the care of, secondary care mental health clinician will be contacted in order for them to document that their patient is entering a clinical trial on the patient's medical records. Additionally, in cases where the patient has an existing secondary care clinician, this clinician will be asked: if they know of any contraindication preventing their patient being entered into the trial and whether they are prepared to prescribe the medication the participant is randomised to which would require them to enter the trial as a trial clinician. Otherwise the medication will be initially prescribed by an existing trial clinician. Trial clinicians will use their clinical judgement to determine whether they believe the randomised treatment is appropriate for the patient entering their care and are under no obligation to prescribe the trial medication if they feel it is not in the patient's best interest. Non-trial clinicians, such as the participant's GP, will be sent a 'Health Provider Information Sheet' about the study their patient is participating in and copy of the signed consent form (post screening assessment).

### Screening / Baseline / Randomisation

Informed consent, screening, baseline and randomisation may occur on the same or different visits. It is essential however that the baseline visit and randomisation occur on the same day (specified as Timepoint 0). This baseline study visit can occur anytime within a maximum of 12 weeks post-informed consent. This is to ensure that where past medical history i.e. access to medical records for a participant is not is available to confirm eligibility, this can be requested and accessed to confirm eligibility. We will also aim to conduct the baseline assessment as close as possible to before the patient's planned visit to a trial clinician where the possible prescribing of the study medication will be considered.

#### *1) Informed Consent Procedure*

At this visit, conducted by trial researchers, the participant will be given the opportunity to ask questions regarding the study and have time to read the participant information sheet again (approved by the REC) if they wish to ensure they understand the objectives, risks and inconveniences of the trial and conditions under which it is to be conducted. The subject will be informed of his/her right to withdraw from the trial at any time without being subject to any resulting detriment, by revoking his/her informed consent. The

patient will participate in the informed consent process and sign and date the consent form before any procedures specified in this protocol are performed. A copy of the information sheet and consent form will be given to the subject, the original will be filed in the Investigator Site file. A further copy will be filed in the subject's medical notes.

We will follow GCP guidelines, which states that 'the investigator, or, a person designated by the investigator should fully inform the subject' and the written informed consent form will be signed and dated by the 'person who conducted the informed consent discussion'. The consent process will be carried out by designated researchers on the study who will be appropriately trained, act in accordance with guidance as set out in GMC "Seeking Patients Consent; the ethical considerations" and familiar with all aspects of the clinical trial including risks (as described in the latest version of the protocol approved by the REC and the SmPCs for the clinical trial). In cases where the informed consent process is not carried out by a study clinician, the participants' eligibility will always be assessed and signed off by a clinician. The patient will be offered the opportunity to discuss the trial and discuss any aspect of the study IMPs with a study clinician should they wish to (and this documented). Non-clinician informed consent will only be carried out with R&D approval at the relevant NHS trust.

Only adults with capacity to give informed consent will be recruited. If a subject is unable to read (e.g. blind, illiterate etc.) an impartial witness will be provided. The impartial witness will ensure that the verbal information correlated to what is written in the information sheet and must sign the consent form as witness to the process. The subject will mark the consent form if able.

In the case of protocol amendments or information becoming available which may affect the subject's willingness to continue in the trial, it may be necessary to re-consent the subject on an updated consent form (after necessary regulatory approvals are obtained).

The consent form will give participants the following options (not essential for taking part in this study):

1) To being re-contacted for future studies in line with NIHR guidance, and may be contacted with invitations to participate in future studies with no obligation to take part in these studies.
2) To provide blood/saliva/hair samples and data for the NIHR BRC BioResource for Mental and Neurological Health as part of a national NIHR initiative to build up a central library of information (or "BioBank)" about people's health
3) In addition, participants who agree to provide samples for the BRC BioResource collaborators, participants will be consented to being re-contacted for future studies, and may be contacted with invitations to participate in future studies collaborating with this project with no obligation to take part in these studies.

After giving informed consent, patients will be registered on the eCRF system by a trial researcher and assigned a unique PIN and complete the following validated self- and clinician-rated questionnaires with a trial researcher:

### ***2) <u>Screening Procedure and Assessment of Eligibility</u>***

If it is determined that a participant does not meet the trial's eligibility criteria (based on the below assessments, in line with Section 6.2) after providing informed consent, the screening procedures outlined below will be stopped and we will record the reason for exclusion in the eCRF. These results will be reported in a CONSORT diagram. The inclusion criteria will be determined via screening procedures as follows:

1) **Age** (above 18 years old) – confirmed via medical record check

2) **Depression severity**: Hamilton Depression Rating Scale-17 item, HAMD-17 (Hamilton, 1960) score of 14 or more and currently meets DSM-5 criteria for MDD as determined via the MINI 7.0). The Mini International Neuropsychiatric Interview, version 7.0 (MINI 7.0) for DSM-5 (Sheehan et al., 1998) is rated by trained investigators to determine current MDD and other comorbid current or past Axis I diagnoses.

3) **Treatment resistance:** meets criteria of failing to respond adequately to at least 2 antidepressants given at a therapeutic dose for at least 6 weeks in the current episode of depression – determined via the Maudsley Treatment Inventory (MTI) and medical records (D. Fekadu, & Cleare, in preparation) and Maudsley Staging Method (MSM) to determine the stage/severity of treatment-resistant depression and duration of the current depressive episode.

4) **Medical contraindication to lithium or quetiapine:** patient does not meet the following, determined via participant self-report and medical record check: known hypersensitivity of lithium or quetiapine or any of their excipients; severe renal insufficiency / impairment; untreated hypothyroidism; severe cardiac disease / insufficiency; low sodium levels e.g. dehydrated patients or those on low sodium diets; Addison's disease; Brugada syndrome or family history of Brugada syndrome; the rare hereditary inborn errors of metabolism galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption; concomitant administration of cytochrome P450 3A4 inhibitors; or QT prolongation.

5) **Augmentation status:** Patient has not previously taken lithium / quetiapine augmentation in the current episode (determined via the MTI and medical records) and/or no ongoing use of another atypical antipsychotic (determined via the MTI).

6) **Psychotic symptoms**: Patient does not currently meet DSM-5 criteria (determined via the MINI 7.0) for: Current Psychotic Disorder and/or Mood Disorder with Psychotic Features (MINI-7).

7) **Diagnosis of bipolar disorder**: Patient does not meets DSM-5 criteria for bipolar I or II on the MINI 7.0.

8) **Not pregnant, breastfeeding or actively trying to get pregnant (females only)**: based on verbal report of the participant.

9) **Patient is not currently participating in another CTIMP**: determined via verbal report of the participant and medical records.

10) **Sufficient degree of comprehension or attention to be able to engage in trial procedures:** This will be determined upon the decision of the trial researcher.

11) **Under the care of a GP and/or adult mental health services** (self-report of participant)

12) **Current antidepressant status**: currently taking an antidepressant, at a therapeutic dose and for a duration of at least 6 weeks (MTI and medical records)

**13) Patient does not wish to withdraw consent**

### *3) Baseline Questionnaires and Physical Assessments (Week 0, time-point 0)*

If the patient meets the above inclusion criteria the following baseline questionnaires and physical assessments will be conducted. We will aim to conduct the baseline assessment as close as possible to the patient's planned visit with a trial clinician e.g. the assessment where the trial clinician will consider prescribing the trial medication the patient is randomised to. If the baseline assessment is more than 7 days after the screening visit, the screening assessments (except demographic information) will be repeated to ensure the participant still meets the required eligibility criteria. The measures to determine eligibility refer to symptoms the patient has experience in the past week (e.g. the HAMD-17), current diagnoses (MINI 7.0) and current concomitant therapy and medical history.

*Sociodemographic questions*: date of birth, gender, relationship status, ethnicity, country of birth, first language, education level (years of education and highest level of education), employment (employment

status, occupational type, number hours paid work per week, number of hours missed work due to ill health), number of units of alcohol and number of cigarettes smoked per week.

*Diagnostic questionnaires*:

- Mini International Neuropsychiatric Interview (MINI), version 7 for DSM-5 (Sheehan et al., 1998): rated by trained investigators to determine current and past Axis I diagnoses (in addition to those outlined in the screening procedures).
- Questions to determine additional medical and psychiatric history e.g. all medical diagnoses, previous and/or current psychotherapy and current medication for all indications (including dose and length of administration).

*Observer-rated depression severity measures:*

- Inventory of Depressive Symptomatology-Clinician Rated (IDS-C){Rush, 1986 #8741}
- Montgomery-Åsberg Depression Rating Scale (MÅDRS) (Montgomery & Asberg, 1979)
- Clinical Global Impressions Scale (GCI) (Guy, National Institute of Mental, Psychopharmacology Research, & Early Clinical Drug Evaluation, 1976) – at baseline, the severity measure of this rating scale will be asked only.

*Self-rated measures:*

- Quick Inventory of Depressive Symptomatology-Self Rated, QIDS-SR (Rush et al., 2003)
- Social functioning (Work & Social Adjustment Scale, WSAS) (Mundt, Marks, Shear, & Greist, 2002)
- Health-related quality of life (EuroQol-5D) (Fryback & Hanmer, 2005)
- Altman Mania Self Rating Scale (E. Altman, Hedeker, Peterson, & Davis, 2001; E. G. Altman, Hedeker, Peterson, & Davis, 1997)
- HCL-16 (16 item Hypomanic Checklist) (Forty et al., 2010)
- Anxiety symptoms (Generalised Anxiety Questionnaire; GAD-7) {Spitzer, 2006 #93}
- Modified version of the CSRI (client service receipt inventory) (Chisholm et al., 2000) with input from the patient's principle carer (if applicable). The carer can complete the relevant sections of the questionnaire via telephone with a researcher or in person and will be allocated an anonymised Carer Identification Number.
- Standard Assessment of Personality – Self Report (SAPAS) (Germans, Van Heck, Moran, & Hodiamont, 2008)
- Amount of concomitant treatment (medication and/or non-pharmacological)
- Maudsley-Visual Analogue Scale (VAS) current (Tsapekos, 2016)
- Digit Symbol Coding Test; DSCT (Wechsler, 2014)
- Medication Adherence Report Scale, 5-item (MARS-5) (Clatworthy et al., 2009) to current antidepressant
- THINC-it tool for Cognitive Dysfunction (http://thinc.progress.im/en/content/thinc-it-tool) to be completed in a subset of patients either on android, windows or mac computer or laptop or ipad. For baseline, this measure can be completed at any time prior to first prescription of the trial medications.

***Physical examination:***

Height (cm), weight (kg), BMI (kg/m$^2$), waist circumference (cm), diastolic and systolic blood pressure (mmHg), pulse rate (bpm), and fasting blood test (for FBC, U&Es, LFTs, TFT, fasting glucose, fasting lipids, calcium, and with additional blood/saliva/hair sample collection for the BRC BioResource for genetic and cytokine analysis if the participant has agreed to taking part in this collaboration and/or study blood tests).

**Additional training:**

Time will also be spent during the first visit to familiarise the patient with the True Colours system which they will be asked to fill in each week to record their depressive symptoms (QIDS-SR); questions to determine study medication status; and social functioning (WSAS).

All trial visits will take place at the NHS Trust or at a University site, depending on local arrangements between the participating NHS Trusts and the associated universities.

***A trial researcher will conduct the randomisation procedure on the same day as the baseline assessment (see section 6.4.1). In order to randomise the patient, all screening measures must be completed and the following baseline questionnaires complete as a minimum requirement: HAMD-17; QIDS-SR and QIDS-C; MADRS; sociodemographic; psychiatric and medical history; concomitant medication use; CSRI; CGI-S; WSAS; EQ-5D and physical examination.***

***Randomisation (see section 6.1.4) – Week 0 (Timepoint 0)***
The participant will be made aware of which treatment group they have been randomly allocated to. Contact will be made by an investigator with the patient's trial clinician regarding the treatment arm the patient has been allocated to and sent a copy of the signed Informed Consent Form. The trial clinician will conduct safety tests, blood monitoring and prescribe the IMP as outlined in the protocol (see sections 5.2 for dosing, 5.7 for concomitant medication and Section 9. for safety and monitoring guidance). Specifically these are:

1) Lithium group only - pre-lithium work up blood tests (unless these tests have already been conducted sufficiently recently in the opinion of the prescribing clinician): Renal function, thyroid function, full blood count, serum calcium.
2) Quetiapine group only - baseline blood tests (unless these tests have already been conducted sufficiently recently in the opinion of the prescribing clinician) for FBC, blood lipids, plasma glucose, LFTs, CPK, and TFTs (note: these are recommended but not essential safety tests, and therefore if a clinician does not conduct these tests it will not be considered a protocol violation)
3) Both lithium and quetiapine: ECG if clinically indicated (recommended for patients who have risk factors for, or existing cardiovascular disease) – unless this test has been conducted sufficiently recently in the opinion of the prescribing clinician
4) Weight (including BMI and waist circumference if possible) and blood pressure, recommended but not essential

Where study baseline blood tests are available, these will be accessible to trial clinicians in the trust for use as quetiapine baseline or pre-lithium work up blood tests. Please note, tests will be done as per NHS Trust practices due to this study being a type A trial and aiming to reflect current standard practice. Any differences in exact tests being part of the blood test profiles at individual Trusts will not be considered as a deviation from the protocol.

Data regarding monitoring and safety tests throughout the trial duration will be recorded where from medical records and entered into the eCRF.

***True Colours weekly monitoring***
Participants will complete weekly self-assessments via the True Colours system and submit them to the True Colours system using mobile phone text-message, email, webform or paper forms (to be sent by post). Automated reminders by text or email (according to patient preference) will be sent out to patients on the day they should complete the questionnaires (day and time of reminder chosen by the participant), with daily reminders if they do not fill them in. The participant will be asked to fill in the questionnaires once a week for the duration of the study and study researchers will enter this data into the study eCRF. The questionnaires to be completed each week using this system are:

- QIDS-SR
- WSAS

- Questions to assess medication status: Which medication are you currently taking? (Quetiapine; Lithium; Not taken either at all in the past week) and what is your currently prescribed total daily dose (mg/day)?

**4 week Research Phone Call**

We will call all patients 4 weeks after randomisation/baseline to determine the date the participant reports they initiated therapy and if they have not started the medication they were randomised to why they have not, If the participant has not yet begun the study medication, these questions will be asked again at follow up visits.

### Visit 2 (8+/-1 weeks post-randomisation):

The second visit will involve the following observer- and self-rated questionnaires and physical examinations:

- Questions to assess concomitant medication use and whether any new (non-study) therapies have been initiated for TRD (determined via patient self-report and medical records)
- The self-report Treatment Satisfaction Questionnaire for Medication (TSQM) (Atkinson et al., 2004)
- Employment status
- IDS-C
- Medication Adherence Report Scale, 5-item (MARS-5) (Clatworthy et al., 2009) to lithium/quetiapine
- CSRI
- SAPAS
- Altman Mania Rating Scale
- EQ-5D
- Generalised Anxiety Disorders questionnaire (GAD-7) Physical examination: weight, height, waist circumference, blood pressure, pulse rate
- Fasting blood tests as conducted at the baseline visit with additional blood tests to monitor levels of quetiapine or lithium (depending on treatment arm and if the participant is currently taking the medication)
- Please note: The measures to be completed via True Colours (QIDS-SR, WSAS, and study specific medication status questions) are only to be completed at study visits if the participant has not completed the True Colours questionnaires that week.
- Maudsley VAS current and change measures
- Digit Symbol Coding Test (DSCT)
- The FIBSER (Frequency, Intensity, and Burden of Side Effects) and PRISE (Patient Rated Inventory of Side Effects) self-report measures will be used to determine side effects (as per the STAR*D project) {Rush, 2004 #8743{Wisniewski, 2006 #8742}}
- THINC-it cognitive tool (to be completed in a subset of participants)

A blinded-assessor (as outlined in Section 4.2) will administer the following clinician rated scales at follow up visits in the order specified:

1) Montgomery-Åsberg Depression Rating Scale (MÅDRS)
2) Clinical Global Impressions scale (CGI)

This blinded assessment will be conducted either face-to-face or over the phone by trained trial investigators.

Additionally, a short qualitative interview will be conducted in a subset of participants at one of either the 8, 26, or 52 week follow up assessments. This will consist of a short interview with the patient focusing on their experience of using the True Colours weekly online monitoring system, in order to establish

whether this is a tool that individuals in this patient group adhere to and benefit from. Additional consent will be sought for this interview.

**Visit 3 (26+-2 weeks post-randomisation):**

This will follow the same procedures as outlined above in Visit 2 (except patients will not have any blood tests at this visit and the IDS-C will not be asked at this visit).

**Visit 4 (52+-2 weeks post-randomisation):**

The same study procedures will be carried out as outlined for Visit 2 (except the IDS-C).
Participants will also be asked in this final session if they wish to receive a summary of the study findings.

## 7.2 Laboratory Tests

Trial clinicians will conduct the following tests before prescribing the trial medications for clinical monitoring and safety purposes (these are separate from the blood tests collected at study visits):

1. Lithium group only - pre-lithium work up blood tests: Renal function, thyroid function, full blood count, serum calcium (required for trial clinicians to conduct in all participants unless these tests were conducted recently enough in their clinical opinion). After prescribing lithium, it is recommended that the dose is adjusted to achieve a serum-lithium concentration of 0.4-1.0mmol/litre 12 hours after a dose on days 4-7 of treatment, then every week until dosage has remained constant for 4 weeks aiming for an optimal therapeutic plasma level of 0.6-1.0 mmol/l.

2. Quetiapine group only - baseline blood tests for FBC, blood lipids, plasma glucose, LFTs, CPK, and TFTs (recommended but not essential for trial clinicians to conduct)

3. Both lithium and quetiapine: ECG should be conducted by trial clinicians if clinically indicated (recommended for patients who have risk factors for, or existing cardiovascular disease) unless conducted recently enough in the clinical opinion of the trial clinician

4. Weight (including BMI and waist circumference if possible) and blood pressure (recommended but not essential for trial clinicians to conduct)

Where study baseline blood tests are available, these will be accessible to trial clinicians in the trust for use as quetiapine baseline or pre-lithium work up blood tests.

In addition to any blood tests for clinical monitoring and safety purposes conducted by trial or non-trial clinicians, participants will have the option of undergoing additional fasting blood tests (no more than 50ml) at study visits: baseline, 8 weeks, and 52 weeks with their consent (recorded in the eCRF). These will be tertiary outcomes to monitor the differential impacts of lithium versus quetiapine on these parameters. We intend to collect FBC, U&Es, LFTs, TFT, calcium, fasting glucose and fasting lipids. Additionally (for those patients currently taking lithium or quetiapine), lithium and quetiapine serum levels will be taken at the 8 week and 52 week study visits to measure adherence to treatment and if the patient meets optimal therapeutic plasma levels of lithium. These tests are for research outcomes only and will be optional for participants, clinical monitoring of the IMPs will be conducted by trial clinicians as appropriate and recorded in medical records and eCRF.

U&Es will indicate changes in renal function that may occur secondary to lithium, specifically alterations in sodium levels and changes in creatinine/eGFR. Glucose will be monitored for signs of raised glucose that may occur with quetiapine. TFTs will be monitored for any signs of hypothyroidism (raised TSH and/or reduced free t4) that may develop with lithium and quetiapine. Lipids will be analysed for signs of hyperlipidaemia (raised triglycerides and raised cholesterol) that can occur with quetiapine. FBC will look for any signs of alteration in red cells, white cells or platelet counts. Serum calcium levels to check for

signs of hypercalcemia, a potential complication from lithium administration.

Blood tests will be undertaken in the NHS laboratories where patients are being treated using their usual SOPs by trained phlebotomists and analysed locally.

We also wish to collaborate with the NIHR BRC BioResource for Mental and Neurological Health in London as part of a national NIHR initiative to build up a central library of information (or “BioBank)” about people's health. This “BioBank” aims to help us better understand why different mental illnesses happen and how we can develop better treatments for them. This patient group is currently under-represented within the BioResource and further exclusion of these patients from the BioResource may place them at a significant disadvantage for future treatment development.

These additional blood and/or hair and saliva samples in this collaboration are optional for patients. Consented samples will be collected by a researcher from the BioResource team in compliance with their ethically approved protocol (Reference Number: 15/SC/0388 | NRES Committee South Central-Oxford). The BRC will be the custodian of the samples received. On receipt, samples will be stored or logged and prepared for extraction of DNA. The BRC will ensure that genetic samples are processed in accordance with strict health and safety guidelines and under the requirements of the HTA. King's College London holds a HTA license, number: 12293. All samples will be stored in tubes labelled with a barcode that includes the participant number. The link between the participant ID and de-identified data will be kept in a secure folder accessible only to the PIs and senior researchers. Samples will be collected as part of this trial, with plasma, RNA and DNA samples which may be stored by the BRC for future analysis and hypothesis testing with appropriate ethical approval in the future, and under existing BRC Bioresource approvals. Additionally, inflammatory markers will be collected to look at the association between an array of cytokines and treatment response and changes with treatment. These will be processed, stored and analysed according to the BioResource’s SOPs.

# 8 Assessment of Effectiveness

## 8.1.1 Primary Effectiveness Parameters

1. **Difference in the area under the curve over 12 months in the self-rated Quick-Inventory of Depressive Symptomatology (QIDS-SR)** assessed weekly via the True Colours system (www.truecolours.nhs.uk) between lithium and quetiapine.

2. **Difference in time to all-cause treatment discontinuation over 12 months** (defined as the time between first prescription and discontinuation) between lithium and quetiapine using survival analysis methods.

## 8.1.2 Secondary Effectiveness Parameters

The secondary outcomes will be as follows; in each case lithium will be compared with quetiapine:

1. **Change in clinician-rated depression severity** (continuous total score on Montgomery-Åsberg Depression Rating Scale, MADRS) from baseline to weeks 8 and 52.

2. **Response rates** at 8 and 52 weeks (proportion with ≥50% reduction in baseline MADRS total score).

3. **Remission rates** at 8 and 52 weeks (proportion with MADRS total score ≤10).

4. **Health-related quality of life** (summary index EuroQol-5D score) measured at 8 and 52 weeks.

5. **Social functioning** (continuous total Work & Social Adjustment Scale score) measured at baseline, 8 and 52 weeks.

6. **Adherence to treatment** using continuous total MARS-5 scores and exploratory cut-offs (categorising participants as either adherent or non-adherent on the MARS-5) at weeks 8 and 52.

7. **Change in weight in kilograms** from baseline to 8 and 52 weeks.

8. **Change in diastolic blood pressure** in mmHg from baseline to 8 and 52 weeks.

9. **Change in systolic blood pressure** in mmHg from baseline to 8 and 52 weeks.

10. **Time to uptake of a new intervention** for depression (pharmacological or non-pharmacological) **over 12 months** defined as any mention of starting a new intervention for depression (we will also summarise the proportion starting a new intervention in each arm as part of this outcome).

11. **Time to initiation of treatment** defined as first date participant takes first dose of the treatment (we will also summarise the proportion initiating the treatment in each arm as part of this outcome).

12. **CGI Global improvement** (proportion of patients with a CGI-improvement score of 'much' or 'very much improved') at 8 and 52 weeks.

13. **Side Effects**, PRISE continuous total score at 8 and 52 weeks.

We do not intend to adjust the following secondary outcomes for multiple comparisons:

14. **Serious Adverse Events –** the number of events and number of people with events in each treatment arm will be summarised as serious adverse events, serious adverse reactions, suspected unexpected serious adverse reactions.

We will also summarise the reasons for not prescribing, reasons for patients not commencing study IMP, reasons for discontinuing study treatment, and withdrawals from the entire trial, and the reasons for withdrawal, but we will not test the difference between the groups on these variables statistically.

**Tertiary outcomes:**

The following outcomes are less important to the main objectives of the trial. We do not intend to report most of these in the primary paper, although we may report a limited number – in particular physical health changes if they are gathered on a sufficient number of participants. All will compare lithium versus quetiapine:

The 26 week time point for the secondary outcomes listed as being analysed at 8 and 52 weeks will be tertiary outcomes.

- **Global severity** (change in CGI-severity) from baseline to 8, 26 and 52 weeks.

- **Global efficacy** (CGI-efficacy score) at 8, 26 and 52 weeks.

- **Side effects** (frequency of individual items on the PRISE) at 8, 26, and 52 weeks.

- **Side Effects** at 8 and 52 weeks rated on the three FIBSER subscales: Frequency, Intensity, and Burden.

- **Physical health changes** from baseline to 8, 26 and 52 weeks (these measures will not be completed for all participants; we will report them if they are completed for a sufficient number of participants):

    - Continuous blood parameters measured in appropriate units
    - Waist circumference in cm.

- **Satisfaction with lithium / quetiapine treatment** at 8, 26 and 52 weeks as assessed using the four subscale scores on the TSQM.

- **Change in self-report manic symptoms** (continuous total Altman Mania Self Rating Scale score) from baseline to 8, 26 and 52 weeks.

- **Change in anxiety symptoms** (continuous total GAD-7 score) from baseline to 8, 26 and 52 weeks.

- **Time to prescription** defined as first date participant is given a prescription for the treatment (we will also summarise the proportion given a prescription in each arm as part of this outcome).

- **Baseline adherence to antidepressant treatment** pre-trial (baseline MARS-5 using continuous total MARS-5 scores and exploratory cut-offs (categorising participants as either adherent or non-adherent on the MARS-5).

- **Change in cognition** (continuous total DSCT score) from baseline to 8, 26 and 52 weeks.

- **Adherence of clinicians** to prescribing and monitoring guidelines for clinical practice as published and recommended (e.g. series of yes/no variables indicating whether recommended tests have been done).

- **Proportion of participants having an adequate acute treatment trial** by 8 week study visit (as defined in Section 5.2).

- **Number of hospital admissions for depressive episode** over 12 months.

- **Change in personality measure** (continuous total SAPAS score) from baseline to 8, 26 and 52 weeks.

- **Social functioning** (continuous total Work & Social Adjustment Scale score) area under the curve, measured weekly over 12 months.

**Ancillary analyses:**

The following analyses will not be reported in separate publications and not reported in the primary trial paper:

1. **Economic analysis** – costs over 12 months from the NHS and Personal Social Services perspective and a secondary analysis from a societal perspective that will include, in addition to the NHS and personal social services, costs to other statutory and non-statutory services, impacts on caregivers and families, days off work due to health problems for those in employment, and

time spent by paid and unpaid caregivers. This data will be gathered from the CSRI, modified for TRD, at baseline, 8, 26, and 52 week study visits.

2. **Predictors of treatment response** e.g. baseline severity of treatment resistance (MSM), baseline depression characteristics (e.g. severity (HAM-D), chronicity (MSM), family history, recurrence (MINI 7.0), psychiatric comorbidity (MINI 7.0), subtype (e.g. typical versus atypical, IDS-C), personality (SAPAS), type of antidepressant (SSRI vs. non SSRI, MTI), smoking status, alcohol use and illicit substance use at baseline, hypomanic screening (HCL-16 at baseline) and sociodemographic factors (e.g. sex, age, ethnicity, BMI).

3. **Exploration of longitudinal depression severity until time to all cause and side effect treatment discontinuation** - for lithium versus quetiapine for the QIDS-SR, assessed weekly via the True Colours system using varying definitions of treatment discontinuation, taking into account that patients may restart the study medications after discontinuation (defined as not taking study medications for at least 2 weeks).

4. **Collection and analysis of biological samples** for those who consented to provide blood/hair/saliva samples to the BRC Bioresource collaboration.

5. **Reliability and validity** of the Maudsley VAS current and change measures compared to the QIDS-SR and MADRS at baseline, 8, 26, and 52 weeks.

6. **Discrepancy between the self-rated and clinician-rated version of the 16 item IDS** at baseline and 8 weeks.

7. **Relationship between quetiapine and lithium serum levels, prescribed dose and depressive symptom severity** and change in from baseline to 8 and 52 weeks (if applicable) on the MADRS.

8. **Exploration of new interventions and amount of concomitant psychological treatment for depression (psychotropic medication and/or non-pharmacological) over 12 months** (determined using questionnaires assessing new/concomitant treatments completed at baseline, 8, 26, and 52 week study visits).

9. Secondary outcomes analysed at 8 and 52 weeks will also be analysed at the 26 week time point additionally.

   Patient rated experience of the True Colours weekly monitoring system, measured using qualitative interview at a follow up appointment (either 8, 26, or 52 week visit)
10. Change in cognitive function (THINC-it composite and individual tests scores)

## 8.2 Procedures for Assessing Effectiveness Parameters

The main effectiveness parameters will be assessed using the self-rated and clinician-rated assessments described in Sections 8.1.1 and 8.1.2.

The self-report depressive symptoms measure (QIDS-SR) used for the primary outcome will be rated weekly by the participants, based on the experience of CEQUEL that this is a feasible and acceptable frequency for patients. Adherence and medication status questions and the WSAS, will also be completed weekly on True Colours. All other measures, including the clinician-based research assessments, will be undertaken at baseline, 8, 26 and 52 week follow up visits.

We will collect economic data using a modified version of the CSRI for use in patients with TRD, developed by the Centre for the Economics of Mental and Physical Health. Data on all concomitant

medication use will also be collected. The main economic evaluation will take the NHS/Personal Social Services perspective preferred by NICE with secondary analyses incorporating all other costs. Costs will be combined with depression symptom improvement (QIDS; MADRS) outcome in a series of cost-effectiveness analysis. Uncertainty around cost-effectiveness estimates will be addressed using cost-effectiveness planes and cost-effectiveness acceptability curves.

Adherence to quetiapine and lithium will be measured via the MARS-5 completed at study visits (weeks 8, 26, and 52).

At every trial attendance there will be a brief clinical assessment for any serious adverse events. Any potentially serious adverse events reported by participants or their clinical teams will be reported and followed up between visits. The research worker will review the adverse events immediately to ascertain whether they meet the criteria for 'serious' and will discuss the event with the site clinician. Clinicians will record serious adverse events, any changes to drug regime, any unplanned admissions to hospital and any new treatments as per standard practice.

Physical effects will be measured using weight, BP and blood parameters at baseline, 8 week and 52 week study visits. Blood will be assessed for changes in full blood count, urea and electrolytes, liver function tests, thyroid function tests, calcium levels, fasting lipids and fasting glucose.

Venepuncture will involve hospital based phlebotomy services, using standard blood draw volumes and tubes as per local policy but no more than 50 ml per visit. Blood parameters will be recorded as per Section 7.2.

Weight will be measured using electronic scales or another method used routinely in the clinic setting patients are seen in.

# 9 Assessment of Safety

## 9.1 Specification, Timing and Recording of Safety Parameters.

Patients with treatment resistant depression are considered a vulnerable population and therefore we will ensure monitoring and safety during the trial, as per GCP guidelines. As the study IMPs are licenced, recommended, and routinely prescribed in patients with TRD in the way outlined in the study (they will not be prescribed to patients who are identified as ineligible for the medications according to the SmPCs – outlined in section 5.4), their safety has already been established. The medications are being initially prescribed by trial clinicians. The primary safety monitoring will be the responsibility of the trial clinicians according to routine clinical practice (e.g. pre-prescribing blood tests and ECGs – these tests are required post-randomisation unless they were conducted in a time period prior judged sufficiently recently to the prescribing clinician). The trial clinicians will also be responsible for safety reporting: informing the core trial team about any serious adverse events. We stress that as this trial is designed to be a pragmatic trial that only essential safety monitoring guidelines will be required to be conducted by trial clinicians before prescribing the medications (as detailed below). Otherwise, the trial and non-trial clinicians should conduct monitoring tests as they would do in their normal clinical practice and as they judge suitable for each individual patient. We outline recommended monitoring below as a reference for clinicians. Failure to follow these (except essential pre-treatment tests) will not constitute a protocol deviation.

Patients will be asked to contact the study team about any adverse events they experience throughout the 12-month study period. A member of the team will speak to the patient and trial clinicians will advise and assess the patient's health and wellbeing. We have access to multiple experienced psychiatrists as part of the research team who can advise and assist if needed and adverse events will be reported as outlined in Section 9.2.

At every trial attendance, there will be a clinical assessment for any adverse events. Any events reported by participants to the research team will be reported and followed up between visits. The research worker will then review the adverse events immediately to ascertain whether they meet the criteria for 'serious' and will discuss the event with a site clinician. Trial clinicians will record adverse events, any changes to drug regime, any admissions to hospital and any new treatments. Any events reported by participants to the research team will be reported and followed up between visits. Adverse events will be reported as per section 9.2 of this protocol.

Additionally, trial clinicians will ensure they ask about and report any SAEs to the core trial team when they meet with a participant on the trial. Trial clinicians will be required to conduct the recommended pre-lithium work up blood tests i.e. renal function, thyroid function, full blood count, serum calcium. Additionally, if ECGs are clinically indicated in patients randomised to either treatment arm i.e. in patients who have risk factors for, or existing cardiovascular disease. These are required safety parameters. Where study baseline blood tests are available, these will be accessible to trial clinicians in the trust for use as quetiapine baseline or pre-lithium work up blood tests. After commencement of the IMP the prescribing and monitoring of the two medications should be conducted as per standard care. The following recommendations are in line with standard NHS guidelines and provided as a reference for clinicians only.

**Recommended and essential treatment safety checks and monitoring for lithium (as defined in Maudsley Prescribing Guidelines):**

| **Indication** | **Treatment resistant depression** |
|---|---|
| Pre-lithium work up | **Essential safety monitoring by trial clinicians** (to be recorded in the eCRF): Renal function, thyroid function, full blood count, serum calcium.<br><br>**Safety monitoring if clinically indicated**: ECG recommended in patients who have risk factors for, or existing cardiovascular disease (to be recorded in the eCRF)<br><br>Weight (or BMI) at baseline (not recorded in eCRF).<br><br>Exclude pregnancy. Women of childbearing age should be advised to use a reliable form of contraception (will be recorded if deemed a reason behind not commencing study IMP). |
| Monitoring<br>(clinician monitoring tests will be recorded in the eCRF) | Serum lithium level: the dose will be adjusted to achieve a serum-lithium concentration of 0.4-1.0mmol/litre 12 hours after a dose on days 4-7 of treatment, then every week until dosage has remained constant for 4 weeks aiming for an optimal therapeutic plasma level of 0.6-1.0 mmol/l.<br><br>Results of any tests or patient refusal should be documented.<br><br>If lithium toxicity suspected or level >1.5mmol/l – STOP lithium immediately and assess patient. Repeat serum lithium, U&Es and creatinine levels and seek hospital advice. Levels >2.0mmol/l consider referral to A&E. |

**Recommended monitoring for quetiapine (as defined in Maudsley Prescribing Guidelines):**

These tests are not essential safety procedures, except ECG (at baseline ) if clinically indicated. These tests will only be done if clinically indicated and, with the exception of ECG, if not done it will not be considered a protocol deviation.

| Parameter/Test | Frequency | Action to be taken if results outside reference range |
|---|---|---|
| **U&Es** (inc. creatinine or eGFR) | Baseline, then yearly | Investigate all abnormalities detected |
| **FBC** | Baseline, then yearly | Stop suspect drug if neutrophils fall below 1.5 x $10^9$/L<br>Note: high frequency of benign ethnic neutropenia in certain ethnic groups |
| **Blood lipids** (cholesterol; triglycerides). Fasting sample, if possible. | Baseline, 3 monthly for first year, then yearly | Offer lifestyle advise<br><br>Consider changing antipsychotic and/or initiating statin therapy |
| **Weight** (including waist size and BMI, if possible) | Baseline, frequently for 3 months, then yearly | Offer lifestyle advice<br>Consider changing antipsychotic and/or dietary/pharmacological intervention |
| **Plasma glucose** (fasting sample, if possible or non-fasting and HbA1c) | Baseline, at 4-6 months, then yearly | Offer lifestyle advice<br>Refer to GP / specialist |
| **ECG** (recommended for patients who have risk factors for, or existing cardiovascular disease) This will be recorded in the eCRF. | Baseline and after dose increases (ECG changes rare in practice) – offered yearly | Discuss with / refer to cardiologist if abnormality detected |
| **Blood pressure** | Baseline; frequently during dose titration period and to generally monitor physical health | Treat hyper/hypotension in line with NICE guidelines |
| **Liver function tests** (LFTs) | Baseline, then yearly as part of a routine physical health check | Stop suspect drug if LFTs indicate hepatitis (transaminases X 3 normal) or functional damage (PT/albumin change) |
| **Creatine phosphokinase** (CPK) | Baseline, then if neuroleptic malignant syndrome (NMS) suspected | If NMS suspected, all anti-psychotic drugs, including quetiapine, should be immediately stopped and urgent medical opinion / treatment sought. |
| **Thyroid function tests** (TFTs) | Baseline, then yearly | Consider thyroxine |

**Additional monitoring recommended for quetiapine and lithium:**

- General Monitoring guidance: Ask about compliance, side effects, adverse events at every consultation.
- Lifestyle factors: Smoking, alcohol, substance misuse, diet, level of physical activity, sexual health, contraceptive advice.
- Response to treatment: Including changes in symptoms and behaviour including suicidal thoughts / clinical worsening.

**Stopping treatments:**

Quetiapine: acute withdrawal symptoms have commonly been described after abrupt discontinuation of quetiapine e.g. insomnia, headache, diarrhoea, dizziness, irritability, nausea and vomiting. It is recommended that quetiapine is discontinued gradually; ideally over a 3-4 week period.

Lithium: it is recommended to reduce the dose slowly over at least 1 month. Avoid incremental reductions in plasma levels of >0.2mmol/L.

## 9.2 Procedures for Recording and Reporting Adverse Events

We will follow the relevant definitions provided by The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 with regards to adverse events:

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

**Adverse Reaction (AR):** Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

**Unexpected Adverse Reaction** (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for that product.

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

**Important Medical Events (IME) & Pregnancy:** Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

King's College London and South London and Maudsley NHS Foundation Trust (the co-sponsors) have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance, as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004, to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24 hours) by the Investigator to the KHP-CTO and CI for review in accordance with the most current version of the Pharmacovigilance Policy.

The KHP-CTO will report SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place. The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:
SUSARs which are fatal or life-threatening must be reported no later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days. SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator and KHP-CTO (on behalf of the co-sponsors), will submit a Development Safety Update Report (DSUR) relating to this trial's IMPs, to the MHRA and REC annually.

### 9.2.1 Adverse events that do not require reporting

As this is a type A trial and the risk associated with the trial is no greater than standard care and the adverse reactions associated with the medications well known, only serious adverse events will be reported in this trial i.e. we will not report non-serious adverse events. Additionally, elective hospital admissions will not be considered as SAEs and therefore will not be reported. After a participant has discontinued the medication they were randomised to we will continue to monitor SAEs for the trial

duration (12 months) for all participants regardless of medication discontinuation.

## 9.3 Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator, or Regulatory Authority on the basis of new safety information or for other reasons given by the Ethics Committee. The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the Trial Steering Committee, Data Monitoring and Ethics Committee or regulatory authorities, who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

Patients may discontinue treatment at any time they choose or as recommended by their clinician.

# 10 Statistics

We have taken multiple measures to reduce bias and in designing this study to be as pragmatic and naturalistic as possible. These include: randomisation of all patients; having lenient inclusion / exclusion criteria (as outlined in Sections 6.1 and 6.2); and treating clinicians and patients not being blinded to the treatment arms. Pre-prescribing safety tests will be operationalised according to best current practice by trial clinicians, but there will not be a rigid control of management thereafter, for example, of frequency of clinic visits, dosing, length or prescribing or monitoring so as to reflect “normal” current clinical practice for the two treatment regimens. Multiple methods of minimising loss to follow-up, including telephone follow-up and reminder letters for study visits and weekly monitoring, will be employed to minimise bias. Observer bias will be minimised by the use of blind raters for the clinician assessed rating scales at follow up study visits.

The main statistical analysis will be carried out on the basis of intention-to-treat (ITT) with consideration of the impact of missing data and the use of appropriate sensitivity analyses. We will follow a Statistical Analysis Plan approved by the Data Monitoring Committee and Trial Steering Committee when analysing the outcomes of this trial.

## 10.1 Sample Size

Based on our power calculation and superiority design, we require 276 patients to be randomised across three centres. We expect recruitment to be split evenly across all sites; however, we will start in one site (London) in order to pilot all procedures including acceptability, practicality, data completion rates, and to assess recruitment rates and barriers, before making any necessary amendment and rolling out to the other sites after an initial 3-month period of recruitment in London. Our estimate of feasible recruitment is 3-4 subjects per centre per month.

This required sample size was calculated based on the following assumptions:

*Drop out:* We estimate a 20% drop out from treatment by the 8 week follow up visit as per Bauer et al (2013), and 50% treatment discontinuation by 52 weeks. We have allowed the discontinuation status at follow-up to be unknown for 10% of the sample.

*Missing data:* Experience from CEQUEL suggests high rates of data return (80%) when using True Colours (Geddes et al., 2016) but we allow for 40% missingness for each of the post-randomisation True Colours scores. While the missingness has been assumed independent over time, the True Colours scores are assumed uniformly correlated 0.6. Imputation will be used for missing baseline data (White & Thompson, 2005). Full information maximum likelihood methods will be used for analysis, which will account for missing data under the missing at random assumption. In the analysis of adherence to treatment time we expect low rates of missingness (power calculations assumed 10%) as the level of information required to determine this outcome is not high, and in many cases partial information will still be available in the form of censored observations. For the analysis of the True Colours outcome the frequent repeated measurement allows the use of a random effects model estimated by maximum likelihood with unbiased estimates under a missing at random assumption i.e. allowing for missingness to be dependent on previous and later observed depression scores. However, with this outcome we expect the rate of missingness to be higher (we assumed 40% in the power calculation) and so will undertake sensitivity analyses of the missing at random assumption. For these analyses, the impact of non-ignorable missingness scenarios will be examined by reporting effect estimates from data where hypothetical systematic bias quantities are added or subtracted to the imputed scores.

*Effect size:* The minimum clinically significant difference for outcomes in depression treatment is widely taken to be 3 points on the HAM-D (NICE 2009, Cleare et al 2015). This corresponds to an effect size of 0.38 between treatments. We wish to see a difference of this effect size in the QIDS-SR score (as measured using the True Colours system) sustained over the period of the trial and follow-up and so will estimate the effect as an area under the curve (a simple average of post-randomization measures if equally spaced). Over the year of follow-up, we expect a rate of discontinuation of assigned treatment of 50% and have powered for an improvement to 30% (i.e. a 20% reduction).

*Power*: All power calculations are for two-tailed tests and alpha=0.05.
When considering the sample size required, we have considered both the primary outcome measure of longitudinal symptom severity as assessed by QIDS-SR score using True Colours, estimated as an area under the curve of the QIDS-SR score over time, as well as all cause discontinuation.

With a sample size of 276 at baseline and 10% loss we expect 248.4 at follow-up. Using a logrank test for the time to discontinuation with 50% (lithium) and 70% (quetiapine) as the proportions remaining on assigned treatment Stata stpower logrank gives a power of 90%. This determined the lower limit of the sample size. Applying this sample size to the self-report True Colours data we also needed to account for the likely haphazard nature of the missingness at each assessment time. We used simulation and the non-central chi-square method for calculating power. Over 1000 samples a simple random intercept model covarying for baseline, a time dummy variable and with a single average combined treatment effect gave 99.7% power for an ES=0.38 (1df, 3.84, and 20.86 for the noncentrality parameter), even with the very pessimistic 40% occasion-wise nonresponse assumed.

Recruitment will be regularly monitored by the TMG, the TSC and the DM(E)C. We have considered the need for a contingency plan in the event of centre recruitment underperformance. If this occurs and there is a failure to respond to corrective measures, then we will consider the option withdrawing 0.5 wte of the research worker post at the underperforming site and redeploying the remaining resource (i.e. the funding rather than the person) at another centre with a higher recruitment rate. As an alternative, additional centres may be approached.

## 10.2 Analysis

The primary outcome will be the self-rated Quick-Inventory of Depressive Symptomatology (QIDS-SR), assessed via the True Colours system (www.truecolours.nhs.uk). This is the system used successfully in the CEQUEL study comparing longitudinal outcomes in patients with affective disorders (Geddes et al., 2016). The use of longitudinal measures of remission in TRD is recommended (A. Fekadu et al., 2011)

given the evidence that patients with TRD move between states of remission and illness (Vergunst et al., 2013) and because TRD is often a chronic, relapsing problem, so that a simple cross sectional outcome measure may miss important differences between treatments. This measure will be rated weekly, based on the experience of CEQUEL that this is a feasible and acceptable frequency for patients. This weekly monitoring using true colours will also be used to measure medication status and adherence and social functioning (WSAS). All other measures, including the clinician-based research assessments, will be undertaken at baseline, 8, 26 & 52 weeks (see Table 1). This weekly measure of adherence is important to minimise recall bias. Adherence will additionally be monitored at study visits (8, 26, and 52 weeks) using the 5-item Medical Adherence Report Scale (MARS-5).

The main analysis will follow the ITT principle, that is, all patients will be analysed in the group to which they were randomised. Participant flow will be presented in a CONSORT diagram. Descriptive data by trial arm will be presented on a complete data basis. For analysis, missing baseline data will be completed using imputation. Models throughout will covary for randomisation stratification factors. For the self-report True Colours QIDS-SR score a linear mixed model covarying by baseline score will be used for the estimation of the mean treatment difference over the course of the trial and reported together with a 95% confidence interval (CI). Estimation will be by maximum likelihood using all the available data allowing efficient and unbiased estimation in the presence of dropout that may be dependent upon observed scores (missing at random assumption). Confidence intervals for the effect size estimate will be obtained using bootstrap. Error distributions will be checked using Q-Q plots. Time from the commencement of the intervention (prescription date) to treatment discontinuation will be analysed using Kaplan-Meier and proportional hazards regression models, treatment difference being described by the relative risk and 95% confidence interval (CI).

Continuous secondary outcomes measured over time will use generalized linear models selected to be appropriate to the distributional form of the outcome variable, and will covary by baseline score if this is appropriate. Where repeated measurement of a continuous variable has been undertaken the analysis will be set in mixed model framework. Estimation will target mean effects at time points as described in Section 8. In view of the large number of secondary outcomes, an overview of the significance after a false discovery rate correction for multiple testing will be presented (Benjamini & Hochberg, 1995). Categorical outcomes will be summarized using frequencies and proportions.

For measures where missingness is above 5% and where the absence of repeated measurement gives less confidence in the adequacy of the missing data properties of maximum likelihood, we will undertake a sensitivity analysis within a multiple imputation framework (White et al, 2011).

The frequency of serious adverse events and side effects (rated on the PRISE and FIBSER) and the number of participants having adverse events and side effects will be tabulated by treatment arm.

A full and detailed Statistical Analysis Plan will be drafted and signed off by the study team and DMEC.

**Economic analysis**

The primary economic analysis will consider costs from the NHS and Personal Social Services (PSS) perspective as recommended by NICE. A secondary analysis from a societal perspective that will include, in addition to the NHS and personal social services, costs to other statutory and non-statutory services, impacts on caregivers and families, days off work due to health problems for those in employment, and time spent by paid and unpaid caregivers. The main categories of NHS and PSS costs that will be analysed will include medication and treatment, inpatient admissions, outpatient appointments, A&E contacts, community-based health and social care. Aggregated health and social care costs, other statutory department costs and, cost of time spent care giving by relatives and friends and lost productivity costs will be analysed in the case of the latter viewpoint.

We will collect economic data using a modified version of the client service receipt inventory (CSRI) for use in patients with TRD and administered at baseline, 8, 26, and 52 week visits. King's Health

Economics in close collaboration with the PI will develop this measure. Data on medication use (lithium/quetiapine, and concomitant medication) and blood tests during treatment will be collected and costs calculated using figures in the British National Formulary in the case of the treatment medication and from NHS Reference costs for blood tests. Costs associated with time spent by friends or relatives providing support will be derived using the most recent unit costs estimates of a local authority home care worker. Lost productivity costs will be derived by multiplying the relevant number of workdays lost with a wage rate estimate, considering the various measurement and valuation methods.

The economic analysis will follow the ITT principle, using the same approach outlined for the analysis of clinical outcomes. Cost and outcomes will be modelled in a multilevel mixed modelling framework. Although the treatment groups are expected to be balanced at baseline, it is possible that baseline costs and outcomes could be predictors of costs at follow-up data collection; therefore, for the adjusted analyses, the total cost model will control for baseline values for the same cost variable and baseline self-rated QIDS and EQ-5D scores. We will also control for age at entry into the study and site.

Costs will be combined with the primary measure of outcome and quality of life measure in a series of cost-effective analysis. Differences in mean total costs between groups will be compared using the standard t-test with ordinary least squares regression used for adjusted analyses and the validity of results confirmed using bootstrapping. The self-rated QIDS will be used as the primary measures of outcome over 52 weeks and appropriate weights will be applied to the EQ-5D (at baseline, 8, 26, and 52 weeks) to derive QALYs over 52 weeks. Uncertainty around cost-effectiveness estimates will be addressed using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

Missing items will be imputed to facilitate the estimation of subtotal and total NHS and PSS costs and societal costs. For measures with missing data above 5% multiple imputation will be used. Where there is an indication that the resource was used and where either the duration of contact or number of contacts was missing, the median value of the other service users in that treatment group will be used. Where it is not indicated that the service was used, it will be assumed that it was not used and a zero cost attached.

# 11 Trial Steering Committee

We will follow NIHR HTA guidance in setting up the TSC. A Trial Steering Committee (TSC) that will meet twice a year, will be set up to monitor, review and supervise the progress of the trial. This will have an independent chair. We will invite two service user representatives onto the TSC. The TSC will set up a Data Monitoring and Ethics Committee (DMEC, see Section 12). Alongside our statistical expertise, the Steering Committee review will ensure that conduct and reporting standards (e.g. stipulated by the Nature Publishing Group) are adhered to. This will include use of appropriate methodology and subsequent reporting (i.e. CONSORT checklist items, design, recruitment, allocation, blinding, ethics, trial registration), and statistical procedures (i.e. stating assumptions, comprehensive reporting of results and providing clearly labelled descriptive statistics and figures, along with a CONSORT flowchart).

The role of the TSC will be to provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. We will carefully monitor adverse events and patient safety, and any concerns in this regard will be promptly taken to the Lead PI and TSC. The main features of the TSC are as follows:

- To provide advice, through its Chair, to the Chief Investigator(s), the Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial
- To concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question
- The rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society
- To ensure appropriate ethical and other approvals are obtained in line with the project plan
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments

- To provide advice to the investigators on all aspects of the trial

## 12 Data Monitoring Committee

A Data Monitoring (and Ethics) Committee (DM(E)C) will be set up by the TSC. The DM(E)Cs main roles will be as follows:

- It will have access to the full data set
- The role of its members will be to monitor these data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. The safety, rights and well-being of the trial participants are paramount
- The DM(E)C may be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies

If funding is required above the level originally requested, the DM(E)C may be asked by the Chief Investigator, TSC/SSC, Trial Sponsor or Trial Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial.

We do not plan an interim analysis given that the medications under investigation are considered relatively safe therapies, and are currently used in clinical practice for the purpose that they will prescribed during this trial, we perceive this not to be a high-risk study.

Membership of the DM(E)C will be completely independent, small (3- 4 members) and comprise experts in the field, e.g. a clinician with experience in the relevant area and expert trial statistician.

Responsibility for calling and organising DM(E)C meetings lies with the Chief Investigator, in association with the Chair of the DM(E)C. We will follow NIHR HTA guidance in setting up the TSC. The project team will provide the DM(E)C with a comprehensive report, the content of which should be agreed in advance by the Chair of the DM(E)C.

The DM(E)C will meet at least annually, or more often as appropriate, with meetings timed so that reports can be fed into the TSC

The statisticians will draft a DMC DAMOCLES charter delineating roles and timings of meetings to be agreed at the first DMC meeting. This charter will sit with the KCTU and will be included in the trial master file.

Minutes of meetings will be sent to all members, the sponsor, the funder, the TSC and the trial master file.

## 13 Direct Access to Source Data and Documents

The study investigators will permit trial-related monitoring, audits, REC review and regulatory inspections by providing the Sponsor(s), Regulators and Research Ethics Committee direct access to source data and other documents (e.g. patients' case sheets, blood test reports, medical test results etc.) when required.

## 14 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use

(Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to the East of England - Cambridge South Research Ethics Committee (REC), Health Research Authority (HRA) and to the Medicines and Healthcare Products Regulatory Agency (MHRA) for Clinical Trial Authorisation. The trial will be registered with the appropriate trial registry. Subsequent protocol amendments will be submitted to the REC and MHRA.

The Chief Investigator will submit a final report at conclusion of the trial to the funders and to the KHP-CTO (on behalf of the Co-Sponsors) and the REC. The KHP-CTO will upload the report on to EudraCT and notify the MHRA within the timelines defined in the Regulations.

# 15 Quality Assurance

Monitoring of this trial, to ensure compliance with Good Clinical Practice and scientific integrity, will be managed with oversight retained by the KHP-CTO Quality Team.

We will ensure that quality is optimally maintained throughout the trial, using methods such as: Trial Steering Committee monitoring, which includes individuals independent from the study team, ensuring regular and experienced supervision for team members, ensuring ongoing support and training for those undertaking research assessments and handling data.

The King's CTU will be responsible for managing the following aspects of the trial: eCRF creation, database design and randomisation.

The Chief Investigator will maintain overall responsibility for the trial working closely with the Trial Manager to ensure that the trial is run in accordance with the protocol and the KCTU Standard Operating Procedures. A Trial Management Group (TMG) consisting of the Chief Investigator, co-investigators, the trial manager and the trial statistician will meet monthly during the first year of the study and then quarterly thereafter. The purpose of the TMG will be to oversee the smooth running of the trial and quality assurance. A full and detailed Data Management Plan will be drafted and signed off by the study team.

During the planning of this research project, we sought informal review by experienced academics, statisticians, and clinicians. This was followed by a stringent peer review process for the funding application by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) funding stream, where the project was judged sufficiently well designed to be funded, and to be worthwhile in terms of future implications and benefits to patients and the NHS.

# 16 Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

- Patient data will be anonymised.
- All anonymised data will be stored on a password-protected computer.
- Paper forms of participant personal data will be stored securely within the recruiting site in locked filing cabinets (the offices will be locked when empty).
- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.

# 17 Data Management

Data will be entered using a secure web-based electronic case report (eCRF using InferMed Macro) hosted at KCTU in which participants will be identified by a unique code and initials with restricted access. We will adhere to NHS confidentiality practice, and to the Research Governance Framework in monitoring and managing the research. As CI, Professor Cleare will undertake overall responsibility for management of the project. A Data Management Plan will detail measures taken to promote data quality, for example, range checks for data values input into the eCRF.

# 18 Publication Policy

It is intended that the results of the study will be published in open access, peer-reviewed journals. The primary report will be attributed to the LQD Investigators and Collaborators. The names of all treating clinicians on the trial and members of the trial management team will be listed at the end of the primary publication. The primary publication will include all primary and secondary outcomes as listed in the protocol. Tertiary outcomes and ancillary analyses will be reported in additional publications.

In addition, we will present the findings at National and International conferences to reach as wide an audience as possible. We will use the university and NHS press offices to publicise findings as widely as possible to the public. We will ensure that a full account of the research is published in the NIHR HTA Journal. The protocol will be publically available but will not grant public access to the participant level dataset and statistical code. Individual participants will not be identifiable from any publication.

Study participants will be asked routinely whether they would like to be informed of the study findings and a summary will be sent to all those who request it. We will provide plain English reports for patient literature, linking with relevant patient organisations to do this, and aim to present the findings at relevant patient and user group meetings.

# 19 Insurance / Indemnity

The trial is co-sponsored by King's College London and South London and Maudsley NHS Foundation Trust. The sponsors will at all times maintain adequate insurance in relation to the study independently. King's College London, through its own professional indemnity (Clinical Trials) and no fault compensation and the Trust having duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient.

# 20 Financial Aspects

Funding to conduct the trial is provided by the National Institute for Health Research (NIHR)
Health Technology Assessment (HTA) programme.

## 21 Signatures

20.12.2016

Chief Investigator
*Professor Anthony Cleare*

Date

# 22 References


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