ATLANTIS

CLINICAL TRIAL PROTOCOL

Title: AnTiconvuLsant AugmeNtation Trial In Schizophrenia: a randomised, pragmatic double-blind, placebo-controlled trial to assess the effectiveness of valproate augmentation of antipsychotic treatment in patients with residual psychotic symptoms

Protocol Short Title: AnTiconvuLsant AugmeNtation Trial In Schizophrenia

Acronym: ATLANTIS

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Trial Identifiers

EudraCT Number - **2020-000420-19.**

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1. Study Synopsis

Title of clinical trial	**AnTiconvuLsant AugmeNtation Trial In Schizophrenia:** a randomised, pragmatic double-blind, placebo-controlled trial to assess the effectiveness of valproate augmentation of antipsychotic treatment in patients with residual psychotic symptoms
Protocol Short Title/Acronym	ATLANTIS
Trial Phase if not mentioned in title	Phase 3
Sponsor name	King's College London and South London and Maudsley NHS foundation trust
Chief Investigator (CI)	Prof Oliver Howes
EudraCT number	
REC number	
Medical condition under investigation	Schizophrenia or schizoaffective disorder
Purpose of clinical trial	To assess the efficacy and cost-effectiveness of valproate when used to augment antipsychotic treatment in patients with schizophrenia or schizoaffective disorder whose illness shows inadequate response to first-line antipsychotics
Primary outcome	The PANSS positive (psychotic) score at the end of the double-blind study (12 months)
Secondary outcomes	The main secondary outcome will be PANSS positive score difference at 3 months Additional secondary outcomes include: – PANSS positive score at 6 months – Change in PANSS factor scores at 3, 6- and 12-

	month follow-up visits – Total PANSS scores at 3, 6- and 12-month follow-up visits – Change in other clinical measures at 3, 6 and 12-month follow-up visits – Patient reported outcome (well-being) at the 3, 6 and 12-month follow-up visits – Cost effectiveness assessment using measures collected at baseline, 3, 6 and 12-month follow-up visits – Adverse effects at baseline, 3, 6-month and 12-month follow-up visits – Discontinuation of the medication at 3, 6 and 12-month follow-up visits – Long-term symptomatic and functional outcomes using the HoNOS in an annual fashion during the extension phase till the end of the trial – starting clozapine treatment
Trial Design	This is a two-arm parallel group randomised 12-month placebo-controlled double-blind trial. Following baseline measures, patients will be randomly assigned 1:1 to either valproate + antipsychotic or placebo + antipsychotic arms. Sodium valproate will be started at a daily dose of 500mg PO and titrated between 500 mg/day to 2500 mg/day of valproate (depending on body weight) over two weeks. The placebo will be titrated in the same way. After the end of one year, each patient in both arms will be down titrated and valproate/placebo augmentation will be stopped over a two-week period. After the 12-month follow up visit, patients will be followed up using electronic databases to capture long-term clinical and functional outcomes using the Health of the Nation Outcome Scale (HoNOS) till the end of the trial.

Sample Size	362 patients We have powered our study based on the superiority of valproate compared to placebo, as determined by the PANSS positive subscale using a clinically meaningful effect size of 0.3. Assuming a two-sided significance level of 0.05 and 1:1 allocation, we will require 290 participants in the analysis dataset to detect an effect size of 0.3 with 90% power. This allows for a correlation between measures (at baseline and three follow-up points) of 0.4. An estimate of attrition of 20% across both arms for the primary end-point at 12 months requires a recruitment total of 362 participants at baseline.
Summary of eligibility criteria	Men and non-pregnant or breastfeeding women 1) aged 18 years and above; 2) diagnosed schizophrenia or schizoaffective disorder, as determined by the DSM-5, are eligible. They should have one or more symptoms of at least moderate severity in the PANSS positive sub-scale despite adequate treatment with at least one non-clozapine antipsychotic drug.
IMP, dosage and route of administration	Oral sodium valproate, dose between 500mg to 2500mg daily (depending on body weight)
Active comparator product(s)	Oral placebo to match sodium valproate 500mg tablets
Maximum duration of treatment of a Subject	12 months (active trial) and an additional 2 weeks for down titration at the end of the 12-month period
Version and date of protocol amendments	Ver 2; Dated 03 January 2020

2. Glossary of Terms

ADR	**Adverse Drug Reaction**
AE	**Adverse Event**
AP	**Antipsychotic**
AR	**Adverse reaction**
ATLANTIS	**AnTiconvuLsant AugmeNtation Trial In Schizophrenia**
BMI	**Body Mass Index**
CDSS	**Calgary Depression Scale for Schizophrenia**
CEAC	**Cost effectiveness acceptability curves**
CGI-SCH	**Clinical Global Impression rating scale – Schizophrenia version**
CI	**Chief Investigator**
Co-I	**Co-investigator**
CONSORT	**Consolidated Standards of Reporting Trials**
CPT	**Carnitine palmitoyltransferase**
CRF	**Case Report Form**
CSRI	**Client Service Receipt Inventory**
C-SSRS	**Columbia-Suicide Severity Rating Scale**
CTCAE	**Common Terminology Criteria for Adverse Events**
DMEC	**Data Monitoring Committee**
DSM	**The Diagnostic and Statistical Manual of Mental Disorders**
HoNOS	**Health of the Nation Outcome Scale**
EC	**Ethics Committee**
eCRF	**Electronic Case Report Form**
EPS	**Extrapyramidal symptoms**
GCP	**Good Clinical Practice**
GP	**General Practitioner**
GPMU	**Guys' & St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit**
ICF	**Informed Consent Form**
IME	**Important Medical Events**
IMP	**Investigational Medicinal Product**
ITT	**Intention to treat**
IUD	**Intrauterine device**
IUS	**Intrauterine hormone-releasing system**
KCTU	**King's Clinical Trials Unit**
KHP-CTO	**King's Health Partners-Clinical Trials Office**
LFT	**Liver Function test**
MOAS	**Modified Overt Aggression Scale**
MHRA	**Medicines & Healthcare Regulatory Agency**
NICE	**National Institute for Health and Care Excellence**
NIHR	**National Institute of Health Research**
OTC	**Over the counter**
PANSS	**Positive and Negative Syndrome Scale**
PIN	**Patient Identification Number**
PO	**Per oral**
POMH-UK	**Prescribing Observatory for Mental Health – UK**
QALYS	**Quality-adjusted life years**
QP	**Qualified person**
REC	**Research Ethics Committee**

RCT	**Randomised controlled trial**
SAE	**Serious Adverse Event**
SAP	**Statistical Analysis Plan**
SAR	**Serious Adverse Reaction**
SCID	**Structured Clinical Interview for DSM-5**
SF-36	**36-Item Short Form Survey**
sIMPD	**Simplified Investigational Medicinal Product Dossier**
SmPC	**Summary of Product Characteristics**
SOP	**Standard Operating Procedure**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
SWEMWBS	**Short Warwick-Edinburgh Well-being scale**
TBC	**Total Blood Count**
TMG	**Trial Management Group**
TRS	**Treatment resistant schizophrenia**
TSC	**Trial Steering Committee**
UAR	**Unexpected Adverse Reaction**
UKU	**Udvalg for Kliniske Undersogelser (side effect rating scale)**
USAR	**Unexpected serious adverse reaction**
YMRS	**Young Mania Rating Scale**

3. CONTENTS

4. Background & Rationale

Background

Schizophrenia is a severe mental disorder, affecting about 1 in 100 people in the UK and costs Europe ~100 billion Euros per year [1, 2]. It is also the primary reason for NHS hospital bed occupancy [3]. The illness is characterised by psychotic (positive) symptoms, which include hallucinations, & delusions, and negative symptoms, such as lack of motivation and anhedonia. The severity of symptoms is commonly measured using a rating scale known as the Positive and Negative Syndrome Scale (PANSS) [4]. In about 1 in 3 cases, schizophrenia does not respond adequately to first-line antipsychotic (AP) treatment [5, 6]. This is termed treatment resistant schizophrenia (TRS) [7]. Hospital admissions and healthcare costs are 311-fold higher in TRS relative to schizophrenia patients who respond to antipsychotics [8]. Moreover, TRS is associated with high on-going illness burden, poor functional outcome, and increased mortality rates due to suicide [8].

Clozapine is the only licensed treatment for TRS. The NICE guidelines recommend offering clozapine to TRS patients [9]. However, its use is limited by contra-indications, the risk of life-threatening and intolerable side-effects, and the requirements for close monitoring & blood tests [10, 11]. Prescribing data indicate that <10% of patients with schizophrenia receive clozapine; less than one-third of the expected rate [12, 13]. Moreover, its use is delayed by >4 years on average and non-evidence based strategies, such as high dose antipsychotics, are commonly used instead [14]. In addition, patient surveys and clinical records indicate that the monitoring requirements and side-effects of clozapine are unacceptable to many patients [15, 16].

However, there are no other treatment options for patients with TRS who cannot or are not willing to take clozapine. Thus, there is a need to develop evidence-based alternate treatment options for TRS patients. In practice, clinicians commonly augment antipsychotic (AP) treatment with an anticonvulsant drug. In a UK audit, we found valproate was the most commonly prescribed adjunctive treatment prescribed to patients with schizophrenia, costing the NHS approximately ~£60 million/year [17]

Twenty-six trials have evaluated the efficacy of valproate as an adjunctive treatment for TRS patients [18, 19]. Meta-analyses of these study findings have demonstrated positive findings, showing that adjunctive valproate relative to placebo significantly reduced psychotic symptom severity [18, 20-22]. The most recent Cochrane review [18] concluded that the adjunctive valproate relative to placebo led to significant improvements in positive (9 RCTs, n=1073) and total symptoms (13 RCTs, n=1363). Adjunctive valproate treatment has also been shown to lead to statistically and clinically significant ~30% greater response rates relative to AP treatment combined with placebo (14 RCTs, n=1049, RR 1.31, 95% CI 1.16-

1.47, I^2=12%). Participants in the valproate group were also found to be less aggressive than the control group (3 RCTs, n=186)). There were no significant differences between groups in drop-out rates due to adverse events, indicating that the tolerability valproate and placebo were comparable (6 RCTs, n = 974)).

In summary, valproate led to significant benefits in reducing positive and total symptom severity, aggression and was well tolerated. However, sensitivity analyses in the meta-analyses showed that effects could be driven by the inclusion of open-label trials. Moreover, many studies had small sample sizes (< 50 subjects/ arm) and included clozapine treated patients. Since we are aiming to identify the efficacy of a treatment option for patients who are either unable or unwilling to take clozapine, we aim to investigate the efficacy of valproate in non-clozapine patients. Moreover, all of the trials conducted previously only followed up the patients for a few months (typically 3 months of less). Only one study was conducted in the UK, but this study aimed to investigate the effect of valproate on tardive dyskinesia, not the effect on symptom severity. The rest of the studies were conducted in countries, such as China and the USA, where health care settings and costs are markedly different to the UK. Moreover, no study to date has investigated the effect of valproate on quality of life or cost-effectiveness [23-25]. A recent Cochrane review concluded that "large, double-blind randomised trials should be undertaken to properly determine the clinical effects of adding valproate to antipsychotic treatment for people with schizophrenia". Our study therefore aims to address the issues raised by the Cochrane review by using a double-blinded, randomised design.

Although other adjunctive treatments have also been used, we selected valproate since the evidence based for its efficacy is superior to other augmentation strategies. In particular, a meta-analysis showed that lamotrigine relative to placebo led to reductions in positive and negative symptoms but not total symptom severity; and lamotrigrine was associated with more adverse events relative to placebo [26]. Although carbamazepine augmentation has been shown to reduce global symptoms relative to AP treatments alone, all of the studies conducted to date have included small sample sizes. [27] The evidence base for the use of other anticonvulsants (e.g. pregabalin) is even more limited and consists of case reports and small studies [28]. Considering this, we aim to investigate the efficacy of valproate.

Rationale

We have also considered current NHS practice in our choice of anticonvulsant to study. We surveyed UK prescribing data from the Prescribing Observatory for Mental Health (POMH-UK) covering 10,072 patients across 761 clinical teams in 58 mental health Trusts across the UK (data on file) [17]. In this sample, 20% of patients with schizophrenia were prescribed valproate in addition to an antipsychotic. Further analyses showed that valproate was the most commonly prescribed anticonvulsant, followed by lamotrigine and pregabalin (both 1% of patients), and carbamazepine (<1% of patients) [17]. We also surveyed prescribing data from one of our NHS Trusts. Our survey showed that 18% of patients on AP medication were prescribed adjunctive valproate. Thus, both national and local audits indicate that valproate

is the most commonly used anticonvulsant adjunctive treatment for patients with residual symptoms. Valproate costs ~£50/month which, taken with the prescribing data indicates that valproate augmentation of antipsychotics costs the NHS approximately £60 million/year across the UK.

In conclusion, valproate is the anticonvulsant most commonly used to augment AP treatment in the UK and meta-analytic findings indicate that it is well tolerated and associated with few adverse effects. Although we estimate that valproate costs the NHS ~£60million/year, existing evidence is largely limited to small, short-term open-label studies conducted outside of the UK. Therefore, we aim to investigate the cost-effectiveness of valproate. Since it is also unclear how valproate may influence quality of life of symptom severity long-term, we aim to conduct a double-blind, RCT investigating the long-term efficacy and cost-effectiveness of valproate, used as an adjunctive treatment to AP treatment, in patients with schizophrenia whose illness has shown an inadequate response to non-clozapine antipsychotics..

As mentioned above, meta-analyses, including a recent Cochrane review, show valproate is potentially effective with a moderate to large effect size. However, the Cochrane review identifies several major limitations: most of the trials are low quality, conducted in very different healthcare settings to the UK, and none has measured quality of life or outcomes beyond 3 months. This means it is not clear if it is effective, or cost-effective in the NHS. There is, thus, clinical equipoise and considerable NHS costs associated with valproate augmentation of antipsychotic treatment in schizophrenia. This indicates the need for a high quality long-term double-blind RCT of valproate in the UK to determine its efficacy and cost-effectiveness.

To address this, our study design is a pragmatic 12-month, parallel group, placebo-controlled double-blind randomized controlled trial of augmenting existing AP treatment with valproate in patients (men and women, above 18 years of age) who fulfil DSM-5 criteria for schizophrenia or schizoaffective disorder and have persistent psychotic symptoms despite adequate (non-clozapine) AP treatment. Patients will be randomised 1:1 to either placebo + continuing antipsychotic treatment arm or valproate + continuing antipsychotic treatment arm. Randomisation will be stratified by diagnosis, sex and site. Valproate will be started at 500mg/day and titrated up to a dose of approximately 15 to 30 mg/kg/day of valproate over two weeks, in line with evidence that this dose range may be effective [18]. The placebo group will receive a matching placebo titration. To ensure treatment is optimised for each patient, and to promote retention in the trial, further dose increments or decrements will be allowed in both arms providing the dose does not exceed 2500mg/day.

The primary outcome is psychotic symptom severity after 12 months, measured using the PANSS positive subscale. Our secondary outcome measures include discontinuation rates, changes in clinical global impression scale (CGI-SCH), the development of adverse effects, cost-effectiveness and quality of life. Cost-effectiveness will be assessed using the Client Service Receipt Inventory; symptom severity will be assessed using the PANSS positive subscale; and quality of life will be assessed using the quality-adjusted life years (QALYS).

Following the completion of the 12-month trial, patients will be down titrated off valproate and discharged to their clinical teams. Following this, we will use an open-label extension to measure long-term outcomes in these patients using electronic healthcare records.

We will use an intention-to-treat analysis as well as linear mixed models to estimate treatment effects (and logistic models for dichotomous outcomes). An effect size of 0.3 is considered the smallest clinically significant effect. Allowing for 20% attrition and for 90% power to detect an effect size of 0.3 or greater, a power calculation shows we need a total sample of 362 patients is needed. Patients will be recruited from sites in the UK over a period of approximately 3 years and the study will be conducted over a period of 4.5 years.

If the study determines that valproate is beneficial and cost-effective, our findings may help promote the widespread use of valproate for TRS patients. This may, in turn, improve long-term outcomes in TR and there will be the potential to improve outcomes and reduce healthcare costs for many patients with resistant schizophrenia who don't want to or are not suitable to use clozapine. Just as importantly, if we show that valproate is not better than placebo, then it will be possible to avoid ineffective treatment with valproate which could save the NHS ~£60 million/year.

4 Trial Objectives and Design

4.1. Trial Objectives

The main aim of the study is to assess the efficacy and cost-effectiveness of valproate when used to augment antipsychotic treatment in patients with schizophrenia or schizoaffective disorder whose illness has shown an inadequate response to non-clozapine antipsychotics.

Objectives:

a) To determine whether adding valproate to treatment significantly reduces psychotic symptom severity relative to placebo in schizophrenia or schizoaffective disorder patients whose illness is resistant to first-line antipsychotic medication.
b) Ascertain the cost-effectiveness of adding valproate to treatment of antipsychotic medication for the management of resistant symptoms.
c) Determine the long-term outcomes of the intervention.

4.1.1 Primary outcome

- Superiority of valproate compared to placebo on the Positive and Negative Syndrome Scale (PANSS) positive subscale at the 12-month visit [4].

The primary outcome is the positive subscale of the PANSS, which measures psychotic symptom severity. The PANSS is a clinician-rated scale that assesses psychotic (positive), negative and general symptom severity in schizophrenia. The PANSS psychotic (positive) rating at the end of the double-blind study (12 months) will serve as the main outcome measure [4]. The positive scale has seven items covering psychotic symptoms (delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspiciousness/persecution and hostility), each rated from 1 (absent) to 7 (very severe). The scale's reliability, criterion-related validity, and construct validity have been well documented [29].

4.1.2 Secondary outcomes

The main secondary outcome will be PANSS positive score difference at 3 months.

Other secondary outcome measures include:

- PANSS positive score at 6 months
- Total symptoms measured using the PANSS at 3, 6 and 12 months.
- Change in PANSS Factor scores from baseline derived from the PANSS scores at 3, 6 and 12 months, an approach used for minimizing pseudospecificity of treatment effects [30].
- Change in Clinical Global Impression scale (Schizophrenia version). This is a brief, stand-alone assessment of a clinician's overall view of the severity of the patient's illness that is designed to identify a clinically significant change prior to and after initiating a medication. It will be carried out at baseline, 3, 6 & 12-month follow-up visits [31].
- Aggression levels will be measured using the Modified Overt Aggression Scale (a brief four category scale to measure aggression in clinical settings. It will be carried out at baseline, 3, 6 & 12-month follow-up visits [32].
- Depression will be measured using the Calgary depression scale for schizophrenia (CDSS) at baseline, 3, 6 & 12-month follow-up visits [33].
- Young's Mania rating scale (YMRS) will be measured at baseline, 3, 6 & 12-month follow-up visits [34]. YMRS is one of the most frequently utilized rating scales to assess manic symptoms.
- Body mass index will be determined at the 3, 6 & 12-month follow-up visits as valproate has the potential for inducing weight gain.
- Patient reported outcomes will be evaluated using the Short Warwick-Edinburgh Well-being scale (SWEMWBS). It will be measured at the 3, 6-month and 1-year time points [35].

- Cost effectiveness will be assessed using measures collected at baseline, 3, 6 & 12-month follow-up visits: the Client Service Receipt Inventory (CSRI) [36], PANSS and the 36-item short form health survey (SF-36)[37]. Adverse effects will be assessed at baseline, 3, 6 & 12-month follow-up visits. We will use the UKU side effect rating scale, a clinician observed rating scale for psychotropic drugs [38]. The Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale evaluates 48 symptoms in 4 categories; psychic, autonomic, neurologic, and other. Using a combination of interview and physical examination, clinicians will assess the magnitude of symptoms, perceived causality and degree of disability.
- The discontinuation of the intervention will be measured at the 3, 6-month and 1-year time points. We will also record the cause of discontinuation under the following categories: (i) lack of efficacy, (ii) adverse effects, (iii) switch to another antipsychotic (including clozapine), (v) lost to follow-up or (vi) personal reasons.
- We will evaluate on an annual basis the long-term symptomatic and functional outcomes beyond the 12-month period primarily using the HoNOS (Health of the Nation Outcome Scales) and service use (admission/crisis/home treatment/other service use) to determine outcomes after patients have finished the trial. HoNOS is a global clinical outcomes tool that is routinely collected across all mental health services in the NHS and can be accessed electronically [39].
- Number starting clozapine treatment

4.2 Trial Design

This multi-site study will use a two-arm, randomized, double blinded, placebo-controlled trial using an intention to treat analysis (ITT). Patients with a diagnosis of schizophrenia or schizoaffective disorder on an antipsychotic (non-clozapine) for at least 6 weeks, continuing to have positive psychotic symptoms, will be randomised 1:1 to either placebo + continuing antipsychotic treatment arm or valproate + continuing antipsychotic treatment arm (**Flow diagram**). Randomisation will be stratified by sex, diagnostic category (schizophrenia or schizoaffective) and site and both in-patient as well as outpatients will be eligible to participate.

Patients must be on one or more non-clozapine oral antipsychotic for at least 6 weeks and should be on a stable dose for at least 2 weeks preceding the screening visit. In case of depot the dose must be stable for at least 2 treatment cycles or at least 30 days (whichever is longer) prior to the screening visit. During the trial, clinicians will also be able to adjust the antipsychotic dose, change formulation, change antipsychotics or even add if needed as this is a pragmatic trial. The addition or change of antipsychotic to clozapine will however be considered as discontinuation of the intervention and patients will be withdrawn from the study medication after down titrating their treatment. All subjects will receive follow-up assessments, including those who discontinue the study medication.

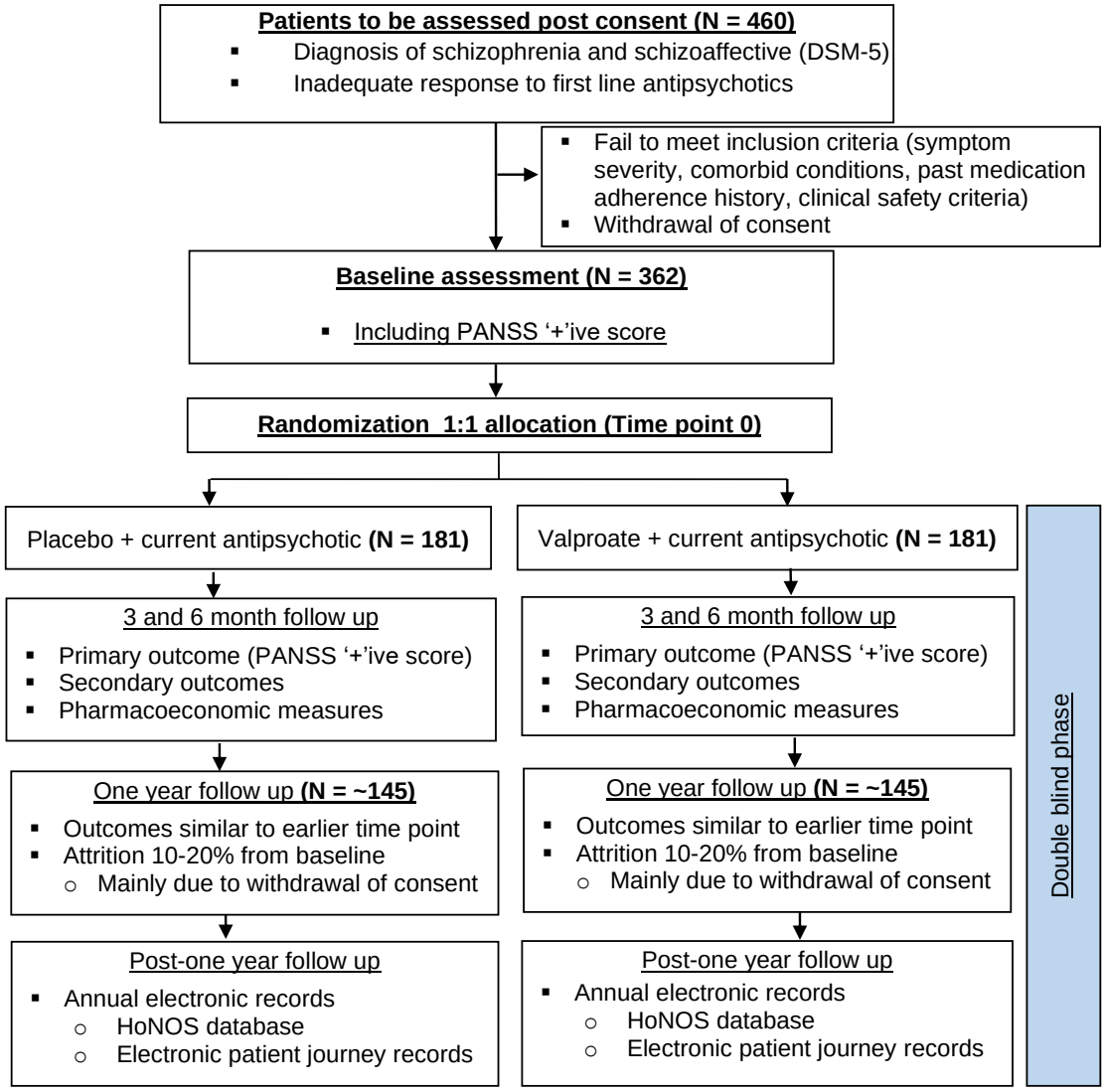
The trial will include a titration phase for the study medication lasting for approximately 2 weeks followed by a maintenance phase for the remaining 50 weeks of the study. At the end of the 52-week treatment period, subjects will be down titrated over 2 weeks. Outcomes will be measured at 3, 6 and 12 months using standard rating scales and after patients have finished the medication phase, follow up study indices will be obtained using electronic health records till the end of the study.

Valproate will be started at 500mg/day and titrated up to a dose of approximately 15 – 30 mg/kg/day (in steps of 500 mg/day), in line with evidence that this dose range is effective and corresponds to the dose range used in clinical practice [18, 23]. The initial titration will occur over approximately two weeks (Refer to Appendix 1). The placebo group will receive a matching placebo titration. To ensure that the treatment is optimised for each patient, and to promote retention in the trial, further dose increments and decrements of valproate will be allowed in both arms at the treating clinician's discretion up to a maximum of 2500mg/day. The side effects will be evaluated by the UKU Side Effect Rating Scale while deciding dose titration or modification.

The primary outcome measure will be change in the PANSS positive subscale at 12 months. Secondary measures as well as pharmacoeconomic measures will be collected at various time-points described later in the trial flow chart section. The study will be conducted over a period of approximately 5 years. If patients consent, then we will also involve their caregivers as part of the study. They will be provided with information about the study and we will involve them in improving study compliance and some of them will be part of the service user and career group that will be set up at each site to advise us on implementation and feedback.

The trial management group (TMG) chaired by the PI will include the co-PIs and KCL clinical trial unit (KCTU) and the King's Health Partners-clinical trials office (KHP-CTO) representatives. Consultants, study staff members and other collaborators will be included as required. The TMG will meet on a bimonthly basis and report to the trial steering committee (TSC). A training and reliability programme under the stewardship of Prof. Barnes will be instituted so that research staff will be consistent in their approach across various sites.

Flow Diagram



Attrition rate of 30% at the randomization step and 20% from allocation based on two similar augmentation studies – Morrison et al, Lancet Psychiatry, 2018. Vol 5:p663 and Cipriani et al, J Clin Psychopharmacology, 2013. Vol 33(4):p533.

DSM-5 - Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (Standard manual for psychiatric diagnosis); PANSS - Positive and Negative Syndrome Scale (Clinical scale for evaluating severity of schizophrenia); HoNOS - Health of the Nation Outcome Scales (a measure of the health and social functioning in psychiatric patients captured yearly by mental health care teams)

4.3 Trial Flowchart

The study will consist of three periods. Screening, a treatment period and a long-term follow-up period. The schematic of the first two periods are shown in Figure 1. The Trial Schedule (Table 1) at the end of this section gives a snap shot of all clinical assessments that will be performed.

Figure 1: Study Schematic

Study visit V3, can take place + / - 3 days from the specified week while study visits V4, V5 and V6 can take place within +/- 2 weeks of the specified week. The same apply to the respective dispensing visits. At the end of the 12-month period, down-titration will take place over approximately two weeks depending on the maintenance dose in steps of 500mg in 3-4 day intervals. V7 is the follow up visit after valproate/placebo has been completely stopped and can take place within one week after the last consumed study drug. Assessments will be conducted as closely as possible to the timeframe mentioned however if a major variation arises, it will be factored in the analysis. A single follow up via telephone or face-to-face, 60 days since their last study drug intake will also be conducted to record for any AEs/SAEs

Screening period (approximately – 8 to 0 weeks)

Clinical teams will first alert suitable patients to the study. If the patients are interested in being contacted by the research team, then the research team will get in touch with them. If patients have already given consent to be contacted for research (for example through a consent-to-consent procedure), then the study team will make contact directly and if the patient consents then the patient's clinical care provider will be informed of their participation. Patients will also be allowed to contact the study team via adverts displayed in waiting rooms, and relevant media (e.g. patient newsletters). When contacted or if the study team has permission to contact the patient then a member from the study team will have a face to face conversation or via the telephone to give the patient more details about the study. If the patient is interested in participating in the study, they will then be invited for consenting and screening where

further details of the study will be discussed and the informed consent form (ICF) of the study will be presented.

Informed consent will be obtained from each subject before any study procedures are performed. Demographics (date of birth, sex, ethnicity, race), prior and current medications, and medical and psychiatric history will be collected. If the subject's historical medical care was provided at another institution or location, the subject's consent will be sought to obtain these outside records where necessary to verify that the subject meets all inclusion and none of the exclusion criteria.

A primary psychiatric diagnosis of schizophrenia or schizoaffective according to DSM-5 must be met. A structured clinical interview for DSM-5 (SCID-5) will be used for the purpose of making a diagnosis. Clinicians administering the SCID should be familiar with the DSM-5 classification and diagnostic criteria and should have the appropriate training. It takes approximately 30 minutes to complete it. The severity of psychopathology will be measured using the Positive and Negative Syndrome Scale (PANSS). A total PANSS score of greater than 70 plus one or more psychotic item rating of moderate or greater severity must be met. Clinicians administering PANSS should be familiar with the scale and it takes 30 minutes to administer it. Subjects must be on at least one antipsychotic at a dose above the minimum therapeutic dose in the approved dose range in the label for a minimum of 6 weeks at the time of screening. Any change to dose must occur 2 weeks prior to screening. The dose and formulation of the antipsychotic can change during the trial. Also switching to a non-clozapine antipsychotic will be allowed. If more than one non-clozapine antipsychotic is needed, then it will be permitted. However, switching to clozapine will result in the patient being discontinued from the study medication.

Subjects should also meet other inclusion and none of the exclusion criteria necessary for the study and, if needed, a blood screen for liver function and full blood cell count will be carried out. Pregnant or breast-feeding women, women of child-bearing potential who do not agree to the contraceptive methods needed for participating in the trial will be excluded. Women of child-bearing potential must meet the MHRA pregnancy prevention programme and agree to an annual risk acknowledgement plan for pregnancy prevention. A pregnancy test must be negative for all women of childbearing potential to participate in the trial. Also, patients who pose immediate or significant risk for suicide will be excluded.

The screening must occur prior to randomization to the study and the study medication will not start within 24 hours of written consent. If the screening could not be completed within 8 weeks from the day of the signed consent, then inclusion criteria will be reassessed by the investigator and clinical tests will be redone if judged necessary by the research team. The eight-week period will then again apply for the reassessment and it will be the final attempt to include the subject under the consent that was obtained. Assessments at the screening stage are described in the Trial Schedule (Table 1).

Treatment period (Week 0 - 52 followed by discontinuation period)

At Visit 2 (Day 1), subjects who continue to meet the study inclusion criteria and none of the exclusion criteria will be randomized to either the placebo or valproate arm. All assessments at baseline (Visit V2) will be done prior to dosing. The study drug will be titrated starting with a dose of 500mg/day to reach a dose between approximately 15mg/kg/day to 30mg/kg/day but not exceeding a total dose of 2500mg per day. Subjects will be asked to take study drug in increments of 500mg (with a minimum interval of 3 days) as illustrated in Appendix 1 over approximately 2 weeks according to their body weight. The placebo arm will also follow the same pattern. An oral gastro-resistant tablet of valproate will be used for the study and the dose may be divided twice daily where multiple tablets are taken. A pragmatic dose escalation or reduction of valproate (in steps of 500mg/day) is permitted in this period based on tolerance to the study medication guided by the UKU side effect scale. Halfway through the titration period (1 week +/- 3 days), the study team will contact the subject to review the titration of the study medication and monitor for any side or adverse effects via a face-to-face (especially in case of in-patients) or telephonic conversation. At the end of two weeks (Visit V3), subjects will continue to receive the dose that they can tolerate for the remainder (50 weeks) of the study. The dose of valproate can be varied in the remainder period, if needed, at the investigator's discretion. If the dose is either increased or decreased after V3, a face-to-face or telephonic conversation will be conducted with the subject between 3 to 7 days after the change of dose to check they have completed the dose titration and assess tolerability.

Clinical assessments will be performed as described in the Trial Schedule (Table 1). Blood samples for determination of liver functioning and full blood counts will be assessed at the 3-month time point (Visit 4) and at the 12-month time point (Visit 6). If a subject were to exit early, then these tests will be conducted at exit. Blood samples for post-hoc analysis of epigenetic changes and drug levels will be collected at V2 prior to the start of medication and then at the end at V6. The rationale for this is that valproate may cause epigenetic changes [40] and we will measure these changes in DNA collected from peripheral blood cells in co-relation to the subject's exposure to valproate and determine if this is linked to clinical response. These samples may not be collected if a site does not have facilities to take or store them.

At the end of the study (Visit 6, 52 weeks), the study medication will be reduced in steps of 500mg, each step over 3-4 days, lasting up to two weeks depending on the maintenance dose of the subject. The study team will organize a follow up visit (V7, 54 weeks) after the trial drug is completely stopped. Results of blood tests (LFT and TBC) done at V6 will also be conveyed to participants and their clinical care team.

In case of early discontinuation from the study medication, the same dose reduction strategy will be followed (unless a more rapid reduction is required for clinical reasons). An exit interview will be conducted (including cases who complete the 12-month

treatment) to assess blinding, experience of participation, and reasons for early termination if applicable. Clinical assessments as described in the Trial Schedule will also be performed (Table 1).

Long-term follow up (approximately annually after 54 weeks till the end of trial)

Patients will be followed up to determine long-term outcomes annually during the course of the study. Consent for this will be sought at the beginning. The main aim is to assess the long-term clinical outcome afforded by the exposure to valproate and the rate of switch to clozapine between the two arms in the follow-up period. We will extract data that are routinely collected by the clinical teams and recorded in clinical notes electronically. The main outcome will be the HoNOS rating. We will also collect data on other important clinical outcomes including the number of hospitalisations, home treatment episodes, and whether they have started valproate or clozapine.

End of trial

Visit 7 of the last patient recruited for the study (including the 60 day follow-up period to assess AE/SAEs after the last day of medication) will end the trial and hence the long-term follow up will be done up to this period for the entire trial. Hence patients who entered the trial earlier will have longer follow up data compared to ones that enter later.

Table 1: Trial Schedule

Study Visit	V1	V2	V3	V4	V5		V6	V7[%]	Post 1-year[%]	Early exit
Study week/month/year	**Screening**	**Baseline[$]**	**2-week**	**3-month**	**6-month**	**9-month**	**12-month**	**Follow up**	**Annually**	
Drug Dispensing session		**DS1**	**DS2**	**DS3**	**DS4**	**DS5**	**DS6**			
Obtain informed consent	x									
Review inclusion/exclusion criteria	x	x[1]								
Demography	x									
Prior/concomitant medication review	x	x[1]	x[4]	x[4]	x[4]	x[4]	x[4]			x
Medical history	x		x[4]	x[4]	x[4]	x[4]	x[4]			x
Medication adherence rating scale (for antipsychotic medication)	x	x	x	x	x	x	x	x		x
Serum Pregnancy test (women)	x				x[2]					
Signed, valid pregnancy risk acknowledgement form as part of the MHRA pregnancy prevention programme		x[2]			x[2]					
Psychiatric history	x						x		x	x
HoNOS	x[&]						x		x*	x
Frailty assessment	x									
SCID-5(Research)	x									
Vital signs	x	x[1]	x	x	x		x	x		x
Height, Weight &BMI	x	x[1]		x	x		x			x
Liver function test	x[£]			x			x			x
Full blood cell count	x[£]			x			x			x
Blood samples (for epigenetic and other analysis)	x	x[5]		x			x			x

…continued

Study Visit	**V1**	**V2**	**V3**	**V4**	**V5**		**V6**	**V7[%]**	**Post 1-year[%]**	**Early exit**
Study week/month/year	**Screening**	**Baseline[$]**	**2-week**	**3-month**	**6-month**	**9-month**	**12-month**	**Follow up**	**Annually**	
Dispensing session		**DS1**	**DS2**	**DS3**	**DS4**	**DS5**	**DS6**			
Urine pregnancy test	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]		
Dispense IMP		x	x	x	x	x	x**			
IMP accountability (pill count)			x	x	x	x	x	x		
PANSS	x	x[1]		x	x		x	x		x
CGI		x		x	x		x			x
YMRS		x		x	x		x			x
C-SSRS		x		x	x		x			x
MOAS		x		x	x		x			x
SWEMWBS		x		x	x		x			x
SF-36		x		x	x		x			x
CSRI		x		x	x		x			x
UKU[#]		x		x	x		x	x		x
Exit interview							x			x

1 – repeated at baseline visit to ensure inclusion/exclusion criteria is met or is a required safety requirement. Please note that inclusion/exclusion criteria should be met throughout the treatment period with the exception of PANSS score which can vary in response to treatment.

2 – the annual pregnancy risk assessment form should be checked for completion at baseline. It is valid for one year from the date of signature by the subject and hence it may need repetition during the course of the clinical trial and hence at V5 make sure it is valid till the end of their medication phase

3 – Optional at clinician discretion (e.g. if there is a gap or change in contraception)

4- Assess changes from baseline that require clinical review (e.g. new onset liver disease, new prescription)

5-To collect a sample if not already collected at screening

[&]Check if subjects have a HoNOS file, if not create one in co-ordination with their clinical team. * HoNOS will be collected on an annual basis till end of trial

** Only if needed to complete the down titration.

£ To be performed at the discretion of the clinician based on clinical history and medical assessment.

Unscheduled UKU should be administered if a subject develops a side-effect requiring treatment.

$ All assessments at baseline (V2) must be performed pre-dose. Also, a minimum of 24 hours between signing of ICF and dosing will be given for subjects to reflect on their participation.

[%] V7 to be scheduled within 1 week after stopping study medication & includes a single follow up via telephone or face-to-face 60 days since their last study drug intake to record for any AEs/SAEs. Most will be further followed up using electronic notes. The last patient who completes V7 (including the 60 day AE/SAE assessment) will result in the end of the trial.

5 Trial Medication

5.1 Investigational Medicinal Product

Investigational Medicinal Product (IMP) – active drug

The Investigational Medicinal Product used in this trial is a gastro-resistant 500mg sodium valproate tablet. A list of excipients can be found in the Summary of Product Characteristics (SmPC) for Sodium Valproate Wockhardt 500mg Gastro-Resistant Tablets, revised on 19/12/2018.

Valproate and its valproic acid, sodium valproate, and valproate semisodium forms, are medications primarily used to treat epilepsy and bipolar disorder and to prevent migraine headaches. There is long history of its use in human subjects however it is unclear exactly how valproate works. Proposed mechanisms include affecting GABA levels, blocking voltage-gated sodium channels, and inhibiting histone deacetylases [41]. Its use in schizophrenia is off-licence [18]. Sodium valproate is the salt form used by most existing trials in the meta-analysis. It is also the form mostly commonly used in clinical practice in the UK, which is why we have chosen to use this form.

Investigational Medicinal Product (IMP) - placebo

To maintain blinding, high quality placebo tablets will be used to provide a complete match with regards to the appearance (e.g. dimensions, colour) of the sodium valproate 500mg tablets being used. The excipients of the placebo will be documented in the simplified investigational medicinal product dossier (sIMPD).

Procurement, manufacture, packaging and distribution of the trial medication has been contracted to Guys and St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit (GPMU). GPMU will arrange the sourcing and purchase of commercially available sodium valproate tablets, placebo manufacture, randomised double-blind IMP packaging, final qualified person (QP) release and storage and distribution of the investigational medicinal products (IMPs).

All active and placebo tablets will be packed in labelled high-density polyethylene (HDPE) bottles with a child-security lid. Each treatment pack will contain 140 tablets and will have a unique treatment pack number.

The Kings Clinical Trials Unit (KCTU) Intervention Management System will be used to allocate blinded supplies to patients. The KCTU trials pharmacist will be unblinded and will have access to the KCTU Intervention Management System to maintain IMP stock levels, both centrally and at investigational sites. This individual will be responsible for placing orders for trial medication for study sites.

Refer to the SmPC and the Simplified Investigational Medicinal Product Dossier (sIMPD) for more details about the active and placebo IMPs.

5.2 Dosing Regimen

The two treatment arms for the trial will be sodium valproate or placebo. The IMP will be started at a dose of 500mg/day and gradually increased to a dose not exceeding 2500 mg/day over two weeks in steps of 500mg depending on body weight over a two week period (Refer to Appendix 1- Dose titration).The placebo group will receive a matching placebo titration. To ensure treatment is optimised for each patient, and to promote retention in the trial, further dose increments/decrements will be allowed in both arms at the treating clinician's discretion depending on side-effects and response and up to a maximum of 30mg/kg/day such that the dose does not exceed 2500mg/day. At the end of the 52-week treatment period, the dose of valproate will be down titrated in steps of 500mg in 3-4-day intervals by patients. The down-titration will also be done when patients exit the trial early. There are no special dietary or life-style requirements that are needed to be adhered to, but patients will be advised that alcohol intake is not recommended during treatment with valproate.

Withdrawal effects have not been reported. Nevertheless, at the end of the study or in the event of a patient wishing to discontinue valproate, the drug will be down titrated over at least two weeks to reduce the risk of a relapse.

5.3 IMP Risks

The Summary of Product Characteristics (SmPC) for 500 mg Gastro-resistant tablets (Sodium Valproate Wockhardt 500mg Gastro-Resistant Tablets, SmPC revised on 19/12/2018) will be the reference document.

<u>Teratogenic risk</u>

There is a potential risk to unborn children associated with valproate treatment. This risk will be minimised in the following ways:

1) Women of childbearing potential will be supported on the Pregnancy Prevention Programme as outlined by the Medicines and Healthcare products Regulatory Agency MHRA [42]. This ensures that they are aware of the potential risks and ensure that they use a highly effective method of contraception that meets the MHRA guidelines. A serum pregnancy test is also conducted as part of the programme. An annual risk acknowledgment form is also needed as part of the programme. The patient's clinical care team and the research team will monitor compliance to the programme. Neither condoms nor oral contraceptives alone are sufficient. Long-term contraceptives (such as copper intrauterine device [IUD] or levonorgestrel intrauterine system and contraceptive implant [progestogen-only implant], or sterilisation) are recommended and patients will be supported to access these if they wish to consider them and are not

already receiving them. If subjects do not meet the pregnancy prevention programme within the screening period after consenting to the study then they will be considered as screen failed and will be rescreened once the requirements are met.

2) An optional urine pregnancy test based on individual patient's risk assessment and circumstances during the trial (e.g. if there is a gap or change in contraception) will be offered.

Abnormal blood cell counts and liver function

There is a potential, rare risk for bleeding, thrombocytopenia, leucopenia and hepatic failure due to valproate. To reduce this potential risk, we will screen-out and exclude people who may be vulnerable to this by reviewing their clinical history and conducting full blood count and liver function tests (LFTs), if indicated, prior to enrolling patients in the study. We will also monitor both tests at 3, and 12 months after initiation of trial drug or if patient exits the trial early.

Other side effects

The use of medications to manage antipsychotic side-effects (e.g. anticholinergics) will be permitted at the clinician's discretion. Patients will be advised that somnolence is a common side effect of valproate that they need to be aware of it. Where this is troubling, dose timing (e.g., scheduled to coincide with bedtime) can be adjusted to minimise these effects. Weight gain is another side effect seen with this drug and BMI will be monitored during the trial. Treating clinicians will be advised to address weight gain using treatment as usual if it occurs.

Overdose

In the unlikely event of an overdose of study drug, guidance in the SmPC for treating excessive ingestion will be followed. These are based on blood levels and hence they will be determined at an A&E centre prior to consequential treatment course.

Cases of accidental and deliberate sodium valproate overdose have been reported. At plasma concentrations of up to 5 – 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. Most patients recover, however, some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral oedema

have been reported. The presence of sodium content in the drug formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 – 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

To reduce the possibility of overdose occurring, we will exclude patients who have active suicidal ideation, as measured by the Columbia Suicide Severity scale, and monitor this throughout the trial.

5.4 Drug Accountability

The pharmacy clinical trials team must maintain accurate accountability records of the IMP, including, but not limited to, the number of bottles/tablets received, the number of bottles/tablets and bottle numbers dispensed to each patient, batch number, expiry date, and the date of the transaction in addition to the quantity of investigational product returned by each patient.

Patients will be asked to return any unused IMP and/or empty packaging at each study visit and at the end of the active study period. The study drug returns will be returned to pharmacy by the research team for accountability. The returns will be verified by the pharmacy clinical trials team and the clinical research associate prior to disposal at site. Destruction of IMP must be in accordance with the site IMP destruction Standard Operating Procedure (SOP).

The pharmacy clinical trials team are required to maintain copies of study drug shipping receipts and drug accountability records in accordance with regulatory requirements.

5.5 Storage of IMP

Sodium Valproate is hygroscopic. Container packs must be stored in a dry place below 25°C. The tablets should not be removed from their pack until immediately before they are taken. Instructions to close the container immediately after each use will be conveyed to patients and displayed on labels.

The investigator or designee is responsible for storing the drug in a secure location, which should always be maintained under the strict control of qualified staff.

5.6 Subject Compliance.

Adherence to the antipsychotic medication will be monitored using the medication adherence rating scale [43]. The patient will be asked to respond to the statements in

the questionnaire by circling the answer which best describes their behaviour or attitude towards their medication during the past week. A rating of at least >4 to their antipsychotic medication will be necessary for the participant to participate in the trial. If compliance to their antipsychotic and/or study medication drops below 4 on the medication adherence rating scale the subject will be counselled, and steps taken to improve compliance will be taken up (e.g. offering reminders or seeking carer's help).

Patients will receive dosing instructions about valproate in a patient diary and be instructed to bring all tablet bottles (opened and unopened) to each study visit for assessment of compliance (based on the tablets remaining in the bottles).

Compliance will be documented on the source record by the research assistant. If compliance is ≤ 80% of the correct dosage as prescribed, the investigator or designee must counsel the patient and ensure steps are taken to improve compliance.

If a patient appears to be taking more tablets than prescribed and the dose taken is greater than 30mg/kg/day or 2500mg/day it will be reported to the trial steering committee.

5.7 Concomitant Medication

Subjects must be on a non-clozapine oral antipsychotic treatment for at least 6 weeks, that is dosed in accordance with its Marketing Authorisation (MA) and The Maudsley Prescribing Guidelines in Psychiatry, and at a stable dose for a minimum of 2 weeks at the time of screening. Depot neuroleptic dose must be stable for at least 2 treatment cycles or at least 30 days (whichever is longer) prior to the screening visit. Subjects who require an increase in dose of their background antipsychotic medication during the study will be permitted. As this is a pragmatic trial changes to antipsychotic dose and formulation will be permitted. Also, a switch to non-clozapine antipsychotic or addition of non-clozapine antipsychotics to the treatment regimen will be permitted. However, switch to a clozapine will lead to discontinuation of the study medication.

The following information will be recorded on the case report form (CRF) for all medication administered between screening and the end of study or at discontinuation Medication name, dose, frequency, route, start date, stop date and indication. Prior treatment with antipsychotic agents including depot neuroleptics will be recorded for at least 3 months prior to screening. Subjects who require treatment with a prohibited concomitant medication in the middle of the trial will be weaned off the study medication but we will continue to monitor their outcomes (based on the SmPC of both the antipsychotic as well as sodium valproate drugs).

Clinicians will be reminded of the potential adverse interactions, as mentioned in the SmPC for sodium valproate while prescribing other medications. Benzodiazepines and anticholinergic medication will be allowed along both arms during the screening and

after enrolment. Clinical teams will not be restricted in prescribing other medications but details of use (irrespective of the randomized arm) and follow-up will be recorded. A secondary /sensitivity analysis will be carried out to determine if this differs between treatment groups.

The date and time of the last dose taken prior to scheduled efficacy assessments must be recorded at each visit. Subjects should be encouraged to avoid taking sedative/hypnotic medications within 8 hours of scheduled efficacy assessments.

Use of non-prescription pain medications (e.g., paracetamol) and other OTC drugs (e.g., to treat seasonal allergies) are allowed during all phases of the study provided these medications do not have a propensity for psychotropic effects and do not interfere with the evaluation of study drug or are contraindicated in the SmPC of the IMP or their antipsychotic drugs.

6 Selection and Withdrawal of Subjects

6.1 Inclusion Criteria

To qualify for participation, subjects must meet all of the following inclusion criteria at screening

1. Subject must be aged 18 and above at the time of consent
2. Subject must have adequate command of English to understand the information leaflet
3. Subject must have capacity to consent to participation in the study
4. Confirmation of DSM-5 diagnosis of schizophrenia or schizoaffective disorder using SCID-5
5. Subject must have a PANSS total symptom severity score >70
6. Subject must have at least one PANSS psychotic item rating of at least moderate severity (>3 on one or more psychotic item rating in PANSS)
7. Subject must have received treatment with at least one non-clozapine antipsychotic drug at adequate dose (as defined by Maudsley guidelines[9])for a duration of at least 6 weeks and in case of a depot be stable for at least 2 treatment cycles or at least 30 days
8. Subject must be on a stable dose of antipsychotic treatment for at least 2 weeks in case of oral dosage forms
9. Subject must have good adherence to antipsychotic treatments as determined by a score >4 (ideally >6) on the Medication Adherence rating scale [43]
10. Female subject of child bearing potential must agree to the MHRA pregnancy prevention programme which includes a negative serum pregnancy test, use of a highly effective form of birth control and signing an annual risk acknowledgement form (refer to section 9.1 – pregnancy prevention and contraception) [42]

6.2 Exclusion Criteria

All participants:

1. Subject aged < 18 years
2. Subject having a rating of 4 or above on the clinical frailty scale [44]
3. Female subject who is pregnant or breast-feeding
4. Subject with a known history of urea cyclic disorder
5. Subject with a known history of porphyria
6. Subject with a known history of severe renal insufficiency
7. Subject with a known history of a mitochondrial disorder and in the opinion of the recruiting physician will impair the safety of the subject and/or the scientific integrity of the study.
8. Subject with carnitine palmitoyltransferase (CPT) type II deficiency
9. Subject currently taking clozapine
10. Subject currently taking valproate.
11. Subject who had stopped taking valproate in the past six weeks prior to screening due to adverse effects
12. Any recent change (<2 weeks) change in antipsychotic regimen
13. Subject answers “yes” to “Suicide Ideation” Items 4 (active suicide ideation) with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSR during the screening visit
14. Subject has attempted suicide within 3 months prior to screening
15. Subject having a known allergy to valproate or other ingredients in the tablet or placebo
16. Significant sustained abnormality when vital signs are measured at screening
17. Patients with a personal or family history of significant liver disease (e.g. severe hepatic dysfunction, cirrhosis)
18. Any other medical condition in the opinion of the recruiting physician that will impair the safety of the subject and/or the scientific integrity of the study.
19. Participation in a clinical trial within 90 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
20. Taking a drug that may have a clinically significant effect on the metabolism of valproate or where valproate may have a clinically significant effect on its metabolism including oxcarbazepine, lamotrigine, phenobarbital, primidone, phenytoin, ethosuximide, rufinamide, phenytoin, carbapenem antibiotics, topiramate, acetazolamide, warfarin and other coumarin anticoagulants and in the opinion of the recruiting physician will impair the safety of the subject and/or the scientific integrity of the study..
21. Any other condition contraindicated in the Summary of Product Characteristics (SmPC) of the study medication.

6.3 Selection of Participants

The study will recruit participants from multi-centre UK inpatient & outpatient mental health services. The recruitment sites will be grouped into hubs, with a PI leading recruitment across the Trusts/boards within each hub. Participant Identification centres around these hubs will further aid in recruitment.
The hubs are as follows:

- South London hub: South London & Maudsley Mental Healthcare NHS trust
- North London hub- West London Mental Healthcare NHS trust
- Cambridge hub- Cambridgeshire and Peterborough NHS trust
- Manchester hub – Manchester Mental health & Social care NHS trust
- Edinburgh hub– Royal Edinburgh Hospital

Additional sites may be added as needed and sites in Wales or Northern Ireland may be added if recruitment were to fall short of targets.

6.4 Randomisation Procedure / Code Break

6.4.1 Randomisation

Randomisation will be undertaken by the local research team at each site once written informed consent has been obtained, eligibility confirmed, and baseline data collected.
Randomisation will be stratified by diagnosis, site and sex and a permuted block randomization will be used for each stratum.

Randomisation will be performed via a bespoke web-based randomisation system hosted by the KCTU. This system can be accessed 24 hours a day. Authorised site staff will be allocated a username and password for the system by the Trial Manager. Authorised staff will log in and enter key information about the patient, including the unique Patient Identification Number (PIN). Once a patient is randomised, confirmation emails will be generated automatically, and appropriate information will be sent to relevant personnel.

The unique treatment pack numbers, batch numbers, expiry dates and last dispense dates for the study drugs will be uploaded into the KCTU Randomisation and Intervention Management System. The system will record the packs delivered to specific site pharmacies and will only allocate treatment packs that are available at that site to participants that are randomised there.

The investigator, research team, pharmacy and the trial manager will be kept blind to treatment allocation.

The system is also programmed to generate a schedule of each participants visit timeline for the entire study, to be sent within the randomisation email. A standard

feature is the ability to download automatically generated recruitment graphs of overall recruitment against target recruitment. The system is tested before the study begins. The system is also programmed to perform validation checks, such as checking for duplicate Participant Identification Numbers and preventing randomisation from proceeding in such cases.

Data will be exported upon request and passed to the trial statistician. Data may be exported in blinded, subgroup blinded, or unblinded formats.

6.4.2 Emergency Code Break

Emergency unblinding of the treatment may be considered necessary when the knowledge of the treatment a patient is or was receiving is essential for further medical care of the patient. This may be because of a serious adverse event arises that clinically requires disclosure, overdose of the trial drug or a clinical need to start the patient on medication which has a risk of interaction.

For the ATLANTIS trial, a 24hr Emergency Code Break and Medical Information will be provided by ESMS Global Ltd. Each randomised patient will be provided with a patient card detailing emergency contact details. Patients will be requested to carry this card with them at all times whilst participating in the trial.

6.5 Withdrawal of Subjects

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAE's, SUSAR's, protocol violations, cure, administrative reasons or other reasons. SAE's and SUSAR's will be followed up until resolution and outcomes will be recorded for the DMEC and TSC to review. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. In the event of hospitalization of patients unrelated to the study drug, patients will be reviewed for their continuation in the study and, if needed, will be recommended for a drug holiday as described in the next paragraph. Should a patient decide to withdraw from the study, the reason for withdrawal will be recorded in the exit interview if they provide us with one. Should a patient discontinue from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

Poor compliance (no minimum threshold) will not merit withdrawal but will be recorded and follow-up data will be continued to be obtained. Study drug holiday is permissible in case of an emergency, or for elective surgery or medical procedures. The process for the drug holiday is that when subjects will undergo a down titration till IMP is completely stopped as described in Section 4.3 and will then be up titrated when they re-join the

study. In such cases their assessments will be delayed depending on the study drug holiday period.

6.6 Expected Duration of Trial.

The total duration of the trial is expected to be 5 years. The end of the trial will be defined as last patient to complete visit 7 (V7), including the 60-day follow-up period to assess AE/SAEs after the last day of medication. Each individual subject will remain on the active trial for 12 months, +/- two weeks for the discontinuation of the treatment at the end. Long-term annual follow-up using clinical and electronic records will be conducted up to the point where the last patient completes Visit 7 for the entire trial.

7 Trial Procedures

7.1 By Visit

ATLANTIS study visits

Visit 1: Face-to-face consenting and screening visit (approximately -8 to 0 weeks)

Following a telephonic or face-to-face conversation and provision of information on the study, subjects will be invited for consenting and screening. A unique screening number will be assigned to each subject.
Subjects will be evaluated during the face-to-face screening visit to determine their eligibility to enrol in the study after obtaining their consent.

The following procedures will be performed at Screening:

- Explain study procedures
- Obtain signed informed consent, capacity assessment and privacy authorization from the subject before conducting any other visit procedures
- Collect demographic information
- Review inclusion and exclusion criteria (conduct clinical interview using SCID-5 and PANSS)
- Conduct frailty assessment if needed
- Record medical and psychiatric history
- Record current and past medication use
- Conduct Medication Adherence Rating Scale (for antipsychotic medication)
- Conduct Risk assessment using the Columbia Suicide Severity Rating scale
- Record vital signs (blood pressure/pulse rate)
- Record height and weight

- Collect blood sample for clinical laboratory assessments (full blood count, liver function test if needed based on medical history)
- For female subjects, collect serum/ urine samples for pregnancy tests
- For female subjects of childbearing potential, review their current choice of contraception
- Complete the pregnancy annual risk Acknowledgement form for female subjects of childbearing potential if not completed yet (if serum pregnancy test needs to be done then conduct one)
- Collect blood samples for pharmacogenomics, epigenetics, antipsychotic drug levels

Visit 2 & DS1: Day 1: Baseline measures and Valproate titration begins (week 0)

- Review inclusion and exclusion criteria
- Review recent medical and medication history for changes since screening visit
- Conduct Medication Adherence Rating Scale (for antipsychotic medication)
- Risk assessment using the Columbia Suicide Severity Rating scale (baseline assessment)
- Conduct clinical interviews/assessments (PANSS, CGI-SCH, CDSS, YMRS, MOAS, SWEMBS, SF-36, CSRI, UKU)
- Record weight
- Record vital signs (blood pressure/pulse rate)
- Collect blood samples for pharmacogenomics, epigenetics, antipsychotic drug levels and other measures before IMP ingestion if not collected earlier
- Ensure female participants use effective long-term methods of contraception during the course of the study
- Explain the drug titration process
- Randomise the patient
- Dispense 2 weeks of medication (completed annual risk acknowledgment form will be needed for female subjects of childbearing potential prior to dispensing)
- Follow up after one week (via telephone/face to face) to check on how the patient is progressing with drug titration and also check if there are any concerns

Visit 3 & DS2: Face-to-face 2-week visit (week 2)

- Review recent medical and medication history for changes since previous visit
- Record vital signs (blood pressure/pulse rate)
- Remind female participants to continue to use effective long-term methods of contraception during the study

- If there is a gap in contraception or if the contraceptive method has been changed then conduct a urine pregnancy test before dispensing study medication
- Conduct Medication Adherence Rating Scale (for antipsychotic medication)
- Conduct a pill count of the IMP
- Dispense 3 months of medication (check if completed annual risk acknowledgment form for female subjects of childbearing potential remains valid)
- Where the target dose has not been reached, and where an increase in dose is executed at this visit then a telephone call/face-to-face visit to check on tolerability to be conducted after approximately three days.

Visit 4 & DS3: 3-month visit (week 13)

- Obtain medical and medication history since the last visit
- Conduct Medication Adherence Rating Scale (for antipsychotic medication)
- Risk assessment using the Columbia Suicide Severity Rating scale
- Conduct clinical interviews (PANSS, CGI-SCH, CDSS, YMRS, MOAS, SWEMBS, SF-36, CSRI, UKU)
- Record weight
- Record vital signs (blood pressure/pulse rate)
- Collect blood sample for clinical laboratory assessments (full blood count, liver function test)
- Collect blood samples for pharmacogenomics, epigenetics and drug levels (antipsychotic and valproate) and other measures
- Remind female participants to continue to use effective long-term methods of contraception during the study
- If there is a gap in contraception or if the contraceptive method has been changed then conduct a urine pregnancy test before dispensing study medication
- Conduct a pill count of the IMP
- Dispense 3 months of medication (check if completed annual risk acknowledgment form for female subjects of childbearing potential remains valid)
- If an increase in dose is executed at this visit then a telephone call to check on tolerability to be conducted after three days

Visit 5 & DS4: 6-month visit (week 26)

- Obtain medical and medication history since last visit
- Conduct Medication Adherence Rating Scale (for antipsychotic medication)

- Risk assessment using the Columbia Suicide Severity Rating scale
- Conduct clinical interviews (PANSS, CGI-SCH, CDSS, YMRS, MOAS, SWEMBS, SF-36, CSRI, UKU)
- Record height and weight
- Record vital signs (blood pressure/pulse rate)
- Remind female participants to continue to use effective long-term methods of contraception during the study
- If there is a gap in contraception or if the contraceptive method has been changed then conduct a urine pregnancy test before dispensing study medication
- Conduct a pill count of the IMP
- Dispense 3 months of medication (check if completed annual risk acknowledgment form for female subjects of childbearing potential remains valid at this time-point but also if it lasts till the end of medication phase and if needed perform a serum pregnancy test and complete a fresh annual risk acknowledgement form)

DS 5: 9-month dispensing session (week 36)

- Remind female participants to continue to use effective long-term methods of contraception during the study
- If there is a gap in contraception or if the contraceptive method has been changed then conduct a urine pregnancy test before dispensing study medication
- Conduct a pill count of the IMP
- Dispense 3 months of medication (check if annual risk acknowledgment form for female subjects of childbearing potential remains valid until end of trial)

Visit 6 & DS6: 12-month visit (week 52)

- Obtain medical and medication history since last visits
- Conduct Medication Adherence Rating Scale (for antipsychotic medication)
- Risk assessment using the Columbia Suicide Severity Rating scale
- Conduct clinical interviews (PANSS, CGI-SCH, CDSS, YMRS, MOAS, SWEMBS, SF-36, CSRI, UKU)
- Record weight
- Record vital signs (blood pressure/pulse rate)
- Collect blood sample for clinical laboratory assessments (full blood count, liver function test)
- Collect blood samples for pharmacogenomics, epigenetics and drug levels (antipsychotic and valproate)

- Remind female participants to continue to use effective long-term methods of contraception during the study
- If there is a gap in contraception or if the contraceptive method has been changed then conduct a urine pregnancy test before dispensing study medication
- For female subjects, collect serum/ urine samples for pregnancy tests
- Conduct a pill count of the IMP
- Dispense medication if needed (check if completed annual risk acknowledgment form for female subjects of childbearing potential is valid till the down-titration is completed irrespective of whether medication is dispensed)
- Explain down titration and advise subject to carry out in steps of 500mg in 3 to 4 days intervals.
- Liase with patient's clinical team to ensure smooth transition after completion of study

Visit 7: End of study (week 54)

- Record vital signs (blood pressure/pulse rate)
- Complete PANSS and UKU
- Conduct a pill count of the IMP
- Collect all unused study medication
- Remind female subjects of childbearing potential to continue using effective long-term methods of contraception until 60 days since their last study drug intake
- If there is a gap in contraception or if the contraceptive method has been changed then conduct a urine pregnancy test
- Complete the exit interview
- A single follow up either face-to-to face or via telephone 60 days since their last study drug intake to record for any AEs/SAEs

Post 1-year (annual)

- Record the HoNOS score
- Record the clinical inputs received by the patient since last assessment (hospitalisation, crisis/home treatment use, relapse & remission phases and medication use including valproate and switch to clozapine)

Early exit (if the patient consents)

- Steps in Visit 6 and Visit 7 to be followed

Participants will be compensated for their time or a pro rata basis When participants discontinue their medication but not withdraw from the study, this payment will still be made for assessments.

7.2 Laboratory Tests

Urine samples for pregnancy will be tested at the local sites using CE marked kits and samples will be immediately discarded. The following blood samples will be collected:

1. Serum pregnancy test – approximately 4ml each time for women of child bearing potential to comply with the MHRA pregnancy prevention programme (testing to be done by local NHS service)

2. Full blood count – approximately 4ml each time (testing to be done by local NHS service)

3. Liver function test – approximately 4ml each time (testing to be by local NHS service)

4. Metabolic and other measures that may influence response including pharmacogenomics – approximately 30ml each time (for post-hoc analysis)

5. Drug levels – approximately 10ml (for post-hoc analysis) each time.

Blood samples with be handled in accordance with the Human Tissue Act (2004). Blood samples will be pseudoanonymised and disposed after analysis. The blood samples will be transferred from the respective study sites to the respective laboratories at each site in blood transportation boxes, complying with the Human Tissue Act (2004). Local laboratory procedures or a lab manual for sample collection and processing will be followed and a site-wise file note will document the process. Samples for metabolic and pharmacogenomics will be transferred to the CI's laboratory at the MRC London Institute of Medical Sciences, Hammersmith campus for storage and post-hoc analysis at a commercial laboratory or at King's College London. These samples will be held up to 10 years after the end of the study.

8 Assessment of Efficacy

8.1.1 Primary Efficacy Parameters

Positive and Negative Syndrome Scale (PANSS)

The primary outcome is the positive subscale of the PANSS, which measures psychotic symptom severity. The PANSS is a clinician-rated scale that assesses psychotic (positive), negative and general symptom severity in schizophrenia. The PANSS psychotic (positive) rating at the end of the double-blind study (12 months) will serve as the main outcome

measure [4]. The positive scale has seven items covering psychotic symptoms (delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspiciousness/persecution and hostility), each rated from 1 (absent) to 7 (very severe). The scale's reliability, criterion-related validity, and construct validity have been well documented [29]. Total time required for PANSS interview and scoring is approximately 30 minutes for the total score of which the positive subscale will form a part. PANSS raters will be required to meet specific training criteria before they are certified for this study. A PANSS rating is valid for seven days from the day it was conducted.

8.1.2 Secondary Efficacy Parameters

PANSS positive subscale and total scores

PANSS is a clinician-rated scale that measures symptom severity in schizophrenia. PANSS total score (including positive subscale) will be measured at baseline, 3, 6 and 12-month time points to measure treatment outcomes.

PANSS Factor score

Transformed PANSS factors intended to reduce pseudospecificity among symptom domains and enhance understanding of symptom change in antipsychotic-treated patients with schizophrenia will be analysed [30]. A significant impediment to correctly characterizing the efficacy of new treatments is the extent to which PANSS factors are correlated with each other. As a consequence, it is difficult to determine whether improvement in the severity of symptoms in PANSS is a domain-specific treatment effect or is a nonspecific effect secondary to observed improvement in correlated PANSS items. Hence this factor analysis approach at the 3, 6 and 12-month time point will help us understand the symptom change related to the adjunctive treatment. Data needed to do the factor analysis will be obtained from PANSS interviews.

CGI (Schizophrenia version)

The CGI-SCH scale is a valid, reliable instrument to evaluate severity and treatment response in schizophrenia [30] . Given its simplicity, brevity and clinical face validity, the scale is appropriate for use in observational studies. It consists of only two categories; severity of illness and degree of change. The severity of illness category evaluates the situation during the week previous to the assessment, while the degree of change category evaluates the change from the previous evaluation (or from the phase preceding the treatment trial). Each category contains five different ratings (positive, negative, depressive, cognitive and global) that are evaluated using a seven-point ordinal scale. Change from baseline will the parameter that will be analysed. It takes approximately 10 minutes to complete this instrument.

Modified Overt Aggression Scale (MOAS)

MOAS rates the patient's aggressive behaviour over the past week under the categories of verbal aggression, physical aggression against objects, physical aggression against self, and physical aggression against others [32]. Scores in each category are summed up, they are multiplied by weight and weighted sums are added for total weighted score. It takes approximately 5 minutes to compile the final score. The reason for its inclusion is to assess the effect of valproate on aggression as it has been shown to improve global measures of aggression and behavioural agitation [45].

Calgary depression scale for schizophrenia (CDSS)

The Calgary Depression Scale for Schizophrenia (CDSS) was developed to assess the level of depression in schizophrenia [33]. It differentiates between depression and the negative and positive symptoms of schizophrenia. It has been extensively evaluated in both relapsed and remitted patients and is sensitive to change. It is a semi-structured, goal directed interview and has 9 items (each rated 0-3). A score above 6 has an 82% specificity and 85% sensitivity for predicting the presence of a major depressive episode. It takes approximately 15 minutes to complete the assessment.

Young's Mania rating scale

The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours [34]. The items are selected based upon published descriptions of the core symptoms of mania. There are four items that are graded on a 0 to 8 scale (irritability, speech, thought content, and disruptive/aggressive behaviour), while the remaining seven items are graded on a 0 to 4 scale. It takes 15 minutes to complete and a single final score is determined. The reason for its inclusion is to assess symptoms of mania in the schizoaffective patient group and if valproate augmentation would have to have any effect on this dimension.

Short Warwick-Edinburgh Well-being scale (SWEMWBS)

The SWEMWBS uses seven statements about thoughts and feelings [35]. The seven statements are positively worded with five response categories from 'none of the time' to 'all of the time'. Patients will be asked to describe their experiences over the past two weeks. The seven items relate more to functioning than feelings and so offer a slightly different perspective on mental well-being. It takes about 10 minutes to complete it.

Client Service Receipt Inventory (CSRI)

The Client Service Receipt Inventory (CSRI) is a research instrument developed to collect information on service utilisation, income, accommodation and other dimensions relevant to the estimation of costs [36]. Its primary purpose is to allow service use

patterns to be measured and described and service and support costs to be derived by combining appropriate unit costs with service use and support data. The CSRI takes around 20 minutes to complete.

Short Form 36 (SF-36)

The SF-36 is a patient-reported survey of patient health and consists of eight scales yielding two summary measures: physical and mental health. The SF-36 offers a choice of recall format at a standard (4 week) or acute (1 week) time frame. We will use the standard (4 week) time frame. Likert scales and yes/no options are used to assess function and well-being. Data generated from this questionnaire will be revised into a six-dimensional health state classification (the SF-6D) and societal weights will be attached [46]. The SF-36 takes around 10 minutes to complete.

Exit interview

An exit interview will be conducted (including cases who complete the 12 month treatment) to assess blinding (including that of the rater), experience of participation, and reasons for early discontinuation if applicable (including lack of efficacy, adverse effects, switch to another antipsychotic or personal reasons). If subject is lost to follow up then loss to follow up will recorded in lieu of an exit interview.

HoNOS

This is a national NHS standard measure of symptoms and function in psychiatric patients. It is measured yearly by mental health care teams as part of routine care and will be assessed annually during the study -extension. It is an instrument with 12 items measuring behaviour, impairment, symptoms and social functioning. We will ensure that all patients have their HoNOS assessments recorded prior to enrolling them.

9 Assessment of Safety

The Investigator or appropriate designee will review results of safety assessments on a regular basis and the Sponsor must be kept fully informed of any clinically significant findings either at Screening or subsequently during study conduct.

9.1 Safety Parameters.

Adverse Events

Adverse events will be collected for each subject. Subjects should be queried in a non-leading manner, without specific prompting (e.g., “How are you getting on with the medication?”). AEs and SAEs will be monitored throughout the study at all visits. Pre-treatment events will be monitored prior to the first dose of study drug.

Clinical Laboratory Assessments

The clinical laboratory tests required by protocol are listed in Section 7.2. Blood and urine samples will be collected for clinical laboratory tests. All clinical laboratory tests will be performed locally except for the post-hoc metabolic, pharmacogenomic & drug level analysis. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the study centre laboratory manual based on local clinical laboratory guidelines. Samples will be processed at a local laboratory and only blood samples for post-hoc analysis will be stored at the MRC London Institute of Medical Sciences (**LMS**), Hammersmith Hospital Campus, London where the CI holds a secondary position. Any value outside the normal range will be flagged for attention of the investigator. The investigator or appropriate designee will indicate whether or not the value is of clinical significance. If a clinical significant abnormality is found in the samples taken during the screening phase then their inclusion should be reviewed. If such were to happen during the treatment phase then they will be recorded as an adverse event (AE) and if needed followed until test(s) have normalized or stabilized.

Vital signs

Measurements will consist of systolic and diastolic blood pressure, respiratory rate and pulse rate. The same arm will be used for all visits to measure blood pressure. Vital signs results assessed as clinically significant by the investigator will be reported as adverse events. Vital signs will be obtained prior to clinical laboratory collections, if any, at their respective time-points.

Height, Weight, and BMI

Height will be measured in meters without shoes and will be recorded at screening. Weight will be measured in kilograms as specified in the Trial Schedule and will be done in street clothes, without shoes and coat/jacket. BMI will be calculated by site staff using the equation BMI = kg/m^2 where kg is a person's weight in kilograms and m^2 is their height in metres squared.

Pregnancy prevention and contraception

Women of childbearing potential must agree to use an acceptable form of birth control. Recommendations related to contraception and pregnancy testing in clinical trials developed by the Clinical Trial Facilitation Group will be followed (Final Version 2014-09-15 [47]) and the MHRA pregnancy prevention programme will be adopted [42]. Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods as per the guidelines. Such methods with low user dependency include:

1. Progestogen-only hormonal contraception associated with inhibition of ovulation

- injectable
- implantable

2. Intrauterine device (IUD)
3. Intrauterine hormone-releasing system (IUS)
4. bilateral tubal occlusion

Hormonal contraceptives have the following time-frame requirements:

a) Contraceptive implant implanted at least 60 days prior to screening
b) Injectable contraception given at least 14 days prior to screening
c) 60 days after completion or premature discontinuation from the study drug

They will be supported on the Pregnancy Prevention Programme as outlined by MHRA [42] and an annual risk acknowledgement plan for pregnancy prevention has to be completed. A serum pregnancy test also needs to be completed.

Hormonal contraception has not been documented to be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method [47]. Antipsychotics are also known to be of low risk for interaction with hormonal contraceptives but should be guided by their respective SmPCs. Any other medication must be assessed for interaction in a similar manner.

Female subjects who are of non-childbearing potential are not required to abide by birth control requirements. Non-childbearing potential is defined as a subject who is surgically sterile, has undergone tubal ligation, or is postmenopausal (defined as at least 12 months of spontaneous amenorrhea or between 6 and 12 months of spontaneous amenorrhea with follicle stimulating hormone [FSH] concentrations within postmenopausal range as determined by laboratory analysis) are not required to remain abstinent or use adequate contraception. Hyperprolactinemia due to antipsychotic treatment can lead to amenorrhea and caution must be exercised in such cases.

An optional urine pregnancy test will be available in case the patient does not want to give blood samples or if there is a delay from when the serum pregnancy test was done at the start of the trial. Pregnancy risks will be reviewed at each time-point and a urine pregnancy test will be conducted based on risk assessment if needed. A valid annual risk acknowledgement plan must be in notes for medication to be dispensed. Pregnancy if it were to occur will lead to rapid down titration and stoppage of medication and though not an SAE it will also be reported via the SAE reporting system (pregnancy is not regarded as an AE unless there is suspicion that the medication may have interfered with the effectiveness of a contraceptive medication). Pregnancy will be monitored till term and if a live birth occurs, the infant may be followed over a period of 5 years and monitored for the detection of birth defects and other functional or developmental deficits. Reporting beyond the study period will be done using the yellow card scheme.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS), an evidence-supported tool, is a simple series of questions that rates suicide risk and is commonly used to identify suicide risk [48]. The C-SSRS will be offered at baseline, 3-month, 6-month and 12-month time point to assess suicide risk. The scale takes approximately 5 minutes to administer it. If the subject answers "yes" to "Suicide Ideation" Items 4 (active suicide ideation) with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSR then the study medication will be discontinued and will be guided to seek appropriate therapy. At screening visit, "Baseline/Screening" version of C-SSRS will be used which includes assessment for lifetime and previous 1 month. For all visits from Visit 2 onwards, the "since last visit" version of the C-SSRS will be used.

UKU Side effect rating scale

The Committee on Clinical Investigations (Udvalg for kliniske undersogelser, UKU), which is a standing committee under the Scandinavian Society of Psychopharmacology came up with this comprehensive side effect rating scale [38]. There are 48 items under (i) Psychic, (ii) Neurological, (iii) Autonomic and (iv) Other categories. Each of the 48 catalogue symptoms are scored on a four-point scale. The scoring steps are individually defined for each symptom, built on the following general principle: 0 = not or doubtfully present, 1 = present to a mild degree, 2 = present to a moderate degree, 3 = present to a severe degree. The scoring is based on all relevant information available, that is, both on what the patient reports, the doctor's observations during the interview, and reports from the ward personnel if applicable. Most symptoms are assessed on a "here-and now" basis. However, where appropriate, the symptoms are rated for severity within the last three days. For some symptoms, the reference period is considerably longer, as stated in the manual (e.g., for weight changes, disturbances of mensuration, epileptic seizures, and dependence).

On the basis of the ratings of the single side effects and of the global side effect assessment, a note is made of any action taken because of the patient's side effects. Four possible alternatives are included in this classification: 0 = No action, 1 = More frequent assessment of the patient, but no reduction of dose, and/or occasional drug treatment of side effect, 2 = Reduction of dose and/or continuous treatment of side effects, and 3 = Discontinuation of drug or change to another preparation. It takes approximately 20 minutes for this scale to be completed and will be done at baseline, 2 week, 3-month, 6-month and 12-month time-point. Also, in subjects who wish to exit the study it will be conducted as part of their exit monitoring. A rating of 2 in any of the

items in the scale will trigger review of dose levels and treatment to mitigate side effects. A rating of 3 in any of the items will trigger review of dose levels, treatment to mitigate side effect and if needed discontinuation of valproate augmentation. Unscheduled UKU should be administered if a subject develops a side-effect especially extrapyramidal symptoms (EPS) requiring treatment.

This scale will be used for dose titration and maintenance of the study drug to assess tolerance.

Liver function

Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported with the use of valproate. In most cases, such liver damage has occurred during the first 6 months of therapy, the period of maximum risk being 2 – 12 weeks (SmPC). A sudden onset of asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain even prior to the onset of jaundice will trigger liver function test in this period else all patients will have their liver function tested at the 3-month time-point. Transaminitis > 5 times the upper limit of normal value (Grade 3 – CTCAE) will result in review of liver function and if it persists with symptoms of jaundice and relevant clinical context, it will lead to their trial medication stopped if determined clinically necessary. Transaminitis > 10 times the upper limit of normal value (Grade 4- CTCAE[49]) and relevant clinical context will result in trial medication stopped [50].

Fulll Blood Cell count

A common side effect of valproate is a decrease in platelet count, seen in 10-15% of patients taking it long term. A normal human platelet count ranges from 150,000 to 450,000 platelets per microliter of blood. Clinically significant spontaneous bleeding does not usually occur until the platelet count is less than 100,000/mm^3. Levels below 75,000/mm^3 (Grade 1 – CTCAE [49]) will be reviewed in the patient's clinical context and if determined clinically necessary the trial medication will be stopped. Leucopenia and agranulocytosis are uncommon and rare side effect respectively (SMPC) and any Grade 3 CTCAE [49] criteria (less than 2 x 10^9/Litre WBCs, less than 1 x 10^9/litre neutrophils) in these parameters will lead to trial medication being stopped if determined clinically necessary.

Pancreatitis

Patients experiencing abdominal pain consistent with a clinical diagnosis of pancreatitis will receive investigation and treatment according to NHS standard of care and trial medication will be stopped pending confirmation or exclusion of diagnosis. Confirmation of acute pacreatitits will result in trial medication being permanently stopped. Patients

found to have an elevation in serum amylase >2.0 x upper limit of normal (Grade 3 – CTCAE [49]) will have their trial medication stopped if determined clinically necessary.

Factors associated with treatment (such as pharmacogenomics, epigenetics and drug levels)

If a subject has consented to have blood samples taken for genetic analysis as well as drug level estimation (and is eligible for randomization) then three blood samples (approximately 30 ml each) will be collected at each visit [baseline, 3-month (main secondary outcome) and 12-month time-point/exit]. The analysis (post-hoc) will occur at the end and will not be used during the trial to maintain blinding. Bloods will be shipped to the CI in batches where they will be frozen until analysis. After unblinding of the main study, the epigenetic signature and the levels of valproate and antipsychotic will be analysed and co-relation with treatment outcomes will be assessed.

9.2 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Averse 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.

Appendix 2 gives a schematic of AE categorization and reporting procedure.

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.

During the study, if the subject has a hospitalization procedure (e.g. elective surgery) that was scheduled before the study entry, i.e. before consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of SAE. However, if the event/condition worsens during the study, it should be reported as an AE (of SAE if the outcome so warrants).

Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system. Each pregnancy will be followed up until the outcome is

known. The CI or PI will liaise with the relevant obstetrician throughout the pregnancy. In the event of a congenital anomaly or birth defect detected in the foetus or live born child it will be reported as an SAE. The database record of all pregnancies will be held by the KHP-CTO, this will include follow up to term and where appropriate, long-term follow up of the baby.

Urgent safety measures

Regulations allow the sponsor and investigator to take appropriate urgent safety measures to protect clinical trial subjects from any immediate hazard to their health and safety. The CI must inform the KHP-CTO as soon as possible after the implementation of the urgent safety measures. The CI or sponsor will phone the MHRA's clinical trial unit on 020 3080 6456 to discuss the issue with a safety scientist, ideally within 24 hours. The MHRA will inform the CI or Sponsor how the submit the substantial amendment to them within 3 days when spoken to them but instructions will be sent by email. The sponsor will then notify the MHRA and the REC in writing, of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment. The decision to undertake appropriate safety measures may be taken by:

- The CI and/or PI
- The KHP-CTO – on behalf of the sponsor and in consultation with the CI or DMC

Ongoing safety

The KHP-CTO will ensure that the CI promptly notifies all other investigators, REC and MHRA of any findings that may affect the health of subjects. A concise safety analysis and risk-benefit evaluation describing all new findings related to the safety of the IMP treatment with respect to their impact for the subjects will be considered by the PIs, CI and DMEC (if applicable).

Reporting Responsibilities

SLAM & KCL 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 will be reported immediately (and certainly no later than 24hrs) by the Investigator to the KHP-CTO and CI for review in accordance with the current Pharmacovigilance Policy. This includes completion of an SAE form and sent immediately to the KHP-CTO

by fax on 020 7188 8330

or by email: jcto.pharmacovigilance@kcl.ac.uk

The original SAE Report Form will be filed in the Trial Master File, with copies filed in the patient's hospital notes, the case record form, the Investigator Site File (if applicable) and the Sponsor file.

The KHP-CTO will report SUSARs to the MHRA. 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 not 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 annual progress report relating to this trial to the REC and will contain a summary of AEs that occur in that period.

Participants will be followed up until clinical recovery and laboratory results have returned to normal baseline values, or until the event has stabilized. If the investigator believes that an SAE is not related to the study drug, but potentially related to the conditions of the study (such as withdrawal), the relationship will be specified in the narrative section of SAE report form. Pregnancy will be monitored till term and if a live birth occurs, we may request the infant to be followed up to a period of 5 years and monitored for the detection of birth defects and other functional or developmental deficits. After the end of the trial, any subsequent events that may be attributed to treatment will be reported to the MHRA using the yellow card system.

9.2.1 Adverse events that do not require reporting

Events or reactions listed in the SmPC of Sodium valproate or that of the antipsychotic drug will not be reported. The period for AE reporting will be from screening until 60 days post final IMP administration.

9.3 Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority based on new safety information or for other reasons given by the Data Monitoring & Ethics Committee / Trial Steering Committee regulatory authority or ethics committee concerned.

If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. All participants will be down titrated in a similar manner discussed in Section 5.2. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

10 Statistics

10.1 Sample Size

We have powered our study on the basis of superiority of valproate compared to placebo on the PANSS positive subscale using an effect size of 0.3. An effect size of 0.3 was selected as, in line with other trials of antipsychotic augmentation for treatment resistant schizophrenia, effects smaller than this are considered unlikely to be clinically meaningful [51, 52]. Assuming a two-sided significance level of 0.05 and 1:1 allocation, we will require 290 participants in the analysis dataset to detect an effect size of 0.3 with 90% power. This allows for a correlation between measures (at baseline and three follow-up points) of 0.4. An estimate of attrition of 20% across both arms for the primary end-point at 12 months requires a recruitment total of 362 participants at

baseline. The attrition rate of 20% is an estimate based on studies of antipsychotic augmentation using a similar design to our proposal, for example, the FOCUS study (Cognitive therapy augmentation of an antipsychotic for treatment resistance) had an attrition rate of ~10% over 21months [53] and the CHAT study (antipsychotic augmentation with a second antipsychotic) had an attrition rate <10% [54]. In this context, a study of a novel drug as an augmentation agent to antipsychotic treatment had a discontinuation rate of 29% at 12 months [55]. This study had a considerably larger burden of measures and higher levels of monitoring than our study. As such we expect our attrition and discontinuation rates to be in the range of 10-20% level in line with the other studies.

10.2 Randomisation

Randomization will be stratified by diagnosis (schizophrenia or schizoaffective), site and sex and a permuted block randomization will be used for each stratum.

10.3 Analysis

Statistical analysis will be done according to the predefined statistical analytical plan (SAP). There is no planned interim analysis unless the DMEC direct us to conduct one. Any deviations will be reviewed by the trial steering committee.

Statistical analysis

The primary analysis will use intention-to-treat principles by including all participants with outcome data in the arms to which they were randomized and follow the CONSORT 2010 statement. Baseline data will be presented using summary statistics with no testing for baseline differences. Treatment effects on the primary and secondary continuous outcomes will be estimated using linear mixed models fitted to outcome variables at all-time points. Fixed effects will be: diagnosis (schizophrenia/ schizoaffective); centre; baseline PANSS psychotic symptom severity rating; treatment; time (categorical); and time*treatment interactions. Marginal treatment effects will be estimated for outcomes at each time point and reported separately as adjusted mean differences in scores between the randomised groups with 95% confidence intervals and two-sided p-values. For binary outcomes, the same approach will be followed using logistic mixed models. All models will be estimated using maximum likelihood estimation, which allows for missing outcome data under the Missing At Random assumption. We may also use inverse probability weighting or multiple imputation to adjust for non-adherence to allocated treatment and other intermediate outcomes as predictors of future loss to follow-up.

Secondary analysis will include accounting for treatment switches from placebo to valproate arms using inverse probability of censoring weighting to estimate the average

treatment effect and longitudinal instrumental variable analysis to estimate the complier average causal effect.

Cost effectiveness evaluation

Costs will be captured from two perspectives: NHS & personal social services (PSS) and a wider societal perspective that will include criminal justice services, caregiver out-of-pocket expenses and lost productivity. The client service receipt inventory (CSRI) adapted for use in this study will be used to collect service use and support data for each participant in the study that will be used to generate cost from these two perspectives [36]. The CSRI facilitates the standardised recording of service use that is commensurate with accurate cost estimation. Through a patient interview, data on service use and caregiver support will be collected for the 3-month period prior to assessment at baseline (for the period prior to entering the study), and at 6 and 1-year follow-up interviews. During the treatment period, we use data collected on the treatment dosages and titration schedules. Also at baseline, 3-month 6-month and 1-year, the SF-36 (36-item short form health survey) will be transformed into a single preference-based measure of health using the algorithm developed by Brazier and colleagues [46]. Using the area under the curve method with linear interpolation between assessment points (and baseline adjustment for comparisons), the quality-adjusted life-year (QALY) gain for each patient will be generated.

From each perspective, in turn, the cost-effectiveness evaluation will compare the comprehensively measured service and support costs between the placebo plus continuing antipsychotic treatment arm and the valproate plus continuing antipsychotic treatment arm with, first, the difference between the treatments in the primary outcome measure (psychotic symptom severity as measured by the PANSS positive subscale), and then with the difference between the treatments in QALYs gained. In each case, an incremental cost-effectiveness ratio (ICER) will be computed as the mean cost difference between placebo plus continuing antipsychotic treatment arm and the valproate plus continuing antipsychotic treatment arm divided by the mean difference in change in primary and secondary outcome respectively. The cost-effectiveness measures will be incremental cost per point improvement in PANSS positive subscale (by 3, 6 month and 1-year) and incremental cost per QALY gain by 12 months. We will use the current standard NICE cost-effectiveness threshold range of £20K and £30K per QALY to determine if the intervention meets cost-effectiveness criteria.

For the base-case models under both perspectives, we will compare costs and outcomes between the treatment arms at baseline, 3-month, 6- month and 12-months follow-up. In these models we will control for baseline costs (only in the cost analysis); centre; baseline PANSS psychotic symptom severity rating; treatment; time (categorical); and time*treatment interactions.

Bootstrapping with mixed effects models will be used to generate confidence intervals that can be used to capture parameter uncertainty around the estimates in the cost-

effectiveness analysis. The 1000 treatment effect replications from this bootstrapping process will be plotted on cost-effectiveness planes and used to construct cost-effectiveness acceptability curves (CEAC). We will use cost effectiveness acceptability curves (CEACs) to explore the nature of the trade-off faced by the decision-maker in situations where one treatment option is both more effective and costly than the other. In this case, the decision maker would need to consider if it is worth incurring the higher costs to improve outcomes. Using this approach, we will be able to show the likelihood of valproate plus continuing antipsychotic treatment arm being seen as cost-effective relative to the placebo plus continuing antipsychotic treatment arm given different (implicit monetary) values placed on incremental outcome improvements. Bootstrapping and regression analysis will be used to generate CEACs. We will also explore the sensitivity of the results to changes in key parameters and the analyses will be repeated. This will include the same control variables as those in the base-case model.

11 Trial Steering Committee

The Trial Steering Committee (TSC) will be constituted in accordance with the NIHR HTA programme guidance before the start of the trial. The TSC chair will be an experienced independent member and the majority of the TSC members (75%) will be independent of the trial. At least one individual who can contribute as a patient or carer perspective will be included. In the initial stage of the trial (first six months) the TSC will review progress with respect to trial recruitment and retention and recommend changes if needed to the protocol and conduct of the trial. Thereafter it will be convened periodically at least once a year to monitor progress. The TSC will provide overall supervision of the trial and monitor trial progress and conduct and advise on scientific credibility. In the event of serious adverse events, or on the advice of the Data Monitoring and Ethics Committee, the TSC will direct action to be undertaken to ensure safety of the participants and will review trial continuation.

12 Data Monitoring Committee

A Data Monitoring and Ethics Committee (DMEC) will be constituted in accordance with the NIHR HTA programme guidance before the start of the trial. It will be the only independent body involved in the trial that will have access to the unblinded comparative data. An independent clinician in the relevant area and an expert trial statistician will be part of the committee. It will meet initially six months after the trial start and then at least once a year to monitor trial data and make recommendations to the TSC with regards to 1) recruitment of patients, 2) ethical issues in the overall conduct of the trial, 3) quality of data (including missing data), 4) incidence of adverse events and 5) any factors that may compromise the progress and satisfactory completion of the trial. The pharmacokinetic and pharmacodynamic interaction between antipsychotics and sodium valproate will be specifically monitored during the trial.

13 Patient and Carer involvement

The study protocol was developed in active consultation with carers and patients at service user meeting at SLAM. Service user and carer groups at each site and an overall study patient and carer advisory board will advise us on national and local implementation of the study and would guide us in our recruitment strategy. They will also provide feedback on issues that arise as the study progresses (including the ICF) and help us write study outcome documents. Feedback from local groups via the patient and carer advisory board will be provided to the Trial management group (TMG) and they will disseminate information to all sites and implementation of actionable items will be decided by the TMG. The TMG will also disseminate information arising from the consultation to the TSG and Data Monitoring and Ethics Committee (DMEC) if needed.

14 Direct Access to Source Data and Documents

The Investigators will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsors, Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, clinical test reports, etc.).

15 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents are reviewed by the UK's Health Research Authority's Research Ethics Committee (REC), and the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation. Subsequent amendments will be submitted to the REC and regulatory authorities for approval. We will also comply with the pharmacovigilance requirements under the Medicines for Human Use (Clinical Trial) Regulations 2004 (as amended).

The Chief Investigator will submit annual progress reports and a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA.

All revisions and/or amendments (substantial or non-substantial) to this protocol must be approved in writing by the sponsor, the REC, the HRA and MHRA (if applicable). Emergency deviations or modifications may be initiated with sponsor, the REC, HRA or MHRA approval or favourable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency

deviations will be reported to the sponsor, REC, HRA and MHRA within five business days.

16 Quality Assurance

KHP-CTO will undertake, on behalf of the Sponsor, independent administrative audits of the trial master file and monitoring at all sites and pharmacies periodically during the trial to ensure compliance with the Medicines for Human Use (Clinical Trials) Regulations 2006 and its subsequent amendments.

17 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.
- 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.

18 Data Management

Paper case report forms will be completed at sites. Data will be transferred to an electronic data management system (Infermed MACRO ver 4). The system is compliant with Good Clinical Practice and is an appropriate system to use for medicinal trials falling under the Medicines for Human Use (Clinical Trials) Regulations 2004 and its subsequent amendments. The web-based system will be available for access 24 hours a day. Roles will be assigned to users, giving the ability to enter data relating to participants or to view data and raise discrepancies, but not amend data. Roles will also be tailored to be blind to treatment allocation where appropriate. The system is programmed to perform validation checks, such as range checks to prevent data entry errors. Missing data codes are routinely programmed into all fields, for ease of analysis. The system is also programmed to flag up when a missing data code is entered, to aid monitoring. The system is also programmed to include e-signatures, where this is required. A standard feature of InferMed MACRO data entry system is the built-in audit trail on all data fields, the automatic saving of data as you leave a form, and the ability to maintain a record of ‘source data verification’ checks. The system also has formal database lock functionality.

The investigator at each study centre will arrange for retention of study records for at least 10 years from time of participation in the study. Precautions to prevent accidental destruction must be taken. All data storage will adhere to General Data Protection Act (GDPR) Act 2018.

19 Publication Policy

The trial protocol will be published in a peer-reviewed open access journal. The results of the study will be disseminated at national and international conferences and submitted for publication in peer-reviewed open access scientific journals. Authorship will be granted to individuals making significant contribution to the design, setup or conduct of the trial and/or analysis and interpretation of trial data. The study findings will also be disseminated to patients and carers through presentations at local service user research networks and through national patient newsletters.

20 Insurance / Indemnity

The lead sponsor, King's College London, will take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting. King's College London also provides cover under its No Fault Compensation Insurance, which provides for payment of damages or compensation in respect of any claim made by a research subject for bodily injury arising out of participation in a clinical trial or healthy volunteer study (with certain restrictions). The basis for damages or compensation shall be in accordance with ABPI guidelines being payable irrespective of fault on the College’s part. The co-sponsor, South London and Maudsley NHS Foundation Trust, takes responsibility for ensuring that appropriate standards, conduct and reporting are adhered to regarding its facilities and staff involved with the project.

21 Financial Aspects

The trial is funded by the National Institute for Health Research as part of a commissioned call under its Health Technology Assessment research programme to address the lack of treatment options for patients with non-response to first-line APs who are not able or willing to take clozapine.

22 Signatures

_____
_____

Chief Investigator Date
Prof. Oliver Howes

_____
_____

Statistician (if applicable) Date
Prof. Richard Emsley

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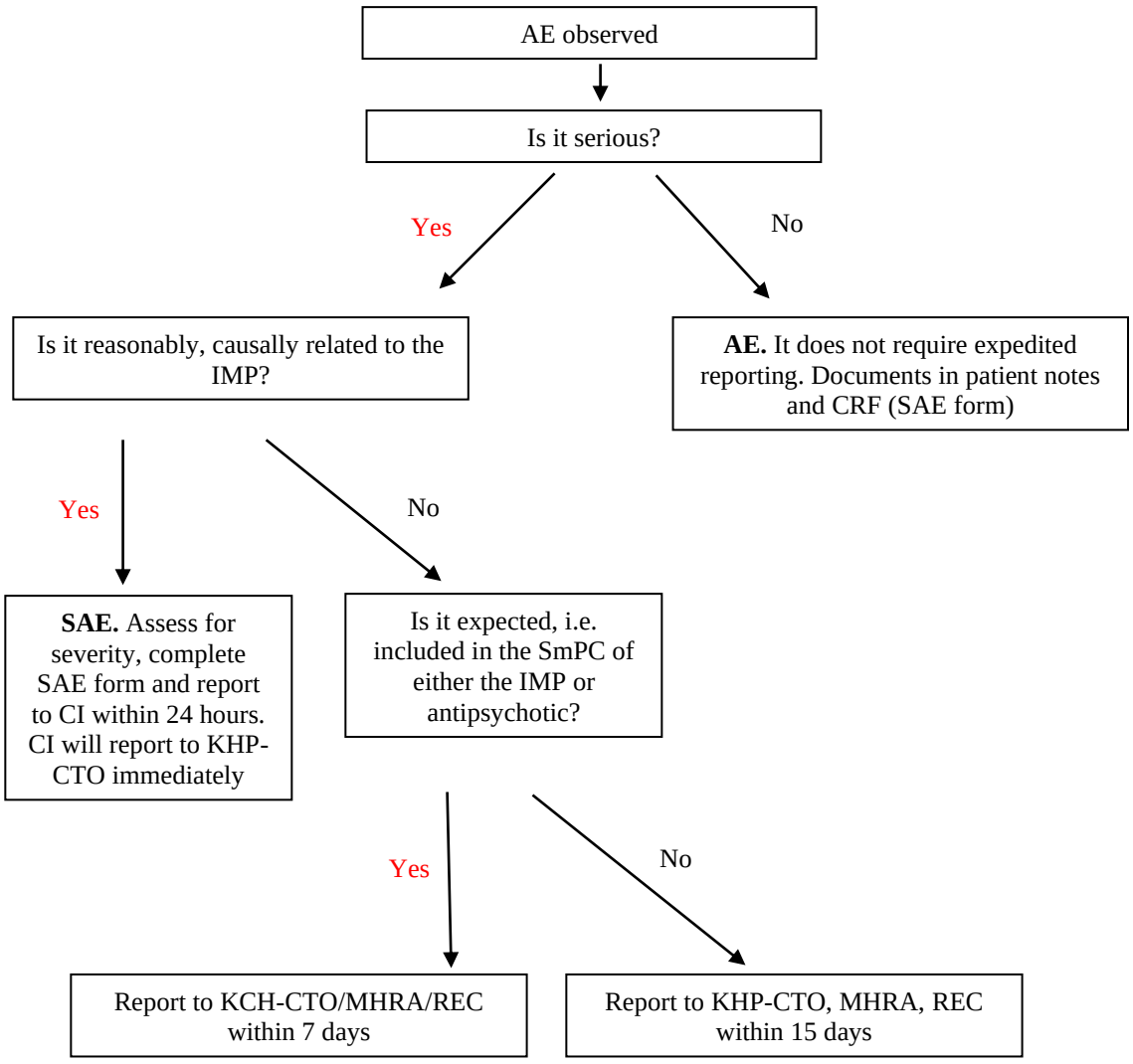
Appendix 1 Dose titration chart for 500mg sodium valproate tablets

Body Weight Range (kg)	**Days 1 -3**	**Days 4 – 6**	**Days 7 – 9**	**Days 10 – 12**	**Days 13 - 15**	**Day 16 onwards**	**Maximum number of tablets that can be taken so it does not exceed 30mg/kg/day or 2500mg/day**
35-49	1	1	2	2	2	2	2
50-69	1	1	2	2	3	3	3
70-84	1	1	2	2	3	3	4
85-99	1	1	2	2	3	3	5
100-134	1	2	3	3	4	4	5
>134	1	2	3	4	4	5	5

The titration is a guideline so that all weight categories exceed 15mg/kg/day. Doses will be guided by individual patient's ability to tolerate the medication. Changes to doses (increase or decrease) in individual patients can be made after the titration phase as long as it does not exceed the 30mg/kg/day or 2500mg/day threshold

After V3 (visit 3 - end of titration phase) any changes in dose will be followed by a telephonic assessment (face-to-face especially for in-patients) after 3 to 7 days on the new dose of medication to assess tolerability and suitability to continue that dose.

Appendix 2 - SAE Reporting schematic



The **AE** event is **SERIOUS** if any of the following criteria applies:

1. The participant died
2. The participant was at risk of death because of the AE
3. The AE lead to admission or extension of admission to hospital
4. The AE resulted in persistent or significant disability/incapacity
5. The AE is an important medical event that may jeopardise the participant (or an unborn child) and may require medical or surgical intervention to prevent one of the outcomes listed above

The event should be classed as a **SUSPECTED ADVERSE REACTION** if a possible relationship with the IMP cannot be ruled out.

If the nature of the adverse reaction is consistent with the SmPC or other relevant product information of the IMP or antipsychotic medication, then the event should be classed as an UNEXPECTED REACTION.