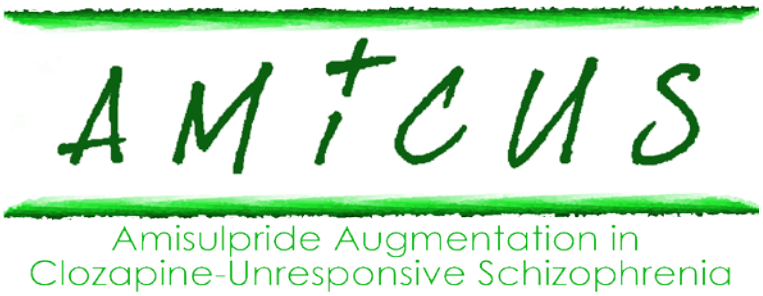
NETSCC, HTA

29th November 2011



Amisulpride augmentation in clozapine-unresponsive schizophrenia
AMICUS

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For general queries, supply of trial documentation, and collection of data, please contact the Trial Manager

Clinical queries should be directed to the local PI, who will direct the query to the appropriate person

Amisulpride augmentation in clozapine-unresponsive schizophrenia
AMICUS

A multi-centre, double-blind, individually randomised, placebo-controlled, parallel arm RCT with 12-week follow-up to establish the clinical and cost effectiveness of amisulpride augmentation of clozapine in treatment-resistant schizophrenia unresponsive to clozapine

Investigator Agreement

I have read this protocol and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

Principal Investigator (Print Name)	Investigator Signature	Date
Co-Investigator (Print Name)	Investigator Signature	Date
Co-Investigator (Print Name)	Investigator Signature	Date

Confidentiality Statement

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

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

This protocol describes the AMICUS study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

1. BACKGROUND AND RATIONALE

In around a third of people with schizophrenia, the illness shows a poor response to standard treatment with antipsychotic medication. While a relatively small proportion will fail to achieve remission even after the first exposure to antipsychotic medication, with either first or second generation drugs (Lambert et al 2008), more commonly the illness becomes progressively more unresponsive to medication with subsequent relapses (Wiersma et al 1998, Barnes et al 2003). This 'treatment-resistant' subgroup of patients represents a major clinical challenge in everyday psychiatry, and consumes a disproportionate amount of NHS funding (Davies & Drummond 1993, Knapp & Kavanagh 1997, Almond et al 2004). Mangalore & Knapp (2006) estimated that the total societal cost of schizophrenia in the UK in 2004/5 was £6.7 billion. The direct cost of treatment and care, falling on the UK public purse, was around £2 billion, while the burden of indirect costs to society was approaching £4.7 billion. The cost of informal care and private expenditures by families and carers was around £615 million, while the loss of productivity due to unemployment, absence from work and premature mortality of people with schizophrenia was estimated to be £3.4 billion and the lost productivity of their carers at around £32 million. Further, Mangalore & Knapp (2006) calculated that in addition to costs to the criminal justice system, around £570 million was being paid out in benefit payments, associated with about £14 million administration costs. Treatment resistant illnesses are the most costly, usually requiring longer term residential and intensive community treatments. There is clinical and economic need to evaluate treatments to improve outcomes in this deprived group of patients.

For treatment-resistant schizophrenia, a common therapeutic approach is to use more than one antipsychotic, although a robust evidence base to justify this is lacking. Recent surveys of prescribing patterns in the US, suggest that about 15% of outpatients, and up to 50% of inpatients, with schizophrenia receive two or more antipsychotics (Freudenreich & Goff 2002). In the UK, national clinical audit data on nearly 3,500 acute inpatients and nearly 2,000 forensic patients prescribed antipsychotics (Prescribing Observatory for Mental Health: POMH-UK 2006, 2007, data on file) revealed that around 40% of patients in both clinical settings were receiving combined antipsychotics. A common reason given by clinical teams for prescribing such a combination was failure of the illness to respond to treatment with a single antipsychotic. In the POMH-UK acute inpatient audit, 13% of prescriptions for combined antipsychotics represented the augmentation of clozapine with another antipsychotic, and the respective figure in forensic services was 37.5%. These figures are in line with other reports of the prevalence of clozapine augmentation, ranging from 18% to 44% depending on the clinical setting and country (Potter et al 1989, Taylor et al 2002, Buckley et al 2001). In summary, it seems that around a third of all clozapine-treated patients receive augmentation with another antipsychotic (Mouaffak al, 2006). This is because it is one of the few therapeutic strategies available to clinicians for those people with schizophrenia that has proved to be poorly responsive to clozapine.

Clozapine is the only antipsychotic with convincing evidence for efficacy in strictly-defined treatment-resistant schizophrenia. But in such cases it has limited efficacy, with 30-40% showing an inadequate response to the drug (Chakos et al 2001). In some patients, a range of potentially serious side effects such as seizures, sedation and tachycardia may prevent the optimal dose being reached. In the short term, metabolic side effects that increase the risk of diabetes and cardiovascular disease become apparent in many.

In an attempt to improve efficacy and limit tolerability problems, clinicians commonly augment clozapine with another antipsychotic, despite limited evidence on the potential risks and benefits of this practice (Remington et al 2005). Kontaxakis et al (2005a) identified 15 case studies of adjunctive agents in clozapine-resistant schizophrenia, 10 of which involved a second antipsychotic (1 using sulpiride, 1 olanzapine, 8 risperidone). They concluded that various methodological shortcomings limited the impact of the findings. These authors came to a similar conclusion after conducting a critical review of randomised controlled trials (RCTs) of clozapine augmentation in treatment-resistant schizophrenia (Kontaxakis et al 2005b), only one of which had used an antipsychotic (sulpiride) as the adjunctive medication. Similarly, Remington et al (2005) noted that the current body of evidence for clozapine augmentation consisted of data from a limited number of small open trials and case series reports. But they suggested that systematic research was warranted and argued for detailed

cost-benefit analysis. Buckley et al (2001) agreed, stating that there was 'a dearth of double-blind studies', and concluding that these adjunctive therapies were worthy of further testing in carefully controlled clinical trials. Recent publication of several new open studies and small RCTs testing the therapeutic value of augmenting clozapine with another antipsychotic prompted us to conduct a meta-analysis of eligible RCTs (Paton et al 2006). A systematic literature search identified 8 open studies and 4 eligible RCTs with a total of 166 participants. The two RCTs that lasted 10 weeks or more gave an odds ratio of response to treatment of 4.41 (95% CI 1.38-14.07). We concluded that for clozapine-refractory schizophrenia, augmentation of clozapine with another antipsychotic drug is worthy of an individual clinical trial, but this may need to be longer than the 4-6 weeks usually recommended for acute antipsychotic monotherapy, a view supported by Correll et al (2008). Mouaffak et al (2006) noted the discrepant results of the published studies of clozapine augmentation with another antipsychotic, identifying methodological shortcomings that related to the heterogeneity of definitions of resistance to clozapine, choice of outcome measures, and the dose and duration of the adjunctive drugs, that they considered 'a major limitation for drawing conclusions'. Clinical response in studies has generally been defined as a 20% reduction in total BPRS/PANSS score. Both the BPRS and the PANSS assess a broad range of symptoms including both positive (e.g. delusions, hallucinations, thought disorder) and negative symptoms. (e.g. blunted affect and emotion, poverty of speech, lack of motivation, and social and emotional withdrawal). Examination of symptom change in studies where augmentation was beneficial suggests a greater improvement in negative symptoms than positive symptoms (e.g. Josiassen et al 2005, Chang et al 2008).

The updated NICE guideline for the treatment of schizophrenia (NICE 2009) supports the augmentation of clozapine with a second antipsychotic in patients with an inadequate response to clozapine alone; advice that is supported by our meta-analysis (Paton et al, 2007). Since the publication of this meta-analysis, data have become available for a further three, short-term, clozapine augmentation RCTs, one each for risperidone (Freudenreich et al, 2007), haloperidol (Mossaheb et al, 2006), and aripiprazole (Chang et al, 2008); all are reported as negative, although the trial by Chang et al showed a statistically significant advantage for augmentation with aripiprazole with regard to reduction in negative symptom score. There is also one essentially negative, 16-week RCT of aripiprazole augmentation (Fleischhaker et al, 2008). Aripiprazole has a different pharmacology to other antipsychotic drugs in that it is a D2 partial agonist. The theoretical basis for augmenting clozapine with another antipsychotic is that clozapine is a weak D2 antagonist, and efficacy may be improved by adding a drug which is a more potent antagonist at this receptor. Negative studies of aripiprazole augmentation of clozapine are therefore difficult to interpret.

Amisulpride has been tested in case reports and case series (Croissant et al 2001, Ziegenbein et al 2002, Kampf et al 2005) and open studies of clozapine augmentation (Munro et al 2004, Ziegenbein et al 2006, Genc et al 2007). Augmentation with amisulpride was found to be well tolerated, and clinical response (again defined as 20% or greater reduction on PANSS total score) in the open studies by Munro et al and Zeigenbein et al occurred in around 70% of patients. There has been one previous 'pilot' double-blind, placebo-controlled RCT of clozapine augmentation with amisulpride (Assion et al 2008) for 6 weeks, in 16 patients with established schizophrenia, partially responsive to clozapine. The primary outcome measures, such as reduction in BPRS total score, failed to show a significant improvement, which the investigators attributed to the study's 'lack of power'. They concluded that 'further investigation requires a larger number of patients to be included'.

1.1 Prevalence of clozapine augmentation with a second antipsychotic in treatment-resistant schizophrenia

Despite the lack of an RCT testing clozapine augmentation with amisulpride, this is a strategy commonly used by clinicians in the NHS. Data from POMH-UK, taken at baseline in quality improvement programmes in acute inpatients (n=3492) in 2006 and forensic services (n=1848) in 2006 and 2007 respectively (POMH data on file) revealed that amisulpride was the antipsychotic most commonly prescribed in association with clozapine. The rationale for choice of an augmenting antipsychotic includes a complementary receptor profile, i.e. potent D2 dopamine receptor blocker (Freudenreich & Goff. 2002, Kontaxakis et al 2006, Genc et al 2007) and robust evidence for tolerability benefits such as a low liability for extrapyramidal side effects, and a low risk of compounding characteristic clozapine side effects such as sedation, weight gain and other metabolic problems. Amisulpride fits this profile. It is a benzamide derivative with selective affinity for human dopamine D3 and D2 receptor subtypes in vitro (Perrault et al 1997). It is classed as a second generation (atypical) antipsychotic on the basis of its relatively low liability for EPS, it causes little or no weight gain and has a similarly low risk for diabetes and lipid abnormalities (Tschoner et al 2007). Further, it is one of the few SGAs with some evidence for benefit on persistent negative symptoms (Boyer et al 1995, Loo et al 1997, Danion et al 1999).

1.2 Risks of clozapine augmentation

When adding one drug to another it is important to consider any potential for interactions that could lead to adverse consequences for the patient. Drug interactions can be either pharmacokinetic where one drug interferes with the way the body handles the other, usually by increasing or decreasing metabolism, or pharmacodynamic where one drug enhances or opposes the pharmacological action of the other.

Case reports have described clinically-significant elevations in serum clozapine after augmentation with the second-generation antipsychotic, risperidone (Tyson et al 1995). The potential relevance clinically of such an effect is, first, that it could cause clozapine plasma levels to reach an individual patient's threshold level for response, a benefit that might be erroneously attributed to a pharmacodymanic synergy between clozapine and the augmenting drug. Secondly, the increased clozapine plasma levels could be associated with the development of serious dose-related side effects. However, clozapine levels have been systematically measured before and after augmentation in four of the clozapine augmentation RCTs mentioned above (Josisassen et al 2005, Yagcioglu et al 2005, Honer et al 2006, Chang et al 2008), and in one the clozapine metabolite norclozapine was also measured, and no significant changes in mean plasma clozapine levels were reported.

In terms of side effects, RCTs and open studies have found clozapine augmentation with a second antipsychotic to be relatively well tolerated. The main treatment-emergent side effects have been predictable from pharmacology of the augmenting drug, with extrapyramidal side effects and prolactin elevation being the most common problems. There are, however, isolated case reports of more serious side effect. Published case reports of clozapine augmentation with risperidone have noted agranulocytosis, atrial ectopics and possible neuroleptic malignant syndrome (Godleski & Serynak 1996, Chong et al 1997, Kontaxakis et al 2002) while case reports of clozapine augmentation with aripiprazole have mentioned nausea, vomiting, insomnia, headache and agitation in the first 2 weeks (Zeigenbein et al 2006), tachycardia (Chang et al 2008) and also modest weight loss (Zeigenbein et al 2006, Karunakaran et al 2007).

Clozapine is commonly associated with sedation, weight gain and postural hypotension. Any augmenting antipsychotic should ideally have a low propensity to compound these side effects. Amisulpride fits these criteria. It is also renally excreted making any pharmacokinetic interaction with clozapine extremely unlikely. The one known disadvantage of amisulpride is that is raises serum prolactin.

2. STUDY OBJECTIVES

The objectives of the study are:

- To test the benefits, costs and risks of augmenting clozapine with amisulpride compared with placebo.
- To add to the clinical and economic evidence base for clozapine augmentation with a second-generation antipsychotic.
- To provide evidence relating to the duration of an adequate trial of clozapine augmentation.

- To examine the potential benefits, costs and risks of clozapine augmentation in treatment-resistant schizophrenia.
- Therapeutic improvement will be assessed in terms of overall symptom severity, but also using broader, clinically-relevant outcome measures of social and occupational function and target symptoms and/or behaviours as well as overall health status and utility. Side effects will be systematically assessed, including the use of a recently-developed scale designed to assess comprehensively the adverse effects of the second-generation antipsychotics.

3. STUDY DESIGN

The study to be undertaken will be a randomised, double-blind, placebo-controlled trial lasting 12 weeks. 230 eligible patients on clozapine will be randomised 1:1 to receive augmentation with either placebo or amisulpride.

3.1 Study outcome measures

Therapeutic improvement will be assessed in terms of overall symptom severity, but also using broader, clinically-relevant outcome measures of social and occupational function and target symptoms and/or behaviours as well as overall health status and utility. Side effects will be systematically assessed, including the use of a recently-developed scale (ANNSERS) designed to assess comprehensively the adverse effects of the second-generation antipsychotics.

The primary outcome measure will be the proportion of 'responders' using a criterion response threshold of a 20% reduction in mental state scale score, i.e. total score on the Positive and Negative Syndrome Scale (PANSS: Kay et al 1987, 1988). This is a commonly used criterion for response in schizophrenia trials, and will allow for comparison with similar published studies. A negative symptom subscale score can be derived from the PANSS, and this will be used to assess negative symptoms, while depression will be assessed using the Calgary Depression Rating Scale for Schizophrenia (CDSS: Addington et al 1993), a scale designed to minimise the potentially confounding symptom overlap between depressive features and both negative symptoms and extrapyramidal symptoms. Aspects of insight the will be assessed using the Schedule for the Assessment of Insight (SAI: David 1990). The impact on social and occupational function will be measured using the Social and Occupational Functioning Assessment Scale (SOFAS: Goldman et al 1992, DSM-IV 1994). For each participant, we will also derive, for each subject, 3 target symptoms and/or behaviours refractory to treatment, which are judged clinically to have compromised social function and community re-integration, been a major cause of distress, and/or precluded discharge from hospital. The level of engagement with clinical services will be assessed,

with the help of a patient's key worker, using the Service Engagement Scale (SES: Tait et al 2002).

The main potential hazards of the treatment strategy being tested are side effects. Non-neurological (weight gain, sexual dysfunction etc) effects will be systematically assessed using the Antipsychotic Non-Neurological Side Effects Scale (ANNSERS: Ohlsen et al 2008), a 44-item scale with good interrater reliability on clinician judged items, that we designed to systematically and comprehensively assess the full range of side effects, other than movement disorders, recognised as occurring with first and second generation antipsychotics. Metabolic side effects will be assessed using an obesity measure (body mass index: BMI) and assessment of blood pressure, serum prolactin, plasma glucose (non-fasting sample) and lipid profile. The motor side effects (extrapyramidal side effects) will systematically assessed using scales of established reliability and validity for drug-induced parkinsonism, akathisia and tardive dyskinesia. An ECG to establish a baseline for any subsequent cardiac monitoring, and exclude cardiac contraindications will also be performed at baseline.

The costs and outcomes for a cost effectiveness acceptability and net benefit analysis will be also measured. The primary economic measure will be the incremental cost effectiveness ratio of clozapine augmentation, estimated as net cost of clozapine augmentation divided by net QALY of clozapine augmentation. The economic evaluation will use a societal perspective and a within trial time horizon of 3 months. The results will be modelled to a time horizon of 1 year.

4. PARTICIPANT ENTRY

4.1 Inclusion criteria

People aged 18-65 years with a schizophrenic illness that has been unresponsive, at a criterion level of persistent symptom severity (as used by Honer et al 2006), to an adequate trial of clozapine monotherapy in terms of dosage, duration and adherence.

Patients must meet the following criteria to be eligible for enrolment:

1. A criterion level of persistent symptom severity despite an adequate trial of clozapine monotherapy in terms of dosage, duration and adherence (as used by Honer et al 2006):
    - Treatment for at least 12 weeks at a stable dose of 400 mg or more of clozapine a day, unless the size of the dose was limited by side effects

- A total score of 80 or greater at baseline on the Positive and Negative Syndrome Scale (PANSS: Kay et al 1987, 1988); the range of possible scores is 30 to 210, with higher scores indicating more severe symptoms.
- A Clinical Global Impressions (CGI: Guy 1976) score of 4 or greater (range of possible scores, 1=not mentally ill to 7=extremely ill)
- A Social and Occupational Functioning Assessment Scale (SOFAS: Goldman et al 1992, DSM-IV 1994) score of 40 or less; range of possible scores, 1 to 100, with lower scores indicating impaired functioning.

2. Age 18-65 years, inclusive
3. Clinically stable for the last 3 months with a consistent clozapine regimen.
4. Competent and willing to provide written, informed consent.

4.2 Exclusion criteria

1. Clinically-significant alcohol/substance use in the previous three months
2. Developmental disability
3. Indication for current treatment with clozapine was intolerance/movement disorder
4. A previous trial of clozapine augmentation with amisulpride.
5. Existing relevant physical health problems: such as cardiovascular disease, previous problems with prolactin, and impaired liver/ renal function.
6. Any woman who is pregnant or planning a pregnancy, and any woman of child bearing potential unless using adequate contraception.

Participants will be required to discontinue any antipsychotic (other than clozapine) and ECT for at least four weeks before entry into the study. Study researchers will discuss with the potential participant whether they are involved in any other study during initial discussion, and should the service user have been involved in other CTIMP's then the guidance from the Association of the British Pharmaceutical Industry will be followed, and study researchers will ensure at least a 4-month gap has elapsed before participation in the AMICUS study is broached.

5. RANDOMISATION AND ENROLMENT PROCEDURE

5.1 Randomisation practicalities

Randomisation will be undertaken by the PRIMENT (www.priment.mrc.ac.uk) Clinical Trials Unit. Equal numbers of participants will be randomised to each arm of the trial using a web based randomisation system. Stratification will occur by centre and halves of the baseline PANSS score. After consenting to participation and completing baseline assessments, patients will be randomly allocated to the intervention or comparator arm of the trial by the

research assistant accessing the randomisation service. They will be given a unique trial identification number for that participant, which will be used on the CRF. A copy of the allocation will be sent automatically by email to the study co-ordinator. Blinding of the allocation code will be maintained until all data entry and processing are complete and the database has been locked. All patients, carers, and study personnel will be blinded to treatment assignment, as will the statistician undertaking the data analysis. The study statistician will also be blind to trial arm allocation and will monitor recruitment rates on a monthly basis.

Each study participant will be assigned a unique trial identification number at the start of the assessment process. This number will be written on all clinical assessment forms/datasheets and databases used to record data on study participants. A hard copy of a record sheet linking patient identity, contact details and trial identification number for all participants will be kept at each site. It will be placed securely in a locked filling cabinet separate from datasheets. The local study co-ordinator will enter the data on to an electronic database, and all such data will be checked for errors before being transferred to the appropriate statistical package. All data will be kept secure at all times and maintained in accordance with the requirements of the Data Protection Act, and archived according to clinical trial GCP regulations.

5.2 Unblinding

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

- A serious adverse event arises that clinically requires disclosure
- Overdose of the trial drug
- Depression warranting treatment with an antidepressant
- There is a clinical need to start the patient on medication which has a risk of interaction

If a participant formally (in writing to the AMICUS office) requests disclosure of their treatment allocation, this will be made available to them alone after they have left the trial or at 12 weeks post-randomisation (whichever is the longer).

5.2.1 Emergency unblinding

In anticipation of an emergency, investigators, clinicians and participants will be provided with the telephone number for a 24-hour emergency unblinding service at the Guy's Medical Toxicology Unit, with medical support This system will allow a medical request for unblinding

in the event of a medical emergency to be responded to 24 hours a day, 7 days a week. Procedures will be put in place to verify the identity of the participant and caller and the decision on whether to reveal the study medication allocation will be based on a set of criteria for judging clinical need and recorded.

5.3 Discontinuation criteria and procedures

In accordance with the current revision of the Declaration of Helsinki (amended October 2000, with additional footnotes added 2002 and 2004), a participant has the right to stop trial treatment and to withdraw from the trial at any time and for any reason, without prejudice to his or her future medical care by the physician or at the institution, and is not obliged to give his or her reasons for doing so. The investigator may withdraw a participant from trial treatment at any time in the interests of the participant's health and well-being or for administrative reasons. The date and reason for termination of treatment will be recorded. Trial follow-up will continue after treatment has been withdrawn unless the participant withdraws consent.

6. TREATMENTS

6.1 Treatment arms

Clozapine augmentation with another second-generation antipsychotic, amisulpride, versus placebo (400mg, 2 x 200mg amisulpride capsules, or 2 matching placebo capsules for the first 4 weeks, then the option of titrating up to 800mg, 4 x 200mg amisulpride capsules, or 4 matching placebo capsules for the remaining 8 weeks). Medication will be supplied as identical capsules containing either 400mg amisulpride or placebo, packaged into monthly (28 tablets) packs. The optimum dose of clozapine at entry and subsequent augmentation will be achieved through a flexible dosing regimen whereby treating psychiatrists will be able to flexibly alter dosage regimens to maximise clinical risk-benefit ratios; an opportunity for clinical titration of clozapine dose will be at two and six weeks. The rationale for avoiding target doses or concentrations of clozapine is because of inter-individual variations in metabolic capacity and therefore serum levels achieved with fixed doses, and uncertainty over the existence of a plasma concentration threshold for response respectively. However, a direct pharmacokinetic effect on clozapine levels will be assessed by pre- and post-augmentation levels of clozapine, samples being taken at baseline and at the end of the 12 weeks.

6.2 Co-prescription and interaction with other drugs

Clinicians will be encouraged not to prescribe any additional medication during the course of the study, and will be reminded of the drugs with potential adverse interactions, as

mentioned in the SPCs for clozapine and amisulpride. Medication returns would be logged as a routine, allowing a 'pill count' check on medication adherence for each study participant. The clozapine/norclozapine ratio derived from a pre-dose ('trough') plasma drug level will also provide some indication of adherence: this ratio should average 1.33 across the dose range, but a ratio of <0.5 suggests poor compliance in preceding day(s). Recommended pharmacovigilance procedures will be followed.

It would be unethical to restrict the therapeutic options of the clinical teams participating. Our approach will therefore be primarily to record the use of all other medication, document details of dosage, and ensure the follow-up of all randomised participants, irrespective of the medication they subsequently receive. However, we will carry out a secondary per protocol analysis in which we will only analyse those individuals in the trial who have received medication we consider to be consistent with our aims. For that analysis, benzodiazepines and anticholinergic medications will be allowed along with the randomised antipsychotic or placebo and the clozapine. However, additional mood stabilisers, antidepressants and antipsychotics will not be included as a per protocol analysis. Clinicians will be asked to indicate the specific reasons for discontinuing the assigned study drug (amisulpride or placebo) during the duration of the study.

6.3 Dispensing and accountability

Once randomisation has taken place, a letter will be generated to confirm the randomisation code that has been allocated to the patient. An AMICUS study prescription form containing the patient's details (including their randomisation code) and details of collection or delivery arrangements will be signed by the site PI or other psychiatrist to whom the task is delegated, and sent to the study pharmacy. Each pharmacy will have a master list containing randomisation codes and treatment arm allocations and, upon receiving the study prescription form, will select the appropriate packs of trial medication blind and dispense it ready for collection. Pharmacy staff will retain the original prescription and complete the medication accountability form. Both will be stored in a pharmacy folder specific to the study.

7. PHARMACOVIGILANCE

The Principal Investigators at each recruitment site and the Chief Investigator will conduct safety monitoring of the trial according to the written standard operating procedures for pharmacovigilance agreed by the Imperial College AHSC Joint Research Office. According to these procedures, the criteria for a serious adverse event are: results in death; is life-threatening; requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; or consists of a congenital anomaly or birth defect.

The clinicians participating in the study will be provided with a list of expected adverse effects associated with the study drugs (see Appendix 2). They will be asked to report all serious adverse events (SAE), and any suspected unexpected serious adverse reactions (SUSARS) to the local Principal Investigator, who will inform the Chief Investigator as soon as possible. The Chief Investigator will inform the sponsor as soon as possible, but no later than 48 hours after first knowledge of the event. Clinicians should indicate the likelihood of a causal relationship with the prescribed study drug, and this will be verified by the Principal Investigator at the local site. The Chief Investigator will also inform the main REC, and copies of the adverse event form will be sent to the chair of the study IDMEC.

7.1. Definitions (See Appendix 3: Classification of adverse events)

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

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

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

7.1.3. Serious or Severe Adverse Events: To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

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

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

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

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

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

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

7.2 Reporting procedures (see flowchart, Appendix 4)

All SAEs whether observed by the investigator or reported by the participant and whether attributed to trial medication or not, will be reported in the CRF, with completion and signing of the Serious Adverse Event Reporting Form. SAEs considered by the Principal Investigator to be related to the trial medication will be followed until resolution or until the event is considered stable. The following attributes must be assigned by the investigator: description, date of onset and resolution date, severity (severity of events assessed on the following scale: 1=mild, 2=moderate, 3=severe), assessment of relatedness to trial medication, other suspect drug or device and action taken. The investigator may be asked to provide follow-up information.

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

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

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

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

All adverse events should be reported. Depending on the nature of the event the reporting procedures in this protocol should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

7.2.1 Reporting by investigator

All SAEs, except those SARs that do not require immediate reporting (see 7.2.3.), must be reported to the Chief Investigator within one working day of discovery or notification of the event. All SAE information must be recorded on an AMICUS SAE form, signed and dated, and emailed/faxed to the Chief Investigator. Additional information received for an event (follow-up or corrections to the original event data) needs to be detailed on a new SAE form and sent/faxed to the CI.

In addition to SAE reporting, investigators should report to the CI all and any non-serious adverse reactions (see 7.2.3. below). Adverse events that lead to withdrawal from the study or termination of the trial treatment during the randomised phase should also be reported.

7.2.2 Reporting by the Chief Investigator

The CI will:

- Report all SUSARs to the Competent Authority (i.e. MHRA) and the REC concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. In addition, a report will be sent to the Sponsor/Joint Research Office.
- Report all SAEs (including SUSARs) to the participant's NHS Trust and to the IDMEC
- Inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

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

- Submit once a year throughout the clinical trial or on request a safety report to the Competent Authority (MHRA), the main REC and participating NHS Trusts and send a copy to the Imperial College Joint Research Office.
- Provide data on all reported AEs to the IDMEC as required.

7.2.3 Suspected serious adverse reactions

Expected Serious Adverse Reactions: Immediate reporting of Suspected Serous Adverse Reactions that are listed in the SmPC for amisulpride will not be required provided that the severity and seriousness are consistent with the information given in the SmPC (see also Appendices 2 and 3). However, these events should be recorded in the patient's medical record/casenotes and on the study SAE form in the normal way, which must be forwarded to the study co-ordination centre within 1 month of the event.

7.2.4 Non serious AR/AEs

All such toxicities, whether expected or not, should be recorded in the patient notes as well as the toxicity section of the relevant case report form and sent to the study coordination centre within one month of the form being due.

7.2.5 Serious AR/AEs

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

8. OUTCOME ASSESSMENT AND FOLLOW-UP

This will be a three-year study: 5 months preparation (materials, research governance, etc.) initially. For the trial to start, the sponsor will need to review and approve all procedures and materials. There will be 24 months for recruitment, plus 3 months for the final follow-up assessments, then 4 months for data analysis and writing up the study report. The assessment measures to be used in the study are listed in Appendix 1. Outcomes scales will be administered at baseline and subsequently at 6 and 12 weeks by research assistants who will have been trained in the use of all the instruments and scales, to achieve a satisfactory level of inter-rater reliability.

8.1 Assessment of primary outcome

The primary outcome measure will be the proportion of patients with a criterion response threshold of a 20% reduction in total PANSS scale score, which will allow for comparison with other published trials (Paton et al 2007) and inclusion of our results in any future, appropriate Cochrane systematic review or similar. The PANSS (Kay et al 1987,1988, National Institute for Mental Health in England 2008) is a 30-item rating scale designed to provide a comprehensive assessment of psychopathology in adult patients with schizophrenia. Five components have been reported: positive, negative, depression, agitation-excitement, and disorganisation.

8.2 Secondary outcomes

8.2.1 Negative symptoms

The PANSS negative symptom subscale score will be used to assess negative symptoms. The validity of this negative subscale has been demonstrated (Gilbert et al 2000).

8.2.2 Social and occupational function

Social and Occupational Functioning Assessment Scale (SOFAS: Goldman et al 1992, DSM-IV 1994) derived from the Global Assessment Scale (GAS) but more focussed on a patient's social and occupational functioning; for an impairment to be rated, it must relate to psychological problems not lack of opportunity. In addition, using the symptom and behavioural assessments, and in discussion with the clinical team, we will identify for each participant the 3 target symptoms and/or behaviours that have proved to be persistent and have made a major adverse impact on the participant's social function and community re-integration, and/or been a major cause of psychological distress, admission to hospital and delayed discharge.

8.2.3 Service engagement

The level of engagement with clinical services will be assessed using the Service Engagement Scale (SES: Tait et al 2002); a 14-item measure consisting of statements that assess client engagement with services, rated on a four-point Likert scale from 'not at all or rarely' to 'most of the time'. Four sub-scales assess availability, collaboration, help-seeking and treatment adherence. High internal consistency and retest reliability, including discrimination between criterion groups, has been demonstrated for SES in a community setting (Tait et al 2002).

8.2.4 Depression

Depression will be assessed using the Calgary Depression Rating Scale for Schizophrenia. (CDSS: Addington et al 1993), a scale designed to minimise the potentially confounding symptom overlap between depressive features and both negative symptoms and extrapyramidal symptoms.

8.2.5 Insight

Insight will be assessed using the Schedule for the Assessment of Insight (SAI: David 1990). This scale comprises a semi-structured interview that obtains measures of three dimensions of insight: (1) awareness of mental illness, scored 0 to 6; (2) the ability to correctly attribute psychotic experiences, scored 0 to 4; and (3) acceptance of the need for treatment, scored 0 to 4. The maximum total score on the three dimensions is 14, but the scale also includes a supplementary question on hypothetical contradiction, scored 0 to 4. Thus, the maximum total score for the scale is 18, which indicates full insight.

8.2.6 Side effects

Non-neurological (weight gain, sexual dysfunction etc) effects will be systematically assessed using the Antipsychotic Non-Neurological Side Effects Scale (ANNSERS: Ohlsen et al 2008), a 44-item scale with good interrater reliability on clinician judged items, that we designed to systematically and comprehensively assess the full range of side effects, other than movement disorders, recognised as occurring with first and second generation antipsychotics.

Metabolic side effects will be assessed at baseline, and 12 weeks follow-up only using an obesity measure (body mass index: BMI +/- waist circumference) and assessment of blood pressure, serum prolactin, plasma glucose (non-fasting sample) and lipid profile. In line with best practice safety monitoring (Royal College of Psychiatrists 2006), an ECG will be carried out and reported on at baseline, before the study medication is initiated. This will be to establish a baseline for any subsequent cardiac monitoring, and exclude cardiac contraindications to potentially high-dose antipsychotic medication, including long QT syndromes.

With regard to extrapyramidal side effects, drug-induced parkinsonism will be assessed using the Simpson and Angus (1970) scale (Janno et al 2005). The Barnes Akathisia Rating Scale (Barnes 1989) will be used to assess akathisia, and the Abnormal Involuntary Movement Scale (Guy 1976, National Institute for Mental Health in England 2008) for rating tardive dyskinesia. Researchers will receive thorough training on the use of these measures and how these motor signs can be distinguished from negative symptoms of schizophrenia assessed when using the PANSS. Videotapes of patients with negative symptoms and

extrapyramidal side effects will be used to illustrated differences between these signs and symptoms and inter-rater reliability of researchers will be formally tested prior to the start of data collection.

8.2 Health economics

Two analytic approaches will be used: a within-trial analysis and a decision analytic model. Both approaches will have the following features. Incremental cost effectiveness ratios (ICERs) will be estimated. The primary health benefit measure for the economic analysis will be quality adjusted life years (QALYs). Cost effectiveness acceptability analysis and net benefit statistics will be estimated to assess the likely cost effectiveness of clozapine augmentation compared to no clozapine augmentation.

For both the within-trial analyses and the economic model, the perspective of the NHS and social care providers and patients, which approximates a societal perspective, will be used. The within-trial economic analysis will use the intent-to-treat sample of trial participants. Resource use and EQ-5D data will be collected for all participants at baseline and scheduled 12 week follow-up.

8.2.1 Data and measures: within trial analysis

Resource use data will be collected for NHS secondary and primary care services, formal, independent and voluntary social care services and patient and family expenditure. The key determinants of total direct costs are expected to be those associated with the use of NHS hospital inpatient, outpatient and clinic services provided for the initial trial interventions and associated follow-up. These items comprised approximately 90% of the total costs for participants in the recent CUtLASS trial (Davies et al, 2007; Davies et al 2008) who were randomised to second-generation antipsychotics (SGAs). Accordingly, these data will be collected for all patients recruited into the trial from baseline to the end of scheduled follow-up. Hospital service use data will be collected from routine hospital information systems and study case record forms by the trial researchers. Use of other services will be collected from resource use questionnaires completed with participants at each scheduled baseline and follow-up assessment. The service use data collection forms will be adapted from those used in previous economic evaluations conducted by the applicants.

Each item of resource use will be multiplied by the unit cost specific to that item. Standard national unit costs will be used. Mental health hospital services will be costed using the relevant national reference costs for each type of admission or ward (published annually by the Department of Health). Medications will be costed using the British National Formulary. Other services will be costed using the most detailed national unit cost available (e.g. Unit

costs of health and social care published annually by the PSSRU, University of Kent).

QALYs gained from baseline to end of scheduled follow-up will be estimated as the number of weeks multiplied by the utility of observed survival. The utility values will be estimated from the Euroqol EQ-5D health status questionnaire completed at each follow-up assessment and the associated published societal utility tariffs. The EQ-5D is a generic and validated health status questionnaire shown to have acceptable validity in people with schizophrenia in European countries (Bobes et al 2005; Prieto et al 2003, National Institute for Mental Health in England 2008). The EQ-5D has been used successfully in two recent UK trials of antipsychotics in schizophrenia (Davies et al, 2007; Davies et al 2008). Data from these trials demonstrated that the EQ-5D correlates with clinical measures of quality of life and effectiveness and is sensitive to change. The EQ-5D will be collected for all participants at baseline and scheduled follow-up.

8.2.2 Data and measures: economic model

The economic model will estimate the expected costs and QALYs of both interventions and the incremental costs and QALYs of clozapine augmentation. The model will synthesise data on resource use, costs and QALYs from the clinical trial and from published systematic reviews of the clinical and economic literature. This will be supplemented where necessary by expert opinion (e.g. to predict the long term impact of clozapine augmentation over 5 and 10 years). A focussed but systematic search and review of the literature will be conducted to identify economic analyses relevant to the target population published in the previous 10 years. If appropriate data are found in the systematic review, meta analytic techniques will be used to synthesise the trial and published data to estimate the probability of events, costs and QALYs. Otherwise, the data from the published literature and expert opinion will be used to generate alternative ranges and distributions for the probabilistic sensitivity analysis.

9. STATISTICS AND DATA ANALYSIS

9.1 Study data analysis

Given the tentative evidence suggesting that a significant clinical response to the intervention being assessed may not be manifest before 10 weeks of treatment, the six-week data will be used to determine whether there is earlier benefit from the intervention. The six-week outcome data will also be examined as a (tertiary) outcome, looking at the data longitudinally using both six and twelve week outcomes and controlling for baseline values of the given measure. The six week data will also be included in the imputation models to help determine values of missing data in other variables for a given person.

All the main analyses will be based on Intention-to-Treat, after appropriately allowing for any loss to follow-up (missing data) using multiple imputations. Analysis will take place after full recruitment and follow-up (i.e. there will be no interim analyses). Group differences in the primary outcome (criterion response threshold of >20% reduction in total PANSS score) and other binary outcome measures will be evaluated through the use of logistic regression after allowing for stratification (treatment centre by sex) and baseline symptom severity (using computationally-demanding exact methods if necessary). Differences in quantitative outcome measures will be evaluated through corresponding analysis of covariance (ANCOVA) model. The results of the trial will be presented following the standard CONSORT recommendations.

9.2 Health economics

9.2.1 Within-trial analysis

The within-trial analysis of data will use an intent-to-treat approach. Incremental cost effectiveness ratios (ICER) will be estimated as the incremental cost of clozapine augmentation divided by the incremental outcome of clozapine augmentation. For the primary within-trial analysis, the outcome measure to estimate the ICER will be the QALY. Within-trial primary and sensitivity analyses will be conducted. The primary and sensitivity analyses will both use the incremental cost per QALY as the primary measure for the cost effectiveness acceptability analyses. Within-trial sensitivity analyses will include use of alternative outcome measures as the denominator in the incremental cost effectiveness ratios (e.g. cost per participant with clinically significant improvement) and the use of alternative unit cost data for key cost events (for example where more than one estimate of the cost per inpatient day is available). Sensitivity analysis will also be used to asses the potential impact of analytic techniques, such as the methods used to impute missing observation and missing follow-up.

The within-trial primary and sensitivity analyses will use ANCOVA to adjust for baseline covariates that may also be determinants of costs and outcomes. The baseline covariates will be identified from those used in previously published economic analyses and are likely to include costs in the period prior to baseline, baseline clinical and socio-demographic characteristics and utility scores.

For both the primary and sensitivity within-trial analyses, cost-effectiveness acceptability curves (CEACs) will be plotted to summarise uncertainty associated with the ICER, rather than using parametric methods of analysis that do not allow variance in the ICER to be interpreted in any meaningful way (Fenwick et al, 2001, Pedram-Sendi and Briggs, 2001,

Briggs and O'Brien 2003). To derive CEACs, the incremental cost and QALY estimates from the ANCOVA (adjusted for baseline covariates) will be bootstrapped to simulate the sample data of costs and QALY (Briggs et al, 2002). The bootstrapped estimates of net QALYs will be revalued, using a range of ceiling ratios or willingness to pay thresholds (WTPT) to gain 1 QALY. For each WTPT, a net benefit statistic (NB) will be estimated as:

NB = E * WTP – C (Where E = incremental QALY gained by FGAs, WTP = willingness to pay to gain 1 QALY, C = incremental cost of amisulpride)

The WTPT values will range from decision makers being willing to pay £0 to gain 1 QALY to decision makers being willing to pay £35,000 to gain 1 QALY. This includes the range of implied values that are acceptable to policy makers in the UK (Rawlins and Culyer 2004).

For those patients who complete scheduled follow-up, missing observations on costs and outcomes will be imputed using multiple imputation. For these patients it will be assumed that any missing observations are missing at random. If the missing data are statistically associated with, or depend on, other observed variables in the data set, then the missing data may be treated as missing at random. The multiple imputation will use multivariate analysis to predict the values of missing observations for each participant with complete follow-up, controlling for baseline characteristics of the patient and treatment allocation. Missing data are typically multivariate, with several variables having missing values. Missing values in a given variable Y will be predicted from an iterative process of regression of the dependent variable Y on the complete cases of all other variables in the dataset. This process will be repeated for each variable with missing values using the complete cases of the other variables, including previously imputed values, until a completed rectangular data set, with a full set of observations for each participant has been generated. It is anticipated that the ICE package for multiple imputation in STATA will be used which implements the iterative multiple imputation process using chained equations. The multiple imputation regressions will be run on bootstrapped samples of the non-missing observations. The use of bootstrapped samples does not assume a normal distribution and is more robust for cost and QALY data that have skewed distributions. The multiple imputation procedure will derive 10 copies of the imputed datasets. The imputed datasets will be stacked and analysed in STATA, to combine the data whilst retaining the uncertainty associated with the imputation process.

For those patients who do not complete scheduled follow-up, the assumption that the missing data are missing at random is weakened, since the reasons for loss to follow-up are unknown. Effectively there is sample selection, which may bias the estimates of costs and

outcomes if not controlled for. For this case, missing data will be treated as censored and imputed using survival analysis. Regression models (e.g. Cox proportional hazard models) will be used to predict the likelihood of key events that determine future costs and outcomes (e.g. survival, relapse, admission to inpatient care). The average cost and outcomes for each of these events will be estimated from the data of participants who complete follow-up. The imputed cost for participants lost to follow-up will be the sum of the cost of each event weighted by the probability that event will occur. The survival models will include patient clinical and socio-demographic characteristics, baseline utility scores and costs prior to baseline.

9.2.2 Economic model analysis

The aim of the economic model will be to supplement the within-trial analysis and assess (i) whether the within-trial results are likely to hold over longer time periods and (ii) highlight any areas of uncertainty. The model type (e.g. decision analytic, markov model) and structure will be developed and validated with reference to published clinical and economics literature, treatment guidelines and expert opinion. The analyses of the model will estimate the incremental cost-effectiveness ratio associated with clozapine augmentation. Cost-effectiveness acceptability analysis and net benefit statistics will be estimated to assess the likely cost effectiveness of clozapine augmentation compared to no clozapine augmentation over the 1-year and 5-year time horizons. Probabilistic and one-way sensitivity analysis will be used to explore uncertainty in the data and structural uncertainty associated with the model structure and data sources.

9.3 Missing data

The methods for dealing with missing data for the economic analysis are described above. For the clinical analysis, it must be accepted that, as in most clinical research studies, it is inevitable there will be some missing data. In this study population it may arise from participants not attending appointments or being fatigued during testing and therefore not completing the battery of tests. It is not known in advance whether there will be patterns in the variables that have missing data. However, this will be checked before more sophisticated techniques are carried out. As described for the economic analysis, it is envisaged that it will be possible to impute the missing data using multiple imputation techniques (for example ice in STATA). The variables placed into the imputation model will be selected in consultation with the study team to ensure that spurious associations are not formed. The resulting imputed data will then be analysed and combined estimates will be obtained using Rubin's Rules.

10. MONITORING AND AUDIT

10.1. Routine monitoring

Day-to day monitoring will be carried out by the central study team: the Trial co-ordinator and Chief Investigator. This will include checking that:

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

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP. The Independent Data Monitoring and Ethics Committee will also have a monitoring and audit role (see section 12.2 above)

10.2 On-site monitoring

On-site monitoring visits to the four study sites by the central study team will be arranged during the study. Arrangements for site visiting may vary from routine visits to all sites, visits to a random selection of sites or visits targeted at less experienced sites or those for which the central monitoring procedures suggest possible problems. The remit of the visiting team will include the following:

- Education of the local site investigators and participating clinicians about the trial
- Review of the understanding of the protocol and trial procedures
- Verification that the study team and staff at the site have access to the necessary documents to conduct the trial
- Ensuring that the required pharmacy resources and arrangements are adequate
- To check adherence to the protocol and GCP by reviewing such things as signed consent forms and patient eligibility
- Verification of selected data items and/or serious adverse events recorded on the CRFs compared with data in the clinical records to identify errors of omission as well as inaccuracies

11. REGULATORY ISSUES

11.1. Declaration of Helsinki

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

11.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that the trial is conducted in full conformity with relevant regulations and with the Medicines for Human Use (Clinical Trials) Regulation 2004

transposed into law from the EU Clinical Trials Directive 2001/20/EC, the EU Good Clinical Practice Directive 2005 and all current and future acts and requirements pertaining to its conduct. A Clinical Trial Authorisation (CTA) application will be made to the MHRA. Imperial College has a Clinical Research Governance Office in place to provide guidance and compliance assessment in relation to all aspects of clinical research regulation, the Research Governance Framework and best practice requirements.

11.3 CTA

Clinical Trials Authorisation will be applied for from the UK Competent Authority, the MHRA.

11.4 Ethical approval

The Study Coordination Centre will apply for approval from a designated Research Ethics Committee. The study will be submitted for Site Specific Assessment (SSA) at each participating NHS Trust, via the CSP system. The Study Coordination Centre will require a copy of the SSA approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

11.5 Consent

Written informed consent will be obtained from each subject prior to their inclusion in this study in line with the Information Sheets and Consent Forms, Guidance for Researchers and Reviewers, Version 3.2 May 2007 (National Research Ethics Service: NRES), and in compliance with those statutory requirements published in Schedule 1 of the Medicines for Human Use (Clinical Trials) Regulations 2004. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage should he/she consider that this is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

11.6 Confidentiality

Participants' identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

11.7 Sponsor

Imperial College would view itself as the primary sponsor. Given that the Department of Heath, with the HTA programme acting as their agent, is prepared, in principle, to be nominated as the sponsor, then co-sponsorship responsibilities could be agreed with Imperial if the application is successful. In accordance with high standards of research governance we would ensure researchers receive training in the International Conference on Harmonisation (ICH) Guidelines - Good Clinical Practice.

11.8 Indemnity

Imperial College holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

11.9 Funding

The National Institute for Health Research, Health Technology Assessment Programme is funding this study. There are no per patient payments included in the award, nor any investigator payments.

11.10 Retention of relevant trial documentation

All trial documentation and data will be retained for a minimum of 5 years, as stated in Clinical Trials Regulations.

12. TRIAL MANAGEMENT

12.1 Trial Steering Group

We will set up a Trial Steering Group (TSC) and an Independent Data Monitoring and Ethics Committee (IDMEC) prior to the start of the study. The TSC (to be chaired by Professor Stefan Priebe, Wolfson Institute of Preventive Medicine, Queen Mary's School of Medicine and Dentistry, University of London) will comprise study applicants, a representative of the HTA, and representatives of service users and providers. Service user input will be organised through the North London MHRN hub Service User Group (www.sunlows.org.uk, lead: Ms Fenella Lemonsky).

12.2 Independent Data Monitoring and Ethics Committee

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

12.3 Criteria for the termination of the trial

Prior to the start of recruitment, the dataset that will be required by the Independent Data Monitoring and Ethics Committee (IDMEC) for interim analyses will be agreed. Stopping rules will also be agreed which specify the point at which interim results will be judged to be sufficiently conclusive for it to be appropriate for the IDMEC to recommend to the Trial

13. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The primary report will be submitted to a high impact medical journal. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

The results will be further disseminated via systematic reviews, guidelines and evidence syntheses. Health economic analyses and results will be reported to field conferences and journals

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APPENDIX 1
AMICUS: PROPOSED RATING SCALES AND ASSESSMENTS

All outcomes scales will be administered at baseline and subsequently at 6 and 12 weeks

Positive and Negative Syndrome Scale (and PANSS negative symptom subscale):

- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schiz Bull* 1987;13:261-76.
- Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the Positive and Negative Syndrome Scale for schizophrenics. *Psychiatry Res* 1988;23:99-110.

Social and Occupational Functioning Assessment Scale (SOFAS):

- Goldman HH, Skodol AE, Lave TR: "Revising Axis V for DSM-IV: A Review of Measures of Social Functioning. *Am J Psychiatry* 1992;149:1148–1156.
- Diagnostic and Statistical Manual of Mental Disorders, 4th ed.: DSMV-IV. Washington, D.C.: American Psychiatric Association, 1994.

Service Engagement Scale (SES):

- Tait L, Birchwood M & Trower P. A new scale (SES) to measure engagement with community mental health services. *J Mental Health* 2002;11:191-198.

Calgary Depression Rating Scale for Schizophrenia. (CDSS):

- Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. *Br J Psychiatry* 1993; Suppl. 22:39-44.

Schedule for the Assessment of Insight (SAI):

- David AS (1990) Insight and psychosis. *Br J Psychiatry* 156:798–808.

Antipsychotic Non-Neurological Side Effects Scale (ANNSERS):

- Ohlsen RI, Williamson RJ, Yusufi B, et al. Interrater reliability of the Antipsychotic Non-Neurological Side-Effects Rating Scale (ANNSERS). *J Psychopharmacol* 2008;22:323-329.

Metabolic side effects: obesity measure (body mass index: BMI +/- waist circumference), assessment of blood pressure, serum prolactin, plasma glucose (non-fasting sample) and lipid profile: baseline and 12 weeks only

Simpson and Angus extrapyramidal side effects rating scale (EPSE):

- Simpson GM, Angus JWS. A rating scale for extrapyramidal side-effects. *Acta Psychiatrica Scand* 1970;212 suppl. 44):11–19
- Janno S, Holi MM, Tuisku K, et al. Validity of Simpson-Angus Scale (SAS) in a naturalistic schizophrenia population. *BMC Neurology* 2005;5:5.

Barnes Akathisia Rating Scale (BARS):

- Barnes TRE. A rating scale for drug-induced akathisia*. Br J Psychiatry* 1989;154:672–6.

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Abnormal Involuntary Movement Scale (AIMS):

- Guy W. ECDEU assessment manual for psychopharmacology, revised edition. Washington, DC: US Department of Health, Education and Welfare, 1976:534–7. (Document no. ADM 76–338.).
- National Institute for Mental Health in England. *Mental Health Outcomes Compendium*, DH Publications 2008
(www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093316)

Resource use data for health economics

Euroqol EQ-5D health status questionnaire

- National Institute for Mental Health in England. *Mental Health Outcomes Compendium*, DH Publications 2008.
(www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093316)
- Bobes J, Garcfa-Portilla P, Sfiiz PA et al (2005) Quality of life measures in schizophrenia. *European Psychiatry*, 20, S313-S317.
- Prieto L, Novick D, Sacristan JA, et al. A Rasch model analysis to test the cross-cultural validity of the EuroQoL-5D in the Schizophrenia Outpatient Health Outcomes Study. *Acta Psychiatr Scand* 2003;107 (Suppl. 416): 24–29).

APPENDIX 2
EXPECTED ADVERSE EFFECTS ASSOCIATED WITH THE STUDY DRUGS

CLOZAPINE

The table below is taken from the SmPC and lists treatment-emergent adverse experience frequency estimate from spontaneous and clinical trial reports. Adverse reactions are ranked under headings of frequency, using the following convention: Very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Investigations		
	Rare:	Increased CPK
Cardiac disorders		
	Very common:	Tachycardia
	Common:	ECG changes
	Rare:	Circulatory collapse, arrhythmias, myocarditis, pericarditis/pericardial effusion
	Very rare:	Cardiomyopathy, cardiac arrest
Blood and lymphatic system disorders		
	Common:	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
	Uncommon:	Agranulocytosis
	Rare:	Anaemia
	Very rare:	Thrombocytopenia, thrombocythaemia
Nervous system disorders		
	Very common:	Drowsiness/sedation, dizziness
	Common:	Blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsions/myoclonic jerks
	Rare:	Confusion, delirium
	Very rare:	Tardive dyskinesia, obsessive compulsive symptoms
Respiratory, thoracic and mediastinal disorders		
	Rare:	Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal
	Very rare:	Respiratory depression/arrest
Gastrointestinal disorders		

	Very common	Constipation, hypersalivation
	Common:	Nausea, vomiting, anorexia, dry mouth
	Rare:	Dysphagia
	Very rare:	Parotid gland enlargement, intestinal obstruction/paralytic ileus/faecal impaction
Renal and urinary disorders		
	Common:	Urinary incontinence, urinary retention
	Very rare:	Interstitial nephritis
Skin and subcutaneous tissue disorders		
	Very rare:	Skin reactions
Metabolism and nutrition disorders		
	Common:	Weight gain
	Rare:	Impaired glucose tolerance, diabetes mellitus
	Very rare:	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypertriglyceridaemia, hypercholesterolaemia
Vascular disorders		
	Common:	Hypertension, postural hypotension, syncope
	Rare: Not known:	Thromboembolism Venous thromboembolism
General disorders and administration site conditions		
	Common:	Fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation
	Uncommon:	Neuroleptic malignant syndrome
	Very rare:	Sudden unexplained death
Hepatobiliary disorders		
	Common:	Elevated liver enzymes
	Rare:	Hepatitis, cholestatic jaundice, pancreatitis
	Very rare:	Fulminant hepatic necrosis
Reproductive system and breast disorders		
	Very rare:	Priapism
Psychiatric disorders		
	Rare:	Restlessness, agitation

Very rare events of QT prolongation which may be associated with Torsades De Pointes have been observed although there is no conclusive causal relationship to the use of this medicine.

AMISULPRIDE

Taken from the SmPC, the following list is of adverse effects that have been observed in controlled clinical trials. It should be noted that in some instances it can be difficult to differentiate adverse events from symptoms of the underlying disease. The rankings of frequency are the same as those for clozapine side effects (see above)

Nervous system disorders
Very common: Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.

Common: Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent. Somnolence.

Uncommon: Tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms. Seizures.

Psychiatric disorders:
Common: Insomnia, anxiety, agitation, orgasmic dysfunction

Gastrointestinal disorders
Common: Constipation, nausea, vomiting, dry mouth

Endocrine disorders
Common: Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction.

Metabolism and nutrition disorders
Uncommon: Hyperglycemia (see 4.4 Special warnings and precautions for use).
Cardiovascular disorders
Common: Hypotension
Uncommon: Bradycardia

Investigations
Common: Weight gain
Uncommon: Elevations of hepatic enzymes, mainly transaminases

Immune system disorders
Uncommon: Allergic reaction

Post Marketing data
In addition, cases of the following adverse reactions have been reported through spontaneous reporting only:

Nervous system disorders: *Frequency not known:* Neuroleptic Malignant Syndrome (see 4.4 Special warnings and precautions for use).

Cardiac disorders: *Frequency not known:* QT interval prolongation and ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death (see 4.4 Special warnings and precautions for use).

APPENDIX 3: CLASSIFICATION OF ADVERSE EVENTS

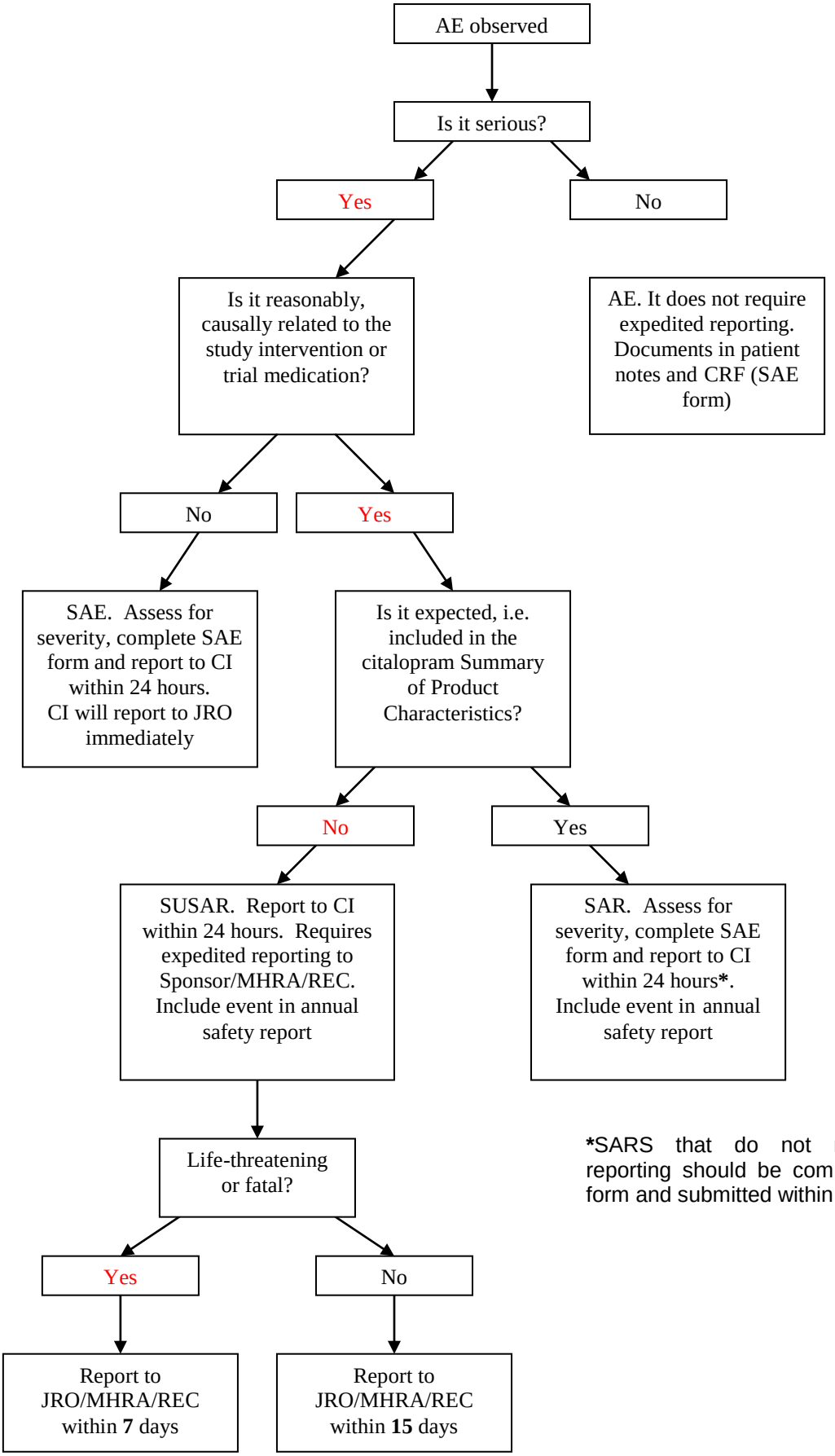
APPENDIX 4

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

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

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

APPENDIX 4: REPORTING SAEs: FLOWCHART



*SARS that do not require immediate reporting should be completed on the SAE form and submitted within 1 month of event