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| Study Analysis Plan | |
| SAP reference: AMICUS/SAP/003 | |
| Version Number: 4.0 | |
| Author: Dr. Louise Marston | |
| Signature: | Date: |

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| Version | Date Implemented | Details of Significant Changes | Author Initials |
| 2 |  | Update All centres included added to the relevant section  Update in IDMEC confidentiality section re blinding of the statistician.  Update how data have been analysed to date for the IDMEC meetings  Update sample size section added |  |
| 3 | 14/11/2014 | Update of how the data have been analysed to date for the IDMEC meetings  Update on the statistical analysis in preparation for final data analysis |  |
| 4 | 03/02/2015 | Update to the statistical analysis in the way centre is taken into account |  |
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**Version History Log**

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

**Introduction**

This analysis plan sets out the methods of analysing the predetermined primary and secondary outcomes, which will be reported in the National Institute for Health Research, Health Technology Assessment (HTA) report at the end of the trial and also in the main peer review paper to result from this randomised controlled trial. It complies with Priment’s SOPs on writing an analysis plan and analysing a randomised controlled trial. This analysis plan does not cover the economic analysis.

**Objectives**

* To determine whether there are any difference in total PANSS score between those randomised to clozapine with amisulpride versus placebo in clozapine-unresponsive schizophrenia at the end of follow up.
* To examine whether there are differences in the PANSS negative symptoms score between the two randomised groups at the end of follow up.
* To investigate whether there are differences in service engagement between the two randomised groups at the end of follow up.
* To explore whether there is a difference in depression between the two randomised groups at the end of follow up.
* To examine whether there is a difference in insight between those randomised to clozapine with amisulpride versus placebo at the end of follow up.
* To investigate whether there are differences in side effects (non-neurological, metabolic or drug induced Parkinsonism) between the two randomised groups at the end of follow up.

**Trial design**

It is a double blind placebo controlled randomised trial comparing clozapine with amisulpride to clozapine with placebo. There will be follow up at six weeks and 12 weeks, with the primary outcome being at 12 weeks.

**Sample size**

The original sample size calculation (prefunding) assumed 30% of participants in the intervention arm and 10% in the placebo arm will have at least a 20% reduction in Positive and Negative Syndrome Scale (PANSS) total score. With 90% power, the study would need 92 people in each arm (184 in total) to complete the study. Assuming 20% dropout this increases to 230 into the study (115 to each arm).

As part of the AMICUS rescue plan submitted to the HTA in March 2013, the sample size was recalculated with the same assumptions but 80% power. This gave 72 in each arm (144 in total); accounting for 20% drop out gives 90 in each group (180 in total). However this total will is unlikely to be reached by the end of recruitment.

**Centres**

*Funded*

West London Mental Health NHS Trust

Camden and Islington NHS Foundation Trust

Manchester Mental Health and Social Care Trust

Oxleas NHS Foundation Trust

*Unfunded*

Avon and Wiltshire Mental Health Partnership

Birmingham and Solihull Mental Health Foundation Trust

Bradford District Care Trust

Central and North West London NHS Foundation Trust

Derbyshire Healthcare NHS Foundation Trust

Devon Partnership NHS Trust

Greater Manchester West Mental Health MHS Foundation Trust

Kent and Medway NHS and Social Care Partnership Trust

Lincolnshire Partnership NHS Foundation Trust

Leeds and York Partnership NHS Foundation Trust

Northumberland Tyne and Wear NHS Foundation Trust

North Essex Partnership NHS Foundation Trust

Nottingham Healthcare NHS Trust

Somerset Partnership NHS Foundation Trust

South Staffordshire and Shropshire Healthcare NHS Foundation Trust

Southern Health NHS Foundation Trust

Tees, Esk and Wear Valleys NHS Foundation Trust

**Inclusion criteria**

* Patients must be aged between 18 and 65 years
* Patients must be diagnosed with a schizophrenic illness that has been clinically unresponsive to clozapine treatment alone
* They must have been prescribed clozapine for at least three months
* They must have been prescribed clozapine at a stable dose of 400mg or more a day, unless dosage was limited due to side effects
* They must have been clinically stable for the last three months
* They must have persistent symptoms (a score of 80 or greater on the total PANSS)1
* They must be at least moderately ill (reach a score of 4 or greater on the Clinical Global Impression)2
* They must have marked social and occupational functioning (a score of 40 or less on the Social and Occupational Functioning Assessment Scale (SOFAS))3
* The patient agrees to participate, providing written consent

**Exclusion Criteria**

* The patient has had significant alcohol/ substance use in the previous three months
* The patient has a developmental disability
* Current clozapine treatment was prescribed due to intolerance/ movement disorder
* The patient has previously taken part in a trial of clozapine augmentation with amisulpride
* The patient is currently taking part in another study
* The patient has existing relevant health problems, such as cardiovascular disease, previous problems with prolactin or impaired liver/ renal function
* Female patients who are pregnant or planning a pregnancy or any woman of child bearing potential not using adequate contraception

**Randomisation**

Randomisation can be carried out once the Referral and Screening Questionnaire (AMICUS/DOC/022) and the Screening Assessment Case Report Form (AMICUS/DOC/023) have been completed, but can also be done after part or full completion of the Baseline Assessment Case Report Form (AMICUS/DOC/024). Randomisation is carried out via a randomisation service in Sheffield and randomisation codes are obtained via a web based system. Randomisation is stratified by baseline PANSS score (high PANSS score versus low PANSS score) and centre. Randomisation is in mixed blocks of 2, 4 and 6.

**Randomised treatments**

Intervention: Clozapine with amisulpride

Control: Clozapine with placebo

The initial dose will be administered as two capsules per day. If the dose is increased then it will be necessary to take four capsules per day.

**Data collection**

*Baseline (identifying variables are not shown on this list)*

Positive and Negative Syndrome Scale Rating Criteria (PANSS)1

OPCRIT4

Social and Occupational Functioning Assessment Scale (SOFAS)3

Randomly assigned treatment arm

Sex

Date of birth (from which and the date of assessment, age can be calculated)

Ethnicity

Inpatient/ outpatient

Date of first presentation to services with schizophrenia

Primary diagnosis

Medication taken in the last three months

Date of assessment

Antipsychotic Non-Neurological Side-Effects Rating Scale-Enhanced (ANNSERS-E)5

MMSE (if known, so not systematically collected)

Service engagement scale (SES)6

Schedule for the Assessment of Insight (SAI)7, 8

Barnes Akathisia Rating Scale (BARS)9, 10

Abnormal Involuntary Movement Scale (AIMS)2

Simpson-Angus Scale for Extrapyramidal Side-Effects (EPSE)11, 12

Calgary Depression Rating Scale for Schizophrenia13

EQ-5D Health Questionnaire (used in the economic analysis only)

Weight

Height

Body mass index

Waist circumference

Systolic blood pressure

Diastolic blood pressure

Serum Prolactin

Plasma Glucose (non-fasting sample)

Total Cholesterol

HDL Cholesterol

LDL Cholesterol

Triglycerides

Economic Patient Questionnaire (EPQ) (used in the economic analysis only)

*Follow up*

*Six weeks*

Date of assessment

Medication taken since the last assessment

Positive and Negative Syndrome Scale Rating Criteria (PANSS)1

Additional Identification of Key Target Symptoms/ Behaviours from PANSS and other behavioural scales

Social and Occupational Functioning Assessment Scale (SOFAS)3

Antipsychotic Non-Neurological Side-Effects Rating Scale-Enhanced (ANNSERS-E)5

Service engagement scale (SES)6

Schedule for the Assessment of Insight (SAI)7, 8

Barnes Akathisia Rating Scale (BARS)9, 10

Abnormal Involuntary Movement Scale (AIMS)2

Simpson-Angus Scale for Extrapyramidal Side-Effects (EPSE)11, 12

Calgary Depression Rating Scale for Schizophrenia13

*12 weeks*

Date of assessment

Medication taken since the last assessment

Positive and Negative Syndrome Scale Rating Criteria (PANSS)1

Additional Identification of Key Target Symptoms/ Behaviours from PANSS and other behavioural scales

Social and Occupational Functioning Assessment Scale (SOFAS)3

Antipsychotic Non-Neurological Side-Effects Rating Scale-Enhanced (ANNSERS-E)5

Service engagement scale (SES)6

Schedule for the Assessment of Insight (SAI)7, 8

Barnes Akathisia Rating Scale (BARS)9, 10

Abnormal Involuntary Movement Scale (AIMS)2

Simpson-Angus Scale for Extrapyramidal Side-Effects (EPSE)11, 12

Calgary Depression Rating Scale for Schizophrenia13

EQ-5D Health Questionnaire (used in the economic analysis only)

Weight

Height

Body mass index

Waist circumference

Systolic blood pressure

Diastolic blood pressure

Serum Prolactin

Plasma Glucose (non-fasting sample)

Total Cholesterol

HDL Cholesterol

LDL Cholesterol

Triglycerides

Economic Patient Questionnaire (EPQ) (used in the economic analysis only)

*Ongoing*

Serious adverse events

Protocol violations

**Trial period**

The trial started recruiting in October 2011 and will recruit until the end of December 2014.

**Primary Outcome**

The proportion of participants with a criterion response threshold of a 20% reduction in total PANSS scale score, which will allow for comparison with published studies. The PANSS1 has 30-items, each of which have a seven point description of severity (1=absent, 7=extreme), with a possible range from 30 to 210. It is designed to provide a comprehensive assessment of psychopathology in adult patients with schizophrenia.

**Secondary Outcomes**

*Negative symptoms*

The PANSS negative symptom subscale score. It consists of seven items (Blunted affect, Emotional withdrawal, Poor rapport, Passive-apathetic social withdrawal, Lack of spontaneity and flow of conversation, Motor retardation, Active social avoidance)1 which are scored on a seven point description of severity with 1=absent and 7=extreme; giving a range of 7 to 49.

*Service engagement*

The level of engagement with clinical services will be assessed using the Service EngagementScale (SES)6; a 14-item measure consisting of statements that assess clientengagement with services, rated on a four-point Likert scale from 0=not at all or rarely to 3=mostof the time, with a range from 0 to 42. Higher scores indicate greater difficulty engaging with services. In development, it was shown to be positively skew. Four sub-scales assess availability, collaboration,help seeking and treatment adherence. They will be explored in analysis. These are broken down as:

Availability

1 The client seems to make it difficult to arrange appointments

2 When a visit is arranged, the client is available (reverse scored)

3 The client seems to avoid making appointments

Collaboration

4 If you offer advice, does the client usually resist it?

5 The client takes an active part in the setting of goals or treatment plans (reverse scored)

6 The client actively participates in managing his/her illness (reverse scored)

Help seeking

7 The client seeks help when assistance is needed (reverse scored)

8 The client finds it difficult to ask for help

9 The client seeks help to prevent a crisis (reverse scored)

10 The client does not actively seek help

Treatment adherence

11 The client agrees to take prescribed medication (reverse scored)

12 The client is clear about what medications he/she is taking and why (reverse scored)

13 The client refuses to co-operate with treatment

14 The client has difficulty in adhering to the prescribed medication

*Depression*

Depression will be assessed using the Calgary Depression Rating Scale for Schizophrenia (CDSS)13, a scale designed to minimise the potentially confounding symptom overlap between depressive features and both negative symptoms and extrapyramidal symptoms. It consists of nine items which are scored 0=absent to 3=very much so; giving a possible range of 0 to 27. Scoring is by the addition of scores from all items.

*Insight*

This is measured using the Schedule for the Assessment of Insight (SAI).7, 8 It consists of three main questions scoring 0=never to 2=often, with supplemental questions if the participant responds sometimes or often to the main question. Finally, there is one additional question “How do you feel when people don’t believe you (when you talk about ... delusional/hallucinatory experience?)”, which has four possible responses, scored 1 to 4. The responses are summed giving a range of 0 to 18, with a higher score indicating a greater awareness of their illness.

*Side effects*

*Non-neurological*

These will be assessed using the Antipsychotic Non-Neurological Side Effects Scale (ANNSERS-E)5, a 44-item scale (although only 43 are used in calculating the scale) and four additional questions. All are scored from 0=absent to 3=severe. The number of side effects is counted. Subtotals of the mild side effects, moderate side effects and severe side effects are calculated (using the scoring schedule above) for the main questions and then totalled (giving a possible score between 0 and 129). The process is repeated for the enhanced questions (giving a possible score between 0 and 12). These two overall scores are combined to give the final score ranging from 0 to 141, with a higher score indicating more and/ or more severe side effects.

*Metabolic side effects*

Body mass index (BMI)

Systolic and diastolic blood pressure

Serum prolactin

Plasma glucose (non-fasting sample)

Total Cholesterol Level

HDL Cholesterol

LDL Cholesterol

Triglycerides

*Motor side effects*

For the following three scales, these will be dichotomised to indicate whether the participant has reached a criterion diagnostic score.

Drug induced Parkinsonism will be assessed using the Simpson-Angus Scale for Extrapyramidal Side-Effects (EPSE) scale.11, 12 It is a ten item scale, with each item scored from 0 to 4, then the total score divided by 10 to give an overall mean score (and therefore the range is 0 to 4). This will be dichotomised to those scoring 3+ versus those scoring less than 3.

Akathisia will be assessed using The Barnes Akathisia Rating Scale (BARS).9, 10 This consists of three questions with response ratings from 0=absent to 3=severe. These are summed to give a score ranging between 0 and 9. There is a further item to globally classify akathisia into six categories. The global item will be dichotomised to those scoring 2+ on the global item versus those scoring less than 2.

Abnormal Involuntary Movements Scale (AIMS)2 for rating tardive dyskinesia. It is a 12 item scale, with the first 10 items being scored 0=absent to 4=severe, and the final two items being scored 0 or 1(no or yes). The scale is made up by adding the scores from the individual items (range 0 to 42). This will be used to identify the presence of tardive dyskinesia using the Research Diagnostic Criteria severity criteria of at least a moderate (coded 3) rating in one or more body areas or mild (coded 2) movements in two or more body areas; a dichotomy will be created using these criteria.15

Using the symptom and behavioural assessments, and in discussion with the clinical team, we plan to identify at baseline, for each participant, the three 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. These will be analysed as a change in the total score for these three symptoms.

**Data entry**

Data, with the exception of the randomisation variable are entered into a web based data entry system, Prospect.16 All individual items of the outcome measures are entered into Prospect and it them calculates the overall score for that measure. Checks for logic, range and missing data are built into Prospect, however, data will be checked by the Statistician and if there are any queries regarding the data, these will be directed to the Trial Manager, Data Manager and/ or Research Associate. Where appropriate corrections are made by the Trial Manager, Data Manager and/ or Research Associate a new copy of the dataset will be sent to the Statistician. The randomisation variable is held separately by the University of Sheffield, and will be requested when appropriate. When appropriate (in good time for analyses to be carried out for the IDMEC and at the end of the trial), data will be downloaded by the Statistician to analyse.

**Data analysis**

The CONSORT flow diagram will be constructed by/ in collaboration with the Trial Manager, Data Manager and/ or Research Associate who will have the numbers of service users who do and do not agree to take part in the study. It will include number of participants randomised to each arm of the trial, and the numbers at follow up. It will also include reasons for not taking part in the trial or dropping out where known.

The main analyses will be based on intention to treat principles. Data will be analysed using Stata version 13.17

*Descriptive analyses*

Initial analyses will look at summary statistics for all variables, both overall and by randomised group. Summary statistics for continuous variables will be mean, median, SD, lower quartile, upper quartile, minimum and maximum. These variables will also be plotted to check the distribution. If variables are skewed, then median and interquartile ranges will be reported, otherwise mean and standard deviation will be reported. Additionally, the outcomes will be plotted against relevant baseline variables (usually the outcome in question and its values at baseline) to assess the relationship between them.

Summary statistics for categorical variables will be frequency and percentage within each category. No statistical significance tests for baseline characteristics by randomised group will be performed.

*Analysis of the primary outcome*

The analysis of the primary outcome will utilise logistic regression, adjusting for baseline PANSS score. The odds ratio for randomised group and 95% confidence interval will be reported. As the study will be underpowered compared with the sample size calculation, no account for alpha spending due to interim analyses will be made in the final analysis.

*Analysis of secondary outcomes*

These analyses will be carried out using linear or logistic regression as appropriate. The models will include baseline measures of the outcome in question and an indicator of the level of PANSS at baseline (the stratification variable). The effect sizes and 95% confidence intervals will be reported; p-values will not be reported as the study is not powered to detect differences between groups with respect to secondary outcomes.

*Sensitivity analyses*

1 The six week data will be used to determine whether benefit from the intervention has been achieved by the sixth week. The data will be analysed longitudinally using both six and twelve week data and controlling for baseline values of the given measure. This will be a two level multilevel model (time points, participants), however, this is unlikely to converge. Randomised group and baseline measure of the outcome will be included in the models.

2 It would be unethical to restrict the therapeutic options of the clinical teams. Our approach will therefore be primarily to record the use of all other medication, documenting details of dosage, and ensure the follow-up of all randomised participants, irrespective of the medication they subsequently receive. 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. Statistical methods will be as for the analyses of the primary and secondary outcomes. For this analysis, the sample size will be further reduced because it will include participants who fulfil stricter inclusion criteria than the whole trial. For this analysis, the effect sizes and 95% confidence intervals will be reported and the emphasis placed on the size of difference in outcome between the randomised groups.

*Missing data*

If the primary outcome is missing for 10% or more of those who were randomised, then analyses to determine the predictors of missingness will take place.

**Interim analyses for the Independent Data Monitoring and Ethics Committee (DMEC)**

**Outcomes to be analysed**

The only outcomes that will be analysed for the IDMEC are:

20% reduction in the PANSS score (study primary outcome)

Adverse events

A graph showing recruitment to date and a consort diagram to date will be produced. Baseline statistics (frequencies (%) for categorical variables or mean (SD) for continuous variables) by randomised group for age, sex, baseline PANSS will be produced to check for major differences at baseline.

**Confidentiality**

Data will be analysed by the study statistician and communicated to the IDMEC. They will not be made available to other members of the study team unless requested by the IDMEC.

Prior to analysis, data will be exported from PROSPECT (the study database system) and the randomisation variable will be sent directly from the Sheffield Clinical Trials Research Unit (CTRU). These will be retained in the original form.

Update: after the IDMEC held on 09/07/2012 it was agreed that the Trial Statistician would analyse the data blind to allocation thereafter and if the IDMEC required the data to be unblinded another statistician would do this task.

**Statistical analyses**

It was planned that the interim analyses would take the same form as the main analyses. However, as there was so little data this was not possible as it is unlikely that planned models would converge. Therefore there have been deviations from this, which are detailed below:

*IDMEC held on 09/07/2012*

As there was so little data (N=5, with n=2 completed the 12 week intervention) only means and frequencies were presented.

*IDMEC held on 29/04/2013*

At this point N=31 had been recruited to the trial and n=12 had completed the 12 week intervention. A Fisher’s exact test was carried out on the primary outcome.

*IDMEC held on 23/09/2013*

At this point N=46 had been randomised and n=26 had finished the 12 week intervention. A chi square test was carried out on the primary outcome and after the IDMEC a chi square test was carried out on the numbers of people who had experienced any adverse event.

*IDMEC held on 16/12/2013*

At this point N=52 had been randomised and n=37 had finished the 12 week interventions. There were no interim analyses by randomised group. However, overall data downloaded from PROSPECT on 09/12/2013 gave the total number of adverse events, people who had adverse events and people who had the primary outcome.

*IDMEC to be held on 14/11/2014*

It is not planned to analyse the data by randomised group for this meeting. However, recruitment and adverse events since the last meeting will be reviewed.

Data analysis will be carried out using Stata version 1317.

**Analysis population**

Data will be included in the analysis for the IDMEC if the participant has had their 12 week assessment (for the primary outcome) and at any time for adverse events and their data have been entered into PROSPECT (this will not include everyone who has some data entered into PROSPECT).

**Stopping rules and type I error**

Using an overall p-value to indicate statistical significance of <0.05, and assuming there are three IDMEC meetings which require interim analyses in addition to the final analysis at the end of the study, then using the program ld98 (DOS version)20, two stopping rules are to be established. The first, for efficacy (the primary outcome) uses the O’Brien Fleming21 type rule while for safety (adverse events) a power family with an exponent of 1.5 is used. These give different p-values at each time point, set out in Table 1.

As recruitment was more difficult than expected, the p-value for the end of the trial will now revert to 0.05 for the primary outcome, although p-values will not be reported (coefficients and 95% confidence intervals only).

Table 1: Timing of interim analyses and p-values to be used to indicate efficacy and safety.

|  |  |  |
| --- | --- | --- |
|  | Efficacy | Safety |
| Time | p-value | p-value |
| 0.25 | 0.00001 | 0.00313 |
| 0.50 | 0.00152 | 0.00571 |
| 0.75 | 0.00812 | 0.00740 |
| 1.00 (end of the trial) | 0.01535 | 0.00876 |

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