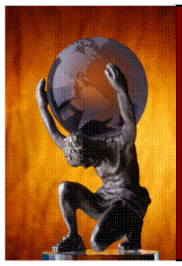

ATLAS A pragmatic randomised double-blind trial of Antipsychotic Treatment of very LAte-onset Schizophrenia-like psychosis

ATLAS

Statistical Analysis Plan

Version Number: 1.0

Prepared by: Rosie Bradley and Richard Gray

1. Introduction

This document gives a detailed statistical analysis plan for the ATLAS trial, and should be read in conjunction with the current protocol.

2. Background

Very late-onset schizophrenia-like psychosis is a common condition, which affects an estimated 34,000 of the UK population aged over 60 and with 2,800 new service contacts each year. After dementia and depression, these patients represent the largest diagnostic group presenting to Old Age Psychiatry services. Impairments in quality of life associated with psychosis are severe and comparable to those seen in younger schizophrenia patients and elderly people with dementia. Patients often suffer the effects of their delusional beliefs for 10 or 20 years and this has a negative impact upon their families, neighbours and local social and housing services.

Antipsychotic drugs are widely used to treat late-onset (i.e. age ≥60) schizophrenia-like psychosis patients but this practice is not evidence-based. A Cochrane review concludes that there is no reliable clinical trial evidence upon which to base treatment guidelines. Potential benefits of antipsychotic drugs cannot currently be quantified without proper clinical trial evaluation and need to be balanced against potential risks of such treatment. A large randomised trial is urgently needed to assess reliably the balance of benefits and risks of antipsychotic drugs in late-onset schizophrenia-like psychosis.

3. Trial objectives and design

ATLAS is a multi-centre randomised controlled trial with the following objectives:

Primary objectives

1) To determine whether 12 weeks' treatment with amisulpride is superior to placebo in reducing symptoms of very late-onset schizophrenia-like psychosis as measured by the Brief Psychiatric Rating Score (BPRS) and by numbers of patients withdrawn to open treatment by their physicians because of perceived lack of efficacy. A prior hypothesis is that benefits of amisulpride will be most apparent on hostility, suspiciousness, hallucinations, tension, uncooperativeness and motor hyperactivity sub-scores of the BPRS.
2) To determine whether any benefits of amisulpride are maintained by prolonging treatment beyond 12 weeks. Duration of stage 2 treatment was initially 24 weeks but was then reduced to 12 weeks, to enhance numbers still on treatment at their final assessment.

Secondary objectives

ATLAS will also investigate:

(i) The associated risks of side-effects and serious adverse events;
(ii) Compliance with allocated treatment;
(iii) The effects of treatment on quality of life;
(iv) The cost-effectiveness of amisulpride treatment.

Trial design

ATLAS is a pragmatic, randomised, 3-arm, double-blind placebo-controlled trial with two stages:

Stage 1 – an initial double-blind placebo-controlled stage to investigate efficacy and tolerability of oral amisulpride (arms A and B) versus placebo (arm C) over 12 weeks.

Stage 2 – a second double-blind stage investigating the effects of treatment continuation (arm A) versus switching to placebo (arm B) over a further 24 (initially, later 12) weeks.

Randomisation (3 Groups)

Stage 1 – Weeks 1-12		**Stage 2 – Weeks 13-24 (or 36)**
(A) Amisulpride	→	**Amisulpride**
(B) Amisulpride	→	**Placebo**
(C) Placebo	→	**Amisulpride**

Outcome measures

Primary Efficacy Parameter – Brief Psychiatric Rating Scale

The first primary outcome measure is the Brief Psychiatric Rating Scale (BPRS), a widely used clinician-rated instrument for assessing positive, negative and affective symptoms in patients with psychotic disorders. The BPRS consists of 18 symptom constructs. Each item is assessed by the rater on a 7-point scale ranging from 1 (not present) to 7 (extremely severe). The total score is obtained by summing the scores from the 18 items. Scores thus range from 18 to 126, with higher scores indicating greater levels of psychopathy. The BPRS will be administered at baseline, at week 4, then again in weeks 10-12, week 16 and the final assessment (weeks 22-24 or 34-36). Change in BPRS score between baseline and the week 10-12 assessment and between the week 10-12 and final assessments are the trial's co-primary outcomes.

The second primary outcome measure is the proportion of patients withdrawn to open treatment by their physicians because of perceived lack of efficacy.

Secondary Efficacy Parameters

(i) Extrapyramidal side effects (EPSE) measured with the Simpson-Angus Scale (SAS). The modified SAS used in ATLAS measures nine extrapyramidal signs: gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, glabellar tap, tremor and salivation, all of which are assessed by direct examination. Each item is rated on a scale of 0-4, with higher scores indicating greater severity of EPSE. The scale range of the modified SAS is thus 0-36. The SAS has been widely used to measure EPSE within clinical trials and will be administered at baseline, then again at week 4, weeks 10-12, week 16 and weeks 22-24 (initially 34-36). The change in SAS between baseline and week 10-12 and between week 10-12 and the final assessment (week 22-24 or 34-36) will be compared between groups to assess EPSE.

(ii) Compliance expressed as treatment discontinuation rates and as percentage of prescribed trial medication taken between weeks 1 and 10-12 and between weeks 13 and the final assessment will be compared in patient allocated to receive amisulpride and those allocated placebo.

(iii) Quality of life measured with the self-rated, 26-item, WHO Quality of Life Scale (WHOQOL-BREF) at baseline, 10-12 weeks and the final assessment. The WHOQOL-BREF includes two items about an individual's overall perception of their quality of life and health and questions assessing four

domains; physical, psychological, social and environmental well-being, which higher scores denoting a better quality of life.

A separate analysis plan for the cost-effectiveness will be drafted.

Sample size considerations

Because of the likely problems with recruitment and retention of patients with late-onset, schizophrenia-like psychosis, ATLAS included an initial Feasibility Phase following which, a pragmatic decision was made to reduce the target sample size from 200-300 to at least 100 participants, to be recruited by mid-2016. The statistical power calculations have been amended with the main emphasis being to answer the primary stage 1 question of whether 12 weeks of amisulpride provides worthwhile benefit. The minimal clinically relevant difference (MRD), given the potential hazards of antipsychotic drugs, is considered to be 5 points on the BPRS. We estimate that the standard deviation of BPRS scores will be 9 points. We are thus powering the trial on a minimal worthwhile standardised effect size of 0.56 (=5/9) standard deviations, a moderate treatment effect.

With 100 patients, allowing for a 10% drop-out rate by 12-weeks, i.e. 90 of 100 with outcome assessments, ATLAS would have 70% power at 2p<0.05 to detect the MRD of 5 points between those taking amisulpride and placebo in stage 1, and ample power to detect larger differences.

4. General considerations

Study population:

Primary analyses of each stage will include all patients who have taken any study treatment in that stage. Participants who withdrew after pack allocation but before receiving any treatment can be safely excluded as treatment allocation is double-blinded so treatment allocation cannot influence the decision to withdraw and so introduce selection bias. Analyses of this population will be by intention to treat (ITT), ie all participants will be analysed in the treatment arm to which they were randomised, whether or not they adhered to the treatment. This is to avoid any potential bias in the analysis. Secondary analysis such as 'per protocol' (only those participants who adhere with the treatment allocation) may be carried out but as a sensitivity analysis only.

P-values:

Unless otherwise specified, estimates of amisulpride efficacy will be presented with 95% confidence intervals. P-values will be from two-sided test. No corrections for multiple testing will be made in the primary analyses.

Missing data:

The primary endpoint will be analysed using repeated measures analyses of all available data, which minimises impact of missing data. If a score is missing for a participant it is just missing. It has no effect on the other scores from the same participant.

Late data:

The week 4 and week 16 assessments should, where possible, be undertaken within ±7 days of the scheduled date. The other assessments (e.g. 10-12 week and 22-24 week) allow a ±14 day leeway. As deviations from scheduled assessments are possible in a study of participants with very late-onset schizophrenia-like psychosis assessments outside these windows will be included as if at the specified time point with no specified time limit.

Timing of interim analyses:

Interim analyses of efficacy and safety will be completed yearly as part of the Data Monitoring and Ethics Committee (DMEC) reviews of accruing data. No formal stopping rules based on interim analyses will be applied. The DMEC will inform the Trial Steering Committee (TSC) if, in their view, information from unblinded analyses of interim data provide proof beyond reasonable doubt that one of the treatments under investigation is either clearly indicated or contraindicated, either for all participants or for a particular subgroup of trial participants. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of the primary endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were adopted, it would have the practical advantage that the exact number of interim analysis would be of little importance, so no fixed schedule is proposed.

Timing of first main analyses for dissemination:

This will be completed once all patients have completed their final assessment.

Unblinding of randomised treatments:

Any unblinding of randomised treatments will be recorded giving randomised group, centre, date and circumstances of unblinding.

5. Proposed Analyses

5.1 Co-primary endpoint:

The main analysis will be undertaken once all patients have reached 22-24 weeks from randomisation. To assess the efficacy of 12 weeks of amisulpride in Stage 1, the primary outcome of BPRS will be compared using repeated measures regression model. Data from week 4 and week 12 will be the outcome variables and baseline scores will be entered into the model as a covariate. Time will be modelled as a categorical variable. The comparison will be between active amisulpride treatment (arms A and B group together) and placebo (arm C). The six minimisation factors (age, gender, home circumstance, BPRS score, time since onset of symptoms and previous antipsychotic treatment) will also be included as covariates in the repeated measures model. A time by treatment interaction parameter will be included to examine if there is any changing treatment effect over time. Treatment effects are presented with 95% confidence interval and associated p-values in each case. For these analyses a p-value of 0.05 (5% level) will be used to indicate statistical significance. This analysis uses all available visit data which will maximise statistical power to detect any difference at visits

To assess the value of continuing treatment in Stage 2, arm A (amisulpride – amisulpride) will be compared with arm B (amisulpride – placebo). Most patients will have only one outcome time point at week 24 or 36; the protocol has now been amended to shorten Stage 2 to 12 weeks with an additional assessment at about week 16. So, an analysis of covariance will be carried out, using the week 12 BPRS as baseline into the model as a covariate. Confidence intervals for the difference in means will be calculated. Participants who withdraw in Stage 1 will not be included in this analysis.

The BPRS covers the important symptoms elicited in very late-onset schizophrenia-like psychosis patients. In particular the Hostility, Suspiciousness, Hallucinations, Unusual Thought Content, Tension, and Uncooperativeness items of the BPRS all assess important areas of psychopathology in

these patients. The 7-point rating of the BPRS on each of these items generates a sub-score for these six symptoms domains that the protocol pre-specified as those most likely to be affected by the disorder. Scores on the subset range from 6 to 42, with higher scores indicating greater levels of psychopathology. The sub-score will be analysed in the same way the full BPRS analysis, for both Stage 1 and Stage 2.

5.2 Secondary endpoints:

The Simpson-Angus Scale (SAS) is used to see if amisulpride is having an effect on Extrapyramidal side effects (EPSE). The change in SAS scores will be plotted over time to see if there appears to be any increases over time. If the SAS scores remain constant over the assessment time points we can assume that amisulpride is having no effect on Extrapyramidal side effects.

Other continuous measures (EQ-5D and WHOQOL-BREF) will be analysed using the same methods specified in section 5.1, analysis of covariance.

5.3 Sensitivity analyses:

For assessment of change at week 12, analyses will be undertaken carrying forward week 4 assessments for patients with week 4 but not week 12 assessments. To evaluate the effect of compliance on treatment efficacy, the primary analysis will be repeated on a sub-group of participants who adhere to their allocated treatment arm but such analyses are prone to bias so will be interpreted appropriately cautiously.

5.4 Planned subgroup analyses:

Subgroup analyses will be limited to the same variables pre-specified in the protocol as minimisation variable used to balance randomisation:

- Age (60-69, 70-79, 80+)
- Gender
- Home circumstance (Living with spouse/partner, living alone, other)
- BPRS score (30-39, 40-49, 50+)
- Time since onset of symptoms (<6 months, ≥6 months)
- Previous antipsychotic treatment (No, Yes >1 month previously, Yes ≤28 days ago)

These exploratory subgroup analyses will be undertaken, appropriately cautiously, to investigate any influence of the prognostic factors. These subgroups will use standard test for significance of the parameter as an interaction in the repeated measures model.

Any deviations from this plan will be described in the final report.