THE LANCET
Psychiatry

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Howard R, Cort E, Bradley R, et al. Antipsychotic treatment of very late-onset schizophrenia-like psychosis (ATLAS): a randomised, controlled, double-blind trial. *Lancet Psychiatry* 2018; published online June 4. http://dx.doi.org/10.1016/S2215-0366(18)30141-X.

Appendix to: **Antipsychotic treatment of very late-onset schizophrenia-like psychosis: a randomised controlled double-blind trial** by Howard R, Cort E, Bradley R, et al.

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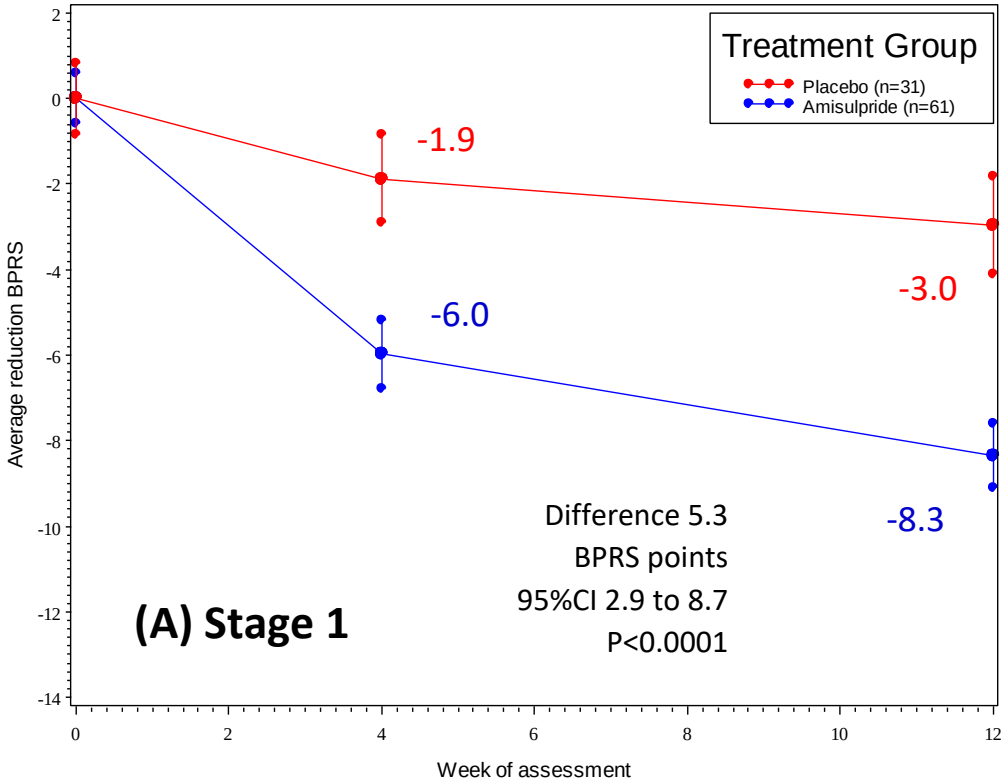
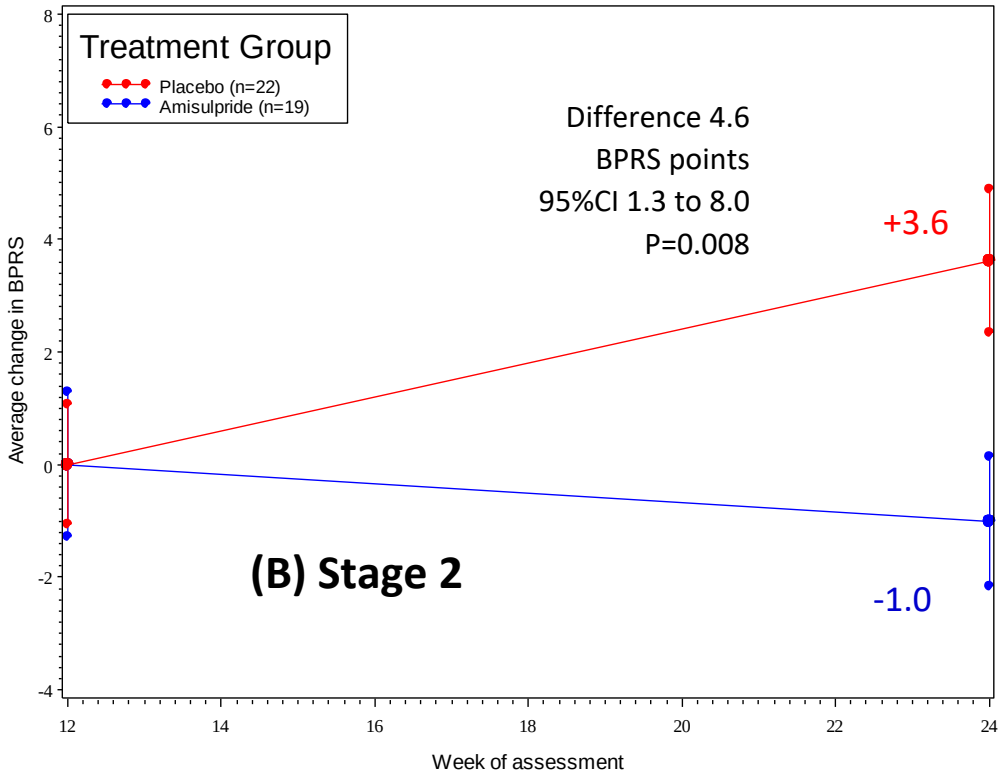
Web figure 1: Change in BPRS six item subscore: (a) from baseline* to 12 weeks in Stage 1, and (b) from 12 weeks to final assessment in stage 2 Graphs show change in mean BPRS scores with standard errors, baseline scores set to zero.

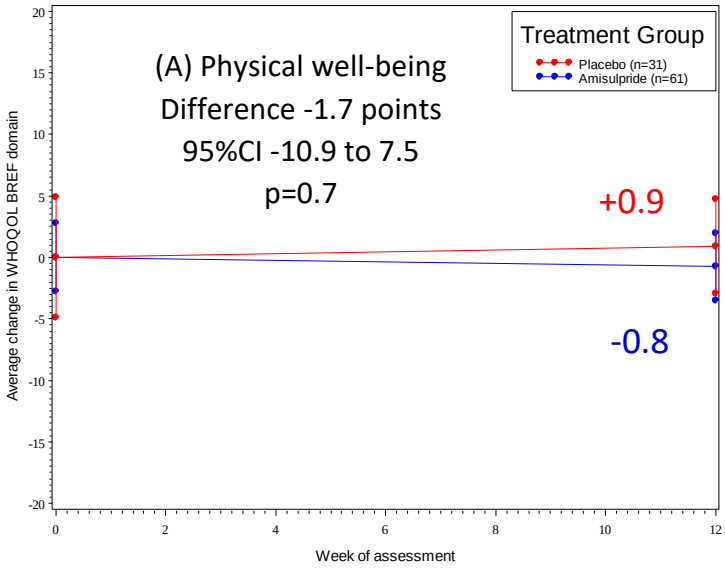


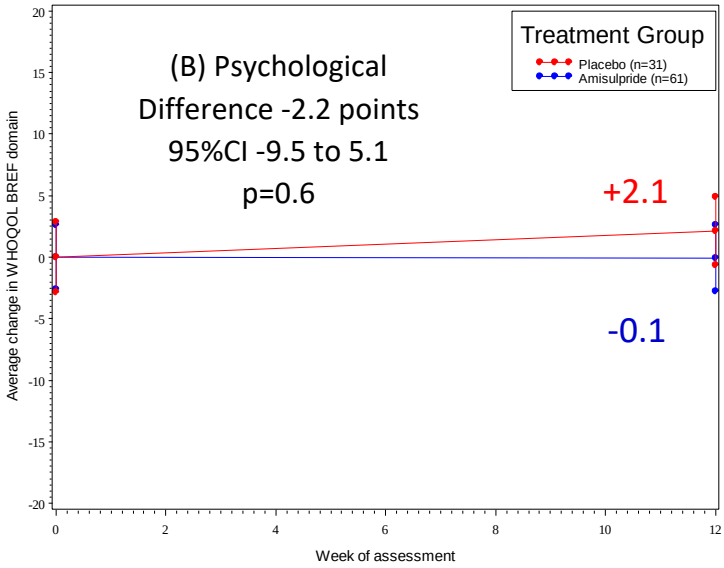


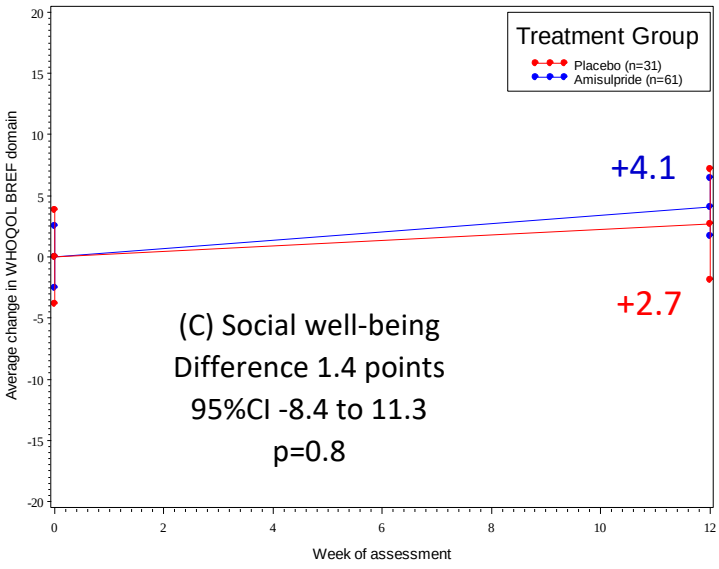
* Baseline scores: Amisulpride 20.2, Placebo 18.6

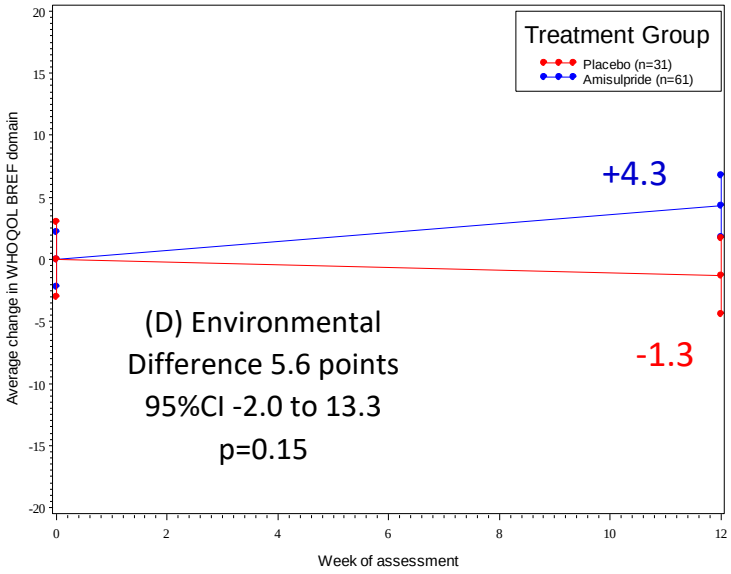
* Baseline scores: Amisulpride 10.5, Placebo 11.3

Web figure 2: Change in WHOQOL-BREF scores from baseline* to 12 weeks in Stage 1: (A) Physical, (B) Psychological, (C) Social, and (D) Environmental well-being Graphs show change in mean WHOQOL-BREF scores with standard errors, baseline scores set to zero.

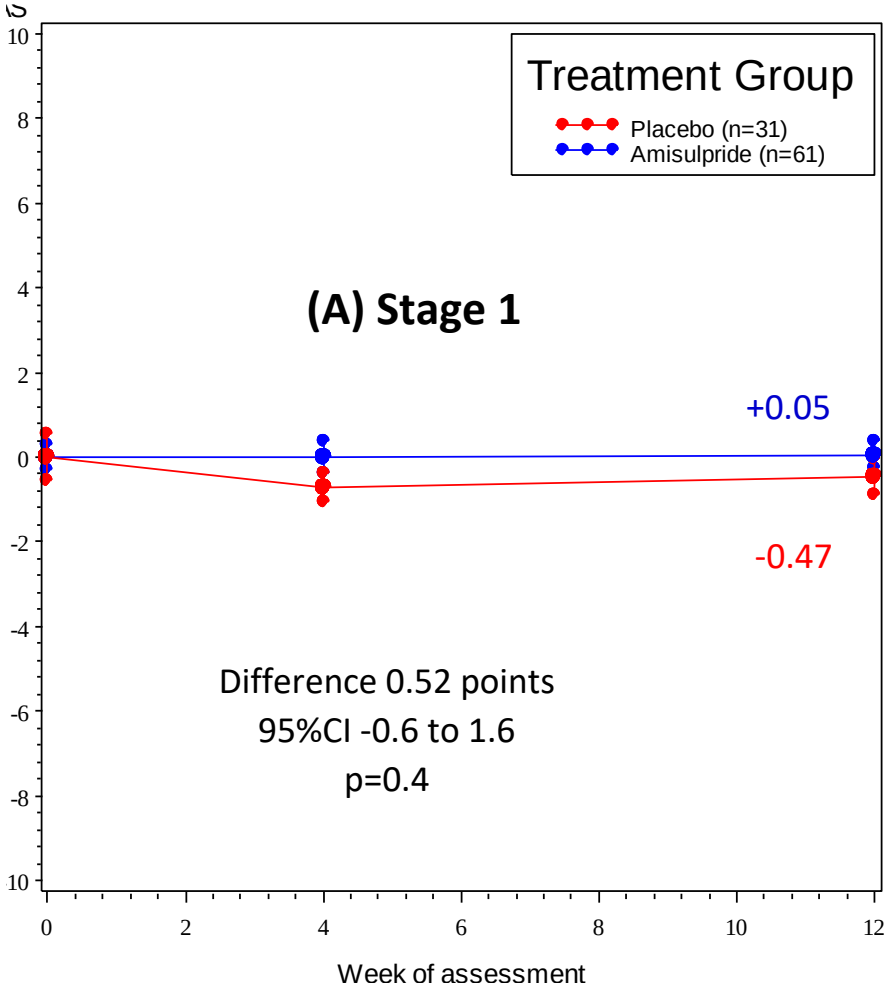




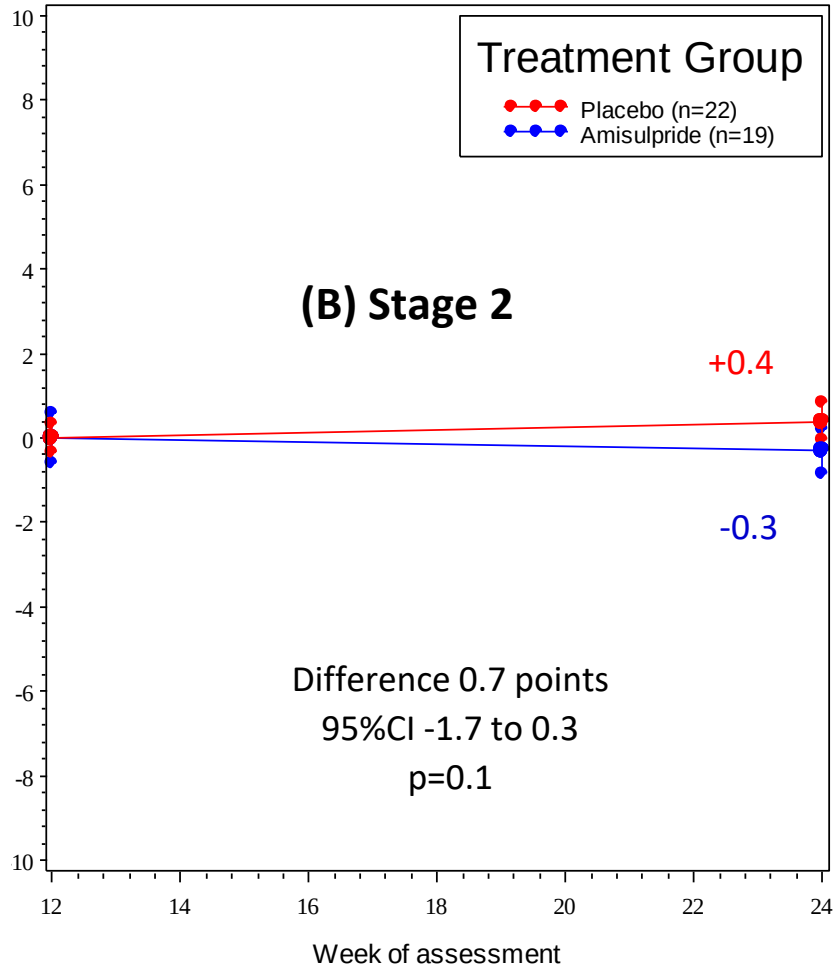




Web Figure 3: Change in SAS score: (A) from baseline* to 12 weeks in Stage 1, and (B) from 12 weeks to final assessment in stage 2 Graphs show change in mean SAS scores with standard errors, baseline scores set to zero.



* Baseline scores: Amisulpride 2.3, Placebo 2.4



* Baseline scores: Amisulpride 2.8, Placebo 1.3

Web table 1a: Results from repeated measures regression analysis for BPRS stage 1, solution for fixed effects. Output from repeated measures model in SAS, using Proc Mixed. Model uses BPRS scores from week 4 and week 12 as the outcome, baseline BPRS fitted as a covariate, with a time by treatment interaction.

Effect	Estimate	95% CI	Std Err	t Value	Pr > |t|
Intercept	13.65	(5.48, 21.82)	4.11	3.32	0.0013
Baseline BPRS	0.54	(0.34, 0.73)	0.10	5.44	<0.0001
Amisulpride	-6.12	(-9.83, -2.40)	1.89	-3.27	0.0015
Control	0	.	.	.	.
Week 4	2.09	(-0.25, 4.43)	1.18	1.77	0.080
Week 12	0	.	.	.	.

Web table 1b: Results from repeated measures regression analysis for BPRS stage 1, test for fixed effects

Effect	F Value	Pr > F
Baseline BPRS	29.64	<0.0001
Treatment	10.97	0.0014
Time	13.16	0.00005
Treatment* Time	6.58	0.4503

Web table 2: Change in BPRS, EQ-5D and WHOQOL-BREF domains from baseline to week 12 (stage 1) and from week 12 to week 24 or 36 (stage 2) by allocated treatment. Average reductions shown for stage 1 and 2 with 95% CI and associated p-values.

Treatment	N	Mean change	95% CI	Std Dev	Std Err	T-statistic	P-value
BPRS Stage 1 (amisulpride vs control) – change from baseline to wk4							
Amisulrpide	56	-9.0	(-11.5, -6.36)	9.3	1.2		
Placebo	31	-2.3	(-4.2, -0.4)	5.2	0.9		
Difference		-6.7	(-10.3, -3.2)	8.1	1.8	-3.73	0.0003
BPRS Stage 1 (aminsulpride vs control) – change from baseline to wk12							
Amisulrpide	58	-11.9	(-14.5, -9.3)	9.9	1.3		
Placebo	31	-4.2	(-6.3, -2.1)	5.8	1.0		
Difference		-7.7	(-11.5, -3.8)	8.7	1.9	-3.96	0.0002
BPRS Stage 2 (continuing amisulpride vs control) – change from wk12 to end							
Amisulpride	16	-1.1	(-4.4, 2.3)	6.3	1.57		
Placebo	21	5.2	(1.1, 9.4)	9.2	2.00		
Difference		6.3	(0.9, 11.7)	8.1	2.67	-2.36	0.0241
EQ-5D Stage 1 (amisulpride vs control) – change from baseline to wk12							
Amisulpride	50	0.027	(-0.032, 0.087)	0.208	0.029		
Placebo	27	-0.009	(-0.087, 0.068)	0.196	0.038		
Difference		0.036	(-0.060, 0.133)	0.204	0.049	0.75	0.46
EQ-5D Stage 2 (continuing amisulpride vs control) – change from wk12 to end							
Amisulpride	16	-0.014	(-0.085, 0.058)	0.134	0.034		
Placebo	18	0.003	(-0.069, 0.075)	0.145	0.004		
Difference		-0.017	(-0.115, 0.081)	0.140	0.048	-0.35	0.73
WHOQOL-BREF Stage 1 Physical well-being (amisulpride vs control) – change from baseline to wk12							
Amisulpride	46	-0.8	(-5.6, 4.0)	16.1	2.38		
Placebo	20	0.9	(-8.3, 10.1)	19.7	4.41		
Difference		-1.7	(-10.9, 7.5)	17.3	4.63	-0.37	0.71
WHOQOL-BREF Stage 1 Psychological well-being (amisulpride vs control) – change from baseline to wk12							
Amisulpride	51	-0.1	(-4.9, 4.7)	17.0	2.38		
Placebo	25	2.1	(-1.9, 6.2)	9.8	1.96		
Difference		-2.2	(-9.5, 5.1)	15.1	3.68	-0.60	0.55
WHOQOL-BREF Stage 1 Social well-being (amisulpride vs control) – change from baseline to wk12							
Amisulpride	52	4.1	(-1.2, 9.4)	19.1	2.65		
Placebo	25	2. 7	(-6.7, 12.0)	22.9	4.54		
Difference		1.4	(-8.4, 11.3)	20.3	4.95	0.29	0.77
WHOQOL-BREF Stage 1 Environmental well-being (amisulpride vs control) – change from baseline to wk12							
Amisulpride	51	4.3	(0.2, 8.4)	14.6	2.0		
Placebo	25	-1.3	(-8.8, 6.1)	18.1	3.6		
Difference		5.6	(-2.0, 13.3)	15.8	3.9	1.46	0.15
WHOQOL-BREF Stage 2 Physical well-being (continuing amisulpride vs control) – change from wk12 to end							
Amisulpride	15	-2.1	(-9.0, -4.7)	12.3	3.18		
Placebo	20	-0.6	(-7.7, 6.6)	15.3	3.42		
Difference		-1.5	(-11.3, 8.2)	14. 1	4.81	0.32	0.75
WHOQOL-BREF Stage 2 Psychological well-being (continuing amisulpride vs control) – change from wk12 to end							
Amisulpride	15	2.7	(-4.8, 10.2)	13.5	3.49		
Placebo	20	3.6	(-3.0, 10.3)	14.2	3.18		
Difference		-0.9	(-10.6, 8.8)	13.9	4.76	-0.19	0.85
WHOQOL-BREF Stage 2 Social well-being (continuing amisulpride vs control) – change from wk12 to end							
Amisulpride	15	0.8	(-10.1, 11.7)	19.7	5.08		
Placebo	16	-4.7	(-13.5, 4.1)	16.4	4.11		
Difference		5.5	(-7.8, 18.8)	18.1	6.50	0.85	0.40
WHOQOL-BREF Stage 2 Environmental well-being (continuing amisulpride vs control) – change from wk12 to end							
Amisulpride	15	1. 7	(-4.8, 8.1)	11.6	3.00		
Placebo	20	1.8	(-5.6, 9.2)	15.8	3.53		
Difference		-0.1	(-10.0, 9.7)	14. 2	4.84	-0.03	0.98

Web table 3: Side-effects believed to be due to trial treatment

Stage 1	Amisulpride (Groups A & B)	Placebo (Group C)
EPSE symptoms		
Tremor	2	1
Increased salivation	4	0
Increased muscle tone	5	0
EPSE subtotal	***11***	***1***
Dry mouth	1	1
Nausea or reduced appetite	2	0
Constipation	3	0
Urinary problems	4	0
Sleep disturbance	3	2
Worsening psychosis	1	0
Headache	2	0
Unsteadiness	3	5
Sedation	5	1
Confusion	1	0
Peripheral oedema	1	0
Total	***36***	***10***
Stage 2	**Amisulpride (Groups A)**	**Placebo (Group B)**
EPSE symptoms		
Tremor	1	0
Increased salivation	1	0
Increased muscle tone	2	0
EPSE subtotal	***4***	***0***
Dry mouth	0	2
Nausea or reduced appetite	1	0
Constipation	0	1
Urinary problems	1	0
Worsening psychosis	0	1
Sedation	1	1
Total	***7***	***5***

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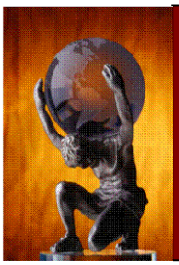
*Rob Jones has since died.



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

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. The National Institute for Health Research's Health Technology Assessment programme has, therefore, funded such a trial: **ATLAS** ("Antipsychotic Treatment of very LAte-onset Schizophrenia-like psychosis").

ATLAS is a double-blind placebo-controlled trial, in patients with very late-onset schizophrenia-like psychosis, to evaluate whether giving 12 weeks treatment with a low dose of the antipsychotic drug, amisulpride, produces sufficient benefit to outweigh the potential risks. **ATLAS** also evaluates whether prolonging treatment for a further 12 weeks among patients who have already been treated with amisulpride for 12 weeks, confers additional benefit. The primary outcome measures are change in the Brief Psychiatric Rating Scale (BPRS) score and the proportions who discontinue treatment because of a perceived lack of efficacy. **ATLAS** will also assess side-effects, safety, compliance, the effects of treatment on quality of life and the cost-effectiveness of amisulpride treatment. As well as evaluating therapeutic approaches, **ATLAS** provides a unique opportunity to obtain a better understanding of the risk factors and natural history of late-onset schizophrenia-like psychosis and to identify patient characteristics predictive of response to antipsychotic therapy.

ATLAS aims to randomise at least 100 patients, in a 2:1 ratio, between 12 weeks of amisulpride and matching placebo. Patients allocated placebo will then switch to amisulpride whereas those receiving amisulpride will be randomised to continuing with either amisulpride or placebo. Thus, all patients receive some active treatment. To make widespread participation feasible, trial procedures and documentation are kept to a minimum. Although recruiting 100 patients is challenging, this is a small number compared to the many tens of thousands of future patients whose treatment will be guided by the results of **ATLAS**. The success of the study depends on the wholehearted support of the old-age psychiatry community. Publication of the main results will therefore be in the names of all collaborators and not those of the central organisers.

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EudraCT number: 2010-022184-35; **MREC number:** 11/LO/1267; **ISRCTN number:** ISRCTN45593573;

CONTENTS

TRIAL DOCUMENTATION: information sheets, consent forms, questionnaires and other forms and information - see separate Appendices

APPENDIX A	Patient Information Sheet Version 3 Date 10/09/15
APPENDIX B	Patient Consent Form Version 3 Date 10/09/15
APPENDIX C	Carer Assent and Consent form Version 2 Date 05/05/2015
APPENDIX D	Registration and Randomisation Form Version 1.2 Date 18/12/2012
APPENDIX E	Brief Psychiatric Rating Scale Version 2 Date 05/05/2015
APPENDIX F	Simpson Angus Scale Version 1.2 Date 18/12/2012
APPENDIX G	WHOQOL-BREF Version 1.2 Date 18/12/2012
APPENDIX H	Client Service Receipt Inventory Version 2 Date 05/05/2015
APPENDIX I	EuroQol EQ-5D Questionnaire
APPENDIX J	GP letter Version 2 Date 05/05/2015
APPENDIX K	**ATLAS** patient follow-up form Version 2 Date 05/05/2015
APPENDIX L	Serious Adverse Event form Version 2 Date 05/05/2015
APPENDIX M	Assay request form for optional blood test Version 1 Date 10/09/15

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1. BACKGROUND AND RATIONALE

There are two main groups of older people with schizophrenia symptoms who use NHS services. The first are patients with onset of their schizophrenia in earlier adult life, and now grown old. Such individuals have usually received several decades of antipsychotic drug treatment and in old age are most seriously disabled by negative symptoms with severe impairments on functional and social measures. The second group - patients with a schizophrenia-like psychosis with onset after the age of 60 years - are the subject of the **ATLAS** study. These patients present with predominantly positive psychosis symptoms, generally persecutory delusions with or without multimodal hallucinations. Symptoms are distressing and persist for many years in the absence of treatment. Very late-onset schizophrenia-like psychosis is a term that has been agreed by international consensus for onset-after-60 cases and has a prevalence of between 0.1% and 0.4% of the elderly population and an incidence of 20 new cases per 100,000 per year (Howard et al 2000) with an estimated 34,000 patients and 2,800 annual new service contacts in the UK. 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. Since increasing age beyond 60 years (Van Os et al 1995) and membership of a migrant group (Reeves et al 2001) are both risk factors for late-onset psychosis, projected changes in UK population demographics will result in more cases.

There is remarkably little good quality evidence to guide physicians' prescribing in patients with late-onset psychosis. Antipsychotic medication has established efficacy in young schizophrenia patients, and in older patients with illness onset before the age of 40 years, but no randomised placebo-controlled treatment trials have ever been conducted in the later onset clinical group. A Cochrane review (Arunpongpaisal et al 2003) identified 38 potentially relevant published trials but most had involved elderly people with chronic schizophrenia and, if patients with later onset had been included, separate outcomes for that subgroup were not reported. The single randomised study in late-onset cases (Phanjoo et al, 1990) was small (n=18) and the treatments that were compared, remoxipride and thioridazine, have subsequently been withdrawn from use. A non-randomised trial in very late-onset schizophrenia-like psychosis (Psarros et al 2009) has recently reported that five weeks of open-label treatment with amisulpiride at a mean dose of 101 mg/day (range 50-200 mg) is well tolerated and led to marked improvement in psychotic symptoms with 30% reductions in BPRS (Brief Psychiatric Rating Scale; Ventura et al 1993) and 47% reductions in total PANSS (Positive and Negative Syndrome Scale; Kay et al 1987) score.

It has generally been accepted by clinicians that antipsychotic treatment improves symptoms (Howard & Levy 1992). Expert opinion and individual clinical experience together currently guide the prescribing behaviour of psychiatrists. An influential expert consensus panel in the United States recommended treatment with risperidone at a dose of 1.6 mg per day for older patients with delusional disorder – a diagnosis sometimes used to describe very late-onset schizophrenia-like psychosis patients (Alexopoulos et al 2004). Some authors have, however, been pessimistic about treatment response rates in comparison with younger patients with psychosis (Raskind & Risse 1986). In the absence of controlled trial data, it is difficult to draw firm conclusions about this or to evaluate the potential contribution of the non-drug components of patient care, including engagement with members of the Community Mental Health Team and Social Services staff (Howard 2008). There is agreement among clinicians that patients with psychosis onset in late life can be treated successfully with much lower doses of

antipsychotic (typically around 25%) than those used in younger patients or older individuals whose psychosis began in early adult life (Howard 2008). For example, the mean dose of depot fluphenazine decanoate prescribed to patients in one naturalistic observational study was only 14.4 mg per fortnight (Howard & Levy 1992).

Typical and atypical antipsychotics are the current treatments of choice for clinicians who manage these patients. The dose ranges reported in practice (Alexopoulos et al 2004, Psarros et al 2009, Howard & Levy 1992) are comparable to those used in trials in patients with dementia and behavioural symptoms (e.g. De Deyn et al 1999) and much lower than those used in schizophrenia, suggesting that the mechanisms of both the antipsychotic effect and extrapyramidal side-effects of neuroleptics in late-onset psychosis patients may be closer to those seen in dementia than in older people with longstanding schizophrenia. Atypical antipsychotic agents in the treatment of behavioural and psychiatric symptoms in dementia have modest efficacy against aggression and agitation, with generally disappointing effects on psychosis symptoms, but this needs to be balanced against small but significant increases in mortality and stroke (Ballard & Howard 2006). A mechanism for this increased mortality has not been elucidated and it is therefore not possible to predict whether or not the same risks will apply in non-demented elderly people treated with antipsychotics.

Although antipsychotic drugs are being widely used to treat late-onset schizophrenia-like psychosis, the benefits and risks of this approach have not been properly evaluated. The Cochrane review (Arunpongpaisal et al 2003) concluded that there is no reliable clinical trial evidence upon which to base treatment guidelines for late-onset psychosis. Antipsychotic drugs may increase the risk of stroke and death and this risk needs to be balanced against potential benefits of treatment which cannot currently be quantified because of the absolute lack of any rigorous clinical trial evaluation. What is urgently needed is a large randomised trial to assess the true value of antipsychotic drugs in late-onset schizophrenia-like psychosis. The National Institute for Health Research's Health Technology Assessment programme has therefore funded **ATLAS** ("Antipsychotic Treatment of very LAte-onset Schizophrenia-like psychosis"), a placebo-controlled trial designed to evaluate whether giving a low dose of the antipsychotic drug, amisulpride, produces sufficient benefit to outweigh the potential risks. Amisulpride is used because its pharmacokinetic and cognition-sparing qualities make it appropriate for use in elderly patients (Leucht et al 2004) and because a case series has reported that amilsulpride, at a mean dose of 100 mg per day, significantly reduced psychosis symptoms in this patient group with no clinically significant adverse events (Psarros et al 2009).

For reliable results, **ATLAS** needs to randomise at least 100 patients and, to make widespread participation feasible, trial procedures and documentation are kept to a minimum. Recruiting one hundred patients will be challenging, but this is a small number compared to the many tens of thousands of future patients whose treatment will be guided by the results of the **ATLAS** study.

2. TRIAL OBJECTIVES AND DESIGN

2.1 Trial Objectives

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

Primary Objectives

1) To determine whether amisulpride is superior to placebo in the treatment of very late-onset schizophrenia-like psychosis as measured by significant differences between amisulpride and placebo treated groups in changes in BPRS score over 12 weeks. A prior hypothesis is that benefits of amisulpride will be most apparent on the hostility, suspiciousness, hallucinations, tension, uncooperativeness and motor hyperactivity sub-scores.
2) To determine whether prolonging amisulpride for a further 12 weeks after an initial 12-week treatment period confers additional benefit, as measured by BPRS scores and by fewer patients in the amisulpride than placebo group being withdrawn to open treatment with amisulpride by their physicians.

Secondary Objectives

ATLAS will 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.

2.2 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 (groups A and B) versus placebo (group C) over 12 weeks

Stage 2 - a second double-blind stage investigating the effects of treatment continuation (group A) versus switching to placebo (group B) over a further 12 weeks.

Randomisation will be carried out centrally by the **ATLAS** randomisation service (tel 0800 585323, e-mail: randomisation@ctsu.ox.ac.uk). A minimisation randomisation procedure will be used to reduce the risk of chance imbalances between arms with respect to known prognostic factors.

The ATLAS Trial: Allocations to amisulpride and placebo in Stages 1 and 2

Randomisation (3 Groups)

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

2.3 Ethical considerations

The presence of significant cognitive impairment is an exclusion criterion for **ATLAS**. However, very late-onset schizophrenia-like psychosis often involves poor insight (Almeida et al 1996), with patients having difficulties in assessing their own need for treatment. Older people with psychotic illnesses participating in trials sometimes have limited understanding of trial design – particularly the use of a placebo control. Failure to understand randomisation, use of placebo control and blinding is ethically problematic (Carpenter et al 2003, Miller et al 2000, Kim 2003) – especially as participants may not recognise how these procedures might affect their treatment and care. This placebo dilemma is especially complex for conditions such as very late-onset schizophrenia-like psychosis for which existing treatments probably have more efficacy than no treatment at all but, on current knowledge, there is great uncertainty about the balance of benefits and risks. To judge whether the net benefits are sufficient to justify treatment, more reliable evidence is required on the effectiveness and side-effect profiles of antipsychotic treatment for this clinical group. However, the process of testing such agents inescapably entails clinical trials in which some patients will receive placebo treatment. Dunn et al 2006 have highlighted the importance of three factors that contribute to how well patients with schizophrenia can be helped to understand the implications of their involvement in such research. These are: (1) the pivotal place of informed consent; (2) the capacity of patients to give informed consent (including understanding of key aspects of the protocol and an appreciation of the significance of the information provided for the individual's situation); and (3) awareness that many participants may confuse aspects of clinical care (e.g. individualisation of treatment) with those of research.

Because of the specific reasoning difficulties that this patient group have with their own assessment of treatment requirements, and the reported difficulties that older people with psychosis may have with the understanding of the randomisation and use of a placebo control in trials, the information about the trial to potential participants will be given in two stages (see section 4). A clinician who sees a patient who meets eligibility for the trial will explain the potential benefits and possible risks of antipsychotic treatment and briefly introduce the option of taking part in **ATLAS**. If the clinician considers that the patient might be interested in participating, then the patient will be given the *Patient Information* leaflet and a second appointment arranged after a delay of at least 24 hours. At the second appointment, the clinician (i.e. doctor, nurse or other suitably qualified trial team member) will go through the information sheet with the patient. If the clinician judges that the patient has the capacity to give informed consent, and the patient consents to take part in the trial (Appendix B), the patient's treatment will be decided by randomisation in **ATLAS**.

All potential participants will be offered the opportunity to discuss their involvement in the trial with a trial doctor before they are randomised.

3. OUTCOME MEASURES

3.1 Primary Efficacy Parameter - Brief Psychiatric Rating Scale

The first primary outcome measure is the Brief Psychiatric Rating Scale (BPRS), a widely used clinician-rated 24-item instrument for assessing positive, negative and affective symptoms in patients with psychotic disorders (Ventura et al 1993). The BPRS (Appendix E) consists of 18 symptom constructs and takes 20-30 minutes for the interview and scoring. 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 psychopathology. The BPRS will be

administered at baseline, at week 4, then again in weeks 10-12, week 16 and weeks 22-24. Changes in BPRS score between baseline and the week 10-12 assessment and between the week 10-12 and week 22-24 assessments are the trial's co-primary outcomes.

The second primary outcome measure is the proportion of patients withdrawn to open treatment with amisulpride by their physicians between Weeks 13 and 24 (Stage 2) because of perceived lack of efficacy, which will be compared in participants randomised to continue amisulpride (arm A) and switch to placebo (Arm B). The difference between groups in the percentage of patients stopping trial treatment because of physician concerns about non-efficacy was used as an outcome measure in the CATIE-AD trial (Schneider et al 2003).

ATLAS uses the BPRS rather than one of the more specific schizophrenia psychopathology scales for the following reasons:

(a) The typical psychopathology of patients with very late-onset schizophrenia-like psychosis is different from that seen in schizophrenia with prominent (generally) persecutory delusions, hallucinations and hostility (Howard et al 1994). These patients characteristically do not have affective blunting, prominent negative symptoms or formal thought disorder and although Schneiderian First Rank Symptoms are seen, these are comparatively rare. Hence the use of instruments such as the Positive and Negative Syndrome Scale (PANSS; Kay et al 1987) would not necessarily be as disease-specific or advantageous as might at first appear.

(b) 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 (1=not present, 2=very mild; 3=mild, 4=moderate, 5=moderately severe, 6=severe and 7=extremely severe) on each of these items generates a subscore for these six symptom domains that are primarily affected by the disorder - with pragmatic clinical relevance and meaning to clinicians - as well as an overall score and separate scores for each of the 18 domains.

(c) The BPRS has already been shown to be sensitive to improvements in symptoms associated with antipsychotic treatment in very late-onset schizophrenia-like psychosis patients. Specifically, Psarros et al (2009) reported that 5 weeks of open-label treatment with amisulpride in the same clinical group led to a 30% reduction in BPRS scores.

(d) Clinicians can be trained to achieve high levels of reliability with the BPRS within a single day. This would not be the case for instruments like the PANSS where training would take much longer and would probably not be realistic for NHS staff to undergo given their other time commitments. A review by Hedlund and Vieweg (1980) identified 10 studies of the use of the BPRS, reporting reliability coefficients of 0.80 or greater for the total psychopathology score. Inter-rater agreement for the six individual BPRS items of most interest to **ATLAS** (listed in (b) above) tends to be high with lower correlations for less relevant items such as Emotional Withdrawal and Blunted Affect. BPRS reliability can be improved and maintained by the use of brief training protocols (Schutzwohl et al 2003) and by holding regular calibration meetings to reduce rater drift (Miller and Faustman 1996). Finally, even clinically inexperienced raters can achieve over 90% levels of test-retest reliability if provided with structured interview guidance to support their use of the BPRS (Crippa et al 2001). In **ATLAS** the BPRS will be administered by a suitably qualified, trained trial team member (e.g. consultant old age psychiatrist, a higher trainee in old age psychiatry, an associate specialist, an experienced specialty doctor in old age psychiatry, or an experienced and trained clinical trials nurse). The rater should be knowledgeable concerning psychotic disorders in older people, able to interpret the constructs used in the assessment and have received appropriate training for the trial assessments. Wherever possible, the same rater will be used for all baseline and follow-up ratings on each individual patient.

3.2 Secondary Efficacy Parameters

(i) **Extrapyramidal side-effects (EPSE)** measured with the Simpson-Angus Scale (SAS; Simpson and Angus, 1970). The modified SAS being 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. The head dropping item is omitted because of difficulties with this assessment in home visits. 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 from 0-36. A standardised description is given of each item to optimise reliability. 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. The change in SAS between Baseline and Week 10-12 and between Week 10-12 and Week 22-24 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 22-24 will be compared in patients allocated to receive amisulpride and those allocated placebo.

(iii) **Quality of life** measured with the self-rated, short, 26-item, WHO Quality of Life Scale (WHOQOL-BREF; WHO 1996,) at Baseline, 10-12 and 22-24 weeks. 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, with higher scores denoting a better quality of life. This instrument has been previously used in studies of older people with schizophrenia (e.g. Ritchie et al 2006, Klug et al 2008) and psychosis patients in residential care settings (Picardi et al 2006).

(iv) **Cost-effectiveness** calculated by attaching nationally applicable unit cost measures to health and social service use and medication data collected for each patient with a modified version of the Client Service Receipt Inventory (CSRI; Beecham and Knapp 2001) at 10-12 and 22-24 and the EQ-5D (EuroQol Group 1990) at Baseline, 10-12 and 22-24 weeks. We will also collect data on informal carer inputs, and attach imputed values.

The cost-effectiveness of oral amisulpride versus placebo over 12 weeks and the cost-effectiveness of treatment continuation for a further 12 weeks versus discontinuing amisulpride treatment at 12 weeks will be investigated. The differences between patient groups in the costs for each Stage (covering health and social care service use, medication and carer support) will be calculated, and an incremental cost-effectiveness ratio estimated using QALYs computed from EQ-5D. We will also examine cost-effectiveness by plotting a cost-effectiveness acceptability curve (CEAC) generated from the net benefit approach using bootstrap regression for a range of hypothesised values for willingness to pay for incremental improvements in psychiatric symptoms measured on the BPRS. Each cost-effectiveness analysis will be conducted from the perspective of (a) the NHS and social services, and (b) society as a whole, the main difference being the exclusion of formal and informal carer costs and out-of-pocket patient or carer payments from (a).

(v) Pharmacokinetic data - an optional biochemistry blood test will be taken at one time point during each of the 2 phases of the trial i.e. W4, or W10-12 (Phase 1) and W16 or W22-24 (Phase 2), to collect information on circulating blood levels of amisulpride, and the hormone prolactin. This data will be combined with clinical information and used to investigate variability and covariate effects on the relationship between blood concentration and response/side effect profile.

4. PATIENT ENTRY

4.1 Screening for eligibility and preliminary information visit

Participants will be patients with very late-onset schizophrenia-like psychosis recruited from the community and inpatient teams of UK Old Age Psychiatry services. Initial assessments can take place either in the patient's place of residence or in a clinic setting. At the first appointment, patients potentially meeting the diagnostic criteria for very late onset schizophrenia-like psychosis will be assessed (diagnosis, eligibility and exclusion criteria).

Eligibility criteria:

i. Diagnosis of very late-onset schizophrenia-like psychosis (defined by International Consensus Group criteria, Howard et al 2000), including onset of delusions and/or hallucinations after the age of 60 years; and
ii. BPRS score ≥30, or active psychotic symptoms of a nature and severity that would be consistent with a BPRS score of 30 or greater; and
iii. Capacity to give informed consent to inclusion in trial (in the view of the responsible physician).

Exclusion criteria:

i. Evidence of significant cognitive impairment and standardised MMSE score <25; or
ii. Uncontrolled serious concomitant physical illness; or
iii. Primary diagnosis of affective disorder; or
iv. Prescribed amisulpride in previous 28 days. (Patients who have been treated with other antipsychotic agents in the previous 28 days but still satisfy the eligibility criteria, and stopping current antipsychotic is considered appropriate, can participate and this will be included as a stratification factor at randomisation); or
v. Contraindication to amisulpride (e.g. phaeochromocytoma, prolactin dependent tumour or potential drug interactions: e.g. with levodopa - see most recent Summary of Product Characteristics http://emc.medicines.org.uk/); or
vi. Participation in another Clinical Trial of an Investigational Medicinal Product (IMP) in the previous 28 days.
vii. Conditions which would prevent participants from having a blood test (eg needle phobia), or may lead to distress during attempts to take blood (eg history of poor intravenous access) will exclude participants from taking part in the optional blood test, but will NOT affect their participation in the trial

Patients who meet the eligibility criteria should have the potential benefits and risks of antipsychotic treatment explained with taking part in the **ATLAS** study introduced as one possible option. Patients who are potentially interested in taking part in the study should be given a patient information leaflet to find out more about the study before deciding whether or not to participate. A second appointment should be arranged in the clinic or the patient's home, after a delay of at least 24 hours, to discuss the trial information and seek the patient's consent to participate. Once a potentially eligible patient is identified, the patient should be registered with the **ATLAS** Study Office and, if not already supplied, an **ATLAS** patient treatment pack will be sent to the hospital pharmacy within two working days so that treatment can be given to the patient at, or following, the second appointment if they consent to be randomised (see section 4.3 Randomisation). A registration number will be given at the end of this call, and this should be cited when calling back to randomise the patient.

4.2 Further information and consent visit

Once a physician has confirmed the diagnosis and eligibility, the clinician (i.e. doctor, nurse or other suitably qualified trained member of the research team) will discuss the **ATLAS** study in detail with the patient at the second appointment. The patient should be given a general outline of the three possible options: choice of treatment (i.e. amisulpride or no antipsychotic treatment), taking part in **ATLAS** with the choice made by randomisation, more time to consider, understanding of the *optional* nature of the blood test. A checklist is provided in the **ATLAS** study folder to facilitate this information appointment. After a full explanation has been given of the treatment options, and the manner of treatment allocation, all suitable patients should be invited to take part in the randomised component of the trial, but it is essential not to put undue pressure on the patient. Written, informed consent will be sought from those agreeing to take part in **ATLAS**. If the patient is dependent on a carer, assent should also be obtained from the carer using the carer assent form in the study folder. Where taking of consent has been appropriately delegated to a non-physician, patients should be offered the opportunity to speak with the study doctor and the study doctor must document that they have confirmed the patient's diagnosis and eligibility. Given the optional nature of the blood test and the fact that this was recently introduced into the protocol (v3), the decision whether or not to approach existing participants will be made on a case by case basis by the local study team. The decision will be based on (i) the presence/absence of medical or other conditions which would make phlebotomy distressing or difficult for the participant (ii) knowledge of the patient's level of engagement with the clinical and study team. Where the study team is of the opinion that an additional procedure may cause distress or be detrimental to the ongoing engagement process, the participant will not be approached to discuss the optional blood test.

All delegation of duties must be documented in the **ATLAS** delegation log – section 10 of the **ATLAS** Investigator File. After obtaining consent, the baseline assessments (BPRS, WHOQoL-BREF, EQ-5D) should be undertaken and the patient examined using the SAS. If BPRS is part of the centre's usual diagnostic work-up, then the BPRS does not need to be repeated as the diagnostic BPRS can be used as the study baseline. After completion of all baseline assessments, patients will be randomly allocated (see below). If the patient declines to take part, the **ATLAS** Study Office should be notified so they know that the treatment pack has not been obtained from the hospital pharmacy. Reasons why eligible patients are not invited, or do not consent to take part, should be recorded on the screening log in the **ATLAS** study folder.

4.3 Randomisation: amisulpride or placebo from ATLAS treatment pack

After informed consent and completion of baseline assessments, randomisation will be carried out centrally by the **ATLAS** randomisation service (tel 0800 585323). The person randomising will need to answer all of the telephone questions and should complete the **ATLAS** randomisation notepad before calling to help in preparing for them. Alternatively, randomisation forms may be faxed - or scanned and e-mailed - to the **ATLAS** randomisation service (fax 01865 743986, e-mail: randomisation@ctsu.ox.ac.uk) who will call back with a treatment allocation. After all the necessary details have been provided, the allocated treatment pack number will be specified. The recruiting PI (or other medically qualified doctor with a substantive or honorary contract with the recruiting NHS Trust and who has signed the 'Recruiting Investigator site delegation of authority form') should complete an **ATLAS** prescription form (provided in the study folder). The first **ATLAS** treatment pack with this number, which will contain the initial 12 weeks' treatment, should be obtained from the hospital pharmacy and given to the patient. Instructions for the trial treatments are available on a label which can be stuck in the patient's clinical notes. The baseline assessments should be labelled with the patient's treatment pack number and copies posted to the **ATLAS** Study Office

in the Freepost envelopes provided in the study folder. Originals should be retained in the trial site study folder. The patient's GP should be notified that they are in **ATLAS** and a specimen "Letter to GP" is provided for this purpose.

5. TREATMENT AND FOLLOW-UP PROCEDURES

5.1 Trial treatment

Trial treatment will be oral amisulpride or identically appearing placebo packed into treatment cartons of 12 weeks' treatment in the form of 3 x 28 blister-packed capsules (for Stage 1 or Stage 2). Trial treatment will be packed, labelled, QP released and dispatched to participating centres' pharmacies by Sharp (Europe) Ltd. As described above, patients will be allocated a treatment pack number following randomisation, which will also be the patient's unique identifying number. This initial 12-week (Stage 1) treatment carton should be obtained from the hospital pharmacy using the **ATLAS** prescription form in the study folder. Treatment should start as soon as possible and should be continued for twenty-four weeks unless a definite contra-indication is thought to have developed. If the patient is still compliant with treatment at the 10-12 week assessment (i.e. taking capsules sufficiently regularly that compliance with weeks 13-24 treatment seems likely), the **ATLAS** Study Office should be informed (tel 0800 585323). The second **ATLAS** treatment pack number will then be allocated. This 12-week (Stage 2) carton, which will contain the patient's treatment for weeks 13 to 24 will be in the same form of 3 x 28 blister-packed capsules (a total of 12 weeks treatment at one capsule a day), again to be obtained from the hospital pharmacy, using an **ATLAS** prescription form, and given to the patient. The second pack allocation must be issued by the ATLAS Trial Office, to ensure that patients are allocated the correct medication in Stage 2. Pharmacy departments in each site will maintain a study medication dispensing log, including date dispensed, batch number, expiry date, and number of capsules dispensed. The study specific prescriptions will be maintained in the pharmacy file for audit purposes.

The dosing regimens for the three treatment arms are:

Group (A) will take one capsule containing 100mg amisulpride orally per day for a period of 24 weeks

Group (B) will take one capsule containing 100mg amisulpride orally per day for a period of 12 weeks, followed by one matching placebo capsule orally per day for a further 12 weeks.

Group (C) will take one placebo capsule orally per day for a period of 12 weeks, followed by one capsule containing 100mg amisulpride orally per day for a further 12 weeks.

Treatment compliance will be monitored by capsule count. Patients should be asked to bring any unused study medication at each follow-up visit and at the end of the trial. The local PI or research worker will log study medication returns, return date and amount of study medication returned and enter the information on the follow-up form. Once returned medication has been logged, it should be destroyed by the local pharmacy.

Arrangements for continued treatment at the end of the trial will be made on an individual patient basis by the Local Investigator or other clinicians responsible for the patient's care at this point. Responsible clinicians will be asked to record on the last patient follow-up form what treatment plan is in place for the individual patient. On present evidence, no recommendation can be made about treatment beyond 24 weeks but the Data Monitoring and Ethics Committee (see section 8.4) will scrutinise the accumulating data from **ATLAS** and, if clear evidence for or against amisulpride treatment emerges, will notify the Steering Committee who will then make appropriate recommendations.

5.2 Randomisation code break

Investigators and patients will remain blinded to the treatment allocation throughout the trial. Unblinding should not normally be necessary as serious side-effects should be dealt with on the assumption that the patient is on active amisulpride treatment. Study medication should be omitted rather than unblinded. Request for unblinding should be directed to the **ATLAS** Study Office during office hours. If considered urgently necessary for patient management, the randomisation service can be telephoned to unblind trial treatments (0800 585323). A medical reason for unblinding must be provided.

5.3 Other treatments

Treatment with other typical or atypical antipsychotic drugs is not allowed during the study period. Patients who are being prescribed other antipsychotic medication at entry to the trial should cease before starting **ATLAS** treatment. Also, when prescribing concomitant medication, investigators should take into consideration the potential for drug interactions – e.g. with levodopa - as described in the most recent Summary of Product Characteristics; see http://emc.medicines.org.uk/. Apart from this, giving out the trial treatments and undertaking the follow–up assessments, all other aspects of patient management are entirely at the discretion of the local doctors. Patients are managed in whatever way appears best for them, with no special treatments, no laboratory or other special investigations, and no extra follow-up required. Concomitant medications should, however, be recorded on the **ATLAS** patient follow-up form. If patients agree to have an optional blood test, these results will not be used to inform management, but will be stored until the end of the trial (see 5.7) and analysed with other collated data.

5.4 Assessments at 4, 10-12, 16 and 22-24 weeks

Assessments will be undertaken prior to randomisation and then at week 4 (+/- 1 week), between weeks 10-12, Week 16 (+/-1 week) and between weeks 22-24 (see flowchart below). The weeks 10-12 and 22-24 follow-up visits are scheduled in the last two weeks before completion of the first and second treatment stages to ensure that the patient is still taking trial treatment at the assessment even if their appointment is delayed for any reason. Follow-up assessments should be undertaken whether or not patients remain compliant with trial treatment. Copies of assessments performed at these visits should be posted to the Trial Office, and the originals retained at site.

ATLAS Study Flowchart

	Eligibility screening	Information & consent	Week4 (±1 week)	Week 10-12	Week 16 (±1 week)	Week 22-24
Diagnosis (ICG criteria)	X					
Standardised MMSE	X					
BPRS	(X)*	(X)*	X	X	X	X
Inclusion Criteria	X					
Exclusion Criteria	X					
Capacity Assessment	X	X				
Patient registration	X					
Informed Consent		X				
Randomisation		X				
Simpson Angus Scale		X	X	X	X	X
Blood test (optional) γ			X		X	
EuroQol EQ-5D		X		X	X	X
WHO QoL Brief Scale		X		X	X	X
Randomisation		X				
Dispense Medication		X		X		
Compliance Check			X	X	X	X
Adverse Events			X	X	X	X
Follow-up form			X	X	X	X
Client Service Receipt Inventory				X		X

* If BPRS is part of the centre's usual diagnostic work-up, then the BPRS does not need to be repeated

γ Venous blood sample to measure circulating levels of amisulpride and prolactin. The blood sample is optional and will be taken at whatever time point is most convenient for the patient (week 4 or 10-12, and week 16 or 22-24).

5.5 Minimising loss to follow-up

The trial aims to minimise the number of patients who discontinue treatment and, especially, the numbers with missing follow-up assessments. However, in some circumstances discontinuation may occur and can be initiated by the patient, their carers, investigators or other responsible physicians.

Discontinuation from treatment only

Patients or their doctors commonly choose to discontinue clinical trial medication, e.g. because:

i. Patient withdraws consent to further treatment.
ii. Intercurrent illness or side-effects prevent further treatment.
iii. Change (or lack of change) in the patient's condition justify discontinuation of treatment in the clinician's opinion.

Most patients who discontinue treatment are happy to continue to be followed up. In this case, **ATLAS** outcome data should be collected in accordance with the protocol. The reason for stopping **ATLAS** treatment (e.g. side-effects, lack of perceived effectiveness, patient choice or other) and the use of other treatments (if any) should be recorded on the patient follow-up form. Unused drugs should be destroyed (see section 5.1) except that, if patients discontinue treatment in the first 12 weeks, the unallocated 13-24 week treatment pack should remain in the pharmacy from where it may be re-allocated to another trial patient.

Discontinuation from treatment and follow-up assessments

Patients may choose to discontinue both treatment and study assessments. In this case, the local PI or research worker should attempt to ascertain the reason for a patient's discontinuation of follow-up assessments, without compromising their right to withdraw at any time without giving a reason, and record this on the patient follow-up form. Note that, unless the patient specifically revokes their earlier consent for information about their progress to be sent to the **ATLAS** Study office, clinical information will continue to be collected and patient information will be retained in the trial database and used for intention-to-treat analyses of study outcome.

Loss to follow-up

Loss to follow-up will be minimised by all available means, including use of centrally held NHS records, and will be monitored both locally and centrally. A patient will only be regarded as lost to follow-up with the agreement of the recruiting PI and the trial manager.

Patient transfers

For patients moving from the area, or to another doctor or hospital, every effort should be made for the patient to be followed up. If another centre agrees to take over responsibility for the patient assessments, it will need to be set up as an **ATLAS** site, a copy of the patient's study documentation sent to the new site, and the patient will have to sign a new consent form. Until this occurs, the patient remains the responsibility of the original centre. The **ATLAS** Study office can help facilitate this process.

5.6 Expected duration of trial

From the regulatory perspective, the end of the trial is defined as the end of the interventional phase, 22-24 weeks after the final patient is randomised. Completion for an individual patient is defined as completion of 22-24 weeks on the trial medication or discontinuation of follow-up for any reason. The trial may, however, be stopped earlier by the Trial Steering Committee if the Independent Data Monitoring and Ethics Committee, in accordance with the DMEC charter, recommend to the Trial Steering Committee that the trial be stopped. The criteria for stopping the trial will be established as part of standard operating procedures of the DMEC (see section 8.4) at their first meeting

5.7 Laboratory tests

Venous blood samples will be taken, in an appropriate container (gold-topped tube) and transported via a courier to Kings College Hospital (Toxicology Unit, Department of Clinical Biochemistry, Third Floor, Bessemer Wing, King's College Hospital, Denmark Hill London SE5 9RS). The address is included on the assay request form (APPENDIX M). Samples will be stored in a refrigerator within a secure CPA accredited laboratory at the Clinical Toxicology Unit within Kings College Hospital, until the end of the study. Each sample will be accompanied by a referral form which will include the following details: study ID, and the date and timing of both the sample and the last dose of study drug. The form will not contain any identifiable information. The analysis will be carried out using a technique called high performance liquid chromatography. This technique will allow concentration of the study drug (amisulpride or placebo) and prolactin (hormone) to be determined. Laboratory staff, supervised by HPC registered scientists, will have access to the samples. Robert Flanagan will act as custodian for the samples during the course of the study. All samples will be analysed at the end of the study, and disposed of in accordance with the Human Tissue Authority's Code of Practice

6. SAFETY MONITORING PROCEDURES

6.1 Specification, Timing and Recording of Safety Parameters

Safety will be assessed at the 4, 10-12, 16 and 22-24 week visits via a face to face interview with the researcher who will systematically enquire about changes in the patient's health state between assessments. Patients will also be examined and rated on the modified Simpson-Angus Scale to detect and quantify the development of extra-pyramidal side-effects (EPSE).

6.2 Procedures for Recording and Reporting Adverse Events

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

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

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

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SPC) for that product (for products with a marketing authorisation) – available at http://emc.medicines.org.uk/ - or the Investigator's Brochure (IB) relating to the trial in question (for any other investigational product).

Serious Adverse Event (SAE), **Serious Adverse Reaction (SAR)** or **Unexpected Serious Adverse Reaction**: Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

1. Results in death;
2. Is life-threatening;
3. Requires hospitalisation or prolongation of existing hospitalisation;
4. Results in persistent or significant disability or incapacity;
5. Consists of a congenital anomaly or birth defect.

A **Suspected Unexpected Serious Adverse Reaction** is usually referred to as a **SUSAR** and requires expedited reporting (see below).

Note the term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

Assessment of Causality

The relationship between study drug and the SAE will be assessed by the local PI and categorised using clinical judgement into one of the following five categories:

1. ***Not related*** – temporal relationship not reasonable or event explained in isolation by another cause
2. ***Unlikely related*** – temporal relationship unlikely or event likely to be explained by another cause
3. ***Possibly related*** – temporal relationship is reasonable but event could be due to another equally likely cause
4. ***Likely related*** – temporal association is reasonable and event is more likely to be due to study drug than other cause
5. ***Definitely related*** – temporal relationship is reasonable and there is no other cause to explain event, or re-challenge is positive

For classification of causality ***possibly***, ***likely*** *and* ***definitely related*** categories should be considered as reactions in the **ATLAS** trial.

Reporting Responsibilities

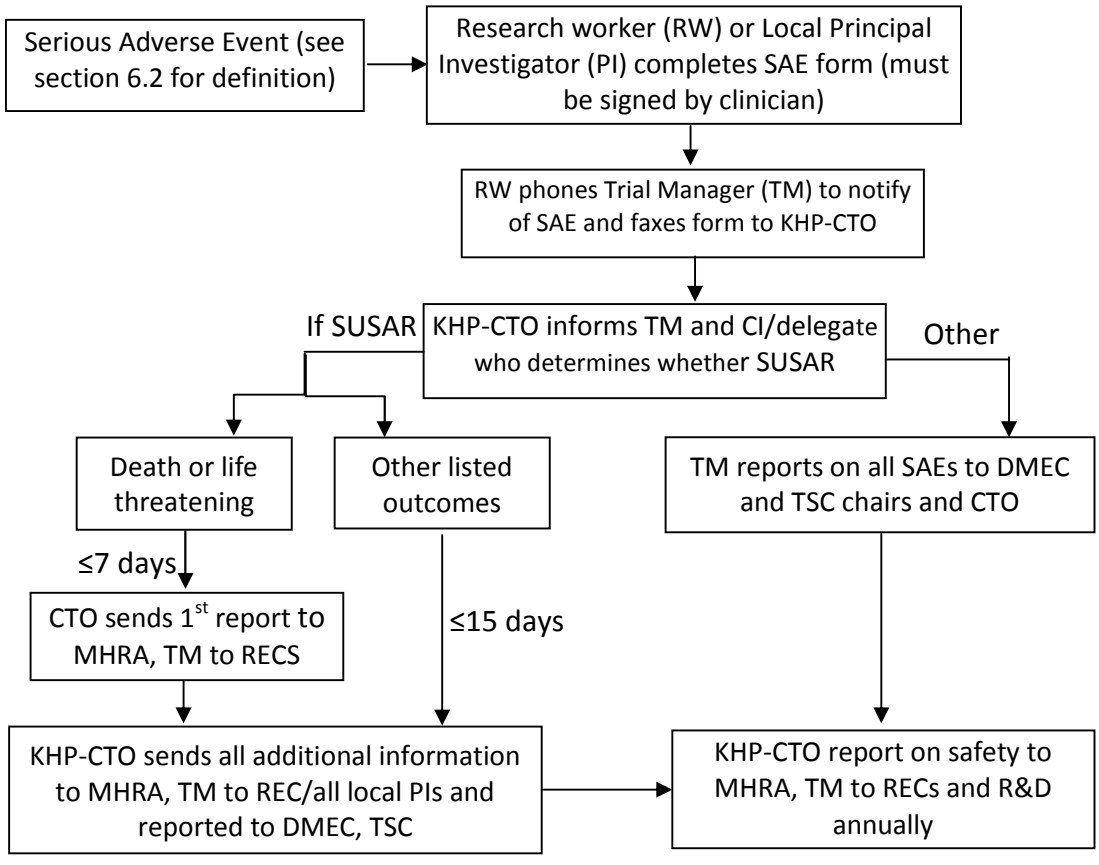
King's College London, as Sponsor, have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance - as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 - to the King's Health Partners Clinical Trials Office (KHP CTO). The Local Principal Investigator or other member of the research team should complete an SAE form for all SAEs, SARs and SUSARs), telephone the **ATLAS** Trial Manager to notify them of the SAE and fax the form to the KHP-CTO and Chief Investigator immediately (and certainly no later than 24 hours after becoming aware of the SAE). The form will be forwarded immediately to the Trial Manager by the KHP-CTO in accordance with the current Pharmacovigilance Policy. The **ATLAS** CI, or delegate, will review these events to determine whether they are SUSARS needing expedited reporting. In addition, AEs that are considered possibly related to **ATLAS** treatment, serious or otherwise will be recorded on follow-up forms and reviewed by **ATLAS**'s independent Data Monitoring Committee at regular intervals.

The King's Health Partners Clinical Trials Office (KHP CTO) will report SUSARs to the MHRA. The Chief Investigator will delegate responsibility to the **ATLAS** Study Office at CTSU for reporting SUSARs and other SARs to the relevant ethics committees, PIs and R&D departments.

Reporting timelines are as follows:

- SUSARs that are fatal or life-threatening must be reported not later than 7 days after the Sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the Sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP-CTO (on behalf of the co-sponsors), will submit a Development Safety Update Report (DSUR) relating to the drug used in the **ATLAS** trial to the REC and MHRA annually.

Reporting Flowchart for SAEs, SARs and SUSARs



7. SAMPLE SIZE, STATISTICS AND DATA MONITORING PROCEDURES

7.1 Sample Size

Patients with very late-onset schizophrenia-like psychosis have very rarely been recruited to randomised controlled trials but, for reasons outlined in this proposal, the conduct of such a trial is an important priority. To assess recruitment and retention, **ATLAS** included an initial Feasibility Phase following which, a pragmatic decision has been made to reduce the target sample size from 200-300 to at least 100 patients, to be recruited by mid-2016. The statistical power calculations have been amended accordingly 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. Since Psarros et al (2009) reported a mean 14-point BPRS improvement over 5 weeks of treatment in an open-label case series, an anticipated treatment effect of at least 5 points is highly plausible. From these same data, we estimate that the standard deviation of BPRS scores will be 9 BPRS 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 (Cohen, 1988, Norman et al 2003).

With 100 patients, allowing for a 10% drop-out rate by 12 weeks, i.e. 90 of 100 with outcome assessments (60 patients in groups A and B combined allocated 12 weeks amisulpride vs. 30 patients in group C allocated 12 weeks placebo), **ATLAS** would have 70% power at $2p<0.05$ to detect the MRD of 5 points (0.56sd) between those taking amisulpride and placebo in Stage 1. If 127 patients can be recruited, **ATLAS** would have 80% power at $2p<0.05$ to detect the MRD.

If, as we hope, the treatment benefit from amisulpride is larger than the minimal difference then statistical power will be substantially higher. For example, 70 randomisations would give 80% power to detect a 7 point drug-placebo difference and 90 randomisations would give 80% power to detect a 6 point difference. These benefits are plausible given the 14 point improvement on BPRS scores with amisulpride reported by Psarros et al (2009).

It should also be noted that these power calculations are conservative in that the principal repeated measures analysis will provide additional statistical power by using all available data (Frison & Pocock, 1992) and because drop-out from treatment will be informative (i.e. a treatment failure) and sensitivity analyses will be undertaken imputing missing outcome assessments, which will also enhance statistical power.

Randomisation will be obtained by telephone, fax or e-mail from the **ATLAS** Study office. A minimised randomisation procedure will be used to ensure balance of treatment allocation overall and by the following variables to be used in the pre-specified sub-group analyses:

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

7.2 Analysis

The trial will comprise two stages (see Flow Diagram, section 2.2). Stage 1 lasts from weeks 1-12 inclusive. Stage 2 lasts from weeks 13-24.

Patients will be randomised between three arms:

(A) Amisulpride 100mg Stage 1 then Amisulpride 100mg Stage 2

(B) Amisulpride 100mg Stage 1 then Placebo Stage 2

(C) Placebo Stage 1 then Amisulpride 100mg Stage 2

The main analysis will be undertaken once all patients have reached 22-24 weeks from randomisation. To assess efficacy of 12 weeks of amisulpride treatment in Stage 1, the primary outcome of the BPRS will be compared using a repeated measures model. Data from 4 weeks and 12 weeks will be the outcome variables and baseline scores will be entered into the model as a covariate. The comparison will be between active amisulpride treatment (i.e. Arms A and B of the trial grouped together) and placebo (Arm C). This will be an Intention-To-Treat (ITT) analysis – all patients who are randomised and take at least one capsule of their treatment will be included in the comparison, analysed according to their randomised allocation, including patients who discontinue **ATLAS** trial treatment and switch to open amisulpride treatment. Wherever possible, we will continue to collect follow-up data from these patients after they move to open-label treatment, so that the dataset will be as complete as possible.

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 36 weeks – the protocol has now been amended to shorten stage 2 to 12 weeks with an additional assessment at about 16 weeks. So, an analysis of covariance will be carried out, again entering the "baseline" (which here will be the 12 week scores) into the model as a covariate. This analysis will again be ITT, except that patients who withdraw from protocol treatment in Stage 1 – and hence do not receive treatment packs after week 12 – will not be included in the Stage 2 comparison. This will not introduce bias: the two arms receive the same treatment regimen in Stage 1 and since neither patients nor their doctors in this double-blind trial will be aware which treatment they would receive in Stage 2, this cannot influence the decision to withdraw and, consequently, result in systematic differences between Arms A and B during Stage 2. Thus, excluding patients who do not reach stage 2 will not introduce selection bias to the comparison at Stage 2.

Other continuous outcome measures will be analysed by similar methods. Exploratory analyses will be undertaken, using standard tests for interaction, of any differential treatment efficacy in subgroups of patients defined by the randomisation stratification variables. Such subgroup analyses will be interpreted appropriately cautiously. Treatment discontinuation rates will be compared using a chi-squared test, or the logrank test if possible (i.e. if accurate data on time of discontinuation can be obtained). Reasons for stopping treatment will be collected and, since stopping **ATLAS** treatment is likely to be informative (e.g. a failure of treatment), this information will be used in sensitivity analyses to investigate and reduce the impact of missing data. Exploratory analysis of blood data will be conducted using non-linear mixed effect modelling to investigate variability and covariate effects on pharmacokinetics (dose-concentration relationships) and pharmacodynamics (prolactin levels, extrapyramidal side effects). This information will also be used to inform future pharmacokinetic modelling of dose-response relationships in older people.

8. ORGANISATION

To ensure the smooth running of **ATLAS** and to minimise the overall procedural workload, it is proposed that each centre should designate individuals who would be chiefly responsible for local coordination of clinical and administrative aspects of **ATLAS**. The **ATLAS** Study Office, working together with MHRN networks, will provide as much assistance as they can to local co-ordinators and investigators in obtaining Trust approval in each centre, identifying, assessing and recruiting patients, distribution of trial treatments, and helping resolve any local problems that may be encountered.

8.1 Local Principal Investigator

Each Centre should nominate one person to act as the Local Principal Investigator (PI). Their responsibilities will include:

1. **Liaising with local GPs, nurses, social services and Clinical Research Networks**
   The PI will need to liaise with all who refer patients to the centre to encourage them to consider suitable patients for **ATLAS**. Local procedures will need to be developed to ensure assessment and discussion of individual patients' suitability for **ATLAS** at Team meetings, providing eligible patients with **ATLAS** information sheets, arranging appointments to discuss taking part in the study, obtaining consent and randomisation, and delivering allocated drug packs to patients. Any member of the clinical team can obtain consent and randomise patients although it is obviously essential that teams liaise closely to agree who randomises and which patients are suitable for **ATLAS**.
2. **To ensure that all medical and nursing staff involved in the care of very late-onset schizophrenia-like psychosis are reasonably well informed about the study**
   This involves distributing the **ATLAS** materials to all relevant staff, and distributing the **ATLAS** newsletters. A regularly updated PowerPoint presentation will be provided to centres so that they can be shown from time to time, especially to new staff.
3. **To ensure compliance with The Medicines For Human Use (Clinical Trials) 2004 regulations and subsequent amendments and research governance requirements**
   This involves obtaining management approval for **ATLAS**, ensuring that all members of the clinical team are familiar with the protocol and trial procedures, in particular serious adverse event reporting, maintaining the Local Study Site File with copies of trial materials, approval documents, consent forms, delegation logs and any other required documents as advised by the **ATLAS** Study office.

8.2 Local Study Coordinator

It is suggested that each Centre should designate one person as Local Study Coordinator. This role might suit a higher trainee in old age psychiatry or other suitably qualified delegated member of the research team (eg a research nurse or clinical studies officer). The Local Study Coordinator would be responsible for ensuring that all eligible patients are considered for **ATLAS**, that patients are provided with **ATLAS** information sheets and have an opportunity to discuss the study as required, registering patients to ensure that **ATLAS** drug packs are available when potential patients are identified, obtaining consent (with the involvement of a study doctor), randomisation, obtaining drug packs from the pharmacy when patients are randomised, giving these to the patient with treatment instructions, and ensuring follow-up assessments are undertaken as scheduled in the protocol. The **ATLAS** Local Study Coordinator will also ensure that **ATLAS** trial forms, questionnaires are completed and treatments are administered as scheduled (unless some contraindication develops). Again, this person would be sent updates and newsletters, would be invited to **ATLAS** progress meetings and appropriately credited in study reports.

8.3 Trial Steering Committee

The TSC is responsible for the independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies. The TSC will review data, blinded to study treatment, on progress of the trial including recruitment, protocol adherence, serious adverse events, trial publications and will determine the future progress of the trial in light of regular reports from the DMEC and Trial Management Group (TMG). The TSC has the power to prematurely close the trial. The TSC will meet annually or more often if the chair determines a reason for doing so. In addition to the independent voting members (listed inside front cover),

the TSC will include the **ATLAS** Chief Investigator, Trial Manager and Statistician, and representatives from the funding body and Sponsor.

8.4 Data Monitoring and Ethics Committee

The independent Data Monitoring and Ethics Committee (DMEC - members listed inside front cover) is responsible for monitoring the unblinded accumulating data from the trial including: protocol adherence, serious adverse events and side effects of treatment as well as the difference between the trial treatments on the primary and secondary outcome measures. Based on the unblinded interim analyses, the DMEC can recommend protocol modifications to the TSC, including premature closure of the trial. The DMEC will agree their structure, organisation and stopping rules in a DMEC Charter (DAMOCLES Study Group, 2005) at their first meeting. The DMEC will meet annually or more often if the chair determines a reason for doing so. The chief investigator (or their representative) and the trial manager will be in attendance for the open session of the DMEC meeting. The trial statistician will be in attendance for the open session and to present and answer any questions on the interim analyses in the closed session. There will then be a session of just the independent members to agree any actions needed and the content of the DMEC report to the Trial Steering Committee.

8.5 Ethics & Regulatory Approvals

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

This protocol and related documents have been reviewed and approved by:

(1) The London and Surrey Borders Multicentre Research Ethics Committee (MREC reference 11/LO/1267).

(2) The Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

The integrated form for both site-specific assessment (SSA) and R&D approval at all participating NHS sites will also be approved prior to recruitment at each site. Annual progress and safety reports and a final report at conclusion of the trial will be submitted to the MREC and the MHRA within the timelines defined in the Regulations.

8.6 Quality Assurance

Recruitment to **ATLAS** and the conduct of trial assessments will be undertaken by senior NHS clinicians or other suitably qualified delegated members of the research team who are experienced in the assessment and rating of psychopathology. All Investigators and staff involved with the trial will undergo appropriate training in GCP, use of the assessment tools and trial procedures before they are able to recruit participants to **ATLAS**.

The Trial Manager will maintain a Trial Master File containing the essential trial documents in accordance with GCP and the EU Clinical Trial Directive. In addition, each site will be provided with an Investigator Site File and a Pharmacy File, which will contain the essential trial documents.

The trial will be carried out in accordance with this protocol and the **ATLAS** Standard Operating Procedures (SOPs). Trial specific functions will be conducted in accordance with these and will ensure the procedures within the trial are carried out in the same way in each centre.

Monitoring of this trial to ensure compliance with the Medicines for Human Use (Clinical Trials) regulations 2004 and amendments, the protocol and Good Clinical Practice will be managed and overseen by the King's Health Partners Clinical Trials Office (KHP CTO) Quality Team, in

accordance with KHP CTO SOPs, on behalf of the Sponsor. Each site will take part in a site initiation, to ensure appropriate staff training, resources, IMP management and essential documents are in place. During the course of the trial the study files will be reviewed for appropriate documentation of patient consent and participation in the trial, and a sample of data will be verified against patient notes in accordance with the risk assessment and monitoring plan for the trial. The Investigator(s) will provide direct access to source data and other documents (e.g. patients' case sheets, etc) to permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate). At the end of the trial each site will be formally closed down once trial activity at the site has ceased.

The Chief Investigator will act as custodian for the trial data. All trial data will be stored on a password-protected computer and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the KHP CTO Archiving Standard Operating Procedure (SOP).

8.7 Publication Policy

The results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. A meeting of the Trial Steering Committee and ATLAS collaborators will be held after the end of the study to allow discussion of the main results prior to publication. The success of **ATLAS** depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have significantly contributed to the study. All grant holders and members of trial committees together with anyone who during the course of the study enters three or more patients into the study and research workers at these centres who have been involved with the trial for more than 12 months would have authorship rights as part of the **ATLAS** Trialists Group. Presentations or publications pertaining to the **ATLAS** trial must not be made without the prior agreement of the Trial Management Group.

8.8 Financial Aspects

Funding to conduct the **ATLAS** trial is provided by the Department of Health's Health Technology Assessment programme (reference number 09/55/06). The duration of the grant is from October 2011 to July 2017 The grant will be administered by King's College London and sub-contracts will be drawn up for the Study Office at CTSU, University of Oxford and for other sites.

9. REFERENCES

Alexopoulos GS, Streim J, Carpenter D, Docherty JP; Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients (2004) Using antipsychotic agents in older patients. Journal of Clinical Psychiatry 65 Supplement 2 5-99.

Almeida O, Levy R, Howard R, David A (1996) Insight and paranoid disorders in late life (late paraphrenia). International Journal of Geriatric Psychiatry 11 653-658.

Arunpongpaisal S, Ahmed I, Aqeel N, Suchat P (2003) Antipsychotic drug treatment for elderly people with late-onset schizophrenia. Cochrane Database Systematic Reviews 2 CD004162.

Ballard C and Howard R (2006) Neuroleptic drugs in dementia: benefits and harm. Nature Reviews Neuroscience 7 492-500.

Beecham J. & Knapp M (2001) Costing psychiatric interventions. In Measuring Mental Health Needs (2nd edn) (ed. G. Thornicroft), pp. 200-224. Gaskell.

Carpenter WT, Appelbaum PS, Levine RJ (2003) The declaration of Helsinki and clinical trials: a focus on placebo-controlled trials in schizophrenia. American Journal of Psychiatry 160 356-362.

Cohen J. Statistical power analysis for the behavioral sciences. 2nd edition. New York: Academic Press, 1988.

Crippa JA, Snaches RF, Hallak JE, Loureiro SR, Zuardi AW (2001) A structured interview guide increases Brief Psychiatric Rating Scale reliability in raters with low clinical experience. Acta Psychiatrica Scandinavica 103 465-470.

The DAMOCLES Study Group. A proposed charter for clinical trial 2005 data monitoring committees: helping them do their job well. Lancet 2005; 365: 711-22

De Deyn PP, Rabheru K, Rasmussen A, et al (1999) A randomized trial of risperidone, placebo and haloperidol for behavioural symptoms of dementia. Neurology 53 946-955.

Dunn LB, Palmer BW, Keehan M (2006) Understanding of placebo controls among older people with schizophrenia. Schizophrenia Bulletin 32 137-146.

EuroQol Group (1990) EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 16 199-208.

Frison L, Pocock SJ. Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design. Statist Med 1992;11:1685-1704.

Hedlund JL, Vieweg BW (1980) The Brief Psychiatric Rating Scale (BPRS): a comprehensive review. Journal of Operational Psychiatry 11 48-65.

Howard R, Levy R (1992) What factors affect treatment response in late paraphrenia? International Journal of Geriatric Psychiatry 7 667-672.

Howard R, Almeida O, Levy R (1994) Phenomenology, demography and diagnosis in late paraphrenia. Psychological Medicine 24 515-524.

Howard R, Rabins PV, Seeman M, Jeste DV (2000) Late-onset schizophrenia and very late-onset schizophrenia-like psychosis: an International Consensus. American Journal of Psychiatry 157 172-8.

Howard R (2008) Late onset schizophrenia and very late onset schizophrenia-like psychosis. In: Oxford Textbook of Old Age Psychiatry (Eds R Jacoby et al.). Oxford University Press. Pp 617-626.

Kay SR, Fiszbein A, Opler LA (1987) The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophrenia Bulletin 13 261-276.

Kim SY (2003) Benefits and burdens of placebos in psychiatric research. Psychopharmacology 171 13-18.

Klug G, Hermann G, Fuchs-Neider B, Stipacek A, Zapotoczky HG (2008) Geriatric psychiatry home treatment: a pilot study on outcomes following hospital discharge for depressive and delusional patients. Archives of Gerontology and Geriatrics 47 109-120.

Leucht S (2004) Amisulpride – a selective dopamine antagonist and atypical antipsychotic: results of a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology 7 (Suppl 1) 15-20.

Miller FG (2000) Placebo-controlled trials in psychiatric research: an ethical perspective. Biological Psychiatry 47 707-716.

Miller LS, Faustman WO (1996) Brief Psychiatric Rating Scale. In LI Sederer and B Dickey (Eds) Outcomes Assessment in Clinical Practice. Baltimore MD. Williams and Wilkins. 105-109.

Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582-92.

Phanjoo AL, Link C (1990). Remoxipride versus thioridazine in elderly psychotic patients. Acta Psychiatrica Scandinavica Supplementum 358 181–185.

Picardi A, Rucci P, de Girolamo G, Santone G, Borsetti G, Morosini P (2006) The quality of life of the mentally ill living in residential facilities: findings from a national survey in Italy. European Archives of Psychiatry and Clinical Neurosciences 256 372-381.

Psarros C, Theleritis CG, Paparrigopoulos TJ, Politis AM, Papadimitriou GN (2009) Amisulpiride for the treatment of very-late-onset schizophrenia-like psychosis. International Journal of Geriatric Psychiatry 24 518-522.

Raskind MA and Risse SC (1986) Antipsychotic drugs and the elderly. Journal of Clinical Psychiatry 47 Supplement 5 17-22.

Reeves SJ, Sauer J, Stewart R, Granger A, Howard R (2001) Increased first contact rates for very late-onset schizophrenia-like psychosis in Caribbean-born elders. British Journal of Psychiatry 179 172-4.

Ritchie CW, Chiu E, Harrogan S, et al (2006) A comparison of the efficacy and safety of olanzapine and risperidone in the treatment of elderly patients with schizophrenia: an open study of six months duration. International Journal of Geriatric Psychiatry 21 171-179.

Schneider LS, Ismail MS, Dagerman K, et al (2003) Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer's Disease Trial. Schizophrenia Bulletin 29 57-72.

Schutzwohl M, Jaroz-Nowak J, Briscoe J, et al (2003) Inter-rater reliability of the Brief Psychiatric Rating Scale and the Groningen Social Disabilities Schedule in a European multi-site randomized controlled trial on the effectiveness of acute psychiatric day hospitals. International Journal of Methods in Psychiatric Research 12 197-207.

Simpson GM, Angus JW (1970) A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavia Supplement 212 11-19.

Van Os J, Howard R, Takei N, Murray R (1995) Increasing age is a risk factor for psychosis in the elderly. Social Psychiatry and Psychiatric Epidemiology 30 161-164.

Ventura MA, Green MF, Shaner A, Liberman RP (1993) Training and quality assurance with the brief psychiatric rating scale: "The drift buster". International Journal of Methods in Psychiatric Research 3 221-244.

World Health Organisation (1996) WHOQOL-BREF Introduction, Administration, Scoring and Generic Version of the Assessment. WHO. Geneva.