Statistical Analysis Plan

Version:2.0
Trial Registration Number: ISRCTN80567433

Approved by:

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1 Amendment History

SAP version	Protocol version	Section number changed	Description	Date changed
V2	V5	4.2 and 4.3	For section 4.2, baseline adjustment added to the analysis description, analysis will only adjust for site and not therapist and how other secondary outcomes will be analysed was included. For section 4.3, how missing baseline data will be handled was included	01/05/2019

2 Introduction

2.1 Aim

Our primary aim is to determine whether it is feasible to conduct a study to examine the effectiveness of psychological therapy, antipsychotic medication or a combination of the two, in adolescents with first episode psychosis.

2.2 Trial design

The study will be a single blind, 3-arm randomised controlled trial comprising of a 6-month intervention and 6 month follow-up period, in seven centres across the UK. The randomised groups will be psychological intervention (PI) alone, antipsychotic medication (AP) alone and a combination of the two.

Randomisation (at the individual level) will be independent and concealed, using randomised-permuted blocks of random size, stratified by site and family contact. Randomisation will be in the ratio of 1:1:1. Randomisation will be administered via a study-specific web-based system developed by the clinical trials unit (CHaRT). Blinding of the allocation code will be maintained for research assistants until all outcome measures for all participants have been collected. The independent Data Monitoring and Ethics Committee (iDMC) and Trial Steering Committee (TSC) will regularly monitor unblindings by each centre, and implement corrective action if necessary.

3 Analysis Objectives

The objectives are to assess, under randomised conditions:

- The proportion of eligible people clinicians are willing to refer, the proportion of eligible people willing to participate and the proportion of participants who comply with their allocation
- The drop-out rate, and the proportion of clinicians willing to refer to the trial
- The characteristics of trial participants to clarify selection criteria
- The appropriateness and integrity of treatment protocols and the feasibility and acceptability of the interventions to participants, parents and referring clinicians
- The randomisation procedures
- The relevance and validity of the measures to assess effectiveness, safety and acceptability in a subsequent definitive trial

We will also:

- Estimate the standard deviation and correlation between time-points of outcome measures, and overall attrition rate to inform the design of a definitive trial
- Clarify training/supervision needs for delivering interventions/assessments
- Finalise treatment manuals and outcome measures
- Assess the possibility for economies of scale and monitor time use of the research assistants

4 Outcomes

4.1 Primary feasibility outcomes

The key outcomes to inform a future trial are referral rates, recruitment, attendance at therapy sessions, compliance with medication and follow-up and questionnaire response rates. Acceptability of treatment will be measured using rates of drop-out from treatment. A specified red/ amber/ green progression criteria which have been agreed by the TSC, iDMC and funder which will be reviewed at the end of trial to inform a recommendation for a definitive trial. The progression criteria are:

- Recruitment $\geq$80% of planned (green), recruitment within 79-60% of planned (amber), recruitment <60% of planned (red)
- Retention of participants within the study with baseline and outcome assessments at primary end point (6 months, end of treatment) $\geq$80% of primary secondary outcome completed (green), 79-60% of primary secondary outcome completed (amber), <60% of primary secondary outcome completed (red)
- Satisfactory delivery of adherent therapy to $\geq$80% of groups receiving PI (green), 79-60% of groups receiving PI (amber), <60% of groups receiving PI (red) Satisfactory delivery of adherent therapy will be operationalised as attending 6 or more sessions of Cognitive Behavioural Therapy (CBT)
- Satisfactory delivery of antipsychotic medication to $\geq$80% of groups receiving AP (green), 79-60% of groups receiving AP (amber), <60% of groups receiving AP (red) Satisfactory delivery of antipsychotic medication will be operationalised as any exposure of AP for 6 consecutive weeks (this would include a dose below British National Formulary (BNF) lower limits given this is a frequent clinical practice for people of this age and the drugs are licensed for adults).

4.2 Secondary clinical outcomes

All secondary outcomes are being collected to determine their suitability for use in a subsequent trial, rather than to draw conclusions about safety or efficacy of treatments. These include:

- The Positive and Negative Syndrome Scale (PANSS) total score (proposed primary outcome for definitive trial) [1]
- PANSS subscales: positive, negative, depression-anxiety, agitation-excitement, and disorganisation
- First Episode Social Functioning Scale (FESFS) [2]
- Questionnaire about the process of recovery (QPR) [3]
- The Specific Psychotic Experiences Questionnaire (SPEQ) [4]
- The Hospital Anxiety and Depression Scale (HADS) [5]
- Alcohol Use Disorder Identification Test (AUDIT) [6]
- 10-item Drug Abuse Screening Test (DAST) [7]
- 10-item adult version of the Autism Spectrum Quotient [8]

- Antipsychotic non-neurological side effects scale (ANNSERS) [9]
- Metabolic side effects including: weight gain, body mass index, waist circumference, blood pressure, fasting estimates of plasma glucose (FPG), HbA, lipids (total cholesterol, LDL, HDL, triglycerides) and, serum prolactin levels
- Hospital admissions
- Potential adverse effects of trial participation measure

4.3 Frequency of Measurements

All measurements will be collected at baseline, 3 months, 6 months (end of treatment), and 12 months (6 months after treatment finishes).

We have designed a variable length follow-up period. We propose a variable follow-up, with participants recruited after 16 months being offered assessments only to end of treatment (6 months). Thus, participants recruited in the first 16 months will receive the full 12 month follow-up, whereas participants recruited thereafter would be offered assessments up to the end of treatment (6 months, our primary end point).

4.4 Adverse events

In research other than Clinical Trials of Investigational Medicinal Products (CTIMPS), a serious adverse event (SAE) is defined by the Health Research Authority (HRA) as an untoward occurrence that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- is otherwise considered medically significant by the investigator

In deciding seriousness, Good Clinical Practice (GCP) guidance suggest that in addition to the above standard definition, researchers should also check the definition of Serious in the Protocol for each study they are involved in. In the MAPS Trial protocol we list: all deaths, suicide attempts, serious violent incidents, admissions to secure units, formal complaints about treatment. In deciding seriousness the Chief Investigator (CI) for MAPS will refer to the above definition from the HRA and from the trial protocol.

In deciding expectedness, the CI for MAPS will refer to the GCP Guidance as follows, Expectedness is determined by comparing the symptoms with the available information related to the study procedures or the IMP. References for all studies are the Protocol and Patient Information Sheet.

An SAE occurring to a research participant will be reported to the main Research Ethics Committee (REC) where in the opinion of the Chief CI and/or the chair of the iDMC the event was:

- Related that is, it resulted from administration of any of the research procedures, and
- Unexpected that is, the type of event is not listed in the protocol as an expected occurrence.

We will also report adverse events (AE) i.e. self-harm.

5 Statistical methods

All the main analyses will be based on the Intention-To-Treat (ITT) principle. Safety and unwanted effects will be analysed based on treatment received rather than as-randomised. PI is defined as any dose of CBT for psychosis (CBTp) or family intervention from the research team therapist. AP is defined as any dose of an antipsychotic as prescribed by the participants clinical team psychiatrist. The analysis will take place after full recruitment and follow-up (i.e. there will be no interim analyses for efficacy). An iDMC will monitor trial progress and any safety issues on a regular basis. The results of the trial will be presented following the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement: extension to randomised pilot and feasibility trials [10].

5.1 Primary feasibility outcomes

Descriptive statistics will be used to summarise the key indicators of the success of the trial, including participant recruitment; checks for absence of selective recruitment of participants; baseline balance and participant flow. Appropriate summary statistics will be the number of participants referred through case managers and mental health staff, number of referrals found to be eligible, and number of consenting individuals and recruited individuals to each arm. Numbers for drop-out from the allocated interventions, withdrawal of consent, and failure to provide follow-up outcome data.

Proportion of participants who received allocated intervention vs not and proportion of participants who moved to combined arm due to deterioration will also be reported.

5.2 Secondary outcomes

To inform a definitive trial analysis of the proposed primary outcome (PANSS) and the secondary outcome (QPR) will be analysed using analysis of repeated measures using a mixed effects model to take into account the discrete timing of the follow-up assessments as well as adjusting for site as well as baseline measure. Other outcomes will be analysed in a similar way. The presentation of the analysis will focus on point estimates and associated 95% confidence intervals rather than statistical significance (p-values); however, we will report p values in the text. Further analysis will assess the correlations of each measure across all time points and the variation within the proposed outcome measure (mean and standard deviation) to inform a definitive sample size calculation for a phase III trial.

To account for departures from the randomised intervention, actual treatment received will be summarised descriptively by arm. We will also summarise treatment compliance. Satisfactory delivery of adherent therapy is operationalised as attending 6 or more sessions of CBT. Satisfactory delivery of antipsychotic medication is operationalised as any exposure of AP for 6 consecutive weeks (this would include a dose below BNF lower limits given this is a frequent clinical practice for people of this age and the drugs are licensed for adults) records.

We will report descriptive statistics for the components of psychological intervention received including number of sessions and milestones achieved, and compliance with between session tasks.

5.3 Missing data

As this is a feasibility study there will be no formal analysis to account for missing data. data missing at baseline will be reported as such. If required for models, continuous data will be imputed with the mean od that variable, missing binary/categorical data will include a missing indicator.

6 CONSORT diagram

See Protocol

7 Dummy tables

Table 1. Baseline characteristics

	AP (N=)	PI (N=)	AP plus PI (N=)
Age (years) - mean (SD)			
Gender - n (%)			
Male			
Female			
Transgender			
Duration of untreated pyschosis (months) - mean (SD)			
PANSS Total - mean (SD)			
PANSS Positive - mean (SD)			
PANSS Negative - mean (SD)			
PANSS Disorganised - mean (SD)			
PANSS Excitement - mean (SD)			
PANSS Emotional Distress - mean (SD)			
QPR - mean (SD)			
First Episode Social Functional[1] - mean (SD)			
Friendships and social activities			
Independent living skills			
Interacting with people			
Family			
Intimacy			
Relationship and social activities at work			
Work abilities			
Relationships and social activities at school			
Education abilities			
The Specific Psychotic Experiences Questionnaire - mean (SD)			
Paranoia			
Hallucinations			
Cognitive disorientation			
Grandiosity			
Anhedonia			
The Hospital Anxiety and Depression Scale - mean (SD)			
Total			
Anxiety			
Depression			
Alcohol Use Disorder Scale total - mean (SD)			
Autism Spectrum Quotient - mean (SD)			
ANNSERS - mean (SD)			
Total			
Number of side effects			

[1] Both ability and frequency scores will be presented

Table 2. Treatment received - safety

	AP (N=)	PI (N=)	AP plus PI (N=)	Total
APs				
PI				
AP plus PI				
None				

Values n (%)

Table 3. Treatment received - compliance

	AP (N=)	PI (N=)	AP plus PI (N=)	Total
APs				
PI				
AP plus PI				
None				

Values n (%)

Table 4. Treatment compliance

	N(%)
Satisfactory delivery of adherent therapy[1]	
Satisfactory delivery of antipsychotic medication[2]	

[1] operationalised as attending 6 or more sessions of CBT

[2] operationalised as any exposure of AP for 6 consecutive weeks (this would include a dose below BNF lower limits given this is a frequent clinical practice for people of this age and the drugs are licensed for adults) records

Table 5. Serious adverse events and potentially unwanted effects of trial participation based on treatment received - n (%)

	AP (N=)	PI (N=)	AP plus PI (N=)	OR	95% CI
Serious Adverse Events					
Participants who had a trial-related SAE					
Total number of SAEs					
Total number of participants with one or more SAEs					
Details					
Death					
Life threatening (suicide attempt)					
Life threatening other					
Voluntary psychiatric admission					
Involuntary psychiatric admission					
Prolongation psychiatric hospital stay					
Admission to general medical ward					
Prolongation of general medical stay					
Results in persistent or significant disability					
Consists of a congenital abnormality or birth defect					
Serious violent incident					
Formal complaint about treatment					
Is otherwise considered medically significant by the Chief Investigator					
Deterioration in PANSS total (rescaled)					
>12.5%					
3 months					
>25%					
3 months					
6 months					
12 months					
>50%					
3 months					
6 months					
12 months					

Table 6. A measure of potential adverse effects of trial participation

	AP (N=)		PI (N=)		AP plus PI (N=)	
	Quite a lot - n(%)	Very much - n(%)	Quite a lot - n(%)	Very much - n(%)	Quite a lot - n(%)	Very much - n(%)
Item 1						
Item 2						
Item 3						
Item 4						
Item 5						
Item 6						
Item 7						
Item 8						
Item 9						
Item 10						
Item 11						
Item 12						
Item 13						
Item 14						
Item 15						
Item 16						
Item 17						
Item 18						
Item 19						
Item 20						
Item 21						
Item 22						
Item 23						
Item 24						
Item 25						
Item 26						
Item 27						

A response of Quite a lot or Very much indicates an improvement. Please see Appendix Table 1 for the definition of the items

Table 7. Adverse physical effects

	AP (N=)	PI (N=)	AP plus PI (N=)	mean difference	95% CI
ANNSERS: Number of side effects - mean(SD)					
ANNSERS: tota - mean(SD) l					
Weight - mean(SD)					
BMI - mean(SD)					
Blood pressure (BP) - mean(SD)					
FPG - mean(SD)					
HbA1c - mean(SD)					
Total cholesterol - mean(SD)					
LDL - mean(SD)					
HDL- mean(SD)					
Triglycerides - mean(SD)					
Prolactin - mean(SD)					

Table 8. PANSS - primary seconday outcome

	AP (N=)	PI (N=)	AP plus PI (N=)	Effect estimare (95% CI)		
				PI vs APs	PI vs APs plus PI	APs vs. APs plus PI
Total - mean (SD)						
Baseline						
3 months						
6 months						
12 month						
Positive - mean (SD)						
Baseline						
3 months						
6 months						
12 month						
Negative - mean (SD)						
Baseline						
3 months						
6 months						
12 month						
Disorganised - mean (SD)						
Baseline						
3 months						
6 months						
12 month						
Excitement - mean (SD)						
Baseline						
3 months						
6 months						
12 month						
Emotional distress						
Baseline						
3 months						
6 months						
12 months						
PANSS % improvement - n (%)						
> 25%						
3 months						
6 months						
12 months						

Table 9. PANSS - primary seconday outcome continued

	AP (N=)	PI (N=)	AP plus PI (N=)	Effect estimate (95% CI)		
				PI vs APs	PI vs APs plus PI	APs vs. APs plus PI
> 50%						
3 months						
6 months						
12 months						
> 75%						
3 months						
6 months						
12 months						

Table 10. Other secondary outcomes

	AP (N=)	PI (N=)	AP plus PI (N=)	Mean difference (95% CI)		
				PI vs APs	PI vs APs plus PI	APs vs. APs plus PI
QPR						
Baseline						
3 months						
6 months						
12 month						
SPEQ: Paranoia						
Baseline						
3 months						
6 months						
12 month						
SPEQ: Hallucinations						
Baseline						
3 months						
6 months						
12 month						
SPEQ: Cognitive disorientation						
Baseline						
3 months						
6 months						
12 month						
SPEQ: grandiosity						
Baseline						
3 months						
6 months						
12 month						
SPEQ: Anhedonia						
Baseline						
3 months						
6 months						
12 months						
HADS Total						
Baseline						
3 months						
6 months						
12 month						
HADS: Depression						
Baseline						
3 months						
6 months						
12 month						

Table 11. Other secondary outcomes continued

	AP (N=)	PI (N=)	AP plus PI (N=)	Mean difference (95% CI)		
				PI vs APs	PI vs APs plus PI	APs vs. APs plus PI
HADS: anxiety						
Baseline						
3 months						
6 months						
12 month						
AUDIT total						
Baseline						
3 months						
6 months						
12 month						
DAST total						
Baseline						
3 months						
6 months						
12 month						
FESFS: Friends and activities[1]						
Baseline						
3 months						
6 months						
12 months						
FESFS Independent living skills[1]						
Baseline						
3 months						
6 months						
12 month						
FESFS Interacting with people[1]						
Baseline						
3 months						
6 months						
12 month						
FESFS Family[1]						
Baseline						
3 months						
6 months						
12 month						

Table 12. Other secondary outcomes continued

	AP (N=)	PI (N=)	AP plus PI (N=)	Mean difference (95% CI)		
				PI vs APs	PI vs APs plus PI	APs vs. APs plus PI
FESFS: Intimacy[1]						
Baseline						
3 months						
6 months						
12 month						
FESFS: Relationships and social activities at work[1]						
Baseline						
3 months						
6 months						
12 month						
FESFS: work abilities [1]						
Baseline						
3 months						
6 months						
12 months						
FESFS: relationships & social activities school[1]						
Baseline						
3 months						
6 months						
12 month						
FESFS: educational abilities[1] -						
Baseline						
3 months						
6 months						
12 month						

Values are mean (SD), [1] Both ability and frequency scores will be presented

References

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8 Appendix

Table A1. A measure of adverse effects of trial participation

Item 1	Taking part hasnt helped me with my problems.
Item 2	Taking part made my problems worse
Item 3	Taking part made me feel more anxious
Item 4	Taking part took up too much time
Item 5	Taking part led to my mood becoming very low
Item 6	Taking part made me feel more angry and irritable
Item 7	I didnt feel ready to talk about my problems
Item 8	Taking part made me think too much about bad things that have happened in the past
Item 9	Taking part meant I stopped looking after myself properly
Item 10	Taking part made me feel more suspicious
Item 11	Taking part required too much energy or motivation
Item 12	Taking part increased my thoughts of killing myself
Item 13	I didnt feel listened to or believed by MAPS staff
Item 14	Taking part made my voices or visions worse
Item 15	Taking part was making me fall out with my family or friends
Item 16	Taking part was having a bad effect on my self-esteem
Item 17	Taking part was making me want to harm myself
Item 18	I didnt like or feel I could trust the MAPS team members
Item 19	I felt embarrassed talking about my problems with people I had not met before
Item 20	Taking part made me have thoughts of harming other people
Item 21	Taking part was making me feel hopeless about the future
Item 22	Taking part meant I had to increase my medication in order to cope
Item 23	Taking part involved too much hard work
Item 24	Taking part made me worry that people would think badly of me because of my diagnosis
Item 25	Taking part made me fall out with my doctor or care team
Item 26	Taking part made me worry about losing control of my mind
Item 27	My problems have improved to the point whereby I no longer feel I need help