Managing Adolescent first episode Psychosis: a feasibility Study (MAPS)

Trial Protocol

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MAPS

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a feasibility Study

Contents

Full title of project:

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Summary of Research:

We aim to assess the feasibility of conducting a definitive trial of interventions for adolescents with first episode psychosis (FEP). We will conduct a 3-arm pilot randomised controlled trial to determine the feasibility of comparing i) antipsychotics (APs) to ii) psychological intervention (PI) and iii) a combined treatment (APs plus PI), in 90 adolescents (aged 14-18) with FEP in NHS services in 4 sites. Randomisation will use randomised-permuted blocks of randomly varying size. Assessors will be masked to allocated treatment. PI consists of Cognitive Behaviour Therapy (CBT) plus family intervention (FI), and allows an individualised approach within clear boundaries, with specific interventions being dependent on an individual formulation (the range of permissible interventions is described in our published manuals (1-3)). Up to 30 sessions of CBT will be delivered over 6 months. FI involves an extra 6 sessions with parents to complement the CBT (as well as regular communication with parents following CBT sessions), improving communication, problem solving and reducing stress. Comparator conditions are APs alone and a combined treatment (APs plus PI). APs will be chosen from those commonly used in the treatment of adolescents and recommended in the recent NICE guidelines, with choice of individual drug made by the managing psychiatrist. Our objectives are to assess feasibility of a definitive trial, including numbers, proportions and characteristics of eligible Adolescents referred by clinicians and adolescents willing to participate, participants who drop out and participants who receive and comply with their allocated intervention. Therapeutic improvement will be assessed in terms of overall symptom severity, but also using broader, clinically relevant outcome measures of social function and target symptoms as well as overall health status and utility. Assessors blind to and independent from randomised treatment group allocation will conduct all assessments at baseline, 3, 6 (immediately post the end of treatment) and 12 months (6 months' follow-up after the end of treatment). In the event of a hospital admission, suicidal or dangerous ideation representing immediate risk, or deterioration at the 3-month assessment, monotherapy participants will be offered transfer to the AP+PI arm. We will also conduct a nested qualitative interview study with a purposive sub-sample of adolescents (n=15-20), parents (n=15-20) and clinicians (n=15-20) to understand experiences and acceptability of interventions and research procedures, which will further inform a definitive trial. We will also evaluate the suitability of outcome measures to assess effectiveness, safety, and acceptability. The 2-year trial will have a recruitment window of 15 months, requiring 1.5 participants per site per month (90 in total); our trial of CBT vs APs vs both in adults is currently recruiting 3 participants per month in a single site, so this is realistic despite lower incidence in adolescents). The proposed sample size is adequate for obtaining reliable parameter estimates for sample size estimates for the definitive trial, and demonstrating the feasibility of such a definitive trial. Our team includes expertise in conducting clinical trials of complex interventions, PI for psychosis, psychopharmacology, mental health in adolescents, nested qualitative research and carer and service user involvement. Five applicants were on the NICE guideline development group for CG155 (5).

Background and Rationale:

What is the problem?

Schizophrenia, a common form of psychosis, is amongst the greatest challenges for the NHS and is associated with significant personal, social and financial costs. Whilst antipsychotics (APs) are the first line of treatment, there is mounting evidence that they are poorly tolerated by adolescents. The NICE guideline (CG155) for treatment of psychosis and schizophrenia in adolescents (5) suggests that treatment options should include the possibility of choice between Cognitive Behaviour Therapy (CBT), APs or both. However, CBT for adolescents with psychosis is currently difficult to access (6) and is excluded from the curriculum for "Children and Young People's Improving Access to Psychological Therapies Programme". CG155 makes an explicit research recommendation to determine "what is the clinical and cost effectiveness of psychological treatment alone, compared with antipsychotic medication and compared with psychological treatment and antipsychotic medication combined?", since there is considerable uncertainty around the efficacy and safety of available treatments in the NHS for adolescents with psychosis.

Why is the research important?

The development of schizophrenia in childhood has a major detrimental effect on a young person's personal, social and educational functioning (7). It is estimated that the total societal cost of schizophrenia in the UK in 2004/5 was £6.7 billion (8), with the direct cost of care falling on the UK taxpayer being around £2 billion, while the indirect costs to society approached £4.7 billion. While much of these costs are associated with adults, a survey of hospital bed use in England and Wales between 1998-2004 found that schizophrenia accounts for 25% of all adolescent psychiatric admissions (9). The nature of the disorder is more severe in adolescents; a recent systematic review of 21 studies of childhood onset schizophrenia found that over 60% of patients had poor long-term outcomes (10), and childhood-onset schizophrenia has longer hospital stays, greater readmission and more days per year in hospital than adult-onset (11). Therefore, evidence based interventions are essential for this population and CG155 notes we have little evidence to draw upon. Our feasibility trial will inform the treatment of this vulnerable group and will help understand the acceptability of the treatments and inform the design of a definitive trial that will answer the question of what treatments should be offered to adolescents with schizophrenia on the basis of safety, clinical and cost-effectiveness.

Does the literature support this?

A systematic review (12) concluded that APs reduce the severity of psychosis in adolescents, but are associated with significant adverse effects and there is no data to support long-term safety. The adverse effects of APs have been underestimated in adolescents, with the recent NICE evidence update concluding there are questions about the long-term safety and tolerability of APs, with adolescents being at greater risk of weight gain, clinically significant lipid disturbance and type 2 diabetes (13). A systematic review also concluded that structural abnormalities in brain volume may result from APs (14), which is of concern for adolescents given their brains are still developing.

Meta-analyses conclude that CBT in combination with APs is effective in adults with psychosis (15, 16), although there is debate about the size of effects, and new evidence shows that CBT can be acceptable and reduce psychotic symptoms in adults with schizophrenia who choose

not to take APs (17); in this RCT, young age (under 21) was a moderator of good clinical response (18).

A Cochrane review concluded that the data are too sparse to assess the effects of APs on clinical outcomes in early episode schizophrenia relative to comparators (19). A systematic review from the CG155 team concluded that, for adolescents, the balance of risk and benefit of APs appears less favourable and research is needed to establish the potential for psychological treatments, alone and in combination with APs, in this population (20).

Rationale and summary

Whilst antipsychotics (APs) are the first line treatment for first episode psychosis (FEP), evidence suggests they are poorly tolerated by adolescents. APs and psychological interventions (PI), specifically, family intervention (FI) and cognitive behaviour therapy (CBT), are recommended treatments for FEP in adolescents (5), but evidence about relative efficacy/acceptability is limited. If PI were non-inferior to APs, within an acceptable margin, this could be a major advance in treating a vulnerable group with high sensitivity to APs. Running a trial to answer this question could prove challenging, since some clinicians and parents have polarised views about APs for adolescents (both for and against) and some adolescents will be prescribed APs at initial presentation to services, limiting recruitment. Key uncertainties are whether recruitment, retention and compliance with allocated treatment are possible, given service structures (including school attendance), relatively low incidence of adolescent FEP and strength of clinician and parent/ adolescent preferences. There is also uncertainty about best outcome measures, relative importance of research questions (non-inferiority of monotherapies or superiority of combined) and magnitude of any non-inferiority margin.

We will address these issues using a 4 site feasibility RCT to compare standardised PI (incorporating CBT+FI) to treatment with APs and a combined treatment (PI+APs) in 90 adolescents with FEP. This will inform the feasibility and design of a future definitive, pragmatic clinical and cost-effectiveness trial. Randomisation using permuted blocks of variable length will be stratified by family contact (i.e. if they are living with their family) and site. Assessors will be blind to allocation. Nested qualitative studies will identify key themes about the acceptability of treatments in adolescents with FEP, as well as experiences of trial involvement, including wanted and unwanted effects. Gauging the opinions of parents and clinicians, in addition to young people themselves, is crucial to assess feasibility of a full definitive RCT.

Aims and objectives:

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.

Specific 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 sample size parameters 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

Research Plan:

Study Design

The study will be a single blind, 3-arm randomised controlled trial comprising a 6-month intervention and 6 month follow up period, involving 90 participants (young people with first episode psychosis) in four centres. 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. Assessors will be masked to allocated treatment. Masking will be maintained using a wide range of strategies (e.g. separate offices for therapists and researchers, protocols for answering phones, message taking and secretarial support, separate diaries and security for electronic randomisation information). The study will be the feasibility phase to prepare for and inform the design of a large multicentre trial. A qualitative sub-study will be embedded within the feasibility trial to evaluate the intervention from the subjective perspectives of young people, their parents and clinicians. The data will be used as stand-alone feasibility study to inform decisions about progression to a definitive trial. The NIHR accredited Aberdeen Clinical Trials Unit (CHaRT) advised on the development of the protocol and will provide ongoing expertise during the conduct of the study.

Project timetable

Weeks 0-6: staff training, finalise protocols and manualise interventions. Months 2-16: recruitment. Months 16-22: final treatment/follow-up. Months 23-24: analyse data and prepare reports.

Randomisation

Following informed and written consent, eligible participants will be randomised within 2 working days. Our Clinical Trials Unit will support the development of the randomisation algorithms and the web-based technology. Randomisation will be in the ratio 1:1:1 to the three groups and will be stratified by centre and family contact (since participants who do not have regular contact with their families will not receive the family intervention components of psychological intervention, although they will still be included). Randomisation (at the individual level) will be independent and concealed, using randomised-permuted blocks of random size administered via a study-specific web-based system developed by the CTU. The allocation is made known to the trial manager (to monitor adherence to the randomisation algorithm), the trial administrator and trial therapists by email and SMS text message. The allocation is made known to the participant by letter from the trial administrator. Blinding of the allocation code will be maintained for research assistants until all outcome measures for all participants have been collected.

Protection against bias

Single blind – assessors will be blind to treatment condition. Blindness will be maintained using a wide range of measures which we have implemented successfully in other single blind trials (EDIE 2; ACTION; FOCUS). These include separate offices for the therapists and research assistants, protocols for answering telephones including reminders for clinicians, participants and family members about the blind, protocols for message taking and secretarial support, separate diaries and pigeon holes and data file security, using passwords and encryption of randomisation information. We will develop a standard operating procedure (SOP) for maintaining, recording and managing blinding, which will outline all of these procedures. This SOP will be reviewed by, and agreed with, our data monitoring committee (DMC)/ trial steering committee (TSC). Each researcher will sign this SOP to confirm they understand and will comply with the blinding procedures. All blind breaks will be recorded by the trial manager and reviewed by the Chief Investigator for patterns in unblindings. There is only one follow-up scheduled during the intervention window (at 3 months). This will reduce the risk of blind breaks occurring because of therapists and RAs crossing paths for visits and it will reduce the opportunity for unblinding to occur because of communication with participants to arrange visits. Maintaining rater blindness to treatment allocation is crucial, and the DMC and TSC will regularly monitor unblindings by each centre, and implement corrective action if necessary. Following eligibility assessment and completion of baseline assessments, participants will be allocated to treatment groups through our web-based randomisation service and the Trial administrator will inform the participants of this decision. All letters to participants and clinicians will contain a standardised statement about the need to maintain the single blinding process. Any accidental unblindings will be recorded. Where possible, we will identify an independent assessor with whom the blind has not been broken to complete subsequent follow-ups, subject to any threats to participant engagement with follow-up. Given each intervention is provided in two arms of this three-arm trial, the blind will also be easier to maintain than in our previous two-arm trials.

Concomitant therapy

It would be unethical to restrict the therapeutic options of the clinical teams participating. Our approach will, therefore, be primarily to record the use of all other medication and psychological therapies, document details of dosage, and ensure the follow-up of all

randomised participants, irrespective of the interventions that they subsequently receive. We will collect participant self-report on the use of medication and psychological therapies and in addition, research assistants will screen the medical records for this information at the end of the study. This will allow us to determine the possibility for economies of scale for data collection. All participants will be eligible to receive medications other than APs (i.e. benzodiazepines, antidepressants etc.) and psychological therapies other than CBT or FI.

Health technologies being assessed:

The PI intervention will use a specific cognitive model (21) to guide both CBT and family intervention. We have used this model successfully in 5 clinical trials with young people with psychosis, and have had successful clinical results and positive feedback regarding acceptability and utility from several nested qualitative studies with the trial participants. CBT is required because there is evidence that it is the most suitable and effective psychosocial intervention to help resolve symptoms, which led to it being NICE recommended in CG155. An element of family intervention is required for two reasons: i) given the developmental stage that our participants are at (adolescence, aged 14-18), it would be inappropriate to work with the participant in isolation from their parents, who are key stakeholders in the health and wellbeing of their child; ii) family intervention is recommended by NICE in CG155 on the basis of ability to prevent relapse. The combination of developmentally-adapted CBT and family intervention represent the best available psychosocial interventions for adolescents with first episode psychosis, as outlined in CG155; therefore, this combination is the appropriate comparator in a head-to-head comparison with pharmacological interventions.

CBT allows an individualised approach within clear boundaries, and incorporates a process of assessment and psychological formulation of problems and goals. The latter is standardised in a manual of agreed components. The specific interventions are dependent on the individual formulation, which focuses on development and maintenance factors, but within a range of permissible interventions described in our published manuals (1-3). Up to 30 sessions will be delivered over the 6-month treatment envelope. Fidelity to the protocol will be ensured by regular supervision and rating recordings of sessions. The overall aims of CBT will be to reduce distress (particularly that associated with psychotic symptoms) and improve quality of life. It is a collaborative therapy that works with the problems and goals that are agreed between patient and therapist. Thus, treatment targets often include positive symptoms, but frequently also include social issues such as improving relationships, maintaining functioning or developing meaningful social roles and issues of comorbidity including anxiety and depression. If comorbidity includes problematic drug or alcohol use, this can also be prioritised. The CBT will be phased as follows: i) assessment, engagement and formulation of problems and goals. Goals could include managing distress and uncertainty, allow for more intense/frequent contact and allow strategies to reassure, calm and activate individuals ii) the use of change strategies derived from the formulation to work towards the particular goals of the individual, including reduction of acute distress iii) a historical formulation phase that focuses on vulnerability factors that led to the development of FEP and includes work on self-esteem and iv) final consolidation phase focusing on staying well and relapse prevention. We have used this approach in previous trials with young people with psychosis (EDIE-2 (22) and

ACTION (17)), and younger age was a predictor of better outcomes in both trials, suggesting it is particularly well-suited to younger participants (the latter trial is particularly relevant as it specifically targeted people who were not taking APs).

Fidelity to the treatment protocol will be ensured by regular supervision of the therapists and assessed by rating audio recordings of therapy sessions using the Cognitive Therapy Scale - Revised (23). This is a widely-accepted approach to the standardisation of CBT, which we have used successfully in previous large-scale trials. All therapists in participating centres will be trained initially, and therapy supervision will be provided by means of weekly meetings. All PI sessions will be taped with the patient's consent (patients will be asked to listen to the tapes as part of their homework) and a random sample of tapes (stratified for stage of therapy) will be rated in order to monitor fidelity and assist supervision; this will be done throughout the lifetime of the trial to provide some quality assurance and ensure corrective action can be taken if required. Following each session, therapists will complete a session record that monitors content of sessions in terms of agenda targets, homework tasks and change strategies used, which is another strategy we have used in previous trials; thus, fidelity can be used as a process variable in analyses.

The family intervention will include psychoeducation, skills building and problem solving components. Sessions will also focus on assessment, formulation, goal setting and communication styles. The six sessions of family intervention will be delivered in tandem with individual CBT and delivered by the same therapist to maintain engagement and consistency of approach. The first FI session will occur within two weeks of randomisation and will focus on reassuring relatives by providing recovery-orientated information, managing uncertainty and distress, discussing confidentiality, assessing the parents' understanding and appraisals of the presenting difficulties and engaging the family in the therapy process. Sessions 2-5 will focus on the (i) development and sharing of emerging psychological formulations, (ii) providing recovery-orientated information to combat stigma and pessimism and (iii) developing new ways of responding to difficulties when they emerge (including promoting personal strengths and reinforcing existing beneficial strategies). These sessions will be scheduled throughout the therapy window to match the pacing and content of the individual CBT sessions and the concerns of family members. Therapists will be flexible with the order that these tasks are covered and adapt the process to the needs and priorities of the parents/carers as long as this does not conflict with the interests of the participant. The final parent/carer session will occur within four weeks of the client finishing CBT. The aim of this final session is to make the family active stakeholders in the client's staying well plans. Ideally both parent/carer and client will be present. All parties will review the formulation, and discuss ways of consolidating the strategies learned during therapy, providing a summary of useful strategies and developing monitoring and action plan for future difficulties.

The focus of the psychological intervention is pragmatic and combines multi-systemic working with use of specific CBT techniques based on the cognitive model. Therapists adopt assertive outreach (or in-reach, for inpatients) youth work principles and also draw from successful social and vocational interventions such as supported education and, where appropriate, employment interventions. The intervention specifically focuses on engaging young people with severe and complex mental health problems into treatment and addresses the presence of multiple co-morbidities and potential cognitive difficulties. This integrated approach combining CBT, family work and multi-systemic working has been fully developed in our manuals and in other trials by this group with young people (e.g. HTA Prodigy).

Comparator conditions are antipsychotic medication (APs) and a combined treatment (APs plus PI). The APs will be selected by the clinician from those commonly used in the treatment of young people with psychosis, with dosages within recommended limits; the responsible consultant psychiatrists will choose the individual AP. The choice of antipsychotic medication should be made jointly with the young person and their parents or carers, and healthcare professionals. Age-appropriate information will be provided by prescribers to facilitate this and the likely benefits and possible side effects of each drug will be discussed. The psychiatrists will initiate the first dose of AP as soon as possible and will be encouraged to keep patients on their AP for a minimum of 12 weeks, and preferably for 26 weeks; however, they will be free to change dose and type of antipsychotic in response to monitoring of efficacy and adverse effects, which is consistent with current NICE guidelines. Treatment with antipsychotic medication will be considered an explicit individual therapeutic trial. This will incorporate: recording the side effects the child or young person is most and least willing to tolerate; the indications and expected benefits and risks of oral antipsychotic medication; the expected time for a change in symptoms and appearance of side effects. At the start of treatment, we will encourage clinicians to prescribe a dose at the lower end of the licensed range. For drugs not licensed for children and young people this would be below the lower end of the licensed range for adults. This will be followed by slow titration upwards within the dose range given in the British national formulary (BNF), the British national formulary for children (BNFC) or the SPC. We will also ask clinicians at each clinical review to record the rationale for continuing, changing or stopping medication, and the effects of such changes. Prescribers will be encouraged to adhere to NICE Guidance parameters about AP choice, dosage and titration. Prescribing information will be recorded for each participant in a clinical form. In order to determine economies from scale we will collect this data in two formats: participant self-report, which will be completed online via the Clinical Trial Unit (CHaRT) secure web-based platform (in order to protect the blind) and via researcher medical record screening. The above represents good practice and NICE guidance; in order to support adherence to these recommendations we will provide prescribers with access to the NICE e-learning tool that accompanies CG155 on prescribing and monitoring APs and the NICE audit tool based on CG155 describing recommended APs, titration and effective dose ranges, monitoring and rules for dose escalation and AP cessation and/or switching. The aim is to ensure that AP prescribing in the trial adheres to current best practice guidelines. In addition, throughout the recruitment phase of the trial, the psychiatrist co-applicants will meet with local psychiatrists at their sites to discuss the trial, inclusion criteria, documentation and any emergent concerns.

APs, FI and CBT are used in NICE-compliant treatment of schizophrenia, but evidence about relative efficacy and acceptability for children and young people is completely lacking.

Target population:

Adolescents, aged 14-18 years, experiencing first episode psychosis (FEP), who have not received antipsychotic medication. There is no diagnosis for FEP in the main diagnostic systems; FEP is defined as 7 or more consecutive days of full threshold positive psychotic symptoms (delusions, hallucinations), operationalized as in inclusion criteria below.

Inclusion/Exclusion Criteria:

Inclusion criteria:

1. aged 14-18 (to ensure adolescent status)
2. In contact with Early Intervention Services/Child and Adolescent Mental Health Services (to ensure appropriate safety considerations can be implemented)
3. Competent to provide written, informed consent, with additional parental consent for those aged <16 (for ethical considerations).
4. Either meet ICD-10 criteria for schizophrenia, schizoaffective disorder or delusional disorder or meet entry criteria for an Early Intervention for Psychosis service (operationally defined using PANSS) to allow for diagnostic uncertainty in early phases of psychosis
5. Within one year of presentation to services with psychosis (to ensure first episode status)
6. Score 4+ on PANSS delusions or hallucinations [for a minimum duration of seven consecutive days] (to ensure current psychosis)
7. Help-seeking (for ethical considerations)

Exclusion criteria

1. A primary diagnosis of alcohol/substance dependence *
2. A diagnosis of moderate or severe learning disability *
3. A diagnosis of ICD-10 organic psychosis *
4. Score 5+ on PANSS conceptual disorganisation / disorganised speech (since majority of participants will be randomised to a talking therapy, we require capacity to answer questions in an interview situation and engage in a conversation)
5. Non-English speaking (since majority of participants will be randomised to a talking therapy)
6. Received APs or structured PI within the last 3 months (to ensure treatment naivety)
7. Immediate risk to self or others (to ensure appropriate safety considerations can be addressed)

* These exclusions are to ensure that the participant population are representative of young people with a primary problem of first episode psychosis

Setting/context:

Child & Adolescent Mental Health Services (CAMHS) or Early Intervention Services (EIS) at 4 UK sites (Manchester, Birmingham, Oxford and Sussex)

Sampling and Feasibility of recruitment

We confidently anticipate that we can achieve the recruitment targets by sampling across early intervention, CAMHS and youth services in our 4 sites. These research sites have successfully collaborated before and participated in a series of related studies. The staff and managers involved in our sites are highly motivated to participate and are familiar with recruiting participants into research trials. The sites have extensive existing links with agencies in primary care, child and adolescent, and adult mental health services, with established referral pathways for recruiting these types of cases into both clinical services and research. The sites have existing services which already receive referrals of adolescent cases with FEP at a rate of around 100 per year (total 400 per year in all centres); it should be noted that all sites cover a large geographical area, and all have possibilities to extend into adjacent mental health NHS Trusts if necessary. Data from related trials suggests that approximately 50% of these existing referrals are likely to meet criteria for the present project. This should facilitate the present study.

We aim to recruit 90 CYP across the 3 conditions (30 per condition) over the 15-month recruitment period. Assuming a recruitment rate of approximately 1.5 cases per month per site, this will be sufficient to recruit to target over the feasibility trial. We are currently randomising 3 per month in a single site RCT comparing APs, CBT and both in adults with psychosis and local audits suggest >100 eligible adolescents per site (we anticipate a lower recruitment rate than our adult trial given the lower incidence and prevalence of adolescent FEP). We will audit reasons among those who decline participation as a learning opportunity to improve recruitment within this feasibility study and for any subsequent trial.

The proposed sample size is adequate to obtain reliable sample size estimates (24), and facilitate the main aims of a pilot trial, including feasibility of trial procedures and a realistic power calculation. Power calculations are not appropriate for a feasibility trial, since hypothesis testing is not the focus of analysis (25): instead, 95% confidence intervals will be estimated to inform likely intervention effects in a definitive trial.

Minimising attrition

A 20% loss to follow up is approaching the upper limit beyond which you would have doubts about the validity of the trial findings (hence this is our proposed threshold for progression to a full definitive trial). Our research group is very experienced in psychological intervention and psychosis trials and we have achieved loss to follow up rates considerably less than 20% - for example, the ongoing FOCUS trial (with the same chief investigator and trial manager combination) has randomised 487 participants with psychosis over 5 sites and have current attrition rates of less than 10% at both end of treatment and final 21-month follow-up. We are, therefore, confident that we can achieve an attrition rate less than 20%, and as indicated we will use a variety of evidence based strategies (including incentivisation / compensation of participants – we are requesting a working budget of £40/head or £3600 to provide the participants with cash or vouchers), along with thank you cards, following the recent systematic reviews of what improves retention in clinical trials (26). This will be complemented by the application of usual good practice in trial management – we will continuously monitor completion of data at all visits, not just the final follow-up visit, and will identify any sites or study personnel that need help in achieving and maintaining high rates of return. Weekly trial management supervision of RAs will monitor compliance to follow-up

rates, problem solving issues relating to attrition as they arise. The best solution to missing data is to avoid it, or at least minimise its occurrence. However, in a cohort with first episode psychosis, it is unlikely that there will be no missing data. We will, therefore, assess the robustness of our findings to any missing data, using multiple imputation techniques (assuming data are missing at random) and if the level of missing data warrants it, models assuming informative missingness (e.g. pattern mixture models) following relevant guidelines (27). We will however be restricted in this feasibility stage by the small sample sizes (~30 in each randomised arm).

Data collection:

Acceptability of treatment will be measured using drop-out rates, and explored in detail using qualitative methods. Therapeutic improvement will be assessed in terms of rate and degree of recovery from psychosis symptoms, age appropriate functioning and overall health status and utility. Assessors blind to randomised group will conduct all assessments at baseline and at 3, 6 and 12 months' post-randomisation. We propose a variable follow-up, with CYP recruited after 10 months being offered assessments only to end of treatment (6 months). Thus, participants recruited in the first 10 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).

We will assess the possibility for economies of scale throughout the trial and we will monitor time use of the research assistants via their regular contact with the trial manager. This will include monitoring of diary appointments, proportions of cancelled and not attended appointments, enquiry to referral and referral to randomisation ratios. We will also collect routine data from the participants' medical records in order to explore the scope for utilising such data in a future definitive trial. We will compare the data collected by our research team to the routine service data to identify any potential for savings (i.e. for reducing the participant burden and required research assistant resources at each site).

Primary outcome:

As this is a feasibility trial, a single primary outcome is not meaningful and 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.

Secondary 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.

The proposed primary outcome measure for a subsequent definitive trial will be total PANSS score (4), a commonly used outcome in psychosis trials, allowing comparison with wider evidence. The PANSS is a 30-item rating scale designed to provide a comprehensive assessment of psychopathology in adults with a diagnosis of schizophrenia. Five components have been reported: positive, negative, depression-anxiety, agitation-excitement, and disorganisation.

In order to test the acceptability and usefulness of potential secondary outcome measures in a trial context, we will also assess: i) social/educational/occupational functioning ii) self-rated

recovery iii) dimensions of psychotic symptoms. Adverse effects (weight gain, sexual dysfunction, metabolic effects and extrapyramidal effects) will be systematically assessed. Hospital admissions, serious adverse events and dose of APs and PIs will also be measured in all groups

Social/educational/occupational functioning

Social and educational/occupational functioning will be assessed using the First Episode Social Functioning Scale (FESFS) (28). The FESFS was developed with over 200 individuals receiving services in first episode psychosis clinics. Subscales include: Friendships and social activities, Independent living skills, Interacting with people, Family, Intimacy, Relationships and social activities at work, Work abilities, Relationships and social activities at school, Educational abilities. This measure has good reliability, convergent and discriminant validity and sensitivity to change. We will also assess time use in constructive economic activity.

Recovery

Recovery will be assessed using the questionnaire about the process of recovery, a user-defined measure (QPR (29)), which is a 15-item questionnaire developed collaboratively with service users with psychosis, measuring subjective recovery.

Dimensions of Psychotic Experiences

The Specific Psychotic Experiences Questionnaire (SPEQ) (30), which was devised with over five thousand 16-year-old twins and their parents, will assess dimensions of psychotic experiences. SPEQ has 5 self-report subscales: paranoia, hallucinations, cognitive disorganization, grandiosity, and anhedonia. These scales showed good internal consistency, test-retest reliability, and convergent validity.

Adverse effects

Non-neurological adverse effects will be systemically assessed using the antipsychotic non-neurological side effects scale (ANNSERS) (31). All participants will also receive a full physical examination: Weight, BMI, waist circumference, BP, fasting estimates of plasma glucose (FPG), HbA^{1c}, lipids (total cholesterol, LDL, HDL, triglycerides) and, serum prolactin levels. If an abnormality of physical health emerges then care teams will be informed and asked to perform subsequent reviews every 12 weeks. We will also record all serious adverse events, regardless of whether they are deemed related to trial participation, and will use a measure developed in our HTA funded FOCUS trial that captures potential adverse effects associated with PIs.

Common comorbidities:

We will also assess anxiety, depression, drug and alcohol use and dimensional ASD symptoms in order to examine the influence of common comorbidities for the benefit of a definitive trial. We will collect demographic information including gender, age, ethnicity, years of education, religion and living circumstances to describe our sample.

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS; (32)) is a 14 item self-report measure; of these items, 7 assess depression, whilst the remaining 7 items assess anxiety, over a period of the preceding week. This scale has good reliability and validity.

Substance Use

Alcohol Use Disorder Identification Test (AUDIT) was developed by the World Health Organisation (WHO). It can be administered via clinical interview or self-report questionnaire. It comprises 10 questions pertaining to harmful alcohol use, hazardous alcohol use, and alcohol-dependence symptoms, with cut-off scores to identify problem drinking related patterns. Scores range from 0-4 on each item, with total AUDIT scores ranging from 0 - 40, the higher the score, the more severe the alcohol use related problems. AUDIT scores are highly predictive of Structured Clinical Interview for DSM-IV (SCID) defined alcohol use disorder in first episode psychosis ((33)).

Drug Abuse Screening Test (DAST (34)) is a 10-item questionnaire. Response format is in the style of dichotomous 'yes'/'no' categories in response to such statements as, "Can you get through the week without using drugs?". Scores range from 0 – 20, with cut-off scores indicating presence of drug-misuse (different cut-off scores are recommended for different populations). A recent review of the DAST confirmed that its psychometric properties of reliability and validity suggest it is a satisfactory screening instrument to identify drug misuse and dependence problems (35). DAST scores are statistically predictive of SCID defined drug misuse problems in psychosis (33).

All measures will be taken by research assistants who will have been trained in the use of all the instruments and scales to achieve a satisfactory level of inter-rater reliability. Participants will be offered choice regarding length of assessments, including the option of breaks and multiple occasions. Assessment measures will be clearly prioritised so that the most important will be collected first to avoid missing data. We will have a standard protocol for managing any distress that is associated with the completion of measures which we gave successfully utilised in several trials and has been developed in collaboration with service users.

Autism spectrum conditions

Common diagnostic symptoms for an autism spectrum condition will be measured at baseline assessment using the NICE-recommended (CG142) 10-item adult version of the Autism Spectrum Quotient (AQ-10) (36).

Health economics

We will collect basic data on health economics in order to scope out range of services used by the participants. This will inform the design of the economic aspect of a full scale application for a definitive trial. Each participant will be asked to complete an economic patient questionnaire (EPQ) and EQ-5D health status questionnaire at baseline, 3, 6, and 12-months assessment.

Assessments: schedule, administration, staff training, reliability and validity

All outcome measures will be administered at baseline and subsequently at 3, 6 (end of treatment) and 12 months by research assistants who will have been trained in the use of all the instruments and scales, to achieve a satisfactory level of inter-rater reliability. Regular training sessions including the use of video and role play will be conducted with all research assistants in order to maintain reliability and prevent rater drift. Participants will be offered choices regarding length of assessments, including the option of breaks and multiple

occasions. Assessment measures will be clearly prioritised so that the most important will be collected first to avoid missing data. We will have a standard protocol for managing any distress that is associated with the completion of measures, which we have successfully utilised in several trials and has been developed in collaboration with service users; this includes telephone contact within 48 hours of assessments in order to check on participant well-being. We will send participants a thank you card at the end of their planned involvement trial as a token of our appreciation of their involvement. For participants who withdraw from the trial, on withdrawal we will ask them if they wish to be sent a thank you card. If they decline then they will not be sent a thank you card.

Data analysis:

The main aims of the feasibility trial will be delivered both via the continued monitoring of descriptive data and the analysis of data at the end of the last follow-up assessment. Analysis will take place after full recruitment and follow-up (i.e. there will be no interim analyses for efficacy, although an independent Data Monitoring Committee will monitor trial progress and any safety issues on a regular basis).

Statistical analysis will use an intention-to-treat approach using all randomised participants. The main focus will be on tabulated and associated graphical summaries of the key indicators of success of the pilot, including participant recruitment; checks for absence of selective recruitment of participants; baseline balance and participant flow. We will report data in line with the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement showing attrition rates and loss to follow-up. Important 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 finally, failure to provide follow-up outcome data, will also be generated.

We will report our feasibility results (recruitment, retention, adherence) overall, in order to inform decisions about the viability of a future definitive trial. However, we will also report our descriptive results and 95% confidence intervals on outcome measures by group. To inform a phase III trial we will conduct the following analysis to ensure the data conforms to the assumptions of the tests which will be conducted at that stage: measures proposed as the primary (PANSS) and secondary outcomes (QPR) for the phase III study 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. The presentation of the analysis will focus on point estimates and associated 95% confidence intervals rather than statistical significance (p-values). The sensitivities of all treatment effect estimates to missing outcome data arising from drop-out will be examined. 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. The primary statistical support will be provided by Norrie and Graeme MacLennan from CHaRT. Secondary, exploratory analyses will involve investigation of treatment effects and possible mediation mechanisms using appropriate statistical methods (37); statistical support for this aspect will be provided by Emsley. At the end of this we will be in a position to design a definitive phase III trial with which to evaluate our intervention rigorously. All statistical analyses will be pre-specified in a comprehensive Statistical Analysis Plan which will be agreed

with TSC and DMC. The results of the trial will be presented following the standard CONSORT recommendations.

We will measure within trial and also explore the literature regarding the possible effects of clustering by therapist and site. We anticipate that the chance of clustering regarding drug outcomes will be negligible, given we are expecting prescribing to follow CG155 NICE guidance, although we will measure this in case of significant differences in prescribing practices between sites. We will adjust for site in analyses (therapist will be nested within site) and examine intraclass correlation coefficients to inform a plan for managing any such impact on design and analysis of a definitive trial.

Intervention and trial acceptability: Qualitative interviews

A nested qualitative study will identify key themes associated with the acceptability of the trial and interventions amongst CYP, carers and clinicians. Individual semi-structured interviews will explore participants' experience of recruitment, random allocation and receiving interventions and identify barriers and solutions to participation, by focusing on e.g. structural issues (access/choice/amenities); process (personalisation, interpersonal quality of care, co-ordination of care) and outcomes (perceived mental and physical well-being). This phase will explore the subjective experience of receiving the treatments, elicit service user views of adverse effects and benefits, and identify themes relating to these issues. Similar interviews will be undertaken with parents and clinicians. As MAPS is a multi-site trial the participants, family members/carers and clinicians will be offered the choice of completing a qualitative interview over the telephone if they wish. The option of a telephone interview would maximise opportunities for participants to take part and capture the views of hard-to-reach participants and their family members/carers as demonstrated by other published qualitative studies [40]. As the MAPS trial is multi-site, participants are geographically dispersed and the qualitative research assistant (RA) is based in Manchester, our interview approach needs to be flexible and offer potential interviewees the choice of a face-to-face or a telephone interview. Telephone interviews have been found to be comparable in quality to face-to-face interviews [41].

Prior to a telephone qualitative interview with a research participant from the main trial, the qualitative RA would conduct a thorough check of risk with the participants care coordinator and with the trial therapist (if allocated to a therapy arm) and establish a clear plan for contingencies if required (access to immediate local info for support and referral access). Participant qualitative interviews are conducted after the 6 month follow-up assessment with the MAPS trial RA and so by 6 months it is reasonable to assume that the participant is well known to the trial including any potential risks. We would offer all trial participants and family members who take part in the qualitative interview the option of a 24-hour-later follow-up call (per previous studies)

Regarding written informed consent for the telephone qualitative interviews, our trial participants provide written informed consent for the qualitative interview under the main trial consent form when they first come into MAPS. Therefore, they have already been through the written informed consent process for this aspect of the project. Prior to a telephone qualitative interview taking place the qualitative RA would verbally re-confirm continued consent for the interview, answering any questions the participant may have, providing them with as much time as they would like to consider the telephone interview and

assuming continued consent is provided the qualitative RA would document this ongoing consent (as they would with a face-to-face qualitative interview). For family member/ carer telephone qualitative interviews the qualitative RA will contact the family member before an interview to talk them through the family member qualitative PIS, answering any questions they may have. Following this, the family member qualitative PIS will be sent in the post or via email to the family member and they will be given at least 24 hours from receiving it to consider the information detailed in the PIS. If the family member is in agreement that they want to take part then the family member will initial the boxes, sign and date the consent form and return it to the qualitative RA and a telephone interview arranged. At the start of the telephone interview the qualitative RA will ask the family member if they have any further questions, verbally check ongoing consent and then to sign and date the form themselves. If a clinician prefers to complete the qualitative interview over the telephone then written informed consent will be taken before the interview takes place by National Institute for Health Research (NIHR) Clinical Research Network (CRN) staff based at the NHS Trust. The clinical research network staff will be trained in the MAPS protocol and will be listed on the delegation log with the specific task of taking written informed consent for clinician qualitative interviews.

This will inform the design of a definitive trial and help further refine intervention, recruitment and retention procedures. Semi-structured interviews will be conducted after 6 month assessments. We will seek a maximum variance sample on key variables (engagement with interventions, symptoms, site, age and gender). These interviews will be conducted with participants allocated to each arm of the trial after completion; this will allow us to explore people's experiences of receiving the treatments. Based on our previous work it is expected that thematic saturation will be achieved with 15-20 CYP (38), 15-20 carers (39) and 15-20 clinicians. All interviews will be audio-recorded and transcribed verbatim. Data will be analysed using thematic analysis (42), which results in a rich and accessible account of qualitative data. The researcher makes sense of the data and reports themes that emerge (42). We will assume a realist perspective and report the experiences of participants. Themes will be coded inductively at a manifest level to inform the design of the definitive trial and refine the therapy protocol. The interviews will be overseen by service user researchers who have a wealth of experience of such qualitative research; transcripts will be reviewed and coded by our service user researchers with input from our service user reference group. Coding will be conducted systematically and iteratively and organised within NVivo.

We will also attempt to capture relevant data from people who decline to participate in the trial (young people, parents and clinicians), either using interview methods or a self-report questionnaire. This will further inform the design of a definitive trial and help further refine intervention, recruitment and retention procedures.

Assessments of moderation and mediation

In order to inform a definitive trial design and analysis plan, we will also address the influence of compliance via causal or 'mediation' models (statistical lead: Emsley). Traditional approaches to mediation (43) assume that confounding between the putative mediator and clinical outcome is absent (i.e. there is no omitted variable bias). We will compare the results of three sets of assumptions: (a) no confounding, (b) that we have measured and are able to adjust for all important confounders (44), and (c) that we are able to effectively adjust for

unmeasured confounders (hidden confounding) using instrumental variable-based methods, specifically analyses based on principal stratification (37).

Measurement of feasibility success criteria:

At 24 months the TSC and DMC will check criteria for progression to a full trial and make recommendations to proceed to a full trial or not. The criteria will be:

i) Recruitment ≥80% of planned (green), recruitment within 79 -60% of planned (amber), recruitment < 60% of planned (red).

ii) Retention of participants within the study with baseline and outcome assessments at primary end point (6 months, end of treatment) ≥80% of primary outcome completed (green), 79 -60% of primary outcome completed (amber), < 60% of primary outcome completed (red).

iii) Satisfactory delivery of adherent therapy to ≥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 CBT.

iv) Satisfactory delivery of antipsychotic medication to ≥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 BNF lower limits given this is a frequent clinical practice for people of this age and the drugs are licensed for adults) records.

Plan of investigation and timetable:

Prior to start of the study: Preparations to be made before the beginning of the study will be a) obtaining ethics and research governance approvals (b) publicising the study to senior managers, clinicians and service users in the sites participating in the study (c) recruiting the members of staff beginning with appointing the trial manager (Pyle, a co-applicant) who will participate in the recruitment of other staff (d) trial therapists will be identified before the start of the study and attend a series of pre-study workshops discussing client information and undertaking their own pilot cases using the therapy manual.

The first 6 weeks (study set up period): The study will begin when the RAs are recruited in each centre. The process of publicising the study will continue. Therapy procedures and the procedures for optimal treatment as usual will be finalised. Training will be provided for therapists in delivering the intervention. Training will be provided for the RAs in undertaking assessments until reliability is established. An intensive, residential training programme will be delivered in month 1.

Study recruitment (Months 2 to 16): In month 2, recruitment to the feasibility study will begin in teams at each site. Randomisation will follow gaining informed consent and an initial interview to determine participant eligibility. Recruitment will continue for 15 months and participants will be followed up at 3, 6 and 12 months. Qualitative interviews will commence in month 6 with clinician interviews.

Study follow up assessments (months 5 to 22):

Trial follow up assessments will end in month 22. Qualitative interviews with participants and parents will be undertaken after end of treatment assessment has occurred (6 month assessments), from month 7 onwards.

Decision making and preliminary trial write up: (months 23 to 24):

In months 23-24 we will present to the HTA data on recruitment and retention in the trial in order to obtain ratification of the recommendations of the TSC and DMC.

Project management

Greater Manchester Mental Health Foundation Trust will be the primary sponsor. In accordance with high standards of research governance we would ensure researchers receive training in the International Conference on Harmonisation (ICH) Guidelines - Good Clinical Practice before recruitment commences. We will set up a Trial Steering Group (TSC) and an Independent Data Monitoring and Ethics Committee (IDMC) prior to the start of the study. The TSC will comprise study applicants, a representative of the HTA, and representatives of service users and providers, and have an independent chairman. It will meet annually, and initially before the trial begins for approval of the protocol and standard operating procedures. The TSC will monitor and supervise progress, consider reports and recommendations. An observer from the HTA will be invited to all meetings. An IDMC will also be established to monitor (1) recruitment of study participants, (2) ethical issues of consent, (3) quality of data (including missing data), (4) the incidence of adverse events, and (5) any other factors that might compromise the progress and satisfactory completion of the trial. This will also have an independent chairman, and include an independent statistician. It will meet on a 6-monthly basis. An evaluation committee (all applicants and at least one independent member of the DMC) will be responsible for the consistency of recruitment, assessments and intervention.

Communication within and between sites

Each site will have a weekly team meeting to ensure regular communication and interaction between site leads, local clinicians and research assistants (measures will be followed to avoid blind breaks). There will be monthly trial management meetings with all applicants via video conference, with 6 monthly extended face-to-face meetings. The trial manager will conduct weekly telephone supervision with all research assistants that will focus on recruitment, liaison with referrers, compliance to follow-ups, and specific scoring queries for interview based measures. In addition, they will chair a fortnightly teleconference that focuses on inter-rater reliability across sites and recruitment during the recruitment window to share best practice and recruitment issue problem solving. The psychological therapists will receive weekly supervision from a central clinical supervisor based in Manchester, which will be focused on fidelity and adherence to the protocol and model. Supervision from site leads focussed on problem solving, risk management and local issues will supplement this. Quarterly triadic supervision involving supervisee, central supervisor and site leads will be used to ensure these arrangements operate smoothly. We have used these processes successfully in several previous multisite RCTs of psychological interventions.

Data management

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

Approval by ethics committees

National Research Ethics Committee approval will be obtained prior to the start of data collection. Only those who agree to provide written informed consent will be included in the study. Each potential participant will be provided with a copy of an information sheet that includes a contact number for the study team.

Correspondence from the Medicines and Healthcare products Regulatory Agency (MHRA) dated 24th March 2016 provided formal Notification that a Clinical Trial Authorisation (CTA) is not required. They confirmed that this proposal is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC and no submission to the Clinical Trials Unit at the MHRA is required.

Risks and anticipated benefits for trial participants

This study will add to the evidence base for the range of medical, psychological and social interventions that should be provided to improve outcomes for adolescents with FEP, who remain among the most socially excluded groups in society. If a subsequent definitive trial found that PI was non-inferior to APs in improving symptoms and quality of life, without a side effect burden, this could have implications for the future evidence-based management of similar service users within primary and secondary care mental health services. Furthermore, if PI were also found to be cost-effective in a definitive trial, this could have implications for the primary care commissioning of local mental health services, and for the development of national guidelines for the provision of care for young people with psychosis or schizophrenia.

Arrangements for participants still at school:

We would ensure that all appointments/interventions are offered at times that as much as possible do not clash with important school commitments (e.g. timed to be after school). With young people's consent, we would inform their school of their involvement in the study and would liaise as required with relevant school pastoral and health care staff, e.g. the school nurse, counsellor, SENCO, to facilitate a joined up and coherent package of support to the young person; parents/carers would also be involved as appropriate. We would also ask school staff to maintain contact with us re: any untoward effects on school attendance/performance etc. as a result of a young person’s involvement in the study.

Information will be age-appropriate for those still at school. Regarding assessment, it should be noted that the time use assessment assesses activity i.e. school or education attendance not simply registration. The aim for participants at school would often be to improve school or education attendance.

Assessment of safety

The following will be considered as adverse incidents; all deaths, suicide attempts, serious violent incidents, admissions to secure units, formal complaints about treatment. We plan to scrutinise any instances of participants being admitted to psychiatric hospital in the period of the trial. These events are likely to come to the attention of the therapists or assessors; however, we will also check medical notes at the end of the participants' time in the trial. The responsible clinical team, the trial management committee and the data monitoring and ethics committee (IDMC) will be informed of any adverse incidents. The response to an adverse incident will be determined on a case by case basis.

Procedures for deterioration

Participants allocated to the PI or Antipsychotic monotherapy arms and whose mental state deteriorates during the course of the study will be offered the option to move into the combined treatment arm and PI or APs will be commenced. Participants will remain in the RCT and continue to follow the schedule of assessments. Participants will be moved into the combined treatment arm if:

- They are subject to involuntary hospitalisation due to a deterioration in mental state
- There is a >12.5% deterioration in PANSS scores at the 3-month assessment.

If >12.5% deterioration in PANSS scores at the 3-month assessment is observed, the client's responsible clinician will be informed.

Informing potential trial participants about known risks and benefits

PI and APs are recommended interventions for adolescents with FEP (44). The investigators have considerable experience of administering the assessments and rating scales included in this study, and are not aware of any risks to participants. During assessment and testing, breaks will be provided to minimise possible fatigue or stress, and if indicated, can be spread over several days. Known adverse effects of APs will be described in advance.

Obtaining informed consent

Written informed consent will be obtained from each subject prior to their inclusion in this study in line with the Information Sheets and Consent Forms, Guidance for Researchers and Reviewers, Version 3.2 May 2007 (National Research Ethics Service: NRES).

Proposed time period for retention of trial material

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

Clinical Trials Unit

The trial will be run under the auspices of the Centre for Healthcare Randomised Trials (CHaRT), a fully registered UK Clinical Research Collaboration Clinical Trials Unit. CHaRT has internationally recognised expertise in the design, conduct, analysis and reporting of multicentre trials. CHaRT has been fully engaged with the CI throughout the planning stage to ensure the optimal scientific design, with the best and most appropriate analysis and suitable methods of managing and conducting the trial. Graeme MacLennan of CHaRT will take responsibility for the conduct of the trial processes. The Data Coordinator will provide clerical support to the trial. The programmer will create, maintain and update all applications programmes for the trial, including the randomisation application and all administrative and analysis databases, while the Senior IT Manager will oversee all IT aspects of the study. The statistician will take responsibility for all aspects of the statistical analysis and the CHaRT Quality Assurance Manager will oversee the demonstration that CHaRT's standard operating procedures for trials have been followed and properly documented, including observance of GCP throughout. This specification fits in with the CHaRT resource model and will adequately support the trial's statistical needs (including the specification of the randomisation system, liaison with the database managers and IT programming of the study databases, preparation of the trial Statistical Analysis Plan, creation and delivery of progress reports to the Trial Steering Committee and independent Data Monitoring Committee, assist in enhancing the quality of the trial data by statistical input to remote central monitoring of accumulating data, and finally the running of all the statistical analyses for the final data set).

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MAPS Trial Protocol Annex 1 (Stakeholder Surveys)

We will survey clinicians working in Child and Adolescent Mental Health Services (CAMHS) or Early Intervention in Psychosis (EIP) services. The aim of the survey is to gather information about treatment options available for young people experiencing a first episode of psychosis. The purpose of the survey is to obtain important feasibility data by surveying opinion on the following information: (1) views regarding treatments, (2) preferences and willingness to participate in, and refer patients to, future research including opinion on future possible trial designs (3) views on important treatment outcomes for future trials. The survey is an opportunity to gather vital feasibility data regarding the opinions of a key stakeholder group, which will inform the design of a future definitive trial. The research team and service user reference group have contributed to the design and content of three surveys (one for each of the stakeholder groups).

No personally identifiable data will be collected as part of the survey and therefore all data collected is anonymous. At the start of each survey the rationale for the survey is provided. Consent is implied by the person completing the survey. Surveys will be administered by National Institute for Health Research (NIHR) Clinical Studies Officers (CSO) who are employed at each MAPS NHS site. CSOs will invite clinicians to complete the survey and discuss with them the rational for the survey, this will include informing the stakeholder that no PID is collected, the surveys are anonymous and that consent is implied by the person completing the survey. Surveys will be administered face-to-face.

Print Name

Signed:

Date: