**Study protocol**

**HTA clinical trials: 09/144/50**

# Randomised controlled trial of the clinical and cost-effectiveness of a contingency management intervention for reduction of cannabis use and of relapse in early psychosis

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## Planned investigation

A multicentre randomised controlled trial will evaluate whether contingency management, reinforcing abstinence with positive incentives in the form of voucher rewards, is clinically and cost effective in increasing time to relapse in a cohort with early psychosis under the care of Early Intervention Services. The NIHR HTA programme funded the study as a feasibility pilot, to proceed to a full trial incorporating the pilot if target numbers were met for feasibility trial recruitment. When the study was discussed with the South-East London Research Ethics Committee by the Principal Investigator, Professor Sonia Johnson, in November 2011, they advised that they would be willing to give approval in the first place for the feasibility pilot, with approval to proceed to the full trial to be sought once the feasibility trial was completed and the funders had approved progress to the full trial. We have just completed the feasibility pilot and received this approval from the NIHR HTA programme.

## Aims and background

### *Research objectives*

Our overall objectives are as follows: 1. To conduct an internal pilot study of a specific intervention based on contingency management for cannabis use in early psychosis, acquiring evidence regarding rates of recruitment and follow-up, as well as feasibility and acceptability of the intervention in an Early Intervention Service context (this objective has now been completed); 2. If pilot trial criteria for recruitment and retention are met, to proceed with a full multicentre pragmatic randomised controlled trial, testing whether the intervention results in an increase in time to relapse compared with a control group. Both experimental and control group will receive an optimised form of EIS treatment as usual for cannabis (OTAU), involving delivery by care coordinators of a standardised psychoeducational package; 3.To test whether the intervention results in a decrease in cannabis use and in positive psychotic symptoms and in an increase in participation in work or education compared with the control group; 4. To assess the cost-effectiveness of the intervention from an NHS perspective.

### *Existing research*

Cannabis is the most commonly used drug in psychotic populations with rates of current use around the time of the onset of psychosis regularly recorded as between 35 and 45% well above use patterns in same age, non-psychotic populations (Lambert et al. 2005, Barnes et al. 2006). There is now overwhelming evidence that continued use following the onset of psychosis is associated with poorer individual outcomes and greater societal burdens. Hazards include delays in remission, suicidal behaviour, violence and homelessness (Lambert et al., 2005, Linszen et al. 1994; Verdoux et al. 2001). In prospective investigations in first episode psychosis, cannabis use is associated with markedly higher relapse rates: an Australian study reported a 51% relapse rate over 15 months follow up among substance users (mostly cannabis) compared with 17% among non-users (Wade et al, 2006), accompanied by a threefold difference in inpatient admission rates. Similarly, a Dutch study reported a 42% relapse rate among persistent cannabis users compared with 17% among those who never used or stopped round the time of first onset (Linszen et al., 1994). A dose-response relationship between severity of cannabis misuse and time to relapse was also reported in this study. Studies of co-morbid substance misuse

among people with established psychosis indicate that people who persist in problematic drug use are heavy users of acute mental health services, are more likely than others with psychotic illnesses to engage in acts of violence, and are less likely to work, sometimes using disability benefits to sustain drug use (Walsh et al., 2002, Kooyman et al., 2007; Marwaha et al., 2007). Thus, if a reduction in cannabis use can be achieved very early in the course of a psychotic illness, this has potential to improve the life experiences and social recovery of young people who develop psychosis, and to reduce the burden on carers, on mental health, criminal justice and welfare services and on the wider society over many years. This is the overall aim of the current study.

Systematic reviews indicate that the evidence on effective interventions for comorbid substance misuse in established psychosis is very limited (Jeffrey et al. 2004; Cleary et al. 2008). Despite a promising pilot study (Barrowclough et al. 2001), a large MRC-funded trial, the MIDAS study, has shown no effect on primary or secondary outcomes from a relatively lengthy intervention involving motivational interviewing and cognitive behavioural therapy. The difficulties in intervening effectively in established psychosis suggest it may be fruitful to target an earlier stage of illness, when several recent studies indicate that patterns of use are in a state of substantial flux (Addington and Addington, 2007; Archie et al. 2006). Many people are ambivalent about persisting with use and have substantial motivation for change, though some who initially abstain soon return to use (Hides et al. 2007). This contrasts with the very limited motivation for change found in established psychosis (Mueser and Drake, 2003), so that early psychosis may well be a stage at which achieving change with a relatively brief intervention is more feasible: we propose to test this.

The very limited benefits achieved from psychological interventions such as motivational interviewing and cognitive behavioural therapy in comorbid substance misuse in psychosis have made us look elsewhere for a potentially effective intervention. Contingency management (CM) is an approach that involves offering rewards contingent on engagement in substance use treatment and on evidence of abstinence. CM is now recognised to have a strong evidence base and its adoption in the UK is advocated by the Naional Institute for Clinical Effectiveness (NICE) guidance (2007). However, with the exception of a small number of recent evaluative studies in Europe (Secades-Villa et al., 2008), the evidence-base is drawn almost entirely in the US. There is very little UK experience of using CM and no evaluations of CM have been completed in in the UK, although several of the current co-applicants are now engaged in the National Institute Health Research Programme Grant-funded CONMAN study, which will provide an evidence base for CM in the UK among opiate users. The NICE review identified 14 trials, all from the US, that met criteria for inclusion, of which 3, as in the current study involved cannabis use. A consistent finding of a benefit for CM was reported, with most studies using abstinence at 12 weeks as their outcome measure. Some studies have reinforced other behaviours, including TB medication adherence, Hepatitis B vaccination and taking antiretrovirals, and in the UK, a trial of the use of incentives to reinforce adherence to antipsychotic medication is currently underway at Barts and the London School of Medicine, led by Professor Stefan Priebe.

Just one North American CM study has so far been reported among people with comorbid substance misuse and psychosis. This was unusual among studies in this population in finding an effect. Bellack et al. (2006) reported that CM, combined with a psychological intervention, resulted in more drug free urines than treatment as usual, and in reduced hospitalisation better quality of life. We have not been able to find any other evidence of current or planned CM studies for this comorbidity in a population with psychosis.

## Research methods

### *Study design*

**Design:** A rater-blind, randomised controlled trial will be conducted to test the acceptability and effectiveness of a cannabis intervention incorporating contingency management (CM) principles (voucher incentives for abstinence) for young, problematic cannabis users with first episode psychosis. Both experimental and control groups will also receive a standardised and manualised psychoeducational intervention delivered by clinical staff: this represents a standardised and manualised form of usual Early Intervention Service management of cannabis use. Having succeeded with recruitment and retention in the pilot phase, we now have approval from the funders to proceed to full trial, and seek ethical approval for this via this amendment.

As feasibility of the pilot study has been shown, we now wish to proceed to a full randomised controlled trial, incorporating pilot participants. We adopted this approach because we are testing an intervention (CM) that has already shown strong evidence of effectiveness in various settings, but not yet in this population. This and the pressing need for evidence in this area make the delays incurred in stopping to seek further funding after a pilot study excessive. The PRIMENT Clinical Trials Unit will support the study throughout. The study forms part of the programme of research of the Mental Health Research Network (MHRN)'s Clinical Research Group on Early Intervention in potentially severe mental health problems (convenor - SJ).

### *Recruitment*

**Setting & Infrastructure:** The initial pilot study was intended to be carried out in three Early Intervention Services (EISs) in Camden and Islington, Hackney, and Coventry and Warwickshire. To meet recruitment targets, we also obtained site specific approvals to recruit in the remaining early intervention services in these Trusts and in two further Trusts All of the teams apporached during the pilot phase agreed to participate in the study, and we succeeded in recruiting 62 participants. In order to meet targets for the full trial, we now wish to add approximately twenty more EI teams to the study, drawn from the North London, South London, Heart of England and East Anglia MHRN Hubs: we aim to recruit 482 participants from these teams.

## Recruitment plans

**Target Population**: Participants will be aged 18-36 years and being seen by clinicians within an EIS. Standard criteria for early intervention services are that they accept people who have developed symptoms of psychotic illness for the first time, with positive psychotic symptoms persisting for at least a week and accompanied by evidence of significant risk and/or functional decline.

**Sample size**: In the pilot study, we recruited 62 participants from the five mental health Trusts in which we eventually obtained site specific approval, and conducted 3 month follow-up interviews with 68% of them. We were also able to assess the feasibility and acceptability of our intervention: some participants dropped out of both experimental and control interventions, but no substantial difficulties arising from the trial were reported by participants, carers, clinicians or researchers during the pilot period. Acceptability, feasibility and any effects on the overall therapeutic programme of the early intervention services participating were assessed throughout. Thus the pilot study showed feasibility of recruitment and retention to the intervention, and a formal report was submitted to the HTA for a decision on proceeding to full trial. This was accompanied by a recommendation from

the trial steering committee (chaired by Professor Thomas Barnes, Imperial College) that the trial should proceed to the full stage.

We are now therefore seeking further ethical approval via a substantial amendment to proceed to the full trial, having received confirmation from the National Institute for health Research that they wish to support the full trial. Our aim in this is to recruit 482 further participants from Early Intervention Services (EISs) in the North London, South London, South-East England, Heart of England and East Anglia hubs of the MHRN. Our power calculation for the main trial is based on data suggesting a usual relapse rate of around 50% over the study timeframe in cannabis users, compared with 20-25% in non-users (Linszen et al, 1994; Wade et al. 2006) (7). We aim for 90% power to detect a 15% increase in time to relapse in the intervention group compared with the control group. This should be achieved by enrolling 272 participants in each group (including the pilot study participants): details of the power calculation are presented below in the Sample Size section.

## Allocation to groups

Following pre-trial assessments, consenting clients will be allocated to sample blocks stratified into groups based on study site and severity of cannabis use (ie., 1-3x per week, >3x per week), then randomised to a group receiving the Contingency Management (CM) intervention, and a group who will not. In each group, clinical staff will deliver a psychoeducational package on cannabis use, supported by a set of six standard modules available on tablet computers. Guidelines on EIS care recommend that such a package should be a standard part of care for service users, although discussions with EIS managers and staff suggest that the extent to which this is realised in practice is very variable. Our aim is thus to standardise the delivery of this intended part of EIS care by providing a brief training, a manual and supporting materials for EIS staff in both arms of the trial to deliver a psychoeducational intervention on cannabis use. Thus this represents an optimisation of standard practice: we have therefore referred to the control arm in the following as the Optimised treatment as usual (OTAU) group. A remote, impartial randomisation service will manage the allocation to groups coordinated by the PRIMENT CTU.

## Blinding

We will not be able to blind participants to treatment group. We will blind primary outcome assessors to group. To do so, following allocation to the treatment or control group, all participants in the study, their care co-ordinator and the service users' clinical team, will be asked not reveal the group to which participants were allocated to their assessor. Secondary outcome assessors will be blinded at the 18 month assessment interview. Interview participants will also be asked at the beginning of each assessment interview not to disclose the group to which the individual was allocated. Outside the assessments, outcome assessors will be shielded from discussion of participants in study forums where the possibility of determining the allocation group of participants could be determined. With the assistance of PRIMENT, we will use a system of web-based data entry to ensure that assessors will not have access to information in the database that would reveal allocation group. To test the success of blinding we will ask the assessor to guess the allocation group for each participant at the end of each assessment.

### Training of trial raters

The trial research assistants will be trained in the use of all measures by members of the team. Joint ratings with one another and with senior members of the team supervising them will be used to establish reliability.

## Planned Interventions

An optimised version of treatment as usual (O-TAU) offered by EISs in the management of cannabis misuse will provide the context in which we will test the impact of a contingency management intervention involving offering voucher rewards for cannabis free urines over a 12 week period to problematic cannabis users with first episode psychosis. We will first describe OTAU, delivered to both experimental and control groups, and then the CM intervention to be received by both groups.

**Optimised Treatment As Usual - to be delivered to both experimental and control group**

Guidance on Early Intervention for psychosis recommends that psychoeducational interventions for cannabis should be an important component of routine care, but consultations with teams and the researchers' experience suggests that the delivery of substance misuse intervention is very variable in practice. CM would be an inappropriate intervention if not accompanied by simple substance misuse interventions that familiarise service users with the rationale for reducing their cannabis use. To be confident that we are measuring the effects of CM, this psychoeducational cannabis intervention needs to be delivered to both experimental and control groups, with the experimental group receiving CM in addition. We will therefore provide training for all care co-ordinators from EI services participating in the study in a structured psychoeducational approach to problematic cannabis use, to be delivered to both experimental (CM) and control (OTAU) groups. A manualised version of this package including educational resources will be made available to all participating services in the form of 6 short modules including video material, short quizzes and a standard format for completing a decision matrix regarding whether to abstain from substances or not.

Optimised treatment as usual for cannabis will be a phase specific, individually tailored, psycho-educational approach to problematic cannabis use for generic EI care co-ordinators that applies general psychoeducational approaches used in first episode psychosis (Edwards et al., 1999). It will draw on the psychoeducational package offered in the control arm of a previous Melbourne pilot study of psychological intervention for cannabis use, the Cannabis and Psychosis trial (Edwards et al., 2006). Full delivery is typically achieved over approximately three hours, normally offered over regularly programmed sessions of 15-30 minutes duration. These will be incorporated in regular care co-ordination sessions provided to services users. The content of the package is as follows:

In the initial phase, participants will be engaged in discussion of their experience of psychosis in order to clarify the individual's explanatory model of their illness and to investigate their view of the reported link between cannabis use and mental health. Psycho-educational materials including a Cannabis and Psychosis DVD 'Back to Reality' and a 'Cannabis and Psychosis Fact sheet' are incorporated in the intervention, with written and web-based materials supporting it. These materials discuss potential concerns about cannabis use in young people with psychosis and provide a platform for care co-ordinators to discuss the service users' cannabis use with them. Care coordinators will explain that they need to discuss service users cannabis with them in order to ensure that they make informed choices regarding future use. The over-arching philosophy underpining the care co-ordinator's position is harm minimisation, with an acknowledgement that in a young person with psychosis, abstinence may be required to ensure that no harm is done.

In middle phases of the package, care co-ordinators will present current information on the potential problems and benefits of cannabis and of a cannabis free lifestyle. This will include discussions of the experiences of service users of achieving abstinence: we have consent to use a number of anonymised audiotapes with EIS users with relevant histories of cannabis use in this phase. Care co-ordinators will explore with their clients the potential risks of continued use and consider strategies for harm minimisation regardless of whether partcipants decide to stop using or not. The material will remain focused on providing information in accordance with psycho-education procedures, and will not act as a psychological intervention.
The final phase of the psychoeducational package will involve presenting material on the challenges of maintaining patterns of cannabis use and explore factors that heighten risk of slips and relapses.

**Contingency Management**

The CM (experimental condition) will involve offering rewards contingent initially on attendance and then on urinalysis results negative for cannabis. The CM procedure is adapted from Budney et al. (2000, 2006). Their care will also include the psychoeducational package described above. Following assignment to the CM group, participants will be introduced to the voucher programme at an initial information and assessment session with their care coordinator. The voucher programme will be described as a "method to enhance and maintain initial motivation to abstain from cannabis use by providing a structure (weekly urine testing) and incentive (vouchers) for doing so" (Budney et al., 2006). Participants will be informed that only reduction in cannabis use from the week before will be rewarded, and that the only way to ensure receiving a reward is to completely abstain. In week 1 of the intervention, participants will receive a £5.00 voucher for attending and providing a urine specimen independent of the drug test results with the aim of familiarising participants with the urine testing and voucher procedures. From week 2 through until week 12 participants will earn vouchers increasing by £5 every two weeks contingent upon consecutive negative specimens. Following the recommendations of Sure Screen Diagnostics, in each centre a small bench-top analyser will be used to test urine for cannabis. To test using this technology, the tester pipettes urine from participants into a tube containing a known quantity of buffer solution and then into a standard 50ng/ml cannabis test cassette. Use of the buffer solution gives a 10:1 serial dilution, so that a standard 50 ng/ml test cassette placed in the analyser will provide a concentration reading of cannabis in urine anywhere from zero through to 500 ng/ml. The analyser provides a reading that allows the tester to determine change in cannabis use, with increasing values indicative of reduction and/or no use, and decreasing values indicative of use in the preceding week. Single use on day one will spike urine cannabis levels to high levels for two days before a gradual reduction commences over the following seven days. Hence, reducing cannabis levels on a week-to-week basis will indicate cannabis abstinence. This has the advantage over dipsticks that we will be able to identify abstinence in people who were heavy users prior to the start of the intervention and whose cannabis levels thus take some time to fall into the undetectable range.

If the participant has a pre-planned holiday or other significant commitment, they will be able on a maximum of two occasions to suspend the intervention for one week, returning after 2 weeks rather than after 1 week. They will still be expected to show evidence of abstinence at this point, and they will need to request this suspension no later than at the time of their previous scheduled appointment. The EI team will also be able to request the suspension of the intervention for a maximum of one month if a participant relapses and loses capacity to decide whether they wish to continue. If capacity is not regained in one

month, the intervention will not continue. If a participant fails to attend on multiple consecutive weeks, or contact is lost between the clinical team and participant, each missed week will be counted as a failure to attend.

Failure to attend intervention sessions, specimens suggesting cannabis use or failure to submit a scheduled specimen (considered a positive result) will reset the value of vouchers back to the initial £5.00. If the particpant attends the next week and provides a negative sample, they will be rewarded with £10. In the third week, if the participant provides a second negative sample voucher values will return to the previous level of reward. Participants will sign an agreement to abide by test results, and vouchers will be from a local supermarket such as TESCO or Sainsburys where participants can choose to use the voucher rewards in-store, or exchange them for other gift cards avaiable (e.g. HMV, JJB Sports, etc.): Participants who abstain from cannabis use for the full duration of the intervention will earn £240, and all participants will receive a £20 voucher at the three assessment interviews as compensation for their time. At follow-up assessments, those participants in both arms will receive an extra £10 (total of £30) voucher for provision of a urine sample.

## Training and delivery

**Selection & Training of clinicians:** Clinicians in the EI services, will deliver the CM intervention. They will also deliver the standardised psychoeducational package (optimised Treatment as Usual for cannabis) in both arms of the trial. A training package will be delivered to all care coordinators in the participating teams by members of the research team over a period of two days.

## Planned inclusion/exclusion criteria

**Inclusion Criteria**

The target group is young people aged 18-36 years with FEP and recent, problematic cannabis use. People being seen within an early intervention service will be eligible. Problematic cannabis use is operationalised as having used cannabis at least once during more weeks than not in the previous 6 months (i.e., at least 12 of the previous 24 weeks). Additional eligibility criteria include having stable accommodation (i.e., not street homeless or roofless), speaking enough English to be able fully to understand and answer the assessment instruments, and being able to give informed consent. In the feasibility study, we have piloted the use of hair analysis as a means of providing additional corroboration of substance misuse histories (we were interested to assess the feasibility and usefulness of doing this, although this was not an element of the study protocol as originally agreed by the funder. However, while we found participants cooperative with this, we have concluded that at this stage in the development of this technology, it does not seem either feasible or useful to include it. We have encountered considerable technical difficulties, especially involving participants being able to provide sufficiently long hair samples and the extent to which relatively low level use is detected. Our recruitment method (via clinicians' referral of participants they belive to be eligible) has also meant that all participants have been individuals whose cannabis history was already well known to early intervention service staff: thus we have not found any suspicions arising that non-cannabis users have sought to enter the study. Following this pilot use of hair analysis, we do not therefore plan to incorporate it in the main trial protocol.
Diagnostic criteria for EIS entry require a first psychotic episode significantly impairing functioning and lasting more than a week. The operational criteria OPCRIT checklist for psychotic and affective illness will assess psychotic diagnosis.

**Exclusion Criteria**

Exclusion criteria include those who fail service inclusion criteria (i.e., are judged not to have a first episode of psychosis), are non-English speaking, or have unstable living arrangements that would compromise participation in the study. Those currently engaged in substance misuse treatment for cannabis use with another agency are also excluded as this may confound results. Those currently detained in hospital or prison, or on probation or Community Treatment Order requiring drug testing, are also excluded.

**Informing potential trial participants of possible benefits and known risks and obtaining informed consent**

All potential trial participants will be approached by care co-ordinators – those principally responsible for the treatment package offered by the service with whom the service user has typically had most contact – from the Early Intervention Service to which they are attached, to enquire whether they are interested in entering the study. Care co-ordinators will be provided with guidelines~~,~~ describing the study and what will be asked of the service user should they wish to participate. They will also be provided with an informational hand-out that they can give to participants, intended to assist them in briefly describing the

study to suitable service users. It will briefly outline the study design, and what participation in the trial will entail. If the individual indicates they are interested, the care co-ordinator will notify members of the study assessment team who will contact the individual. The research assistant, who will have been carefully trained by the applicants in procedures for eliciting informed consent, will make an appointment to see the service user and will discuss the study with them in detail, answering their questions and checking that they have understood what is proposed. Researchers will provide the individual with a participant information sheet, written in plain English, and will explain all aspects of the study to the person at the initial meeting. All benefits of the study and known risks to the individual will be explained in that meeting with the researcher. Forty-eight hours will be allowed to consider participation further: if following this they remain willing, an appointment will be made at which the consent forms will be completed and assessment initiated. At baseline and follow-up assessments, all participants will be given £20 voucher for their time, and at follow-up assessment all participants will be given an extra £10 for the provision of a urine sample. We will not include individuals who do not have capacity to consent to participation or who are currently detained in hospital.

## Proposed sample size

We are aiming in the full trial for a total sample size of 544 (incorporating the initial pilot study sample of 62), based on the following power calculation. Assuming that 50% of the subjects in the control arm will not relapse during follow up (Wade et al., 2006, Linszen et al., 1994), a 15% increase in this percentage due to intervention is clinically beneficial, and using a power of 90% and a significance level of 5%, a total sample size of 460 subjects will be required. This sample size is based on an analysis of time to relapse and will allow us to detect a 37% decrease in the hazard of relapse (hazard ratio of 0.63) in the intervention group using a Cox proportional hazards model. This sample size has been calculated using the STATA software version 11. The sample size is inflated by a factor of 1.06; assuming that the 120 care co-ordinators see an average of 4 service user participants in the trial and an intraclass correlation coefficient of 0.02, this gives a total sample size of 488. Finally, the sample size is inflated by 10% to account for drop outs (the primary outcome is obtainable from routine data), giving a total sample size of 544. Based on our recruitment experiences in the pilot study, we estimate that approximately 30 early intervention services will need to participate to achieve this goal. We are already in contact with and have received expressions of interest from in excess of this number, so that we are confident, subject to receive all the relevant local central and local approvals, of being able to recruit the numbers required.

## Statistical analysis

The main analysis will compare time to relapse over 18 months between treatment arms. All analyses will be via intention to treat. Baseline data will be compared with descriptive statistics. Kaplan Meier survival curves by randomised allocation will be produced. After checking the assumptions of proportional hazards, we will carry out Cox Proportional Hazards modelling to compare the intervention and control groups. This will be adjusted for clustering (care co-ordinator). Both primary and secondary outcome analyses will control for important demographic factors to be decided at the onset of the trial, before the detailed analysis plan is written with clinical consultation with the study team.

It is expected that there will be little missing data for the primary outcome as data for this will be extracted from the participants' medical records. There is likely to be more missing

data for the secondary outcomes as the majority require the participant to be interviewed to complete the measure. For both the primary and secondary outcomes we will check the extent and patterns of missing data and use multiple imputation if it is felt necessary. Factors to include in the imputation model will be those that are likely to be related to the outcomes (a clinical decision) and those related to missingness (a statistical decision). The analysis using imputed data will be a secondary analysis with complete case analysis being the primary analysis.

For the health economic analysis, intervention costs will be calculated using data on staff costs, incentives, oncosts, other overheads, and activity levels. These will be added to the costs of other health and social care services derived from the Client Service Receipt Inventory and records combined with nationally applicable unit costs (e.g. Curtis, 2009). Cost comparisons at 3 and 18 months will be made using similar regression models to those described above, with bootstrap methods used to generate confidence intervals around the cost differences. Cost-effectiveness from an NHS perspective at 3 and 18 months will use three outcome measures: number of cannabis negative urines, days of reported cannabis abstinence and QALYs (primary measure for economic evaluation). If for any of these the intervention has higher costs and better outcomes than usual treatment then cost-effectiveness will be expressed in the form of incremental cost-effectiveness ratios, estimated by dividing the incremental costs by the incremental benefits of the intervention. Uncertainty around cost-effectiveness estimates will be explored using cost-effectiveness planes (through generating a large number of cost-outcome combinations using bootstrap methods) and cost-effectiveness acceptability curves (showing the probability of the intervention being cost-effective at various levels of willingness to pay for health benefits). The range of values for QALYs will be £0 to £100,000 so as to include the threshold used by NICE. The values for the other measures will be chosen so that the points at which one arm has 50%, 60%, 70%, 80% and 90% of being the most cost-effective can be observed. It will then be a value judgement as to whether these values are acceptable. Cost-effectiveness will be investigated regardless of clinical outcome.

### *Proposed outcome measures*

Measures will be taken at baseline, 12 weeks after baseline following the intervention, and at 18 months after baseline a time at which a significant proportion of young persons with psychosis will relapse if they are going to do so (Robinson et al., 1999; Gitlin et al., 2001). At baseline, relevant demographic and clinical characteristics will be recorded, along with the following measures:

**Cannabis use** Relevant sections from the Time Line Follow Back (TLFB) (Sobell & Sobell, 1992) will be used to establish eligibility in terms of cannabis use and extent of recent use. Part E of the Structured Clinical Interview for DSM IV (SCID) will be used to assess substance misuse. Specimens for urinalysis will be obtained with the threshold set at a level for detecting cannabis use in the previous 28 days (i.e., 50 ng/ml cannabis metabolites).
**Diagnostic assessment:** The OPCRIT online tool will be used to assess psychotic diagnosis
**Psychotic symptoms:** The Positive and Negative Syndrome Scales (PANSS) (Kay et.al., 1987) will be completed at interview.
**Social functioning:** Employment status will also be assessed in interviews with patients using questions from the CSRI measure already being used for health economics.
**Service use and health economic analysis** . Service use over the preceding 18 months will be recorded with a version of the Client Service Receipt Inventory (CSRI) tailored to the

study (Beecham & Knapp, 2001). Quality adjusted life years (QALYs) derived from the SF-12 and EQ-5D will be used in the cost-effectiveness analyses (Brazier and Roberts, 2004; McCrone et al, 2009).

**Follow-up assessments:**
These will take place at 3 months and at 18 months. The primary outcome will be assessed at 18 months, secondary outcomes at both 3 and 18 month follow up points.
**Primary outcome:** The primary outcome will be time to relapse in each group. Admission to hospital or to a crisis resolution team or crisis house will be used as a relapse marker. Our hypothesis is that experimental group members will have a longer mean time to relapse.

**Secondary outcomes**
The measures completed following the intervention and 18 months after baseline will be:

- How many urines obtained at follow-up points are cannabis-positive.
- Positive symptom severity (Positive and Negative Syndrome Scale (Kay et al, 1987)
- Social functioning, based on self-reports regarding engagement in work or study
- Quality adjusted life years (QALYs) (SF-12 and EQ5D) (Jenkinson et al., 1999) and CSRI will be used in the cost-effectiveness analyses with costs assessed from an NHS perspective, as described in the analysis section above. Service utilisation data will be derived, where possible, from participants' medical records and will be checked against the CSRI. Quality adjusted life years (QALYs) derived from the SF-12 and EQ-5D will be used in the cost-effectiveness analyses (Brazier and Roberts, 2004; McCrone et al, 2009).

## Qualitative data collection

Previous versions of the CIRCLE protocol (v.1-5) included collection of data from all key stakeholders, including participants, clinicians, and carers, in order to investigate the usefulness and acceptability of the contingency management (CM) intervention and to explore its possible mechanism. This qualitative data collection received ethics approval and began alongside the pilot study data collection. A sufficient sample for analysis and publication was not obtained at this stage, but we have reviewed the data obtained and further developed our data collection tools and methods to allow us to realise more fully the qualitative study objectives. We have therefore revised our materials to collect more in depth data from a larger sample of the participants and clinicians. We will continue to collect qualitative data from participants and clinicians, but not carers. We had limited success during the pilot with collecting data from carers, partly due to few participants consenting to us contacting their family and carers, and secondly because many carers felt they did not know enough about what the study had involved. The qualitative data that we now collect will address the following questions:

1. What is the feasibility of implementing a CM intervention for cannabis use in psychosis in NHS settings? We will investigate views of the procedural aspects of the intervention, its acceptability and the barriers and facilitators to its implementation. Data to address this question will be from Early Intervention in Psychosis (EIP) teams participating in CIRCLE and participants in the experimental arm of CIRCLE.

2. Do CM interventions encourage long-term abstinence? CM is criticised as failing to motivate patients to abstain beyond the period in which incentives are offered. We will explore service user views of the impact of CM on cannabis use since the end of the intervention. Data for this topic will be collected from participants in both the experimental and control arms of CIRCLE.

3. Are psychoeducation (PE) treatments beneficial to service users? Psychosocial interventions, such as PE, are a mainstay for treatment of substance misuse (NICE, 2007). However, there is little qualitative research exploring subjective service user experiences of these interventions. (Childs et al, 2011; Lobban et al 2010). We will explore participants' views about the strengths and weaknesses of the CIRCLE PE package, including its impact on behaviour and attitudes around cannabis use following completion of the package. Data will be collected from participants in the control arm of CIRCLE.

**Methods**

Setting:

Qualitative interviews will take place in EIP services participating in CIRCLE. EIP teams will be selected from across a range of research centres; thereby allowing us to consider how the context and delivery of the intervention may vary between geographical regions and impact trial outcomes, as well as affect implementation of CM interventions in EI services. We will aim to include teams based in a range of rural and urban areas, with a mix of gender, age, ethnicity, job role and years of experience working in EIP settings.

Sampling:

Qualitative data will be collected through interviews with 3 groups:

- Clinical staff from EIP services that took part in CIRCLE: Data will be collected through focus groups with 6 EIP teams who have delivered or observed the CM intervention, with purposive sampling used to represent a range of professional and demographic characteristics. Each focus group will comprise of approximately 8-10 participants and will be conducted by the researcher within the EIP services. They would be expected to last approximately one hour. Separate one to one interviews will be performed with the team managers or consultants of included EIP teams, with the aim of interviewing 10 participants in one-to-one interviews. These interviews would aim to gauge a more detailed perspective of implementation issues from a service level and an overview of how it was perceived by the teams.

- Experimental arm participants: Views of participants in the CIRCLE experimental group will be explored regarding two topics: the procedural aspects and the acceptability of the CM intervention, which will be used to assess the feasibility of and acceptability implementing CM in NHS settings (question 1). Secondly, the cognitive-behavioural impact of the CM intervention (question 2). Data will be collected from 15-20 participants through one to one, semi-structured interviews, with the possibility of further sampling to achieve saturation. Purposive sampling will be used to include participants with varying degrees of education, work experience, and living circumstances, as well as to include a mix of those who quit cannabis use during the CM period and those who did not. Participants will be

recruited after they have finished the CM intervention and prior to the 18 month follow up. Participants who did not attend any CM sessions will be excluded.

- Control arm participants: As above, data will be collected from 15-20 CIRCLE control group participants through interviews, with the possibility of further sampling if needed. Participants will be invited to participate following the 3 month follow up assessment, and before the 18 month follow up. To explore the views of participants with different experiences of cannabis smoking and abstinence over the study period, a mix of participants based on their smoking status at baseline and 3 month follow-up will be included.

Interviews:

Focus groups and one to one interviews will be conducted by a member of the CIRCLE research team. Interviewers will be guided by semi-structured interview schedules. Memory aids, including a poster of the CIRCLE study design and a copy of the psycho-education handout, will be provided during interviews and focus groups. All interviews and focus groups will be digitally recorded and are expected to last approximately 45-60 minutes. CIRCLE participants will be able to take breaks as required, and informed that the interview can be split over 2 sessions if preferable. Participants will be thanked for their time with a voucher worth £20.

- Focus groups and interviews with EIP staff: Staff attitudes to CM after experiencing it, their experiences of contextual, practical and attitudinal factors which impede or facilitate its implementation, and their views about sustaining the intervention in the long term will be explored. We will also ask about any previous experience of using or delivering a CM intervention, and issue a short questionnaire to obtain demographic details. We will aim for each focus group to have a mixture of job roles and levels of experience of working within the service. Interviews with team managers will explore attitudes and knowledge of the intervention, and ask for an overview of how it was received by the team.

- Interviews with experimental participants: Since experimental participants received both CM and PE, service users' views will be sought on the benefits and limitations of each, as well as the impact of receiving CM in combination with PE. Subjective experiences of the CM and PE will be explored, including how attitudes towards the treatments changed over time. Perceived changes in cognitive, behavioural, and social factors related to cannabis use will be discussed, including changes to motivation to abstain, social/family support, and cannabis expectancies. Focus will be given to changes both during and since treatment. Experiences of other support offered within mental health services for cannabis use and how this compares will also be examined.

- Interviews with control participants: Interviews will be similar to those for experimental participants. Interviews will focus on the impact of PE on perceived changes in cognitive, behavioural, and social factors related to cannabis use, as well as knowledge regarding cannabis and mental health. Its impact both during and since treatment will be explored.

**Analysis**

Interviews and focus groups will be digitally recorded and transcribed verbatim. Data will be analysed using thematic analysis, a systematic method for identifying patterns across the data set by organising them into a thematic framework (Braun & Clarke, 2006), which will be performed using the NVivo 11. Thematic analysis will allow exploration of questions relating directly to our research questions and themes arising more inductively from the data. The analysis will be a collaborative process conducted by members of the CIRCLE research team, to enhance the validity of the analysis. Data will contribute both to the study report and to work submitted for PhD or MSc degrees by members of the CIRCLE a research team.

**Cognitive-Behavioural Process Evaluation:**

**Overview:**

A second sub-study will be performed as a process evaluation of the mechanism of cognitive and behavioural change associated with contingency management (CM) interventions. This will constitute part of the required research for a PhD for Luke Sheridan Rains, the CIRCLE Trial Manager.

The primary objective is to investigate the impact of CM on intrinsic motivation to abstain from cannabis use. It is also hypothesised that this relationship will be mediated by treatment engagement (Carroll et al. 2006, Tevyaw et al. 2009) and perceived competence in being able to abstain (Deci, Koestner, & Ryan 1999). Secondary objectives for the study include investigating the relationship between intrinsic motivation at treatment end and cannabis use in the 6 months following treatment. It is expected that higher self-reported intrinsic motivation at treatment end will be associated with lower rates of cannabis use over the 6 month post-treatment period. The study will also explore whether commonly identified barriers to successful abstinence, including cravings and environmental cannabis use, are also impacted by CM interventions. Finally, it will identify the principle reasons participants have for taking part in the contingency management intervention, and consider how they impact cannabis use during and following treatment.

**Background:**

Budney et al. (2006) describe CM as a ‘method to enhance and maintain initial motivation to abstain from cannabis use by providing a structure (weekly urine testing) and incentive (vouchers) for doing so’. However, some critics (e.g. Deci and Ryan, 1971) of financial rewards for motivating behaviour change argue that if an individual is encouraged to perform a particular behaviour by extrinsic motivational factors, their intrinsic motivation to perform that behaviour will be undermined. In support of this view Deci, Ryan, and Koestner (1999) published a meta-analysis of 128 studies investigating the effect of tangible rewards on participant’s intrinsic motivation to perform a study task. They found that receiving rewards reduced the likelihood that participants would continue performing the task during a ‘free choice’ period following cessation of the rewards. They argue that this results from the rewards making the individual feel like they are being externally controlled, and that their control over their own behaviour has been undermined. Deci and Ryan (2008) argue that contingency management (CM) type interventions are likely to produce only short lived behavioural change, and that they could undermine any motivation

the patient had pre-treatment to adopt healthier behaviours. If correct, this would be major problem for the long term efficacy of CM interventions, and may be a significant concern for mental health practitioners considering adopting CM type interventions to reduce substance use.

Contrary to Deci and Ryan it appears that abstinence does not rapidly fall for CM post-treatment in all cases. In a review of CM for substance misuse literature, Prendergast et al. (2006) found that CM was associated with significantly reduced cannabis use at 3 months (d=0.37) and 6 months (d=0.45) post treatment. Several publications since (Kadden et al., 2007; Carroll et al. 2006; Stranger et al. 2009; Litt et al. 2008) have reported that CM compared to a treatment as usual condition had reduced rates of substance use at up to 9 months post-treatment. Possible explanations for the impact of CM post-treatment are varied. Cognitive Evaluation Theory (CET) (Deci & Ryan 1986) suggests that financial rewards can improve the individual's sense of competency in performing the desired behaviour, and this may lead to improved intrinsic motivation. Alternatively, it may be that CM raises overall motivation to abstain sufficiently during treatment to resist or change certain cognitive-behavioural predictors of relapse. Coffey et al. (2002) found that 75% of people who met the criteria for dependency reported withdrawal symptoms such as cravings, anxiety, or sleeplessness. 38% of those with withdrawal symptoms reported using to avoid those symptoms. CM may benefit such individuals by giving additional motivation to endure withdrawal symptoms while recently abstinent. Given a sufficiently long period of treatment these factors are likely to decline in severity or disappear, thereby aiding long term abstinence without necessarily increasing intrinsic motivation.

While there is evidence of the benefits of CM post-treatment, Kadden et al. (2007) and Litt et al. (2008) found that CM alone failed to produce significant results on reducing cannabis use at 6 and 8 months respectively. Secondly, there is a perception amongst some researchers that CM alone has a relatively short term impact on substance use post-treatment (see Prendergast et al. 2006). It may be that while CM is effective at reducing cannabis user for up to 3-6 months post-treatment, CM alone may not be sufficient to produce longer term abstinence. Kadden et al. (2007), Carroll et al. (2006), and Litt et al. (2008) found that a CM intervention combined with Motivational Enhancement Therapy/Cognitive Behavioural Therapy (MET/CBT) produced longer term effects on cannabis use than CM alone. One explanation for the increased benefit of CM and MET/CBT combined is that each intervention is likely to address different factors influencing relapse. CM is effective at quickly reducing use during treatment compared to MET/CBT alone (Carroll et al. and Litt et al.). Thereby it may also be effective in terms of reducing cravings and other symptoms of withdrawal by treatment end. The aim of MET/CBT interventions meanwhile typically include: 1) to provide educational materials on the likely consequences of continued use; 2) to evoke and strengthen the patient's own motivation for change; 3) to assist the individual in developing effective coping strategies and harm reduction strategies (Thombs & Osborn 2013). Carroll et al. further found that CM improved engagement with treatment offered alongside CM. A CM plus MET/CBT intervention may therefore improve long term treatment outcomes partially through the benefits of CM and MET/CBT as standalone treatments, but secondly through CM improving engagement with MET/CBT treatments compared to MET/CBT alone.

For CIRCLE, CM is being offered alongside a manualised psycho-education package intended as an Optimised Treatment as Usual (OTAU) intervention. As described in the 'planned interventions' section for CIRCLE, it is intended to provide information about the likely consequences of continued cannabis use; to aid the participant in making a decision about their cannabis use; and to help them achieve those goals through strengthening their

motivation and helping them develop effective coping and harm reduction strategies. Based on the above model, one would expect the group receiving CM to show greater engagement in the psycho-education, and to be associated with greater long term abstinence compared to the control group.

**Aims:**

The overall objective of the present sub-study is to investigate the mechanism of cognitive and behavioural change underlying CM. The aim is to improve our understanding of its efficacy in treating substance use, both during treatment and post-treatment, when used in combination with a psycho-education intervention. The primary objective is to investigate the impact of adding CM for cannabis to routine clinical care on participants' intrinsic motivation to abstain. The expectation is that participants in the experimental group will show greater intrinsic motivation, and that this relationship will be mediated by engagement in the psycho-education and their perceived competence in abstaining. It is hypothesised that CM will improve intrinsic motivation by treatment end by: 1) encouraging increased engagement in the psycho-education. 2) Improving perceived competence in being able to abstain.

Secondary objectives include: 1) to investigate the impact of adding a CM intervention to routine clinical care on cravings and social networks/environmental cannabis use. 2) To investigate the impact of an added CM intervention at treatment end and 6 months post-treatment on self-reported overall motivation to abstain and cannabis use. 3) To investigate the relationship between self-reported intrinsic motivation at treatment end and post-treatment abstinence. 4) To consider the reasons patients have for taking part in treatment, and explore how they relate to successful long term abstinence. It is predicted that the experimental group (CM plus psycho-education) will display reduced cravings, reduced exposure to environmental cannabis use, and greater motivation at treatment end. Secondly, greater intrinsic motivation will be associated with longer periods of abstinence post-treatment. Thirdly, that health concerns (Copersino et al. 2006) and the prospect of receiving the financial rewards will be the primary reasons participants give for taking part.

**Method:**

Study Design

The process evaluation will be performed as part of CIRCLE. CIRCLE is a rater-blinded randomised controlled trial of contingency management (CM) offered alongside an optimised treatment as usual intervention. The aim is to investigate how CM offered as an addition to routine clinical care impacts service user motivation to abstain from cannabis use both during the intervention and in the months following treatment cessation. Furthermore, it will explore some of the cognitive and psychosocial processes expected to be underlying this relationship, and consider how this fits with current models of how CM interventions work. Finally, it will investigate the long term benefits of CM interventions compared to treatment as usual type interventions in terms of abstinence from cannabis use and motivation to abstain, and consider how this can inform future applications of CM type interventions for promoting behavioural change.

Once approval has been received, the outcome measures for the process evaluation will be conducted alongside the CIRCLE outcome measures at CIRCLE baseline and 3 month follow up assessment interviews, but not at the 18 month follow up. An additional assessment interview for the process evaluation will be performed at 9 months following

study induction (6 months following intervention cessation) as a telephone interview. This assessment will be performed for approximately 1/3 of participants recruited after approval has been received. This will happen through 1/3 of study sites conducting the 6 month follow up assessment.

Recruitment:

All participants eligible for CIRCLE will be included in the process evaluation. Participants will be informed of its aims as part of the consent process for CIRCLE. Details of the process evaluation, including objectives and information about the 9 month telephone interview, are included in the participant information sheet. They can opt out of the follow up telephone interview without being excluded from participation in any other part of CIRCLE.

Sample Size:

Outcome data will be collected for the process evaluation for all service users consented into CIRCLE once ethical approval has been received. It is estimated that outcome data will be collected for approximately 400 CIRCLE participants at baseline assessment. Based on the 3 month follow up rate achieved during the pilot phase of 70%, primary outcome data is expected to be collected for approximately 280 participants.

Outcome Measures:

The following measures will be included in the baseline and 3 month follow up assessment interviews for CIRCLE. In total they comprise 32 items, each of which are rated with a Likert type scale. They take around 15-20 minutes to complete in total.

Intrinsic motivation: Reasons for Quitting (RFQ) (McBride et al., 1994). Some changes have been made to the items in the assessment to accommodate better the likely concerns of patients with psychosis and a history of psychosis. Secondly, 4 items have been added explicitly referring to the vouchers participants will receive as part of the intervention.

Motivation and competence: 1) Chung et al. (2011) validated a 3 item measure of motivation to abstain, perceived difficulty of abstaining, and confidence in being able to abstain. The original measure targeted cigarette smoking, and has been adapted for the present sub-study by changing references to cigarette smoking to cannabis use. 2) Readiness Ruler (Heather, Smailes, & Cassidy 2008) is a single item measure of readiness to change. The original measure targeted alcohol use, and as above the measure has been adapted for the present sub-study by changing references to alcohol use to cannabis use.

Cravings: Mood and physical symptoms scale (MPSS) (West and Hajek, 2004) cravings subscale only (2 items). These items have been adapted to refer to cannabis use instead of cigarette smoking.

Environmental/social cues: The Wisconsin Predicting Patients' Relapse questionnaire (WI-PREPARE) (Bolt et al. 2009) environmental use subscale only (1 item in total), which has been adapted to refer to cannabis use instead of cigarette smoking.

Engagement with services: Engagement will be judged based on the number of CIRCLE psychoeducation sessions each participant attends. The number of contingency

management sessions attended will not be included, since there isn't a comparable measure for the control group.

The following will be co-opted for the procedural evaluation study from the current CIRCLE outcome measures. Cannabis use: the Timeline Follow Back (TLFB) will be used for self-reported cannabis use. Cannabis free urines will be used for a biometrically verified measure of cannabis use.

Data Collection:

Data for the process evaluation will be collected following ethical approval for the present amendment. The following outcome measures will be collected as part of the CIRCLE baseline and 3 month follow up assessment interviews: RFQ, Chung et al., Readiness Ruler, MPSS, and WI-PREPARE. TLFB and urinalysis outcome data is already collected for CIRCLE and will be co-opted for the present sub-study. Engagement data will be collected as part of the interventions for CIRCLE.

The 9 month follow up will consist of a single telephone interview during which the Timeline Follow Back and the adapted Chung et al. (2011) items will be collected. The telephone interviews are expected to take approximately 15–20 minutes to complete. Only participants who have previously discussed and agreed to being contacted by telephone by a researcher will be contacted. A cluster design will be used, with approximately 1/3 of study sites randomly selected to conduct telephone interviews. All sub-study participants from the selected sites and who have not opted out of the telephone interview will be contacted.

Statistical Analysis:

The primary outcome is the impact of treatment on intrinsic motivation at the end of the intervention period. This relationship is hypothesised to be mediated by treatment engagement during the period of the intervention, and by self-reported competence at treatment end. For the analysis, intrinsic motivation will be rated using the RFQ, treatment engagement will be measured as the number of psycho-education sessions attended by the participant, and competence will be assessed using the self-reported confidence measure from Chung et al. The relationship will be tested using linear regression analysis. The regression model will include 3 coefficients: group allocation, competence, and treatment engagement.

The following power calculation was performed to confirm that the predicted sample size should provide sufficient statistical power for the primary outcome: Tevyaw et al. (2009) reported an effect size of 0.44 for the effect of CM on intrinsic motivation. Based a more conservative estimate of 0.3 for the effect size, power of 0.8, and significance level of 0.05, the statistical test for the primary outcome would require a sample size of 82. Following an alternative method, based on Harrell (2001) 15 observations are required for each coefficient for a linear regression analysis. Based on this, a sample size of 45 would be adequate. The expected sample size of 280 should therefore be sufficient for the primary outcome analysis.

## *Research Governance*

### Data Monitoring Committee

We will assemble a Data Monitoring Committee (DMC) that will have access to all trial data. The DMC will have a key role in considering interim analysis and data review from the pilot trial and in advising the Trial Steering Committee (TSC) on the decision to step up from the pilot to the full trial. The DMC will also consider whether any interim analysis is warranted, review data from any analysis and consider requests for data release, again acting to advise the TSC on these issues. Finally, the DMC will be tasked with advising the TSC on any ethical or safety reasons why the trial should not continue giving due consideration to the safety, rights and well-being of participants.

Membership of the DMC will be completely independent of the study and comprise at least two clinical academics with experiences of trials, a service user with substantial experience of research, recruited via the MHRN, and an independent statistician. Professor David Kingdon, from the University of Southampton has agreed to be the chair of the DMC. This group will meet before the study begins with the chief investigator to consider activity of the DMC and set an agenda of meetings of sufficient frequency and at strategic points to fulfil the duties and responsibilities of the DMC. Administrative support will be provided to the DMC from the study team. Additional travelling and meeting expenses have been added for this additional committee, for which we have budgeted 3 meetings.

### Trial Steering Committee

The TSC will meet every six months in the early stages of the study, moving to annually once recruitment for the trial has begun if it goes ahead. It will be closely linked to the Service User and Carer Steering Committee (see below).. Professor Thomas Barnes at Imperial College, a renowned expert in the field of comorbidity and in conducting trials in this population, will be the independent chair person. Other members will include Dr Jonathan West, an independent consultant EI psychiatrist with considerable research experience, Dr Sara Brooks, independent statistician, and a representative of the service user and carer steering group (see below). The PI, trial manager and representatives from all the participating sites will also sit on the TSC.

The role of the TSC is to provide overall supervision for the trial, concentrate on the progress of the trial and adherence to the protocol and provide advice through its independent Chair. The ultimate decision for the progress from the pilot phase to the full trial and continuation of the trial at any time in the course of the trial lies with the HTA, but they will be advised on this by the TSC, in consultation also with the DMC. The TSC will report to the sponsors (University of College London) and the HTA.

### Project timetable and milestones:

**Project Timetable**:

**Prior to start of 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, EIS clinicians and service user and carer groups in the sites participating in the pilot study, (c) recruiting the first three members of staff, beginning with the trial manager who will participate in recruitment of other staff.

**First 3 months (study set up period):** The study will begin when the trial manager comes into post, and the second research worker in London and pilot study researcher in Warwick will also come into post during this period. The process of publicising the study will continue. The CM schedules and psychoeducational package will be finalised. Training will be provided for care coordinators in the three pilot study teams in delivering the intervention.

**Pilot study recruitment (Months 4 to 13 of study):** In month 4, recruitment to the pilot study will begin in teams in Camden and Islington NHS Foundation Trust, East London Foundation Trust, and Coventry & Warwickshire Partnership Trust. Randomisation will follow gaining informed consent and an initial interview. Recruitment will continue for 6 months, and patients will be followed up initially at 3 months.

**Pilot study follow up assessments (Months 7 to 16):** Participants in the pilot trial will initially be assessed at 3 months. At this point we will examine the feasibility of proceeding to a full trial, based on recruitment during this period. Pilot study follow up assessments will end in month 12. Qualitative interviews will be conducted following the 3 month assessments.

**Decision making and pilot study writing up (months 13 and 14):** In months 13 and 14, we will consult the Data Monitoring Committee and Trial Steering Committee, as described above, in order to decide whether to proceed to a full trial. We will present to the HTA data on recruitment and retention in the pilot study, in order to obtain ratification of the decision, and if necessary, guidance. If the decision is not to proceed to a full trial, research assistant staff contracts will expire at the end of month 15 and the trial manager's contract at the end of month 18, allowing time for analysis, writing up and dissemination of the pilot study results and qualitative study.

**Set up for full trial (months 15 to 18):** As soon as a decision has been made (by the end of month 15) regarding proceeding to a full trial, the set up period for a full trial will begin. During this four month set up period we will (a) obtain final ethics and research governance approvals to proceed to the full trial; (b) recruit further staff in North London and Warwick and research assistants for the East Anglia and South London centres; (c) confirm which further 20 EISs are participating, publicise the study to teams and senior managers in these centres, and (d) train staff in the intervention; and (e) make any modifications to trial methods that appear indicated following the pilot study.

**Recruitment for full study (months 19 to 33):** Recruitment will take place for the main trial for 15 months in all 30 participating EISs. The 11 pilot teams will continue to recruit during this period and the 62 pilot study participants will be included in the main trial, leaving an additional 482 to be recruited in the main study. In each of the 30 EISs, an average recruitment level of 1 participant recruited per month will need to be achieved to reach this target: if any sites appear to be finding this target difficult to meet, we will recruit further local teams early in the main trial recruitment period.

**Follow up assessments (Months 22 to 52)** Follow up assessments will be at 3 months (following the initial abstinence oriented intensive phase) and 18 months after baseline. 18 month assessments for the 62 pilot participants will take place from Month 22 to 27 inclusive. For the main sample, 3 month assessments will be from month 22 to month 36 inclusive and for those in the main sample, the 18 month assessments will be from months 35 to 52 inclusive.

**Final analyses and writing up (Months 53-55):** The final 3 months of the study will be dedicated to analysing all data and writing up results.

**Dissemination:** Specific dissemination strategies are likely to include the following. A study website will be developed and will be central to dissemination.

- For clinicians: articles in professional periodicals, updates about the study on relevant websites (e.g. www.psychminded.co.uk) and via regional EIS networks.
- For service users and carers: updates sent to prominent websites and blogs that report on mental health, e.g. MIND, Time to Change, the National Survivor User Network, presentations to MHRN and local user groups.
- For researchers: papers reporting our findings in peer reviewed journals with good impact and presentations at high profile conferences. We will publish an interim paper reporting on a pilot study in a journal of good impact, and anticipate that the full trial will result in a publication in one of the highest impact medical journals.
- For policy makers and planners: articles in relevant periodicals and updates sent to relevant websites e.g Health Service Journal, World Class Commissioning website. Previous experience of participating in Department of Health consultations will help us to contact key policy groups to whom we can delivery important messages regarding our work, especially to those developing national quality standards and care pathways.

## Expertise:

Contributions and roles of the members of the study team are as follows:

- SJ (PI) has a strong track record of researching complex interventions, including leading trials of crisis team care, of alternative EIS models, and of a training intervention for substance use in psychosis. She will oversee all aspects of the trial and supervise the Trial Manager.
- MH is an experienced EIS psychologist and researcher who worked on the CAP study of a cannabis intervention in early psychosis in Melbourne. He will lead on training and implementation of the intervention.
- MK is a psychiatric epidemiologist with extensive experience of large multicentre trials in primary and secondary care, and is Co-Director of the PRIMENT CTU, which specialises in mental health and primary care. PRIMENT will provide statistical and methodological expertise throughout the trial and have advised on the power calculation.
- PMcC, lead for the economic evaluation, has extensive experience of assessing the cost effectiveness of complex mental health interventions.
- JS is Director of the National Addiction Centre, Europe's highest rated addictions research centre. He provides expertise from an addictions perspective.
- JS and SP bring expertise from development of the NICE Guidelines for Psychosocial Treatments in drug use and DH Guidelines on drug use (both chaired by JS).
- SP is experienced in developing, delivering and evaluating innovative psychological treatments, and will advise on this and on dissemination.
- TC has extensive experience of multicentre trials in severe mental illness and will supervise a researcher in the full trial.
- SM is an Associate Professor in Social Psychiatry and BM an EIS consultant with research experience. He will coordinate the Heart of England sites in the pilot and full trial.
- BM is a consultant psychiatrist in early intervention with research experience, and is Chair of the London Early Intervention Network. He will support implementation of the study at the Hackney pilot and full trial study and will link to services across London.

- DF is a Professor of Social Psychiatry and senior EIS clinical psychologist with extensive experience in conducting trials of complex interventions in psychosis. As well as contributing to development and monitoring of the intervention, he will oversee the East Anglia site in the full trial.
- LM is an experienced medical statistician with the PRIMENT Clinical Trials Unit who will be the study statistician, designing and conducting analyses and contributing to paper writing throughout.
- TW is a social scientist who currently has a lead role in a trial of contingency management for substance misuse with JS and SP. He is an expert in qualitative research methods and will oversee the qualitative aspects of the pilot study, and he is also an expert in comorbidity in psychosis.
- RO is a very experienced medical statistician, including substantial trial expertise. She will provide additional senior oversight of the development of analysis plans and conduct of the trial.

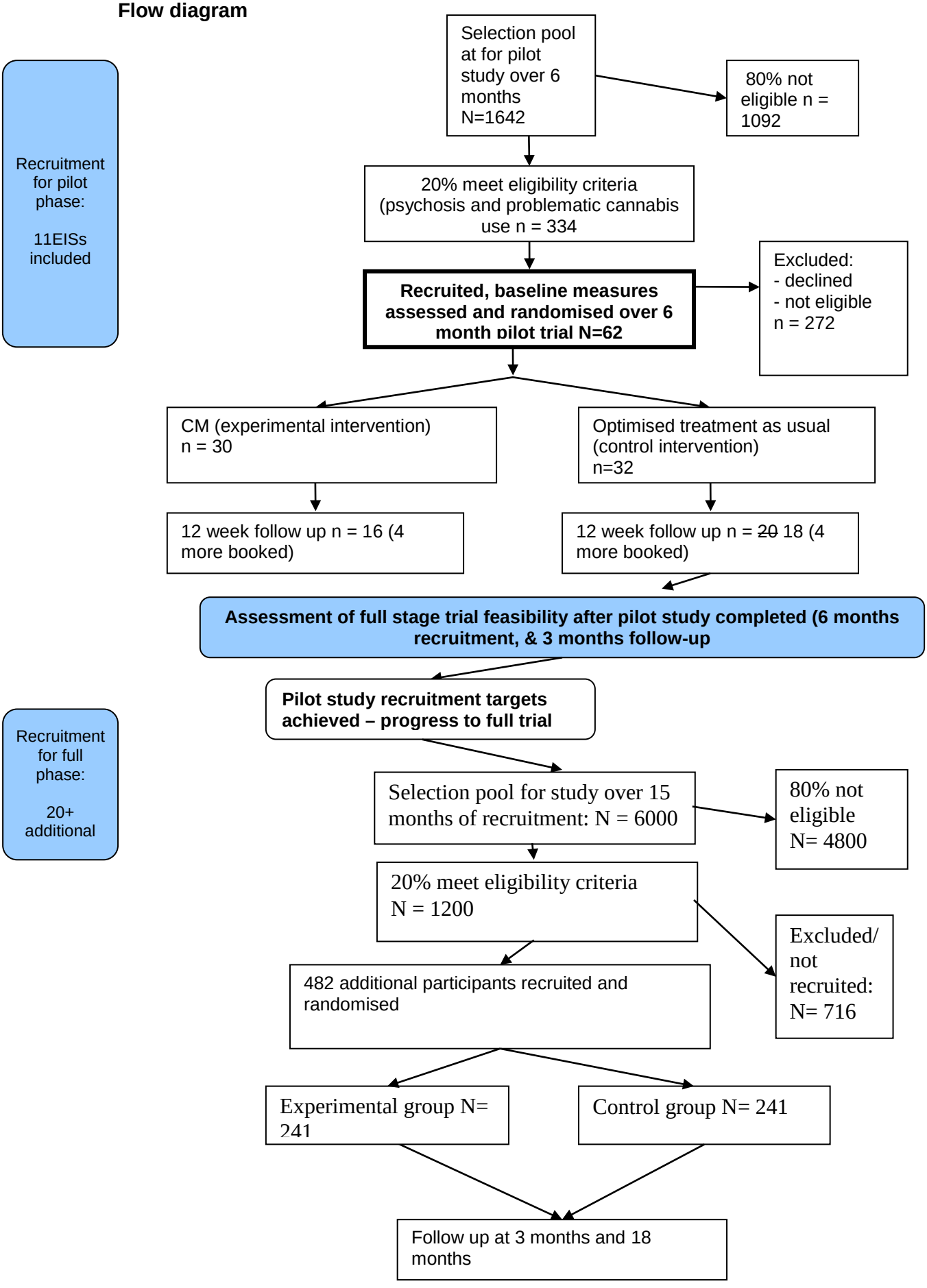
PRIMENT Clinical Trials Unit, as described in our responses to the committee, will support the trail throughout, roles including randomisation, methodological advice, database development, protocols for data entry and statistical input.

## Service Users:

We have consulted service users in the course both of preparation of the outline and the full proposal, and we are also planning considerable input to the main study. In the course of preparing the outline, we consulted service users in the Camden and Islington Early Intervention Service regarding the study, focusing especially on the feasibility and acceptability of the intervention and how best to implement it. In the course of preparing this full proposal we have had a further group discussion with Early Intervention Service users in Camden and Islington, and have consulted service user researcher meetings in Hackney and Camden and Islington (SURF, the service user research forum). The main topics in our consultation, which has informed preparation of the proposal and decisions about the intervention, have been the content, presentation and acceptability of the intervention, best methods for recruiting to the trial, and the best way of engaging service users in the research process.

Once the study begins, we plan to convene a service user and carer researcher steering group. This will meet up to 8 times a year at stages of the study when there are many decisions to be made, and will send representatives to the study steering group. We propose a minimum membership of this group of 4 service users and 2 carers, half recruited from among current EIS service users and half via the MHRN service users and carers who have substantial experience in contributing to research and service development. Throughout we will consult this group on final version of study materials, interventions and methods, on methods of publicising and recruiting to the study, and on interpretation and dissemination of our findings. 100 hours has also been budgeted for one of the members of this group to spend time on disseminating findings through channels accessible to service users.

**Flow diagram**



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