NIHR Health Technology Assessment programme

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NIHR HTA programme

06 August 2012

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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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Version 2: 02.04.12

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 current application is for the pilot trial designed to establish feasibility and acceptability of the intervention: we have resources available to proceed to a full trial if appropriate, and will return to the committee if it does appear appropriate. We are also seeking approval to conduct the qualitative work that accompanies the pilot trial.

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; 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 care coordinators: this represents a standardised and manualised form of usual Early Intervention Service management of cannabis use. We propose initially to conduct a pilot trial in 3 sites: this is what we are currently seeking approval for.

If this confirms feasibility of recruitment and retention, a full randomised controlled trial will follow, incorporating pilot participants. We adopt 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 will be in three Early Intervention Services (EISs) in Camden and Islington, Hackney, and Coventry and Warwickshire. EISs have had important roles as research settings, as they provide excellent access to incident cases of psychosis, and often have well-motivated staff who are interested in innovation. All three services involved in the pilot study have strong research cultures and have hosted several studies. Management teams at each centre have been consulted and expressed support for the study, perceiving it as relevant to their service. If criteria for the success of the pilot (see below) are met, we will add a further nine teams to the study, drawn from the North London, South London, Heart of England and East Anglia MHRN Hubs: we will return to the Committee with details of this in the form of a substantial amendment if the pilot indicates we should proceed.

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: When the study begins, the three pilot services will have around 640 clients in their first two years of follow-up. At least 40% are expected to meet cannabis eligibility criteria, yielding around 250 potential participants at baseline. We expect a further 90 eligible patients to enter the 3 services over the next 6 months. Of the 340 eligible in the first six months, we aim to recruit at least 68 into the trial and to obtain 3 month follow up data on at least 60% of these. If we fall more than 20% short of these targets, the full trial will not proceed. If we are within 20%, we will seek ways of improving recruitment and present our plans to the HTA for a decision on proceeding. Also taken into account in deciding whether to proceed will be the views of the Trial Steering Committee, service user and care working groups, and the outcomes of the qualitative work on the acceptability of

the intervention and whether it results in any problems. Summaries of these discussions and the research team's view will be presented to the HTA to inform a final decision on proceeding to a full trial.

If the full trial proceeds, we will seek further ethical approval via a substantial amendment. Our current plan for this is to continue to recruit participants in the 3 pilot services and add a further 9 EISs, drawn from the North London, South London, Heart of England and East Anglia hubs of the MHRN (in all 4 N London Hub teams, 3 each from S London and Heart of England, 2 from East Anglia). 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: details of the power calculation are presented below in the Sample Size section.

Feasibility of recruitment

An internal pilot study has been included to establish that recruitment and retention are feasible: as noted above, if recruitment falls more than 20% below target in this study, the full trial will not proceed.

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, care coordinators 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 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. 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. Qualitative interviews will be carried out by a researcher from another service. 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.

3d. Planned Interventions

An optimised version of treatment (OTAU) as usual 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 the 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 they will need to achieve two weeks of abstinence to return a cannabis free urine. 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 £2.00 each week 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 whether the cannabis level is falling or zero (due to abstinence) versus steady or rising (due to re-use). 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.

A bonus voucher to the value of £10.00 will be earned each time two consecutive specimens suggesting abstinence are provided. Failure to attend therapy 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, returning to the previous level of reward once two consecutive urine results negative for cannabis are recorded. Participants will sign an agreement to abide by test results, and vouchers will be from a local pharmacy (e.g. Boots), music (e.g. HMV) or catalogue store (e.g. Argos). The maximum achievable reward will be £300 (inclusive of three £20.00 vouchers received at assessments).

Training and delivery
Selection & Training of clinicians: Clinicians in the EI services, primarily care coordinators, 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. MH, who has extensive experience of training EIS care coordinators on cannabis use, will lead on this.

3e. 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. Hair analysis will be used in the pilot study to confirm compatibility between the history given by participants and a toxicological screening.

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, are currently engaged in substance misuse treatment with another agency and have unstable living arrangements that would compromise participation in the study.

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 an information sheet, written in plain English, describing the study and what will be asked of the service user should they wish to participate. All benefits of the study and known risks to the individual will be explained in that interview with their care co-ordinator. 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. 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. We will not include individuals

who do not have capacity to consent to participation or who are currently detained in hospital.

Proposed sample size

Participants will be aged 18-36 years and being seen by an EIS. The initial pilot trial for which we are currently seeking approval will be run in three services. If thresholds are met for progress to a full trial, a further nine teams will be added. 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.

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). At baseline, hair samples will be analysed to ensure evidence of problematic cannbis use (defined as use on more weeks than not in previous 24 weeks).
Diagnostic assessment: The OPCRIT online tool will be used to assess psychotic diagnosis
Psychotic symptoms: The Positive and Negative symptom 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).

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 time to relapse in each group.. Admission to hospital or to a crisis resolution team 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 instruments shown 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 sub-study

Alongside the pilot study, we will conduct a qualitative investigation regarding the usefulness and acceptability of the intervention from the perspective of participants and of clinicians, and of potential mechanisms for change. We will also investigate the views of potentially eligible people who choose not to participate. TW will supervise study research staff in carrying out this component of the study. The following forms of data collection will be used to sample all major perspectives on in the intervention:

Focus groups with staff will be used to assess participating clinicians' views regarding the intervention in the four teams participating in the pilot study. Topic guides will include their experiences of implementing CM schedules and any impediments encountered, the impact of the organisational context and culture on CM delivery, their views regarding the ethical and clinical implications of CM, and their perceptions of service users' responses to the intervention.

Individual semi-structured interviews with pilot study participants will elicit the service user perspective. Topic guides, refined in collaboration with the service user and carer steering groups, will include service users' perception of the effects on them of being offered incentives, their views regarding ethical aspects of this, and suggestions for improvements.

Focus groups with staff: We will hold three carer focus groups, two in London and one in Coventry. Our aim will be for at least half the participants to be carers of study participants. The groups will be used to explore carer participants on the intervention, including their views on use of voucher rewards and how these should be presented.

Analysis: A framework analysis approach will be taken. Interviews and focus groups will be digitally recorded and transcribed, and imported into the NVivo7 package which facilitates data coding. The key principle of the framework analysis is a thematic framework, developed and applied by charting themes in a matrix against individual cases, thus preserving case integrity while generating a thematic analysis. Data coding will operate at 3 levels

1 Each transcript will be retained as an individual data source and coded using case variables (i.e. treatments received, service-user demographics etc.) facilitating analysis within and between defined groups

2 Descriptive categories used to label themes identified in sub-sections of transcript that relate to research questions. For example, user responses to reward schedules, high frequency urinalysis etc

3 Descriptive sub-categories of descriptive categories or emergent themes identified through the analysis

Coding frames will classify and index text on-line, enabling flexible data retrieval and cross-referencing. Emergent finding will inform the final version of the trial intervention and training for staff and management protocols in the full trial.

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 be recruited 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. It will be closely linked to the Service User and Carer Steering Committee (see below). in the early stages of the study, moving to annually once recruitment for the trial has begun if it goes ahead. 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 9 of study): In month 4, recruitment to the pilot study will begin in teams in Camden and Islington, Hackney and Coventry. 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 12): 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 14) 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 9 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 12 participating EISs. The 3 pilot teams will continue to recruit during this period and the 60 pilot study participants will be included in the main trial, leaving an additional 502 to be recruited in the main study. In each of the 12 EISs, an average recruitment level of 2.36 participants 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 60 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 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.

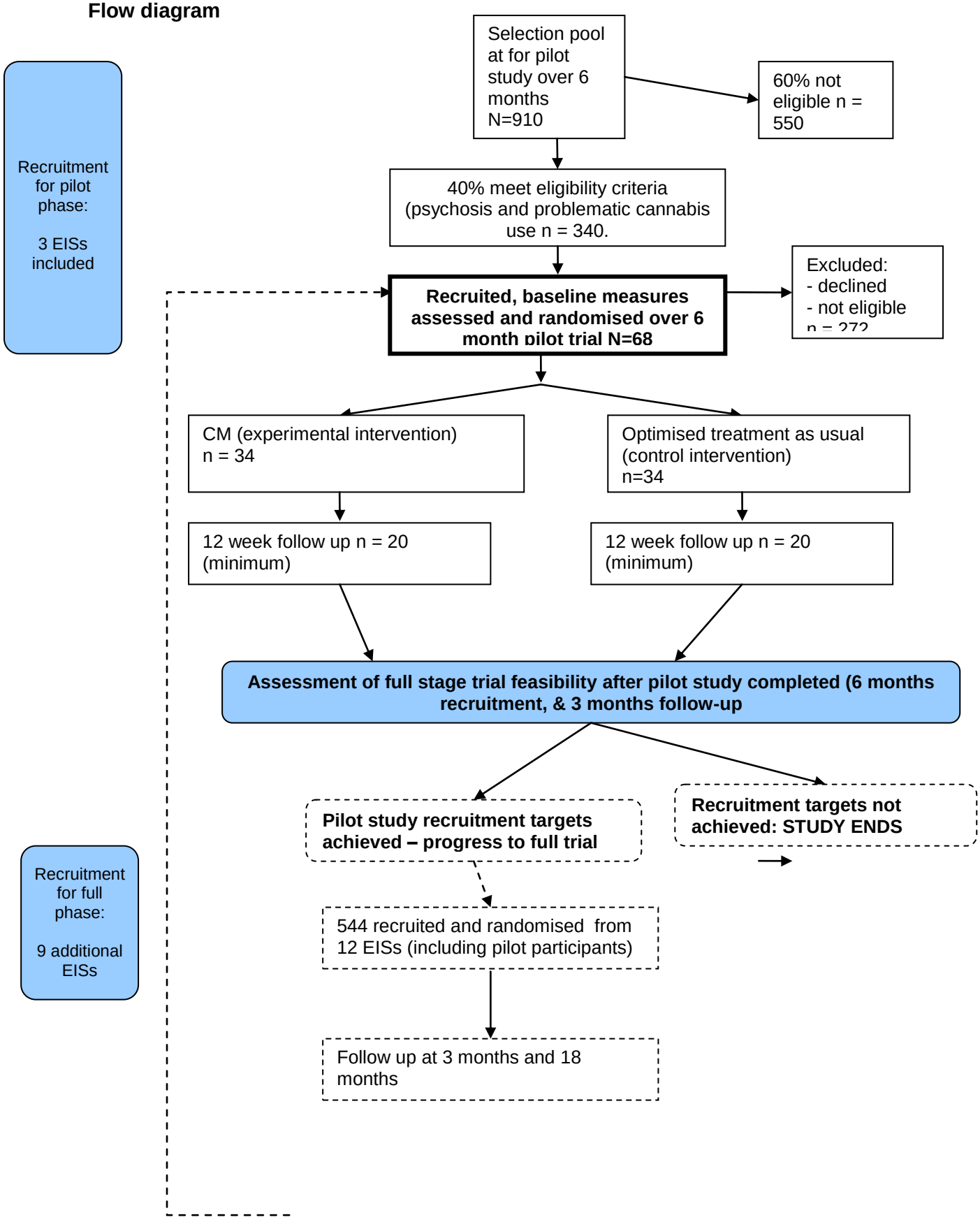
PRIMENT Clinical Trials Unit, as described in our responses to the committee, will support the trail throughout, roles including randomisation, methodological advice, database development, protocols for data entry and statistical input.

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



References:

Addington J, Addington D. Patterns, predictors and impact of substance use in early psychosis : A longitudinal study. Acta Psychiatrica Scandinavica. 2007;115:304-309.
Archie S, Rush BR, Akhtar-Danesh N, Norman R, Malla A, Roy P, Zipurshy RB. Substance use and abuse in first-episode psychosis: Prevalence before and after early intervention. Schizophrenia Bulletin. 2007; 33(6): 1354-1363.
Barnes TE, Mutsatsa SH, Hutton SB, Watt HC, Joyce EM. Comorbid substance use and age at onset of schizophrenia. British Journal of Psychiatry. 2006;188:237-242.
Barnett JH, Werners U, Secher SM, Hill K, Brazil R, Masson K, Pernet D, Kirkbride J, Murray G, Bullmore T, Jones PB. Substance use in a population-based clinic sample of people with first-episode psychosis. British Journal of Psychiatry. 2007; 190: 515-520.
Barrowclough C, Haddock G, Tarrier N, Lewis SW, Moring J, O'Brien R, Schofield N, McGovern J . Randomized controlled trial of motivational interviewing, cognitive behavior therapy, and family intervention for patients with comorbid schizophrenia and substance use disorders. American Journal of Psychiatry. 2001; 158: 1706-1713**.**
Bellack AS, Bennett ME, Gearon JS, Brown CH, Ye Yang MS. A randomized clinical trial of a new behavioral treatment for drug abuse in people with severe and persistent mental illness. Archives of General Psychiatry. 2006; 63: 426-432.
Brazier, JE, Roberts, JR,. The estimation of a preference-based index from the SF-12. Medical Care, 2004;42(9):851-859.
Budney A, Higgins S, Radonovich K, Novy PL. Adding voucher-based incentive to coping skills and motivational enhancement improves outcomes during treatment for marijuana dependence. Journal of Consulting and Clinical Psychology. 2000; 68:1051-1061.
Budney AJ, Moore BA, Rocha HL, Higgins ST. Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. Journal or Consulting and Clinical Psychology. 2006; 74: 307-316.
Cantwell R, Brewin J, Glazebrook C, Dalkin T, Fox R, Medley I, Harrison G. Prevalence of substance
Carroll KM, Easton CJ, Nich C, Hunkele KA, Neavins TM, Sinha R., Ford HL, Vitolo SA, Doebrick CA, Rounsaville BJ. The use of contingency management and motivational/skills building therapy to treat young adults with marijuana dependence. Journal of Consulting and Clinical Psychology. 2006; 74(5): 955-966.
Christine Barrowclough (MIDAS PI) Personal communication. April 2010
Cleary M, Hunt GE, Matheson SL, Siegfried N, Walter G. Psychosocial interventions for people with both severe mental illness and substance misuse. The Cochrane Library, Issue 3. Wiley & sons 2008.
Cleary M, Hunt GE, Matheson S, Walter G. Psychosocial treatments for people with co-occurring severe mental illness and substance misuse: Systematic review. Journal of Advanced Nursing. 2008; 65(2): 238-258.
Edwards JE, Cocks J, Bott,J. Preventative case management in first-episode psychosis. In McGorry PD, Jackson HJ (eds). The Recognition and Management of Early Psychosis: A Preventative Approach. Cambridge: Cambridge University Press: 1999.
Edwards J, Elkins K, Hinton M, Harrigan SM, Donovan K, Athanasopoulos O, McGorry PD. Randomized controlled trial of a cannabis-focused intervention for young people with first-episode psychosis. Acta Psychiatrica Scandinavica. 2006; 114:109-117.
Glasziou P, Chalmers I**,** Altman DG, Bastian H, Boutron I, Brice A, Jamtve**d**t G, Farmer A, Ghersi D, Groves T, Heneghan C, Hill S, Lewin S, Michie S, Perera R, Pomeroy V, Tilson J, Shepper**d S**, Williams JW. Taking healthcare interventions from trial into practice. British Medical Journal. 2010; 341: c3852
Hides L., Dawe A . Kavanagh DJ, Young RM. Psychotic symptom and cannabis relapse in recent onset psychosis. British Journal of Psychiatry. 2006; 189: 137-143.
Higgins ST, Alessi SM, Dantona RL. Voucher-based incentives: A substance abuse treatment innovation. Addictive Behaviours. 2002; 27(6): 887-910.
Jeffery D, Ley A, McLaren S. Siegfried N. Psychosocial treatment programmes for people with both severe mental illness and substance misuse. In: The Cochrane Library: Issue 3: Chichester, UK: John Wiley 2004
Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. Journal of Epidemiology and Community Health. 1999; 53: 46-53.
Kay S, Fiszbein R, Opler,L. The positive and negative syndrome scale for schizophrenia. Schizophrenia Bulletin. 1987; 13 : 261-276.
Kooyman I, Dean K, Harvey S, Walsh E. Outcomes of public concern in schizophrenia. British Journal of Psychiatry. 2007; 191: s29-36.
Lambert M, Conus P, Lubman DI, Wade D, Yuen H, Moritz S, Naber D, McGorry PD, Schimmelmann BG. The impact of substance use disorders on clinical outcome in 643 patients with first-episode psychosis. Acta Psychiatrica Scandinavica. 2005; 112:141-148.

Linszen D, Dingemans P, Lenior M. Cannabis abuse and the course of recent-onset schizophrenic disorders. Archives of General Psychiatry. 1994; 51: 273-274.
Litt M, Kadden R, Kabela-Cormier E. Petry N. Coping skills training and contingency management treatments for marijuana dependence: Exploring mechanisms of behaviour change. Addiction. 2008;103: 638-48.
Lussier JP, Heil SH, Mongeon JA, Badger GJ, Higgins ST. A meta-analysis of voucher-based reinforcement therapy for substance use disorders. Addiction. 2006;101:192-203.
Marteau T, Ashcroft R, Oliver A. Using financial incentives to achieve healthy behaviour. British Medical Journal. 2009; 338: 983-985.
Marwaha S, Johnson S, Bebbington P, Stafford M, Angermeyer MC, Brugha T, Azorin J-M, Kilian R, Hansen K, Toumi M. Rates and correlates of employment in people with schizophrenia living in the UK, France and Germany: findings from the EuroSC study. British Journal of Psychiatry. 2007; 191: 30-37.
Mazzoncini R, Donoghue K, Hart J, Morgan C, Doody GA, Dazzan P, Jones PB, Morgan K, Murray RM, Fearon P. Illicit substance use and its correlates in first episode psychosis. Acta Psychiatrica Scandinavica. 2009; 121: 351-358.
Mueser K, Drake R. Integrated dual disorder treatment in New Hampshire. In: Graham H, Copello A, Birchwood M. Substance Misuse in Psychosis: Approaches to Treatment Delivery. London : Wiley 2003
National Institute for Health and Clinical Excellence (NICE). Clinical Guideline on Drug Misuse: Psychosocial Interventions. London: NICE 2007.
Paul-Ebhohimhen V, Avenell A. Systematic review of the use of financial incentives in treatments for obesity and the overweight. Obesity Review. 2008; 9: 355-367.
Petry NM. A comprehensive guide to the application of contingency management procedures in clinical settings. Drug and Alcohol Dependence. 2000; 58 (1-2): 9-25.
Petry N, Simcic F. Recent advances in the dissemination of contingency management techniques: clinical and research perspectives. Journal of Substance Abuse Treatment. 2002; 2: 81-86.
Robinson D, Woerner M G, Alvir J M, Bilder R, Goldman R, Geisler S, Koreen A, Sheitman B, Chakos M, Mayeroff D, Lieberman JA. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Archives of General Psychiatry.1999; 56: 241–246.
Secades-Villa, R García-Rodríguez, O;. Higgins, S et al (2008) Community reinforcement approach plus vouchers for cocaine dependence in a community setting in Spain: Six-month outcomes. Journal of Substance Abuse Treatment, 34, 202-207
Sobell L, Sobell M.Timeline Follow-back. In: Allen J, Litten R. (eds.) Measuring alcohol consumption: Psychosocial and biological methods. New Jersey:Humana Press 1992.
Verdoux H, Liraud F, Gonzales B, Assens F, Abalan F, Van Os J. Predictors and outcome characteristics associated with suicidal behaviour in early psychosis: a two-year follow-up of first-admitted subjects. Acta Psychiatrica Scandinavica. 2001;103:347-354.
Wade D, Harrigan S, Edwards J, Burgess PM, Whelan G, McGorry PD. Substance misuse in first-episode psychosis: 15-month prospective follow-up study. British Journal of Psychiatry. 2006; 189: 229-234.
Walsh E, Buchanan A, Fahy T. Violence and Schizophrenia: Examining the evidence. British Journal of Psychiatry. 2002; 180:490-495.
Weaver T, Madden P, Charles V, Stimson G, Renton A, Tyrer P, Barnes T, Bench C, Middleton H, Wright N. Comorbidity of substance misuse and mental illness in community mental health and substance misuse services. British Journal of Psychiatry. 2003;183:304-313.