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 (CIRCLE)

Final statistical analysis plan

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Introduction

This analysis plan sets out the methods of analysing the predetermined primary and secondary outcomes of CIRCLE, which will be reported in the National Institute for Health Research, Health Technology Assessment report at the end of the trial and also in the main peer review paper to result from this randomised controlled trial.

The analysis of this trial will conform to the CONSORT statement[1-3] and the appropriate standard operating procedures written by Priment Clinical Trials Unit.

Further information on this trial can be found in the protocol version 6 (12/05/2014).

Trial summary

Aims

The aims of the main trial are to test whether the intervention results in an increase in time to relapse compared with the control group. Also 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.

Objectives

- To determine whether there is a difference in time to relapse in those randomised to the intervention compared with those randomised to optimised treatment as usual
- To investigate whether there is a difference in cannabis taking at follow-up between the randomised groups.
- To explore whether there is a difference in positive symptoms score at follow-up between the two randomised groups.
- To examine whether social functioning as defined by employment status is different between the two randomised groups.

Study population

Inclusion criteria

- Aged 18-36 years
- First episode psychosis and recent problematic cannabis use (having used cannabis at least once a week in more weeks than not over the previous six months)
- Being seen in the Early Intervention Service
- Having stable accomodation (not street homeless or roofless)
- Having sufficient command of English to give informed consent, to understand and answer the assessment instruments.

Diagnostic criteria for Early Intervention Service entry require a first psychotic episode significantly impairing functioning and lasting more than a week.

Exclusion criteria

- Not first episode psychosis
- Non-English speaking
- Currently engaged in substance misuse treatment with another agency
- Have unstable living arrangements
- Currently detained in hospital or prison, or on probation or Community Treatment Order requiring drug testing

Trial design

A single blind (assessors only) individually randomised controlled trial comparing contingency management to optimised treatment as usual. Initially this study was conducted in 11 Early Intervention Services (Camden and Islington, Hackney, Coventry, Tower Hamlets, Newham, north Warwickshire, south Warwickshire, Barnet, Enfield, Haringay, Kensington Chelsea and Westminster) as a pilot. This part of the study recruited 62 participants and aimed to obtain three month follow up on at least 60% of these. The full trial took place with those recruited to the pilot incorporated to the main trial and more sites from North London, South London, Heart of England, Surrey, Sussex MHRN Hubs. The main trial aimed to recruit 544 participants (including the 62 from the pilot trial). There were 42 Early Intervention Services (including the 11 that took part in the pilot) taking part in the trial. They aimed to recruit 13 on average per service.

The pilot trial recruitment ran from 01/06/2012 to 28/02/2013. The full trial, recruitment ran from 01/08/2013 until March 2016, with follow up ongoing until September 2017.

Randomised treatments

Intervention:

Contingency management involved offering rewards contingent initially on attendance and then on negative urinalysis results for cannabis. Following assignment to the contingency management group, participants were introduced to the voucher programme at an initial information and assessment session. Participants were informed that they needed to achieve two weeks of abstinence to return a cannabis free urine. In week 1 of the intervention, participants received 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 until week 12 participants earned vouchers contingent upon consecutive negative specimens or specimens that indicated a reduction in cannabis use.

If the participant has a pre-planned holiday or other significant commitment, they were able, on a maximum of two occasions, to suspend the intervention for one week, returning after 2 weeks rather than after 1 week. They were still be expected to show evidence of abstinence

at that point, and they needed to request this suspension no later than at the time of their previous scheduled appointment. The Early Intervention team was also be able to request suspension of the intervention for a maximum of one month if a participant relapsed and lost capacity to decide whether they wished to continue. If capacity was not regained in one month, the intervention was not continued.

Optimised treatment as usual (to be delivered to the intervention and control groups)
Optimised treatment as usual for cannabis was a phase specific, individually tailored, psycho-educational approach to problematic cannabis use for generic early intervention care coordinators that applies general psycho-educational approaches used in first episode psychosis[4]. The full delivery was typically achieved over approximately three hours, normally offered over regularly programmed sessions of 15-30 minutes duration.

Sample size
Assuming that 50% of the subjects in the control arm will not relapse during follow up,[5 6] 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 version 11[7]. The sample size is inflated by a factor of 1.06; assuming that the 120 care coordinators 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.

Randomisation
Participants were individually block randomised using blocks of size 2, 4 and 6 to either contingency management or optimised treatment as usual, stratified by severity of cannabis use (one to three times a week versus four or more times a week). Randomisation was carried out remotely and with impartiality by Sealed Envelope[8].

Blinding
This was a single blind trial. Participants could not be blinded to their allocation as they will be participating in an interactive intervention. Outcome assessors were be blinded to allocation. However, this relied on participants, their care coordinators and clinical team not telling the assessors the.

The statisticians and health economists will remain blind to allocation until the primary analyses have been verified.

Outcomes

Primary Outcome
Time to relapse defined as admission to hospital, crisis house or crisis resolution team for mental health related problems. Data for this outcome were obtained from the informatics department of the relevant Trusts. This was in the form of the date of admission and which service admitted in the 18 months following baseline. Those that did not have any data recorded were assumed to not have any admissions and their data were censored 18 months after entry into the trial. If a participant died within the follow up period, the study team had this information and follow up will be censored at the date of death if they have did have a relapse before then. Likewise if their drop out date was known, this will be used as the date of censoring. Everything possible was done to trace people who dropped out to ensure that it was ascertained whether they had a relapse and if so when. This is because

drop out may be related to the outcome and therefore introducing informative censoring. [outcome type: time to event]

Secondary Outcomes
Secondary outcomes were measured at 12 weeks and 18 months. Analysis will be separately at these time points to match the clinical question of examining the outcomes at each of these time points rather than over time.

Cannabis positive urine sample at follow up. This will be a dichotomous outcome, positive versus negative.

Positive symptom score using the positive scale of the Positive and Negative Syndrome Scale (PANSS)[9]. This consists of seven items: Delusions, Conceptual disorganization, Hallucinatory behaviour, Excitement, Grandiosity, Suspiciousness and Hostility. Each item is scored on a scale from one to seven with one indicating absent and seven indicating extreme. These are summed to give an overall score which ranges from 7 to 49. [outcome type: continuous]

Negative symptom score using the negative scale of the PANSS. This consists of seven items: Blunted affect, Emotional withdrawal, Poor rapport, Passive-apathetic social withdrawal, Difficulty in abstract thinking, Lack of spontaneity and flow of conversation, Stereotyped thinking. Each item is scored on a scale from one to seven with one indicating absent and seven indicating extreme. These are summed to give an overall score which ranges from 7 to 49. [outcome type: continuous]

Social functioning, based on self-reports regarding engagement in work or study, defined as any work (including sheltered or voluntary) or study (full or part time). [outcome type: dichotomous]

Number of days cannabis is used in the previous 12 weeks for follow up at 12 weeks and previous six months for 18 month follow up [outcome type: count]

Number of admissions over 18 months follow up. The primary analysis of this outcome will be operationalised to include those who provided a full 18 months follow up and those who died during follow up [outcome type: dependent on number of events. It may be possible to use this as count data else it will be dichotomised to none versus any]

Data collection
Data were collected at three time points, baseline, 12 weeks and 18 months post baseline.

Baseline
Demographic and social information (age, gender, ethnicity, social standing, living arrangements, employment, benefits received)
Clinical characteristics
Cannabis use using Time Line Follow Back[10]
Part E of the Structured Clinical Interview for DSM IV[11]
Urine sample results
The Positive and Negative syndrome scales (PANSS)[9]
Employment status using questions from the Client Service Receipt Inventory (CSRI)
SF-12 (to be used in health economic analysis)[13, 14]
EQ-5D (to be used in health economic analysis)
CSRI tailored to the study[13] (primarily for health economic analysis)

12 weeks and 18 months
Urine sample results

Positive and Negative Syndrome Scale (PANSS)[9]
Engagement in work or study from the CSRI
SF-12 (to be used in health economic analysis)[13,14]
EQ-5D (to be used in health economic analysis)
CSRI (to be used in health economic analysis)

18 months
Date of admission to hospital or crisis resolution team

Data entry
Data were entered using a web based system set up by Sealed Envelope[8]. This was set up so that, it mirrored the data collection sheets in order. It also had range checks, consistency checks and for closed questions gave a number of options plus "other" where appropriate. Assessors who entered the data will had no access to the group allocation through this system.

Data were checked by the statistician and health economists before analysis and any problems reported to the Trial Manager, who will rectify them as appropriate before data analysis.

Statistical analyses
The CONSORT[1-3] flow diagram will be constructed by/ in collaboration with the Trial Manager who will have logs of service users who do and do not agree to take part in the study. It will include number of service users randomised to each arm of the trial, and the numbers who have follow up data available.

All analyses will be on an intention to treat basis and data from the pilot trial will be incorporated into the main trial.

Data will be analysed using Stata version 14[15].

Descriptive statistics
Initial analyses will look at summary statistics for all variables, both overall and by randomised group. Summary statistics for continuous variables will be mean, median, SD, lower quartile, upper quartile, minimum and maximum and reported appropriately according to distribution. Summary statistics for categorical variables will be frequency and percentage within each category.

Summary statistics of baseline variables by whether a participant has dropped out of the study will also be examined to determine whether the drop outs had similar characteristics to those who remained in the study at baseline.

Analysis of the primary outcome
The primary outcome will be initially examined using Kaplan Meier survival curves by randomised allocation. If the assumptions of proportional hazards is satisfied, Cox Proportional Hazards modelling to compare the intervention and control groups will be carried out, adjusting for severity of cannabis use at baseline (the stratification variable, dichotomous – 1 to 3 times a week versus 4+ times a week) and whether the participant was part of the pilot trial. If the assumption of proportional hazards is not fulfilled, alternative modelling strategies will be employed. Robust standard errors will be used to account for clustering by therapist; which should account for most of the centre effects in this multicentre individually randomised trial. Hazard ratios and 95% confidence intervals will be presented.

Analysis of the secondary outcomes

These will be analysed separately for data collected at 12 weeks and 18 months. Models will include severity of cannabis use at baseline and whether the participant was part of the pilot trial. For the dichotomous outcomes (cannabis positive urine, engaged in work or study), logistic regression with robust standard errors to account for clustering by therapist will be used. If there are too few participants engaged in work or study for logistic regression to be possible then results will be reported descriptively. For continuous outcomes (positive and negative symptoms), linear regression with robust standard errors will be used.

For count outcomes, Poisson regression with robust standard errors will be used for count outcomes (number of cannabis days and number of admissions over follow up). If there are excess zeros for either count outcome, then the use of zero inflated Poisson regression will be explored.

Appropriate estimates and 95% confidence intervals will be presented for all analyses.

Missing data
There is not much missing data for the primary outcome since it is an objective outcome collected from the appropriate informatics departments.

There is missing data for other variables, especially at follow up. This may be because of non-attendance at the follow up appointment or non-response to specific questions. The extent and patterns of missingness will be assessed. Potential predictors of missing values that are related to the outcomes will be identified. .

Multiple imputation[16] may be used if it is felt to be necessary. We will only impute outcome data if surrogate outcomes or variables closely related to the missing outcome(s) are available. Otherwise there is no gain in imputing outcomes[17].

The primary analysis will be complete case analysis with analysis using multiple imputation being a supportive analysis if it is carried out.

Supportive analyses
There will be up to six supportive analyses for the primary outcome:
1. Analysis of all outcomes with their baseline predictors of missingness, that is modelling including the randomised allocation, whether the participant was in the pilot trial and the level of cannabis use at baseline

2. Analysis of the primary outcome excluding those participants who have no follow up secondary outcome data (for 12 weeks and 18 months separately) because those who drop out or die may be different to those who remain in the study and/ or survive. Before doing this, some demographic statistics comparing those who remained in the study and those who dropped out will be produced.

3. Analysis of those in the main trial only as some changes were made to the protocol at the end of the pilot before the main trial commenced, which might mean the participants behave differently to those in the pilot trial.

4. Analysis of the primary outcome controlling for the same factors as in the primary analysis plus the number of psychoeducation sessions attended (which is being offered in both arms of the trial).

5. Analysis of the primary outcome controlling for the same factors as the primary analysis and number of admissions in the six months prior to baseline.

6. Analysis of the primary outcome controlling for the same factors as the primary analysis, but using centre as the clustering variable not therapist.

There will be up to two supportive analyses for the number of admissions during follow up:
1. In addition to the factors included in the main analysis, this will include predictors of missingness.

2. Including those who were discharged within 18 months and assuming they had no admissions over the follow up time.

There may be supportive analyses for secondary outcomes collected at 18 months, as outlined in the missing data section.

Exploratory analysis:
We will investigate potential patterns and degree of non-compliance using clinical definitions of compliance and descriptive analysis. We will perform a Complier Average Causal Effect (CACE) analysis if feasible.

There are no subgroup analyses planned.

Health Economic analyses
The objective of the cost effectiveness analysis is to establish the relative cost-effectiveness of contingency management versus optimised treatment as usual at 18 months. The primary outcome will be QALYs (Quality Adjusted Life Years) calculated using EuroQol EQ-5D (3L) health profiles combined with health state preference values from the UK general population[i]. The resultant mean Quality of Life utility scores of the two treatment groups will be compared at eighteen months using unpaired *t*-tests. QALYs will be calculated using the area under the curve method and compared between groups adjusting for baseline EQ-5D utility scores[ii].

Costs will be calculated based on resource use gathered from an adapted version of the client services receipt inventory (CSRI)[iii]. The primary analysis will take an NHS and personal social services perspective[iv].

Costs of the contingency management intervention and optimised treatment as usual will be calculated using the salaries of staff delivering the intervention, plus employer on-costs, overhead costs, the cost of providers of supervision, and the cost of any equipment or consumables. A ratio of direct face-to-face to indirect non-face-to-face time will be applied.

Total costs at 18 months will be calculated by combining resource use with unit costs at 2016 prices. Unit costs will be derived from PSSRU and NHS reference costs. Medications will be costed using NHS prescription cost analysis data. Costs and QALYs will be discounted at 3.5% per year.

Costs will be compared, adjusting for baseline differences. Patient level costs and quality of life data will be bootstrapped with replacement (N = 10,000) to populate incremental cost effectiveness (ICER) planes, to estimate median cost-effectiveness and (pseudo) 95% confidence intervals. The probability of the intervention being cost-effective at different levels of willingness to pay for health benefits will be shown by generating cost-effectiveness acceptability curves (CEACs).

No subgroup health economics analyses are planned. The CHEERS statement will be completed[v].

Additional health economics analyses

1. Cost effectiveness at 3 months will be reported.
2. Results from a broader perspective including costs from criminal justice and cost of unpaid lost productivity due to illness will be reported.
3. Cost-effectiveness using alternative outcomes will be reported:
   - QALYs calculated using SF-12 data
   - Time to relapse (to 18 months)
   - Number of cannabis-negative urine samples
   - Days of reported cannabis abstinence

4. Missing data in baseline resource use, quality of life, and other covariates will be handled with multiple imputation using chained equations, using guidelines from Gabrio, Mason and Baio[vi].

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