

**Statistical and health economics analysis plan:**

**Trial Name**: Optimising team functioning, preventing relapse and enhancing recovery in crisis resolution teams: the CORE programme (CRT Optimisation and RElapse prevention) – Phase 3

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**Part I – Statistical Analysis Plan**

**Introduction**

The analysis of this trial will conform to the CONSORT statement1-3 and the appropriate standard operating procedures written by Priment Clinical Trials Unit. Further details on the trial can be found in the protocol version 3, dated 17/11/2013 on http://www.ucl.ac.uk/core-study.

This analysis plan includes the health economic evaluation in Part II.

**Trial summary**

**Aim**

The aim of the randomised controlled trial is to test whether a peer-provided, self-management programme for people leaving Crisis Resolution Teams (CRTs) can reduce relapse and promote recovery.

**Objectives**

* To discover whether there are differences in levels of readmission to acute care between the two randomised groups during follow up.
* To evaluate whether inpatient bed use during the study period is different between randomised groups.
* To determine whether satisfaction with services differs between randomised groups.
* To ascertain whether self-rated recovery differs between randomised groups.
* To discover whether the extent of symptoms are different between the two randomised groups.
* To evaluate whether loneliness is different between the randomised groups.
* To determine whether perceived level of social support is different between randomised groups.

**Study population**

*Inclusion criteria*

* Been on the caseload of one of the participating CRTs for at least a week
* Have capacity to give written informed consent to the study

*Exclusion criteria*

* People who in the view of the clinical team present such high risk to others, it would be unsafe for peer support workers to meet them even in a mental health service setting.
* People who are discharged to addresses outside the catchment area.
* People who cannot understand English

Participants will be identified by clinicians from study site CRTs at the initial screening stage as: either having psychosis or bipolar disorder; or not.

**Trial design**

This is an individually randomised multicentre randomised controlled trial. The intervention group will receive up to ten sessions with a Peer Support Worker and a structured workbook to fill in. The participants in the control group will be offered the structured workbook but no guidance on how to use it and no Peer Support Worker contacts. Participants will be followed up at four months post baseline and data will be collected from the trust records for the 12 months post baseline. Additional funding was provided to follow up participants at 18 months post baseline.

Recruitment ran from March 2014 until 440 participants had been recruited (July 2015), with 12 month follow up to July 2016 and 18 month follow up to January 2017.

**Sample size**

The sample size is based on readmission to acute care during follow up of 50% versus 35%, with 80% power and 5% significance using unequal allocation of 217 in the control arm and 159 in the intervention arm. The intervention arm is then inflated for clustering (peer support worker) using an intraclass correlation coefficient of 0.03, after rounding this gives 220 participants in the intervention arm and 220 participants in the control arm (a total of 440 participants) from five Crisis Resolution Teams, all in different NHS Trusts. It is expected that on average, there will be four peer support workers within each Crisis Resolution Team, with an average cluster size of 11.

**Randomisation**

Randomisation will be conducted by an independent randomisation service, Sealed Envelope4. It will be stratified by Crisis Resolution Team. Randomisation will be 1:1 using in blocks randomisation with varying block sizes.

**Outcomes**

Outcomes are defined in detail in the appendix at the end of this document.

*Primary outcome*

* Readmission to acute care during the follow-up period (from the date of study entry)

*Secondary outcomes*

* Time to first readmission to acute care
* Days in acute care during one year follow-up (from the date of study entry)
* Any compulsory admission to hospital during follow-up period
* The Client Satisfaction Questionnaire (CSQ-8)
* Social Outcomes Index (SIX)
* Illness Management and Recovery Scale - patient version (IMR)
* A Questionnaire on the Process of Recovery (QPR)
* Brief Psychiatric Rating Scale (BPRS)
* UCLA Loneliness Scale (ULS-8)
* Lubben Social Network Scale (LSNS-6)
* HLS Social Capital Questionnaire
* Employment status at follow-up (question 1 from SIX)

**Data collection**

*Baseline from the participants*

Socio demographics (age, gender, ethnicity, accommodation, living situation, marital status, employment status and GP contacts over the previous three months)

The Client Satisfaction Questionnaire(CSQ-8)

Social Outcomes Index (SIX)

The Illness Management and Recovery Scale- patient version (IMR)

A Questionnaire on the Process of Recovery (QPR)

The Euroqol 5-Dimension Health Questionnaire (EQ-5D)5 – to be used in economic analysis only (See Part II)

UCLA Loneliness Scale (ULS-8)

Lubben Social Network Scale (LSNS-6)

HLS Social Capital Questionnaire

The Brief Psychiatric Rating Scale (BPRS)

Alcohol Use Questionnaire (AUDIT-C)

Drug Use Questionnaire (DAST-10)

*Baseline from participants’ notes*

Current diagnosis

Use of acute care services during the previous year

Mental Health Act admission or Community Treatment orders during the previous year

Use of community mental health services during the previous year

Care Plan Approach status at baseline

Did the participant have a care coordinator at baseline?

*Four months after baseline*

The same measures as at baseline apart from demographics, Audit-C and Dast-10. Participants in the intervention group will also be asked to complete the Recovery Promoting Relationships Scale (RPRS) in a separate phone interview with an unblinded researcher, following the main follow-up interview.

*12 months from the Trust records*

All readmissions to acute care over the previous 12 months (to enable time to readmission and the number of days spent in acute care during follow up to be calculated).

*18 months after baseline*

As at four months with the addition of the Connor-Davidson Resilience Scale (CD-RISC-10) and the exclusion of the Recovery Promoting Relationship Scale.

**Data entry**

Data will be entered using a web based system set up by Sealed Envelope4. This has been set up so that, it mirrors the case report forms in order. It also has range checks, consistency checks and for closed questions gives a number of options plus “other” where appropriate. Assessors who will be entering the data will have no access to the group allocation through this system. The stratification variables are held in the Sealed Envelope database with the randomisation variable.

With the checks in place, there should not be any issues with illegal values being entered or inconsistent data being entered so necessary cleaning should be minimal. However, data will be checked by the Statistician before analysis and any problems reported to the Assistant/ Trial Manager, who will rectify them as appropriate before data analysis.

Peer support worker ID and participant identification numbers for those in the intervention group are held in a separate datasheet in the trial office.

**Statistical analyses**

*General principles*

The assumptions underpinning each statistical method will be checked. For example, normality and equality of variances will be checked for t-tests. The use of transformations or non-parametric methods will be considered if assumptions do not hold. Adjusted analyses will be performed if baseline imbalances are observed. The impact of missing data will be explored in all analyses. Supportive analyses will be performed if non-compliance is considered to be a problem.

The primary analyses will be complete case. All analyses will be on an intention to treat basis. Data will be analysed using Stata6.

*CONSORT*

The CONSORT1-3 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.

*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 (SD), median (lower quartile, upper quartile), minimum and maximum. These variables will also be plotted to check their distribution. If variables are skewed, then median and interquartile ranges will be reported, otherwise mean and standard deviation will be reported. Summary statistics for categorical variables will be frequency and percentage within each category. No statistical significance tests for baseline characteristics by randomised group will be performed, but balance will be assessed visually.

*Primary Outcomes*

For the dichotomous outcome readmission during the study period, data will be analysed using random effects logistic regression, with clustering by peer support worker being modelled using random effects. Those in the control group will be considered to be clusters of size one for analysis purposes. Condition (psychosis versus no psychosis) and centre will be entered into the model as fixed effects. This analysis will be reported in terms of an odds ratio and 95% confidence interval.

*Secondary Outcomes*

For the analysis of the scales, random effects linear regression will be utilised (with peer support worker as the random effect), controlling for the baseline value of the outcome, condition (psychosis versus no psychosis) and centre. These will be reported in terms of mean difference in outcome between the two randomised groups with associated 95% confidence intervals. For days in acute care, we will perform random effects linear regression analysis with the peer support worker being entered as a random effect. Centre will be entered into the model as a fixed effect. This analysis will be reported as coefficient and 95% confidence interval.

SIX, which will be analysed using random effects ordinal regression; odds ratios and 95% confidence intervals will be reported from this analysis.

Time to first readmission during the study period will be analysed using Cox regression frailty model. However, if the frailty model fails to converge, then Cox regression with robust standard errors will be used. The condition (psychosis versus no psychosis) and centre will be added as fixed effects.

*Supportive analyses*

Supportive analyses using analogous statistical methods to the primary analyses will be conducted on the primary outcome, adjusting for any marked differences in randomised groups in terms of demographic characteristics, service use in the year preceding entry to the study and scores on outcome measures; amount of improvement for both groups between baseline and follow-up; analyses of outcomes adjusting for non-compliant participants in the treatment group using a dichotomous variable compliant is defined as three or more meetings attended. Those in the treatment as usual group will be assigned to the same category as those who are non-compliant in the intervention group.

Participants attending fewer than three meetings with a peer support worker will be defined as non-compliant. Non-compliance will be examined using Complier Average Causal Effect (CACE) analysis. We will look at baseline predictors of attending fewer than three meetings using random effects logistic regression (those in the intervention group only).

Additional analyses of the primary outcome, which will include the randomisation variable are:

* Existing peer support versus not (SLaM and West London versus others)

*Process analysis*

The following descriptive information will be provided about the content of the intervention and the degree of match between the peer support workers and the participants. The following will be reported:

*Use of the recovery plan:*

a) From participant data at follow up: the proportion of participants in the treatment and control groups discussing or reading each of four sections of the recovery plan. A composite score of 0-4 will be reported for overall extent of awareness of the recovery plan, combining participants’ reports of whether they had looked at each section of the workbook.

b) From participant data at follow-up: the proportion of participants in the treatment and control groups making a written plan for each of four sections of the recovery plan. A composite score of 0-4 will be reported for overall extent of development of a written recovery plan by combining participants’ reports of whether they had looked at each section of the workbook.

*PSWs’ style*

The mean RPRS total and subscale scores and range of mean scores among PSWs will be reported.

Degree of match between PSW and participant

The proportion of participants who were matched with their PSW will be reported regarding:

a) Diagnosis

b) Experience of hospital admission (ever admitted yes/ no)

c) Gender

d) Ethnicity

e) Age

In the event of positive study outcomes, an exploratory regression analysis will be conducted to model the relationship of these process factors to study outcomes.

*18 month follow up analysis*

The scales will be analysed descriptively. Comparisons between randomised groups will be made using t-tests or non-parametric equivalents as appropriate. The questions related to the use of the recovery plan will be scored in a similar way to the data collected at four months and reported descriptively.

*Missing data*

It is not expected that there will be much missing data for the primary outcomes, as these data will come from the trust’s informatics department. There will only be missing data when it is known that the participant is no longer residing in the area. In this case, the date of last known contact with services and data up to that point will be collected and used in analyses where possible.

However, there may be missing data for other outcomes. All items within a scale may be missing, or individual items within a given scale may be missing. Some scales have recognised ways to impute missing items up to a given number of items; these have been noted with the relevant scales in the appendix of this document. The extent and patterns of missingness will be evaluated to determine whether it is associated with any of the outcomes. If variables are associated with missingness, these will be controlled for in complete case analysis to maintain the missing at random assumption.

*Participants who have more than one peer support worker during the intervention*

Participants in the intervention group are permitted to change peer support worker if they request it, have disengaged from peer support, the peer support worker became ill or left their post so that all participants in the intervention group are offered the full intervention package. As peer support workers form a cluster, statistical contingencies need to be in place for such occurrences. Therefore, one peer support worker will be designated the “main” based on the number of sessions with the participant.

**Part II: Economic Evaluation**

**Aim**

The aim of the economic evaluation is to calculate the probability that peer-provided self-management is cost-effective compared to control over (i) 18 months and (ii) 12 months for a range of values of willingness to pay for a quality adjusted life year (QALY) gained.

**Outcomes**

* Mental health service use (community and acute services) during 18 months follow up period
* EQ-5D at baseline and 4 months and 18 months

**Analyses**

All analyses will follow the assumptions made in Part I regarding missing data, loss to follow up and clustering. In line with the statistical analysis the primary economic evaluation will be a complete case analysis. Sensitivity analyses will be conducted accounting for loss to follow up and missing data as described below (Sensitivity Analyses).

*Cost of the intervention*

Information on peer support worker costs (salaries and oncosts) and time spent with patients on peer support will be used to calculate the average cost per patient of the peer-provided self-management intervention.

*Cost of 12 and 18 month mental health service use*

Acute and community mental health service use for the intervention and control groups will be collected from electronic patient records held by the mental health trust. These will be costed for each patient using unit costs from the most recent Unit Costs of Health and Social Care published by the Personal Social Services Research Unit7. Mean cost per patient for intervention and control groups will be reported by type of service use and at 12 and 18 months.

*QALYs*

We will calculate the mean cost per quality adjusted life year (QALY) gained of peer-provided self-management compared to control over18 months. QALYs will be calculated using the EQ-5D and the formula developed by Dolan and colleagues8. We will calculate the mean area under the curve for each group from baseline to 4 months and 18 months, controlling for any baseline differences using regression analysis. Confidence intervals will be constructed using non-parametric bootstrapping. A secondary analysis will calculate QALYs over 1 year, where we will assume both groups have a linear progress to their 18 month EQ-5D, unless they have had an acute readmission. Participants with an acute readmission between 4 and 12 months will have a QALY decrement attributed calculated using regression analysis and 4 month and 18 month patient data.

*Confidence intervals*

Confidence intervals for mean costs and QALYs will be calculated using non-parametric bootstrap with replacement.

*Incremental cost-effectiveness ratio (ICER)*

The mean costs and QALYs calculated above will be used to calculate the mean incremental cost per QALY gained of peer-provided self-management compared to control.

*Cost-effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC)*

The results of the non-parametric bootstrap will be presented on a CEP. A CEAC will also be constructed using the bootstrap data from a range of values of willingness to pay for a QALY gained. The probability that the peer-provided self-management is cost-effective compared to control at a willingness to pay for a QALY gained of £30,000 will be reported. CEACs will be reported for (i) 18 months and (ii) 12 months.

*Supportive Analyses*

The following sensitivity analyses will be conducted and the new ICER and CEAC reported:

* Cost-effectiveness complete case analysis at 4 months.
* Housing, employment and GP contacts are recorded at baseline and 4 months only. Two analyses will be conducted, one including employment and one excluding employment, using the 4 month data only for the 3 variables, each costed using PSSRU and assuming mean national values for wages.
* Accounting for missing data in line with the statistical analysis plan.
* Testing the impact of a range of assumptions about QALYs over the 4-18 month period.
* Different values for the QALY decrement as a result of an inpatient admission.
* Any sub-group analyses identified including the ICER for different levels of engagement with the peer-support worker in the intervention group, including CACE analysis.

If any key assumptions become apparent during the analysis these will also be tested for as part of the sensitivity analyses.

**References**

1 Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomised controlled trials. The CONSORT statement. JAMA 1996;276:637-639.

2 Moher D, Schulz KF, Altman DG, CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001;357:1191-1194.

3 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332

4 Randomisation and online databases for clinical trials 2013 <http://www.sealedenvelope.com/> accessed February 2013

5 EuroQol Group EuroQol: -a new facility for the measurement of health-related quality of life Health Policy 1990;16:199-208

6 StataCorp Stata Statistical Software: Release 14. 2015 College Station, TX: StataCorp LP

7 Curtis L (2013) Unit Costs of Health and Social Care 2012. Personal Social Service Research Unit, University of Kent, Canterbury.

8 Dolan P (1997). Modelling valuations for EuroQol health states. Med Care 35(11):1095-108.

**Appendix**

Further details on the outcome measures

**Primary Outcomes**

Readmission to acute care during the follow-up period (from the date of study entry). Data for this outcome will be obtained from the informatics department of the relevant Trusts. Those that do not have any data recorded will be assumed to not have any admissions. As these data do not rely on direct interaction with the participant by the study team, the data for this variable should be complete. This will be a dichotomous yes/ no variable. This is operationalised as readmission to any acute service – that is, inpatient ward, Crisis Resolution Team, crisis house or acute day centre. Some participants may have some days in acute care but no new admissions, if they were recruited before CRT discharge. If **acute\_study\_entry\_12**, **admis\_acute\_12**, **psych\_hosp\_12**, **crt\_12**, **acute\_day\_hosp\_12**, **crisis\_house\_12** in the 12 month patient records datasheet are all no, then no readmission to acute care.

**Secondary outcomes**

Days in acute care during one year follow-up (from the date of study entry) Data for this outcome will also be obtained from the informatics department of the relevant Trusts. Those that do not have any data recorded will be assumed to have spent no (0) days in hospital during follow up. As these data do not rely on direct interaction with the participant by the study team, the data for this variable should be complete. It is likely this outcome will be right skewed, that is many participants will have spent no or a small number of days in hospital, but some will have spent substantially longer in hospital. The possible range for this variable is from 0 to 365 for the main trial (as follow up is for a year).

Time to first readmission to acute care using the variable **days\_study\_entry\_acute\_12** from the 12 month patient records datasheet.

Any compulsory admission to hospital during follow-up period is operationalised using **detain\_mha\_12**.

*Satisfaction with services*

The Client Satisfaction Questionnaire (CSQ-8). This is an eight item questionnaire, with four possible answers given which participants have to circle one of them. Each question is scored from 1 to 4, with 1 indicating least satisfied and 4 indicating most satisfied. Individual item scores are summed to give an overall score between 8 and 32, with higher scores indicating greater satisfaction. It is expected that this measure will have a mean score slightly above the midpoint, although normally distributed. The usual practice with regard to missing items on the CSQ-8 is to impute pro rata a maximum of two items using the mean of the other items.

*Atkisson C, Zwick R The Client Satisfaction Questionnaire: Psychometric Properties and Correlations with Service Utilisation and Psychotherapy Outcome. Evaluation and Programme Planning 1982;5:233-237.*

Time to first readmission to acute care. Data will be obtained from the informatics department of the relevant Trusts. Participants that do not have any records of an acute admission in the relevant time window will be assumed not to have had any. This will be censored at 12 months from baseline or death if readmission has not occurred before that time (date of death will be known). As these data do not rely on direct interaction with the participant by the study team, the data for this variable should be complete.

*Self-rated recovery*

Illness Management and Recovery Scale - patient version (IMR). This is a 15 item questionnaire, each item has five forced responses with the exception of question 13 “How often do you take your medication as prescribed?”, which has an additional tick box to indicate that no psychiatric medication has been prescribed. The responses are scored from 1 to 5 with 1 indicating little sign of recovery and 5 indicating good signs of recovery. Responses are summed, so that the scale ranges between 15 and 75.

*Mueser K, Gingerich S, Illness Management and Recovery (IMR) scales. In Campbell-Orde, T et al eds. Measuring the promise: a compendium of recovery measures Volume 2. Human Services Research Institute, Cambridge Mass; 2005.*

A Questionnaire on the Process of Recovery (QPR). This consists of 22 items, with likert scale responses ranging from “strongly disagree” (scored 0) to “strongly agree” (scored 4); with the total measure ranging between 0 and 88, with higher scores indicating a more positive outlook and being further along the recovery process.

*Neil S, Kilbride M, Pitt L, Welford M, Nothard S, Sellwood W, Morrison A The Questionnaire about the Process of Recovery (QPR): a measure developed in collaboration with service users Psychosis 2009;1:145-155*

*Social Outcomes*

Social Outcomes Index (SIX). This is a brief, four-question index rating employment, accommodation and living situation on a scale of 0-6.

*Priebe S, Watzke S, Hansson L, Burns T Objective social outcomes index (SIX): a method to summarise objective indicators of social outcomes in mental health care. Acta Psychiat Scand 2008, 118:57–63.*

UCLA Loneliness Scale (ULS-8). This consists of an eight-item, self-report questionnaire which is responded to using a four-point likert scale which is scored 1 for “never” and 4 for “always”, giving a total range of 8 to 32.

*Hays RD, DiMatteo MR (1987). A short-form measure of loneliness. Journal of Personality Assessment, 51,69–81.*

Lubben Social Network Scale (LSNS-6). This is a six-item, self-reported scale measuring the level of perceived support received from family and friends. Each item is scored on a scale from 0 for “none” to 5 for “nine or more”, giving a range of 0-30.

*Lubben J, Blozik E, Gillmann G, Iliffe S, von Renteln Kruse W, Beck JC, Stuck AE. Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations. Gerontology 46(4) 503-13*

Health and Lifestyles Survey Social Capital Questionnaire. This is a six-point questionnaire designed to assess the social capital of the respondent’s neighbourhood. Each question can be answered “yes”, “no”, or “don’t know”. Answers of “yes” score 1 point; answers of “don’t know” or missing data score 0; answers of “no” score -1, giving a range of -6 to +6 for total score.

*Health Education Authority Health and Lifestyles: a survey of the UK Population – Part 1 London, Health education Authority 1995*

Employment status. This will be operationalised as the first question from SIX, which asks “Are you currently employed?” with response options of; 0 = No; 1 = in voluntary, protected or sheltered work; 2 = in regular employment. This will be dichotomised to not employed versus in voluntary, protected, sheltered or regular employment.

*Symptoms*

Expanded Brief Psychiatric Rating Scale (BPRS-E). This consists of 24 symptom constructs which are responded to using a seven point likert scale which is scored 1 for “not present” and 7 for “extremely severe”, giving a total range of 24 to 168. There is also a “not assessed” option if any of the symptom constructs could not be assessed from the interview for an individual participant.

*Lukoff D, Nuechterlein KH, Ventura J Manual for the Expanded Brief Psychiatric Rating Scale**Schizophrenia Bulletin 1986;13:261–276*

*Overall K, Gorham D The Brief Psychiatric Rating Scale. Psychological Reports 1962;10:799-812.*

*Relationship with service provider*

Recovery promoting relationships scale *(*RPRS) is a 24-item measure of patient-rated relationship with a service provider. Items are rated on a four point scale, providing a total score of 24-96. Subscale scores may be generated for general therapeutic alliance (items 5, 10, 13, 16, 17, 18, 21 and 24) and specific recovery orientation (other items).

*Russinova Z, Rogers S, Cook K, Ellison M, Lyass A (2013) Conceptualization and measurement of mental health providers' recovery-promoting competence: the recovery promoting relationships scale (RPRS) Psychiatric Rehabilitation Journal 36(1) pp7-14*

*Health related quality of life*

EQ-5D consists of 5 domains each with 3 levels, no problems, moderate problems and severe problems, scored 1-3 for each domain, 1 being no problems. The questionnaire is converted to a utility score, where 1 is perfect health, 0 is death and negative scores are for states worse than death, using the algorithm from Dolan (1997).

*EuroQol Group EuroQol: a new facility for the measurement of health-related quality of life Health Policy 1990;16:199-208*

*Dolan P (1997). Modelling valuations for EuroQol health states. Med Care 35(11):1095-108.*

*Resilience*

Connor-Davidson Resilience Scale (CD-RISC-10) is a 10 item measure where each item is scored 0 (not true at all) to 4 (true nearly all the time). These are summed to give a score ranging from 0 to 40.

*Campbell-Sills L, Stein MB Psychometric analysis and refinement of the Connor–Davidson Resilience Scale (CD-RISC): validation of a 10-item measure of resilience Journal of Traumatic Stress, 2007; 20:1019–1028*