Statistical Analysis Plan

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Version history

Version	Version date	Changes
1.0	2014.03.31	See Section 12
2.0	2014.04.22	

1. Introduction

Preface

This document was prepared by Maria Vazquez-Montes (Senior Statistician (Methodologist), NIHR Oxford BRC Research Fellow, Nuffield Department of Primary Health Care Sciences) in collaboration with Constantinos Koshiaris (Medical Statistician, Nuffield Department of Primary Health Care Sciences). The content will be discussed with Prof. Tom Burns, Chief Investigator; Jorun Rugkåsa and Ksenija Yeeles, Trial Managers; and Tanya Smith, Data Manager. Maria, Tom, Jorun, Ksenija and Tanya will review and sign off the final version of this Statistical Analysis Plan (SAP). Constantinos will be responsible for implementing the SAP. Any decisions that need to be made during the analysis will be discussed with Jason Oke, Constantinos' line manager.

Purpose and scope of the plan

This document was prepared as a continuation of the Statistical Analysis Plan for the Oxford Community Treatment Order Evaluation Trial (OCTET) (SAP v.4 2012.06.29). As such, it follows the same principles stated in Section 1.2 of the SAP v.4 2012.06.29. It covers the analyses for the trial's follow-up study (OCTET follow-up study) i.e. the evaluation of disengagement and readmission in the 36 month period following randomisation.

This statistical analysis plan will be available on request when the principal papers are submitted for publication in a journal.

Changes from planned analysis in the protocol

The proposed analyses for OCTET Follow-up Study are described in the NIHR grant application form RP-PG-0606-1006. This SAP presents the analyses in more detail following the principles and amendments indicated in the SAP v.4 2012.06.29. In particular, the types of statistical models or tests performed have been changed for more sophisticated adjusted regression models to be used as the primary comparisons with the simpler unadjusted tests used for secondary sensitivity analyses. The adjustment will be done for the variables used in the stratified block design method of randomisation. No minimisation process took place.

All analyses will be done over the entire 36-month follow-up period from randomisation (i.e. from INDEX to 1095 days) and are not limited to the 24 months after the OCTET RCT ended as the RP-PG-0606-1006 form indicates.

Given that OCTET showed no difference between the two randomisation arms for most outcomes,[15, 93] we have changed the primary objective for the OCTET Follow-up Study to investigate the association of compulsion and disengagement for the whole sample as a primary objective, and investigating the effect of randomisation arm as a secondary objective. The aims and objectives indicated in the NIHR grant application form RP-PG-0606-1006 and discussions previous to the preparation of this SAP, the analyses will be divided into the following four categories:

Primary analysis: To investigate the association of compulsion and levels of disengagement;
Secondary analysis: To investigate the effect of randomisation arm on levels of disengagement and readmission rate;
Tertiary analysis: To investigate the association of compulsion and readmission to hospital;
Exploratory analysis: To investigate the differential impact of baseline characteristics on the effect of duration of compulsion on discontinuity of care.

2. Trial overview

Trial summary

The purpose of Community Treatment Orders (CTOs) is to ensure a period of improved mental health that optimally leads to subsequent voluntary engagement and treatment concordance. OCTET tests the effectiveness of CTOs using readmission to hospital over 12 months as the primary outcome. Further details and results from the trial can be found in Burns and colleagues' paper.[15]

Serious concerns have repeatedly been expressed that a potential increase in coercion due to the use of CTOs (particularly if it is excessively prolonged) might lead to greater disengagement from services. The OCTET trial provides a unique randomised

sample that can be used to measure the long-term effects of CTOs on disengagement and clinical outcomes.

OCTET Follow-up Study adds a fourth time-point in order to collect data over 24 additional months from the end of the initial 12 months follow up. The aim is to investigate the effect of compulsion on disengagement (or poor continuity of care (CoC)) in the 36 month period following randomisation. OCTET Follow-up Study also aims to compare disengagement and readmission data between the two trial arms. This will establish whether, in the long term, there is a difference in rates and duration of readmission between patients who have had a period on CTO compared with those in the control arm and whether, in the long term, there is a difference in the engagement with services and in service use between patients in the two arms.

Study objectives

Primary objective: Association between compulsion and disengagement

To test the hypothesis that longer time under compulsion increases disengagement from mental health services.

Secondary objectives: Comparison of randomisation arms

To test the hypothesis that compared to leave, the use of CTOs in patients with psychosis and a history of compulsory admissions will result in:

1) an increased disengagement;
2) a reduction in readmissions to hospital;

at 36-month follow up.

Tertiary objectives: Association between hospitalisation and duration of compulsion

To test the hypotheses that patients with any period under compulsion (e.g. Section 2, 3, 4, 136, 37, CTO and 40/48 of the Mental Health Act) will have

1) a reduced hospitalisation rate;
2) a longer time to readmission;
3) and a shorter duration of admissions

compared to those with no period under compulsion.

Exploratory analysis

Sub-group analysis

To use subgroup analysis to identify the baseline characteristics of patients which are associated with a differential effect of duration of compulsion on discontinuity of care.

Outcome measures

Primary outcome

The primary outcome is level of disengagement during the 36-month follow-up period, from index leave date (date when initially left hospital after randomisation) to 1095 days. A patient will be considered as disengaged if he/she had no contact with services for 90 days or more. Patients who reengaged after this absence period will not be counted as disengaged.

Two variables will be used to measure the level of disengagement:

a**) Time to disengagement** – number of days from index leave date to the last contact, when the last contact occurred at least 90 days (3 months) before the end of the follow-up period (i.e. T4 date). This is a continuous variable expected to be skewed. Data will be censored for patients discharged or lost to follow-up.

b) Discontinuity of treatment over time - number of time periods of 60 days or more in community care without a contact with services. This is a continuous variable expected to be skewed. Time in community care will be measured only for periods at risk (i.e. hospitalisation periods will be excluded) as follows.

Time in community: a) Subtract time in hospital from time between index leave date and end of study (36 months) or time when patient was lost to follow-up.

b) A period of 3 months or more with no hospitalisations and no contact with services will indicate that the patient disengaged and data will be censored up to the last contact.

According to the primary objective, level of disengagement will be compared to duration of compulsion. This variable is defined as follows.

Duration of compulsion - number of days under any legal compulsion (e.g. Section 2, 3, 4, 136, 37, CTO, and 40/48 of the Mental Health Act) during the 36-month follow-up period, which includes time under initial Section 3 between index and first change of legal status.

- This variable will include inpatient and outpatient compulsion times (i.e. total duration of periods when patient is in hospital under section (e.g. Section 2, 3, 4, 136, 37, 40/48) or in the community (under CTO)).
- Time under 'voluntary' status is not included in this variable.

Secondary outcomes

Readmission to hospital - Psychiatric hospitalisation in the 36-month follow-up period is defined as the binary outcome:

1 = Patient readmitted to hospital during the study period;

0 = Patient never readmitted.

A hospitalisation episode will be defined as the period between the patient's readmission date and the date on which the patient leaves hospital, which should include at least one overnight stay. Hospitalisations can be either voluntary or involuntary.

Recall to hospital of a patient on CTOs will not be classified as readmission (it will be understood as part of the treatment regime). If a recall ends in the CTO being revoked, this will be calculated as a readmission from the date of recall.

Any patient who was never initially discharged from hospital after randomisation and remained hospitalised for 1095 days after randomisation will be defined as readmitted.

Other variables related to readmission to hospital are:

Number of nights in psychiatric hospitalization from INDEX LEAVE DATE to 1095 days - This will include voluntary and involuntary

hospitalizations. Nights on recall will not be included unless the recall ends in revocation.

Number of nights to first readmission from INDEX LEAVE DATE to 1095 days - For patients (in both arms) that remained in hospital for the duration of the trial time to first readmission will be counted as zero. Nights on recall do not count as a readmission unless revoked.

Number of readmissions from INDEX LEAVE DATE to 1095 days - This will include voluntary and involuntary hospitalisations but not recalls that did not end in revocation.

Tertiary outcomes

a) Duration of compulsion will be defined as in Section 2.3.1;
b) Hospitalisation rate will be given as the proportion of patients readmitted to hospital, according to the constraints stated in Section 2.3.2;
c) Time to readmission is given by the variable "**Number of nights to first readmission from INDEX LEAVE DATE to 1095 days**" defined in Section 2.3.2;
d) Duration of readmissions is given by the variable "**Number of nights in psychiatric hospitalization from INDEX LEAVE DATE to 1095**" defined in Section 2.3.2.

3. Study methods

Overall study design and plan

The OCTET study was a randomised, parallel arm, non-blinded study of the effect on hospital readmissions for psychiatric treatment of discharge on CTO versus discharge on non-CTO. The target for randomisation was 330 patients. The first randomisation took place on 10 November 2008 and the last on 22 February 2011. Follow up continued until 22 February 2014.

Target population

Inclusion criteria

Patients were eligible if they were:

- Aged 18-65 years (in line with local administrative procedures for adult mental health services);
- Diagnosed with psychosis;
- Currently admitted under section 3 or section 37 (without restrictions) of the MHA;
- Not currently subject to any other legal restrictions;
- Judged by their clinicians (RC and AMHP) to need ongoing community treatment, but, having considered the relevant legal standards and clinical indicators, clinicians are genuinely uncertain as to which treatment mechanism would be appropriate;
- Able to consent to take part in research and give written and informed consent;
- Not having participated in the study (i.e. people with multiple admissions throughout the recruitment period should only participate in the study once).

Exclusion criteria

Patients were not eligible if they were:

- Unable to give informed consent (e.g. advanced dementia or mental disorder too severe to give informed consent);
- Subject to incompatible legal restrictions on treatment;
- Considered by their clinicians to be clear candidates for either a CTO or leave;
- Considered to be clear candidates for immediate discharge to voluntary treatment.

Method of treatment assignment and randomisation

Randomisation was a stratified block design, with a 1:1 allocation ratio and stratification factors gender (male/female), schizophrenic status (yes/no), and duration of illness (< 2yrs, ≥ 2yrs). Sequence assignment was unknown to all active members of the trial team until recruitment and data collection were completed. Participants were assumed to remain in their trial arm during the 36-month follow up period.

Treatment masking

Treatment masking was ensured through the use of sealed envelopes stored and opened by an independent researcher after consent and baseline interview took place, and participant's trial number and randomisation date properly recorded.

Sample size determination

Sample size calculation was performed based on readmission rate as explained in the SAP v.4 2012.06.29.

4. Data collection

All data for OCTET Follow-up Study were collected from medical records.

Timing of data collection

Recruitment took place from 10 November 2008 to 22 February 2011. Follow-up data for OCTET were collected at 6 months and 12 months after randomisation. Data collection from medical records for OCTET Follow-up Study continued until 22 February 2014.

Database

Description

Data were collected by research assistants from medical records. Data for the first 60 participants were collected on paper forms and entered into ACCESS database. Data for all other participants were collected directly into ACCESS database on laptops and later uploaded and merged to a master ACCESS database.

Data quality

Data collected on paper forms were double entered by different researchers. Double entered data will be compared against each other and discrepancies will be discussed and corrected by the research assistants, supervised by KY. Data entered directly into Access database will be cleaned in Excel by the data manger (TS) with support of the research assistants.

CK, the statistician responsible for conducting the analysis, will perform additional data quality evaluations. These include range checks, logical and consistency checks which may not be picked up by checks at the individual patient level by the research staff that collected and entered the data. In the case of variables that are function of

other variables (e.g. length of a particular hospitalisation), these will be checked by automatic calculation of its values.

Database freeze

The final cleaned data will be frozen before we start analysing the data.

5. General issues for statistical analysis

Blinding of the statistical analysis

The consultant statistician (Jason Oke) will remain blind to the treatment allocation until data are locked and final data analysis is to be conducted.

Analysis populations

Intent-to-treat population

The Intention-to-treat population will include all randomised patients. Data from crossovers, drop-outs, or patients who never received the intervention assigned will be analysed according to their randomised group.

There were three withdrawals during the OCTET study: one was already on CTO, one self-withdrew, and one had been spending a long time (one month or longer before randomisation) on Section 17 at time of randomisation. All available data from these patients will be included in analyses.

There will be no per-protocol population as the trial was designed in a pragmatic way in which it was necessary that treating clinicians could change the legal status of the participant after their enrolment in the trial, if this was clinically appropriate in the opinion of the clinician at the time.

Major protocol violations

Potential protocol violations:

- Discharge from section 3 on the wrong arm (no matter when patients leave hospital).
- Patient never left hospital
- Patient withdrawn.

- Patient not eligible. Possible reasons:
    - Patient not eligible for CTO.
    - Patient already on CTO.
    - Patient not fulfilling inclusion/exclusion criteria.
    - Patient too long on Sec 17 (one month or longer before randomisation).

Identified protocol violations:

- One patient self-withdrew – Withdrew before T1 interview was completed.
- One patient had been on Section 17 for over a month before randomisation – T1 CRF is still available.
- One patient was already on a CTO – T1 CRF is still available.

Methods for handling missing data

As an intention-to-treat analysis will be performed, data from all randomised patients will be included. As data for OCTET Follow-up Study is collected directly from medical records, any missing values are expected to occur completely at random. Analysis of data missing completely at random returns unbiased estimates, thus no imputation method will be used in the main analysis.

Method for handling centre effect

Sub-group analysis comparing London versus other sites will be performed for the primary and secondary outcomes.

Method for handling randomisation, stratification or minimisation factors

Stratification variables (gender (male/female), schizophrenia status (yes/no), and duration of illness (< 2yrs, ≥ 2yrs)) will be adjusted for in the main analyses.

Multiple comparisons and multiplicity

Comparisons will be carried out between the two randomisation arms, between patients with any versus no compulsion, and between patients with any vs no disengagement. Multiplicity of secondary outcomes will be managed by conservative reporting and interpretation of results. There will be no adjustment of p-values.

Method for handling time-varying interventions

Similar to the analysis for the OCTET study, sensitivity analyses adjusting for number of recalls will be performed when analysing readmission to hospital variables (secondary and tertiary objectives).

Method for handling outliers

Potential outliers will be identified by the use of graphical methods. Any values that are too large or too small will be checked by reviewing the relevant patient's data. If the value is correct, a sensitivity analysis will be performed excluding it from the analysis to evaluate its effect on the outcome.

Derived and computed variables

Contact with services will be obtained by examining patients' notes and medical records. The total number of contacts with carers of any profession will be calculated.

The following variables will be automatically calculated by CK and TS separately and compared previous to locking the dataset by comparing readmission and discharge dates from index leave date to 1095 days:

- Number of nights to readmission;
- Total number of nights in hospital (readmissions only);
- Total number of involuntary readmissions. A readmission will be considered involuntary if the patient was hospitalised under the MHA Sections 2,3,4,136,37 and 40/48 or there is at least one change of legal status to "involuntary" between the readmission and readmission discharge dates;
- Total number of voluntary readmissions;
- Total number of CTO recalls;
- Total number of periods of 60 days or more in community care without contact with service;
- Total time in community care;
- Patients disengaged;
- Disengagement date;
- Duration of compulsion.

Planned sub-groups

Sub-group analysis for baseline socio-demographic characteristics will be performed only for primary outcome, using discontinuity of care as a measure of disengagement. The subgroups to be tested are as follows:

- Age: ≤ 40 years *vs.* > 40 years;
- Gender: male *vs.* female;
- Ethnicity: white *vs.* others;
- Born in UK: born in UK *vs.* born in another country;
- Marital status: (single + separated/divorced) *vs.* married/co-habiting;
- Accommodation: independent *vs.* (supported + homeless);
- Living status: living alone (living alone +homeless + living in supported housing) *vs.* living with others (living with partners/family + with others e.g. friends);
- Diagnosis: schizophrenia *vs.* other;
- Duration of illness: <2 years *vs.* ≥2years;
- Educational level: ≤12 years *vs.* > 12 years; Tertiary education y/n;
- Scales:
    - BPRS: ≤ 33 *vs.* > 33;
    - GAF: ≤ 49 *vs.* > 49.

Centre effect will be evaluated through a sub-group analysis for both primary and secondary outcomes. The sub-groups will be defined by the variable:

- Centre (London vs. other sites).

6. Descriptive analysis

Participant flow

Participant flow will be summarized in a CONSORT diagram.

Description of interventions received during the 36-month follow up

For CTOs, the number of recalls and their duration will be summarized. For both trial arms and for the whole sample, the time from index leave date and subsequent occurrences will be summarized according to:

READMISSIONS

For total sample:

- Number of readmitted patients;
- Number of nights in hospital (readmissions only).

For those who were readmitted:

- Number of readmissions;
- Number of nights in hospital (readmissions only).

For all readmissions (not per patient):

- Number of voluntary readmissions
- Number of involuntary readmissions;
- Number of initially voluntary readmissions turned to involuntary.

OTHER INTERVENTIONS RECEIVED

- Total number of tribunal hearings (MHRT);
- Total number of Managers Hearings;
- Number of recalls;
- For all recalls, distribution of their outcomes (i.e. revocation, discharge or back to CTO);
- Total number of CTOs for the total sample (not per patient);
- Average duration of CTOs for two groups of CTOs (First we will calculate number of days between start and end date of each CTO episode. For each episode of CTO we will record whether it was completed during the study period (CTO end date is before T4 date) or it was an on-going CTO at T4 time point. This will enable us to divide all CTO episodes to two groups: 'CTOs completed during the OCTET Follow-up Study period' and 'on-going CTOs at the end of the OCTET Follow-up Study period'. Average duration (number of days) for each group of CTOs will be calculated);

- Number of people who never left hospital during the trial period;
- Average number of service contacts per month received in the community;
- Time under legal compulsion.

Baseline comparability of randomised groups

The baseline comparability of the two randomised groups was assessed in OCTET study. No differences were found.[15]

Comparison of losses to follow-up

As the main outcomes relate to contact with service and hospital admissions data obtained from medical records, it is not expected that there will be any missing data for these outcomes, apart from those occurring completely at random.

Tabulation of protocol violations

No further protocol violations are expected. If any are found, besides those analysed in the OCTET study, protocol violations will be tabulated by trial arm and overall.

7. Interim analysis and safety monitoring analyses

No interim analyses or safety monitoring analyses were conducted for the 24-month follow up period of the OCTET Follow-up Study.

8. Analysis of primary outcome

Descriptive statistics for outcome measure

For both the variables that measure the primary outcome, 'time to disengagement' and 'discontinuity of treatment over time', we will report the number and percentage of observed values, mean and standard deviation, median and inter-quartile range, and range, by arm and full sample.

Primary analysis

'Time to disengagement' is a time to event outcome and analysis will be performed using a proportional hazards model adjusting for duration of compulsion and stratification factors (gender (male/female), schizophrenia (yes/no), and duration of

illness (<2yrs, >2yrs)) with results presented as hazard ratios with 95% confidence intervals. Kaplan Meier plots will also be presented and the median time to disengagement calculated with 95% confidence intervals.

'Discontinuity of treatment over time' is a count outcome and will be analysed using Poisson or negative-binomial regression models depending on data dispersion and adjusting for duration of compulsion and stratification factors. Results will be presented as incident-density ratios, which are interpreted in the same way as relative risks.

The primary analysis will be conducted on the total sample (not splitting it by trial arm).

Other analysis supporting the primary (including sensitivity analyses)

A sensitivity analysis will be conducted for the variables measuring the primary outcome which will consist of repeating the above analyses without adjusting for the stratification factors.

9. Analysis of secondary outcomes

Descriptive statistics for outcome measures

For all secondary outcomes, we will report the number and percentage of observed values, mean and standard deviation, median and inter-quartile range, and range, by arm and full sample.

Secondary analysis

Secondary analyses will be conducted using the ITT population. No adjustment for missing data will be performed when analysing these outcomes as no missing data is expected for them.

Secondary outcomes will be analysed in the same way as primary outcomes using multiple regression models with adjustment for stratification factors. The type of regression model will depend on the data distribution. All model assumptions will be assessed.

The comparison of time to disengagement between trial arms will be achieved fitting the same proportional hazards model as in the primary analysis adding trial arm as explicative variable. The coefficient (and corresponding 95% confidence interval and 2-sided p-value) of the latter variable will be the parameter of interest interpreted as a hazard ratio.

Similarly, the model used in the primary analysis for discontinuity of treatment will be adjusted for trial arm, reporting its coefficient (and 95% confidence interval and 2-sided p-value) interpreted as an incident-density ratio.

The binary secondary outcome of psychiatric hospital readmission in the 36-month follow up period will be analysed using log-binomial regression adjusted for the trial arm indicator and stratification factors (gender (male/female), schizophrenia (yes/no), and duration of illness (<2yrs, >2yrs)). Results will be presented as the relative risk of readmission under CTO compared to non-CTO, with appropriate 95% confidence interval and 2-sided p-values. If log-binomial modelling is not possible due to model instability then other alternatives will be explored such as Poisson regression with robust error variances[199] a method which has the advantage of presenting results as relative risks; or logistic regression with associated odds ratios.

Number of readmissions and number of nights in psychiatric hospital are count outcomes and will be analysed using Poisson or negative-binomial regression models depending on data dispersion and adjusting for trial arm indicator and stratification factors. Results will be presented as incident-density ratios.

The number of nights to first readmission from INDEX LEAVE DATE to 1095 days is a time to event outcome and analysis will be performed using proportional hazards model adjusting for the trial arm indicator and stratification factors, with results presented as hazard ratios with 95% confidence intervals. Kaplan Meier plots will be presented and the median time to readmission calculated with 95% confidence intervals.

10. Analysis of tertiary outcomes

Descriptive statistics for outcome measures

For all tertiary outcomes, we will report the number and percentage of observed values, mean and standard deviation, median and inter-quartile range, and range, by duration of compulsion group (i.e. any compulsion *vs.* no compulsion). Descriptive statistics for the full sample for these variables have been included as part of the analysis of secondary outcomes.

Tertiary analysis

Tertiary analyses will be conducted using the ITT population once again. No adjustment for missing data will be performed when analysing these outcomes as no missing data is expected for them.

The association of compulsion and psychiatric hospitalisation in the 36-month follow up period will be analysed using a log-binomial regression for psychiatric hospitalisation adjusted for duration of compulsion and stratification factors. Results will be presented as the relative risk of readmission for patients with any compulsion compared to those with no compulsion, with appropriate 95% confidence interval and 2-sided p-values. Once again, if log-binomial modelling is not possible due to model instability then other alternatives will be explored such as Poisson regression with robust error variances.[199]

As before, the analysis for number of nights to first readmission from INDEX LEAVE DATE to 1095 days will be performed using a proportional hazards model adjusting for duration of compulsion and stratification factors, with results presented as hazards ratios with 95% confidence intervals. Kaplan Meier plots will also be presented and the median time to readmission calculated with 95% confidence intervals.

Similarly, duration of admissions will be analysed using Poisson or negative-binomial regression models depending on data dispersion and adjusting for duration of compulsion and stratification factors. Results will be presented as incident-density ratios.

11. Analysis of exploratory objectives

Sub-group analysis

Sub-group analyses will be conducted for the primary endpoint to test the hypothesis that the levels of disengagement (two variables: time to disengagement and discontinuity of treatment over time) differed according to factors measured at baseline. The subgroup analysis will involve fitting the same model as for the primary outcome (Section 8.2) with the inclusion of an additional interaction effect for the interaction between duration of compulsion and the relevant subgroup variable. The p-value for the interaction test will be the p-value of interest as this is the test of the stated hypothesis. The significance of compulsion variable will not be considered of interest.

Centre effect will be evaluated through a similar subgroup analysis for both primary and secondary outcomes.

12. Amendments to version 1.0

1) Index date was changed to be Index Leave Date (date when the patient left hospital following randomisation) in relevant variables.
2) The effect of Metropolitan vs. non-Metropolitan sites will not be analysed (only London vs. other sites).
3) Four category ethnicity variable (white *vs.* black *vs.* Asian *vs.* other) and Type of service were excluded from Sub-group Analysis.

Characteristics of the readmission sub-sample, recall outcomes, and CTO duration were added to the list of intervention characteristics to be described.