Oxfordshire and Buckinghamshire Mental Health NHS

Oxford Community Treatment Order Evaluation Trial

Statistical Analysis Plan

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Version history

Version	Version date	Changes
1.0	2012.03.04	Design used clarified (stratified block design and not minimisation design). No information on discipline of clinical supervisor will be available thus the analysis to test its effect was excluded.
2.0	2012.04.30	Tertiary objectives specified
3.0	2012.05.25	Subgroup analysis described. Statistical methods edited.
4.0	2012.06.29	Schedule of procedures and Consort diagram inserted. Bibliographic referenced reviewed.

1. Introduction

1.1 Preface

This document was prepared by Maria Vazquez-Montes (Statistician) in collaboration with Merryn Voysey (Medical Statistician at the Centre for Statistics in Medicine, CSM). The content will be discussed with Professor Tom Burns, Chief Investigator, Jorun Rugkåsa, Trial Manager, and Ksenija Yeeles, Data manager. Merryn, Tom, Jorun, and Ksenija will review and sign off the final version of this Statistical Analysis Plan (SAP). Maria will be responsible of implementing the SAP. Ksenija will be responsible of calculating total scores of the different instruments assessed in the RCT (described in Section 4). Any decisions that need to be made during the analysis will be discussed with Merryn.

1.2 Purpose and scope of the plan

This document was prepared following the Primary Care Clinical Trial Unit (PC-CTU) Statistical Analysis Plan template (ref. TEMST01-A; version 1.0), which is based on ICH Topic E9 Statistical Principles for Clinical Trials, Step5, September1998; ICH Topic E3 Structure and content of Clinical Study Reports, July 1996; and PSI Guidelines for Standard operating procedures for good statistical practice in clinical research, version 6, 2000. It details the proposed analysis of primary, secondary and exploratory objectives for the Oxford Community Treatment Order Evaluation Trial (OCTET). Most of its content is derived from the OCTET Protocol Version 6.[92] Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The statistical analysis plan will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged. Any deviations from the statistical analysis plan

will be described and justified in the final report of the trial. The analysis of health economic data is not included in the scope of this document.

1.3 Changes from planned analysis in the protocol

The analyses detailed within this document are in line with the spirit of the analyses detailed in the protocol however changes have been made to the types of statistical models or tests performed to allow for more sophisticated adjusted regression models to be used as the primary comparisons with the simpler unadjusted tests used for secondary sensitivity analyses. Adjusted regression models have more statistical power (are more precise) than unadjusted tests such as t-tests and thus make better use of the data collected.

The protocol makes reference to minimisation factors. However no minimisation procedure was carried out during treatment assignment. Instead a stratified block design was used.

Tertiary outcomes were specified. In particular, satisfaction with service is now being considered a tertiary outcome instead of a secondary outcome.

Analysis excluded:
There will be no analysis of the effect of discipline of clinical supervisor in readmissions as information on this outcome was not available.

2. Trial overview

Trial summary

Different forms of compulsory supervision and treatment of outpatients with severe mental illness have developed internationally in the wake of widespread deinstitutionalisation. Community Treatment Orders (CTOs) for patients with psychiatric illness became available in 2008 as a treatment option in England and Wales under the amended Mental Health Act 2007. There is no convincing experimental evidence for the efficacy of compulsory outpatient treatment, so current clinical guidance and decision making is not based on firm evidence. Section 17 Leave remains a lawful option for supervision of patients in the community. OCTET

aims to demonstrate whether CTOs reduce readmissions to hospital in patients compared with patients not subject to CTOs.

Study objectives

Primary objective

To test the hypothesis that the use of CTOs in patients with psychosis and a history of compulsory admissions will result in a reduction in readmissions to hospital compared to treatment on leave.

Secondary objectives

To investigate whether the use of CTOs in patients with psychosis and a history of compulsory admissions, compared to leave, will improve treatment adherence with a consequent reduction in relapse and readmission rates and improvement in social stability.

Exploratory objectives

Sub-group analysis

To identify the baseline characteristics of patients which are associated with differential treatment effect in subgroup analyses.

Readmission predictors

To examine the factors (other than treatment group) associated with readmission.

Mediation analysis

To explore the effect on readmission of process variables such as rate of contact and type of contact (i.e face-to-face vs. telephone contact).

Outcome measures

Primary outcome

The primary outcome measure is: psychiatric hospitalisation in the 12-month follow-up period (i.e. from INDEX to 365 days). This is a binary outcome: 1=Patient readmitted at all; 0=Patient never readmitted. A hospitalisation will be defined as the period between the patient's admission 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. Any patient who was never initially discharged from hospital after randomisation and remained hospitalised for 365 days after randomisation will be counted as a readmission.

Secondary outcomes

Secondary outcomes related to readmission follow the same readmission definition and constraints stated for the primary outcome. Secondary outcomes considered in this study are mainly obtained from medical records. They represent patterns of readmission and are listed next.

Number of nights in psychiatric hospitalization from INDEX to 365 days. This will include voluntary and involuntary hospitalizations. Nights on recall will not be included.

Number of nights to first readmission from INDEX to 365 days. Time to first readmission for patients (in both arms) that remained in hospital for the duration of the trial will be counted as zero. Nights on recall do not count as a readmission.

Number of readmissions from INDEX to 365 days. This will include voluntary and involuntary hospitalisations but not nights on recalls.

Time under legal compulsion. This will be measured by time being subject to the Mental Health Act (i.e. under sections 2, 3, 17, 37 or on a CTO).

Tertiary outcomes

Tertiary outcomes considered in this study are mainly self-reported patient outcomes. These are:

Adherence to treatment. This will be obtained from two self-reported variables recording how often, over the past month, the patient

- took his/her prescribed medication
- attended his/her planned appointment.

Satisfaction with service. This will be measured through the Client Satisfaction Questionnaire (CSQ-8) total score and Scale to Assess Therapeutic Relationships – Participant Version (STAR-P).

Social and clinical outcomes. These will be measured by the following instruments

- Brief Psychiatric Rating Scale (BPRS-24)
- Global Assessment of Functioning (GAF)
- Substance misuse history (CAGE)
- Health Related Quality of Life (EQ-5D)
- Insight and Treatment Attitudes Questionnaire (ITAQ)
- Drug Attitude Inventory (DAI-10)
- Psychiatry Autonomy Preference Index (API).

Service usage. This will be measured by the Client Service Receipt Inventory (CSRI).

Patient rated experiences of pressure. This will be measured by

- Mac Arthur Admission Experience Survey (AES)
- Index of fairness
- Index of effectiveness
- Experience of specific types of leverage questions.
- Types of pressure.

Safety outcomes

Safety outcomes include those self-reported items under Section 4 (Crime) of the CRF. These data, collected at 180 and 365 days, record whether the patient, in the previous six months,

- has been the victim of a non-violent crime;
- has been the victim of violent crime;
- has been self-harming;
- have harmed others

and if so how many times. Additional safety outcomes will include death and cause of death.

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 section 17 leave. The target for randomisation was 330 patients. The first randomisation took place on 10 November 2008 and the last on 22 February 2011.

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 sequence assignment was unknown to all active members of the trial team until recruitment and data collection were completed. Eligible participants have an equal probability of assignment to each arm of the trial and the allocation ratio is 1:1. Participants are randomised individually to either CTO or Section 17 by an independent researcher using block randomisation with stratification factors for gender (male/female), schizophrenic status (yes/no), and duration of illness (< 2yrs, ≥ 2yrs). The randomisation code was developed using a computer random number generator to select random permuted blocks. The block lengths were 2, 4, and 6 varied randomly.

Treatment masking

An independent statistician enclosed the treatment assignments in sequentially numbered, opaque, sealed envelopes which were stored by a researcher independent to the trial team. The details of the sequence remained unknown to all members of the trial team until recruitment and data collection were completed. The sealed envelope was labelled with the stratum number, gender, schizophrenic status, duration of illness and an envelope number. A matching label inside, also numbered, specified the intervention arm. Randomisation took place after consent was obtained and the baseline interview was performed. The envelope was opened following the interview by the independent researcher and communicated to the recruiting researcher by telephone. That researcher then informed the treating Responsible Clinician. The participant's trial identification number and date of randomisation were recorded on the appropriate envelope before it was opened.

Sample size determination

Of the two previous RCTs on CTO, the study by Swartz and colleagues (1999) is considered the most rigorous. They reported a difference of 16% in the proportion readmitted to a psychiatric hospital within 12 months in patients under outpatient commitment compared to control. The sample size of 288 patients was determined as sufficient to detect a similar difference with a significance level of 5% and power of 80%, assuming rates of readmission were comparable in the control group. With this

number of patients, the following differences would also be detected as statistically significant, at the 5% level with 80% power:

- A 14-day difference in the mean number of days spent in hospital over 12 months;
- A difference of 0.43 in the mean number of readmissions over 12 months.

4. Data collection

All primary outcome data were collected from medical records. Client Service Receipt Inventory was initiated from interview with patients but confirmed from case note examination. Notes from other hospitals and from the criminal justice system will be pursued when applicable.

A range of the secondary measures rely on patient interviews which are administered by the research assistants by reading out the questions contained in booklets specially designed for the RCT and recording the patient's reply. These booklets contain detailed assessment of demographics, clinical history, prior MHA use and criminal justice system contacts. They also record the assessment date, patient ID, interviewer ID, and time point. Current status will be assessed using the following well validated and widely used structured questionnaires:

- Mac Arthur Admission Experience Survey (AES)
- Index of fairness
- Index of effectiveness
- Psychiatry Autonomy Preference Index (API)
- Insight and Treatment Attitudes Questionnaire (ITAQ)
- Scale To Assess Therapeutic Relationships -Participant Version (STAR-P)
- Client Satisfaction Questionnaire (CSQ-8)
- Health Related Quality of Life (EQ-5D)
- Client Service Receipt Inventory (CSRI)
- Drug Attitude Inventory (DAI-10)
- Brief Psychiatric Rating Scale (BPRS-24)
- Global Assessment of Functioning (GAF)
- Substance Misuse History (CAGE).

The following non-validated instruments were also recorded:

- Experience of specific types of leverage;
- Patient Capabilities Questionnaire (PCQ), Quality of Life, which was applied in order to investigate its validity within the health economy analysis (not within the scope of this SAP);
- In addition, new items recording 'Types of pressure' in relation to experience of Leverage were included;
- A very small response rate is expected in the following validated questionnaire: Scale to Assess Therapeutic Relationships – Clinicians Version (STAR-C). It will be excluded from the analysis;
- The carer questionnaires will also be excluded from analysis as the patients in general did not have carers, and among those who had there was a low response rate ending up with only 30 questionnaires completed.

Timing of data collection

Recruitment took place from 10 November 2008 to 22 February 2011. Potential participants were identified, informed of the trial and asked for consent prior to randomisation. The follow-up data were planned to be collected at six months after randomisation and at 12 months after randomisation.

Database

Description

Data will be recorded in the CRFs by hand and double entered in SPSS.

Data quality

Double-entered data will be compared against each other and discrepancies will be discussed and corrected by the research assistants, supervised by Ksenija Yeeles.

Database freeze

MVM, the statistician responsible for the analysis will conduct 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, except for total scoring of the individual instruments which will be performed automatically by Ksenija Yeeles using a validated code. The final cleaned data will be frozen before analysis starts.

5. General issues for statistical analysis

Blinding of the statistical analysis

The consultant statistician (MV) will remain blind to the treatment allocation until data are locked and final data analysis is to be conducted. The analysis statistician (MVM) carried out the two interim analyses but has remained blinded to the data collected since March 2011.

Analysis populations

Intent-to-treat population

The Intention-to-treat population will include all randomised patients. Data from crossovers, drop-outs, or patients that never undertook the intervention assigned will be analysed according to their randomised group. Only one single withdrawal occurred during the trial. All available data from this patient 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 on the wrong arm (no matter when patients leave hospital);
- Patient withdrawn;
- Patient not eligible. Possible reasons:
    - Patient not eligible for CTO
    - Patient already on CTO
    - Patient not fulfilling inclusion/exclusion criteria.

Identified protocol violations:

- One patients self withdrew – Withdrew before T1 interview was completed;
- One patient had been on Section 17 for too long – T1 RCF is still available;
- One patient was already on a CTO – T1 RCF is still available.

Methods for handling missing data

Given that the analysis is planned as an intention-to-treat analysis, data from all randomised patients will be included. Tertiary self-reported outcomes are likely to have missing values. For analysis involving these variables, missing data will be handled by multiple imputations using the *ice* stata command to generate a suitable number of imputed data sets and then using the *mim* stata command to automatically analyse each dataset and pool the results. The number of imputations will be chosen as follows:

1) The proportion of observed data will be calculated;
2) Assuming a tolerance for preventable power falloff <1%, a number of imputations m_1 will be selected using Table 5 of Graham and colleagues' paper;[115]
3) The proportion of information available will then be estimated using m_1;
4) Table 5 will be used once again to obtain the final number of imputations m needed for the analysis.

The imputation model will potentially include all predictors of missing values (identified by fitting a logistic regression to each baseline variable on an indicator of missingness, for each variable with missing values), the primary, secondary and tertiary outcomes, and the stratification factors.

Method for handling centre effect

Subgroup analyses comparing London versus other sites and Metropolitan versus non-metropolitan sites will be performed.

Method for handling randomisation, stratification or minimisation factors

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

Multiple comparisons and multiplicity

Comparisons will only be carried out between the two intervention groups. 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

CTO is a time varying intervention. The MHA permits a CTO recall to continue for up to 72 hours (i.e. up to 3 nights in hospital) after which the patient either returns to the community on the CTO or the CTO is revoked and the patient remains in hospital under section 3. Recalling patients is therefore a part of the CTO treatment regime which sometimes results in an overnight stay at hospital and thus could be a confounder for the primary outcome. A sensitivity analysis will be carried out adjusting for the number of recalls in the CTO arm.

A secondary sensitivity analysis will be conducted adjusting the primary outcome by the time spent on Section 17 before starting on CTO for those patients with a delayed initiation after allocation.

Method for handling outliers

Ranges will be calculated for all variables and contrasted with a list of possible values for each of them. Any values that resulted too large or too small will be checked by reviewing the relevant patient's booklet. If the value is correct, a sensitivity analysis will be performed excluding it from the analysis to evaluate its effect on the outcomes.

Derived and computed variables

Total scores for the following instruments will be automatically calculated previous to handing the data to the statistician:

- Substance Misuse History (CAGE) –Two scores will be calculated from 2x4 questions: 1) Positive for alcohol (y/n), and 2) Positive for drugs (y/n);
- Leverage - no total score but frequencies of those experiencing each type of leverage;
- MacArthur Admission Experience Survey (AES) –only total scores will be calculated for each of this instrument's subscales: 1) Perceived Coercion Scale; 2) Negative Pressures Scale, and 3) Procedural Justice Scale;

- Index of fairness;
- Index of effectiveness;
- Insight and Treatment Attitudes Questionnaire (ITAQ);
- Scale to Assess Therapeutic Relationship in Community Mental Health Care – Participants version (STAR –P) total score –and three subscale scores: 1) Positive Collaborations, 2) Positive Clinician Input, and 3) Non Supportive Clinician Input;
- Autonomy Preference Index (API) – only total scores will be calculated for the two subscales 1) Decision-making scale, and 2) Information Seeking Scale;
- Client Satisfaction Questionnaire (CSQ-8);
- Health Related Quality of Life Questionnaire (EQ-5D);
- Drug Attitude Inventory (DAI);
- Brief Psychiatric Rating Scale (BPRS);
- Global Assessment of Functioning (GAF).

Contact with service will be obtained by summing up questions 1-6 and 10 from the Client Service Receipt Inventory section of the CRF. The total number of contacts with carers of any profession will be calculated as well as the total number of phone and face-to-face contacts.

The following variables will be manually calculated previous to locking the dataset by comparing admission and discharge dates from (a) Index to 180 days; (b) 181 days to 365 days; (c) Index to 365 days:

- Number of nights to readmission;
- Total number of days in hospital;
- Total number of involuntary readmissions. A readmission will be considered involuntary if there is at least one change of status to “involuntary” between the admission and discharge dates;
- Total number of voluntary readmissions;
- Total number of CTO recalls.

Planned sub-groups

Sub-group analysis will be performed only for primary outcome and all secondary outcomes apart from time under compulsion. The subgroups to be tested are as follows:

- Age: ≤ 40 years *vs.* > 40 years;
- Gender: male *vs.* female;
- Ethnicity: white *vs.* black *vs.* Asian *vs.* other; and black *vs.* other;
- 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;
- Type of service: Assertive Outreach and Forensic *vs.* CMHT *vs.* Learning Disability *vs.* Crisis Intervention teams *vs.* Rehabilitations *vs.* EIS *vs.* Other;
- Scales:
    - BPRS: ≤ 33 *vs.* > 33;
    - GAF: ≤ 49 *vs.* > 49.

6. Descriptive analysis

Participant flow

Participant flow will be summarized in a CONSORT diagram.

Description of treatments received

For CTOs, the number of recalls and their lengths will be summarized. For both treatments, the time to initial discharge after randomisation and subsequent occurrences will be summarized according to:

- Number of hospitalisations;

- Average length of hospital stays;
- Changes to legal status;
- Total number of tribunals (MHRT);
- Total number of Managers Hearings;
- Number of recalls and revocations;
- Discharges;
- Average duration on CTO and on Section 17 Leave;
- Number of people who never leave hospital during the trial period;
- Number of patients whose voluntary hospitalisation is made involuntary during admission;
- Average number of service contacts received;
- Time under legal compulsion (including recalls);
- Number of
    - Face-to-face contacts with service;
    - Phone contacts with service.

Baseline comparability of randomised groups

The baseline comparability of the two randomised groups will be assessed by tabulating patient characteristics and treatment experiences. No statistical tests on baseline data will be performed.

For continuous variables, normality will be assessed using plots. For normally distributed continuous variables, mean and standard deviation will be reported. For non-normally distributed continuous variables, median and interquartile range will be reported in addition to the mean. For binary and categorical variables, number of cases and percentages over non-missing observations per category will be reported. However, some data will be presented based on the format that will convey most information which may involve collapsing some variable with large numbers of possible categories (such as self-reported ethnicity) into a smaller list of categories (e.g. white/black/Asian/mixed/other). Collapsed categories will be identified (such as in a footnote to the table) so that it is known what is included in each category. Similarly although age and other variables are measured on a continuous scale, it may be more informative to present the percentages at different age intervals.

Summary of all baseline characteristics will be presented by treatment group and overall.

Tables will include:

- Socio-demographic characteristics;
- Employment, family and living situation;
- Clinical and medical history;
- Substance Misuse History (CAGE for alcohol and CAGE for drugs);
- Legal history;
- Leverage;
- AES (Perceived Coercion, Negative Pressures, and Procedural Justice);
- Index of fairness;
- Index of effectiveness;
- Types of pressure;
- Psychiatric Autonomy Preference Index (API);
- Insight and Treatment Attitudes (ITAQ);
- Therapeutic relationships (STAR-P);
- Client Satisfaction Questionnaire (CSQ-8);
- Global Assessment of Functioning (GAF);
- European Quality of Life Questionnaire - 5 Dimensions (EQ-5D);
- Brief Psychiatric Rating Scale (BPRS-24);
- Drug Attitude Inventory (DAI).

Current psychiatric medication

Current medication will be summarized at each time point by treatment group, tabulating the number of psychiatric medications per person; the generic name of the medication, and average daily dose (mg).

Characteristics of care providers where applicable

Baseline number of care providers (1. Assertive Outreach and Forensic, 2. CMHT, 3. Learning Disability, 4. Crisis Intervention teams, 5. Rehabilitations, 6. EIS, 7. Other)

will be tabulated by treatment group and full sample as well as number of patients under each care type.

Comparison of losses to follow-up

As the main outcomes relate to hospital admissions data obtained from medical records, it is not expected that there will be any missing data for these outcomes. Participant self-reported outcomes derived from interviews and questionnaires are expected to contain substantial missing data.

The baseline characteristics of patients with and without data will be tabulated by treatment group and overall at each follow-up point for participant self-reported outcomes.

Tabulation of protocol violations

Protocol violations will be tabulated by treatment group and overall.

7. Interim analysis and safety monitoring analyses

Purpose of interim analyses

Two interim analyses were reviewed by the Data Monitoring Committee (DMC), which forms part of OCTET's governance structure. The purpose of the interim analyses was to judge whether it was ethical and desirable to continue the trial by examining interim data.

Monitoring plan

The first interim analysis was carried out in May 2010; the second, in February 2011. Each of these interim analyses reported:

- Overall progress;
- Participant accrual;
- Data quality, availability and completeness;
- Baseline data;
- Comparison of primary and secondary outcomes (including EQ-5D and GAF).

Stopping rules

The DMC was asked on the basis of the interim results to assess whether the trial should be stopped because:

- There are unanticipated adverse outcomes clustered in one arm;
- The result already is clear (i.e., statistically clear advantage to one arm because of massive effect size).

The stopping rules were not statistically defined a-priori and thus there will be no adjustment of p-values in the main analysis as this would constitute a post-hoc decision.

In both interim analyses the DMC unanimously recommended the continuation of the trial.

8. Analysis of primary outcome

Descriptive statistics for outcome measure

Number of patients readmitted to hospital in the 12-month follow-up; the proportion these patients represent and a 95% confidence interval for this proportion, by treatment group and overall.

Primary analysis

The primary outcome, psychiatric hospitalisation in the 12 month follow-up period, will be analysed using log-binomial regression adjusted for stratification factors (gender (male/female), schizophrenic status (yes/no), and duration of illness (< 2yrs, ≥ 2yrs)). Results will be presented as the relative risk of readmission under CTO compared to Section 17, 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.

The primary analysis will be conducted on the ITT population. There will be no adjustment for missing data as it is not expected that there will be any.

Other analysis supporting the primary (including sensitivity analyses)

A sensitivity analysis will be conducted for the primary outcome which is unadjusted for any 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.

Number of readmissions and number of nights in psychiatric hospitalization are count outcomes and will be analysed using Poisson or negative-binomial regression models depending on data dispersion. Results will be presented as incident-density ratios, which are interpreted in the same way as relative risks.

The number of nights to first readmission from INDEX to 365 days, and time under compulsion, are time to event outcomes and analyses will be performed using proportional hazards regression, with results presented as hazard ratios with 95% confidence intervals. Kaplan Meier plots will also 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 arm and full sample.

Tertiary analysis

Tertiary analyses will be conducted using the ITT population once again. Where patient self-reported outcomes with missing data are analysed, these data will be imputed using multiple imputations (see Section 0).

For categorical outcomes such as self-reported adherence to treatment, substance misuse (CAGE), experience of specific types of leverage, and types of pressure chi-squared tests will be performed and no adjustments for stratification factors will be possible.

For continuous or pseudo-continuous outcomes (satisfaction with service (CSQ-8 and STAR-P), social and clinical outcomes (BPRS-24, GAF, EQ-5D, ITAQ, DAI-10, and API), service usage (CSRI), AES subscales, Index of fairness, and Index of effectiveness) linear regression models will be used.

Other analysis supporting the tertiary analysis (including sensitivity analyses)

A repeated measures sensitivity analysis will be conducted for endpoints measured at multiple time points using multivariable mixed-effects regression models. All available data from all participants will be included with missing values intrinsically imputed within the model rather than requiring multiple imputations. Treatment, stratification factors and time point (time since randomisation) will be entered into the model as fixed effects and the model will contain a patient specific random intercept. An interaction between time point and treatment group will be fitted as a fixed effect to allow estimation of treatment effect at each time point. We will also assess whether time should be included in the model as a random slope and different covariance structures will be explored to determine which model best fits the data.

11. Safety analyses

Binary safety variables such as self-harm, death, harm to others or being a victim of crime will be analysed in the same way as the primary outcome using log-binomial regression.

Counts of safety variables (such as number of self-harm episodes, number of times a victim of crime, etc.) will be analysed as per secondary count outcomes using Poisson or negative binomial regression models. Cause of death will be tabulated descriptively by treatment group.

12. Sub-group analyses

Sub-group analyses will be conducted for the primary endpoint to test the hypothesis that the treatment effect differs according to factors measured at baseline. The subgroup analysis will involve fitting the same model as described for the primary outcome with the inclusion of an additional interaction effect for the interaction between treatment group 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 the treatment variable within each subgroup separately will not be considered of interest.

13. Analysis of exploratory objectives

Predictors of readmission

A risk prediction model for readmission will be developed after a more thorough literature search in order to review other potentially available models.

Mediator effects

The mediator effect of contact with service (rate of contact and type of contact) will be assessed for the primary outcome (readmission to psychiatry hospital) and the secondary outcomes 1) number of nights in psychiatric hospitalization; 2) number of nights to first readmission; and 3) number of readmissions, from INDEX to 365 days.

This analysis aims to explain how the difference of treatment between the two groups occurred based on the contact with service experienced.[324]

This analysis will consist of fitting the same models as described for the primary outcome and secondary outcomes adding each contact with service variable independently as a fixed factor. Results will report the treatment effect after this adjustment, together with 95% confidence intervals whenever possible.

14. Amendments to version 3.0

Statistical methods edited and references added. Schedule of procedures and Consort diagram inserted.