CaFI Trial Statistical Analysis Plan

Project Details

Project Title: The effect on relapse of Culturally-adapted Family Intervention (CaFI) compared to usual care among African & Caribbean people diagnosed with psychosis in the UK: a Randomised Controlled Trial

ISRCTN Registry: ISRCTN12622538

Statistical data analysis plan (SAP)

Statistical analyses will be performed on an intention-to-treat basis and will follow the CONSORT statement for non-pharmacological interventions. Within the first six months of the trial, the trial statistician will develop a detailed statistical analysis plan, which will be presented to and agreed with the DMEC and TSC prior to the allocation codes being released and commencement of any data analysis.

A consort diagram will be presented detailing participant flow and reasons for drop out where available. Baseline socio-demographic data will be presented by arm to demonstrate the extent of comparability between randomised groups.

For the primary outcome, a log-rank test will be used to compare the survival distributions of the two arms. If its assumptions are met, Cox's proportional hazards model will be fitted, allowing adjustment for covariates used in the minimisation process. All analyses will be appropriately adjusted for therapist clustering.

Secondary outcomes as defined above will be analysed using linear mixed models, adjusting for baseline outcome and minimisation covariates, with random effects for therapist and treatment allocation. Where residuals are found to be skewed, standard errors and confidence intervals for the treatment effects will be estimated by applying a bootstrap procedure using the percentiles based on the results of 5000 replications (using the trial participant as the sampling unit).

Qualitative data will be digitally-recorded, transcribed verbatim, and analysis will occur blind to trial outcomes to avoid biased interpretation of the findings. Anonymised transcripts will be thematically analysed using a modified framework approach. This produces a matrix of summarised data providing a structure for analysis and interpretation. We will initially take an inductive approach to theme generation, with subsequent deductive theme refinement, guided by Normalisation Process Theory.

An economic evaluation comparing the cost-effectiveness of CaFI with usual care will be performed and reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. The perspective for the primary analysis will be that of the NHS and Social Care for direct costs (as recommended by NICE) and patient participants for health benefit. The time horizon will be 12 months from baseline to end of follow up.

When the data are analysed, the most recent, published, national unit costs will be used to cost each of the services used. The costs of the intervention will be estimated from staff time (training, delivery, and supervision), facilities, and consumables and costed using national unit costs.

The measure of health benefit for the primary analysis is the QALY (EQ-5D-5L and the published utility tariffs recommended by NICE at the time of the analysis). Single imputation will be used to account for missing cost data at baseline and missing data from the outcome measures used at baseline. A missing indicator will be used to account for missing data about a participant's demographic characteristics (e.g. age, gender, ethnicity) at baseline. The methods used to deal with missing follow-up data will be determined according to the extent and pattern of missing data (e.g. multiple imputation, missing indicator or propensity score methods). A pooled descriptive statistical analysis of baseline data will be combined with information from previous economic evaluations to inform the final methods used for (i) methods to account for missing follow-up data (ii) the type of regression models and key covariates for the analyses of the 12-month follow-up data. Regression analyses will be used to estimate net costs and net QALYs (or health benefit) for the intervention compared to TAU. All analyses will be adjusted for key covariates which will be identified prior to analysis of the follow-up data.

The estimates of net costs and QALYs from the regression analyses will be bootstrapped to simulate 10,000 pairs of incremental cost and QALY outcomes of the CaFI intervention. These capture the relationship between costs and QALYs and will be used to generate cost-effectiveness acceptability analyses to capture both parameter uncertainty and uncertainty about the value to decision makers of an additional QALY gained. This will include: (i) plotting the distribution of pairs of net costs and QALYs on a cost-effectiveness plane, to assess parameter uncertainty, (ii) generate a cost-effectiveness acceptability curve to estimate whether the additional cost of a QALY gained by an intervention is acceptable to decision makers (iii) estimate the probability that the CaFI intervention is cost-effective compared to TAU (iv) estimate a net benefit statistic. The cost-effectiveness acceptability approach requires revaluing QALY by an estimate of how much decision makers are prepared to pay to gain one QALY. However, there is no universally agreed threshold willingness to pay value and reported thresholds for the UK range from £8,000 to £30,000 per QALY gained. Accordingly, we plan to use a mid-estimate willingness to pay threshold value of £15,000 per QALY gained to estimate the probability that CaFI is cost-effective

and the net benefit statistic, with a range of £0 to £30,000 threshold values for the cost-effectiveness acceptability curve. The final mid-estimate and range of threshold values will be determined on the basis of published guidance at the time of analysis.

Sensitivity analysis will be used to test the impact of assumptions and data on The Incremental Cost-Effectiveness Ratio (ICER) and results of the cost-effectiveness acceptability analysis. The planned sensitivity analyses will explore the intervention's cost-effectiveness using (i) cost per relapse avoided and cost per relapse free year; (ii) broader cost perspectives to include non-NHS and social care costs and indirect costs of lost productivity; (iii) broader health benefit perspectives to include family health benefits; (iv) complete case analysis (v) alternative methods of dealing with missing follow-up data.

Interim analyses and Stop/Go guidelines

Based on our sample size calculation, we will need to recruit 17 participants per month across all participating NHS Trusts to reach target. Recruitment will be rigorously monitored throughout the recruitment period. We expect to have recruited 60-80% of our total year 1 target (202 family units) into the Stop/Go internal pilot within twelve months from starting recruitment. As with most trials, we anticipate recruitment may be slow initially. We have increased monitoring in-line with recent changes to study design, specifically – offering a CaFI:Digital version. The Trial Steering Committee (TSC) will meet at least twice within the first 6 months at the start of recruitment, by which time at least 60 families should have been recruited. We will also monitor engagement and participation in therapy sessions during this time. In the feasibility study attendance rate at therapy sessions was 80%. At each review point during the 6 months period if attendance rates are 50% or less this would be cause for concern. At the 9 months review, if we have recruited less than 60% of the 9-month target, we shall consider opening one or both contingency sites. If we have achieved 80% or more of the 12-months target, we will continue without change. If, however, recruitment is less than 50% at the 12-months review, the trial may be stopped after discussion with the Trial Steering Committee Data Monitoring and Ethics Committee (DMEC), and funders.

Data management

A web based electronic data capture (EDC) system will be designed, using the InferMed Macro 4 system. The EDC will be created in collaboration with the trial analyst/s and the CI and maintained

by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

The CI or delegate will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g. Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g. Trial Manager) in the first instance.

Each participant's initials and date of birth will be entered on the EDC. NHS number, email address, participant names and addresses, and full postcodes will not be entered into the EDC. No data will be entered onto the EDC system unless a participant has completed a consent form with the researcher, agreeing to participate in the trial. Source data will be entered by recruiting site staff according to the KCTU guidelines by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. A full audit trial of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

The CI will undertake appropriate reviews of the entered data, in consultation with the trial statistician for the purpose of data cleaning and will request amendments as required. No data will be amended independently of the study site responsible for entering the data. At the end of the trial, data will be reviewed for each participant. After review, all data will be formally locked for analysis.