Focusing on Clozopine Unresponsive Symptoms (FOCUS)

Economic evaluation protocol

1. Overview

The following section briefly paraphrases and summarises background section and study overview in the study protocol (Pyle et al, 2016).

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1.1 Background

Around a third of people with schizophrenia experience a poor response to standard treatment with antipsychotic medication. In some cases the illness becomes progressively more unresponsive to medication and patients experience subsequent relapses. This subgroup of patients is known as “treatment-resistant”. The total societal cost of schizophrenia in the UK in 2004/5 was £6.7 billion, with the direct cost of treatment and care around £2 billion. Treatment-resistant schizophrenia is more costly, as it usually requiring longer term residential and intensive community treatments.

Clozapine is the only antipsychotic with convincing evidence for efficacy in strictly-defined treatment-resistant schizophrenia. But even in people in this category, clozapine has limited efficacy, with 30-40% showing an inadequate response to the drug. Long-term effects of antipsychotics can be very serious and so alternatives, like cognitive behavioural therapy (CBT), are sought after. The literature demonstrates that there are significant numbers of patients with a schizophrenia spectrum disorder who either fail to respond to an adequate trial of clozapine or are unable to tolerate such medication due to adverse reactions. CBT has the potential to help alleviate symptoms and improve quality of life in people with treatment-resistant schizophrenia.

The FOCUS trial will address the question of whether CBT is a clinically and cost-effective treatment for the population with confirmed treatment-resistant schizophrenia that is poorly responsive or not tolerated to an adequate trial of clozapine.

1.2 Overview of trial design

The FOCUS trial is an integrated clinical and economic study to evaluate the effectiveness and cost effectiveness of the addition of a standardised CBT intervention to treatment for individuals who are unable to tolerate or have an inadequate response to clozapine. The comparator group will receive treatment as usual. Full details of the trial design are reported elsewhere (Pyle et al, 2016).

The study will be conducted in secondary care, specifically mental health services (community mental health, residential rehabilitation and inpatient settings), at five UK centres (Manchester, Edinburgh, Glasgow, Newcastle and Southampton).

The target population includes people aged 16- 65 years with a schizophrenic illness that has been unresponsive to clozapine. Non-response is defined as a criterion level of persistent symptom severity, to an adequate trial of clozapine in terms of dosage, duration and adherence.

Therapeutic improvement in the trial will be assessed in terms of overall symptom severity, but also using broader, clinically-relevant outcome measures of social and occupational function and target symptoms and/or behaviours as well as overall health status utility. The primary outcome measure will be the total score on the Positive and Negative Syndrome Scale (PANSS). This is a commonly used outcome for response in schizophrenia trials, and will allow for comparison with relevant published studies. Both positive and negative symptom subscale scores can be derived from the PANSS, and these will be used to assess specific symptoms. Other outcomes include the Calgary Depression Rating Scale for Schizophrenia (CDSS), the AnTi measure of self-reported anxiety, dimensions of psychotic experiences such as severity and distress (PSYRATS), health status and health related utility (EQ-5D) quality of life (QLS), social functioning (PSP), a user-defined measure of recovery (QPR). In addition, alcohol and illicit drug use will be measured using the AUDIT and DAST. We will also measure psychological factors as potential mediators of treatment outcome, including appraisals of psychotic experiences using the Interpretations of Voices Inventory for voices (IVI) and the beliefs about paranoia scale for paranoia (BAPS). We will also assess beliefs about self and others using the brief core schema scale (BCSS), attachment style using the psychosis attachment measure (PAM) and experience of childhood trauma using the childhood trauma questionnaire (CTQ).

Follow up is planned to occur at 9 months and 21 months.

1.3 Economic evaluation

Economic evaluation compares the costs and health benefits (such as symptoms cured, life years gained, improvements in overall health) of different care or treatments. The aim is to help patients, practitioners and commissioners choose care that offers value for money. A key concept is that care should be selected to give the most health benefit within the budget available. This is often translated to giving the most health benefit for the lowest cost. It is important to remember that if care does not benefit the person who needs it, then it cannot be cost effective.

An economic evaluation compares two or more types of care or treatment by looking at their costs and benefits. A simple example is shown in the table below. In this example treatment A costs more than treatment B. However, it is also more effective and there are gains in health. If decision makers are willing to pay £8,988 for one additional year in full health then treatment A is cost effective:

Table 1 example cost-effectiveness analysis

	Treatment A	Treatment B	Treatment A minus B
Cost of all services	£2,279	£1,560	£719
Quality-adjusted life-years (QALY)[a]	1.36	1.28	0.08
Incremental cost effectiveness ratio[b]			£719 divided by 0.08 = £8,988 per QALY gained
[a] A QALY is a joint measure of quantity of life and health-related quality of quality (represented by utility). The equation for a QALY is provided in Section 2.4 (measure of health benefit). [b] The ICER is equal to the change in cost for each additional unit of health outcome when an intervention is introduced.			

1.4 Aims and objectives

The aim of the economic evaluation component is to estimate the cost-effectiveness of the addition of CBT intervention to the treatment of individuals who are cannot tolerate or have an inadequate response to clozapine versus usual care, in a UK secondary care setting. This will consist of a within trial analysis using patient-level data collected during baseline and follow-up study time points.

The primary objectives for the trial analysis are to:

- Estimate the costs of health and social care in the intervention and usual care groups, and assess whether there are differences between groups
- Estimate the QALYs of patients in the intervention and usual care groups, and assess whether there are differences between groups
- Assess whether any additional benefit is worth any additional cost.

1.5 Overview of within trial economic evaluation

The economic analysis will use a cost-effectiveness acceptability analysis to assess the cost-effectiveness of CBT for people who cannot tolerate or have an inadequate response to clozapine. The intervention is usual care plus CBT and comparator is usual care. The perspectives for the primary analysis are health and social care service providers (costs) and services users (health benefits). The analysis will use individual patient-level service use and health benefit data from all participants recruited and allocated to a management arm in the FOCUS trial. The time horizon for the primary analysis will be 21 months (with shorter time horizons tested in the sensitivity analysis), which is the total duration of scheduled follow-up in the trial. Costs and outcomes will be discounted at a rate of 3.5% in line with UK guidelines (NICE, 2013).

The measure of health benefit for the primary analysis will be QALYs, based upon the premise that the intervention and control arms will have differences in patient health status.

An improved health status would generate more QALYs over the study duration, which will be reflected in the primary analysis. Changes on key clinical measures from baseline to follow up will be used in secondary analyses (defined in Section 2.8).

The analysis will control for key covariates that are predictors of costs, QALYs or the secondary outcome measures. Bootstrap techniques will be used to estimate a cost-effectiveness acceptability curve, displaying the likelihood that the intervention could be cost-effective, and the measure of net benefit.

Descriptive analysis and data manipulation will be conducted using SPSS version 23. The main statistical analyses and estimation of net benefit statistics and cost-effectiveness analysis will be conducted using STATA version 14.

2. Detailed methods

2.1 Study sample

People aged 16- 65 years with a schizophrenic illness that has been unresponsive, to an adequate trial of clozapine in terms of dosage, duration and adherence. The FOCUS trial will recruit participants meeting the following criteria:

1. A criterion level of persistent symptom severity despite an adequate trial of clozapine in terms of dosage, duration and adherence (Honer et al, 2006):
   - Treatment of clozapine at a stable dose of 400 mg or more (unless limited by tolerability) for at least 12 weeks, or if currently augmented with a second antipsychotic that this has been given for at least 12 weeks, without remission of psychotic symptoms, or have discontinued clozapine due to adverse reactions (including agranulocytosis) or lack of efficacy in the past 24 months.
2. Presence of at least one psychotic symptom with severity ≥4 (for hallucinations/delusions) or ≥5 (for suspiciousness/grandiosity) on the Positive and Negative Syndrome Scale (PANSS) in addition to a PANSS total score of at least 58, which is equivalent to a clinical global impression (CGI) of being at least mildly ill (Leucht et al, 2005).
3. Be in contact with mental health services and have a care coordinator.
4. Either meet ICD-10 criteria for schizophrenia, schizoaffective disorder or delusional disorder or meet entry criteria for an Early Intervention for Psychosis service (operationally defined using PANSS) in order to allow for diagnostic uncertainty in early phases of psychosis.
5. Aged at least 16 years' old
6. Competent and willing

Participants were excluded if they had a primary diagnosis of alcohol/substance dependence where this is clearly the cause of their psychotic symptoms, a developmental disability, were non-English speaking, and if they were receiving or had received structured CBT from a qualified psychological therapist in accordance with NICE guideline recommendations within the last 12 months.

2.2 Time horizon

The time horizon of the analysis will be 21 months (in line with the final trial follow-up). Costs, QALYs and the secondary outcome measures will be estimated from baseline to end of scheduled follow-up, to estimate incremental cost-effectiveness of the CBT intervention.

2.3 Intervention and comparator

The analysis will compare CBT plus usual care with usual care alone. The intervention and usual care are summarised and described in detail in the trial protocol (Pyle et al, 2016).

2.4 Measure of health benefit

The measure of health benefit for the primary analysis will be the QALY (calculation shown below). This will be estimated from the EQ-5D-5L and associated utility tariffs (Devlin et al, 2016) completed at baseline and end of scheduled follow up. The EQ-5D is a validated, generic health status measure, allowing for the comparison of health outcomes across different disease areas. The EQ-5D has been shown to be a valid and responsive measure of health in patients with psychosis (Barton et al, 2009; Bobes et al, 2005). Without a generic

measure of benefit it would be impossible to compare condition-specific outcomes such as severity of depression (depression) and progression-free survival (oncology). Furthermore, the QALY and the EQ-5D are the measures recommended for economic evaluations by NICE (NICE, 2013).

The EQ-5D-5L captures the following five domains of health status: mobility, self-care, usual activity, pain/distress, and anxiety/depression. Each domain is rated on a five-point scale of levels: no problems, slight problems, some problems, severe problems or unable to do activity. Resulting health status profiles will be converted to utility values using published utility tariffs for the EQ-5D-5L (Devlin et al, 2016). These utility values represent the weight of preference for each health state of a sample of 912 adults in England.

Total QALYs will be estimated as follows:

$$QALY = \Sigma[(U_i + U_{i+1}) /2] \times (t_{i+1} - t_i)$$

Here, U = utility value and t = time between assessments. The time between assessments is the time from baseline data collection to follow-up.

2.5 Resource use and costs

Direct costs of healthcare services used by trial participants will be estimated for the primary analysis. The total direct costs of service use for each trial arm will be estimated by summing the costs of each resource used to provide health and social care. Data on the resources used for each participant will be collected using a bespoke patient service utilisation questionnaire at baseline and follow up. Services covered by the questionnaire include the following items:

- Primary care services e.g. GP surgery or walk-in centre
- Community care services e.g. community-based mental health care and social support
- Hospital inpatient visits (overnight stays)
- Hospital day case visits (not staying overnight)
- Hospital outpatient services e.g. elective clinics
- Accident and emergency services

The cost of providing CBT intervention in the FOCUS intervention arm will be added to the costs of other services used by participants in the FOCUS arm to estimate the total costs of usual care plus CBT. The number of CBT sessions attended by each participant has been collected in the trial. Note that the protocol specified that participants would receive up to 30 hours of CBT (rather than a certain number of sessions) as shorter sessions may be more appropriate for certain participants. CBT sessions were delivered at home, thus the cost of a home-based CBT session will be sourced and applied to the number of sessions to calculate a per participant cost of CBT.

The unit costs of NHS and social care services will be derived from national average unit cost data. These unit costs are published annually in the NHS reference costs database, and in the Unit Costs of Health and Social Care document published by the Personal Social Services Research Unit (PSSRU), University of Kent. The price year for all costs will be 2015/16, as this will be the price year of the most recent unit costs.

2.6 Missing data

Analysis of the economic data will be based upon intent-to-treat principles, namely that outcome data for all services users will be included in the analysis regardless of whether they completed the planned treatment. It is expected that data will be missing, either from loss to follow-up or incomplete data collection.

Multiple imputation (MI) will be used to derive values based on available data for each participant for the primary analysis of costs and QALYs. MI of both costs and QALYs is increasingly recognised as an appropriate approach to deal with missing observation and missing follow-up data (Faria et al, 2014). Missing values will be imputed for each time point, rather than as total values covering the whole follow-up period. Missing cost and utility data will be treated as missing at random. To ensure that all available data is used we aim to impute values by healthcare category for costs (inpatient, outpatient and primary/community care) and individual EQ-5D domain (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), rather than as totals. However, this may depend on any patterns that exist within the data when we come to review it.

Imputations will be conducted in STATA version 13, using predictive mean matching and sequential chained equations. Regression models used to impute missing data will be based on initial descriptive analyses and regression analyses to identify key baseline and follow-up variables (e.g. age, gender, PANSS score) that were associated with either costs or outcomes. These will be included in the chained equations to iteratively impute missing cost categories and utilities.

2.7 Primary analysis

The primary measure of interest for the economic analysis is the incremental cost-effectiveness ratio (ICER). Rather than considering cost and health outcomes separately, the ICER is a joint measure of both. It is calculated by dividing the difference in costs (net costs) by the difference in QALYs (net QALYs) between any two interventions. The ICER represents the additional cost of an intervention per additional QALY gained (in our analysis of the FOCUS intervention and usual care):

$$\text{ICER} = \frac{\text{Cost}_{\text{FOCUS intervention}} - \text{Cost}_{\text{usual care}}}{\text{Utility}_{\text{FOCUS intervention}} - \text{Utility}_{\text{usual care}}}$$

Regression analysis will be used to estimate the net costs and QALYs of the FOCUS intervention. Key covariates will be included in the regression models to control for factors that may influence costs or QALYs. The covariates for these analyses will be identified using the approach outlined for the multiple imputation described in the previous section.

Based on published literature it is anticipated that relevant covariates will include one or more of the following patient characteristics:

- Age
- Gender
- Ethnicity
- Service use costs prior to baseline
- Duration of mental health problems
- Diagnoses
- Medication at baseline

- Employment status*
- Living arrangements (e.g. living alone, living with partner, etc.)*
- Level of education.
- Site location (Manchester, Edinburgh, Glasgow, Newcastle and Southampton)

*Note that these were not collected during the trial but will be sourced from case notes.

The estimates of costs and health outcomes from the regression will be bootstrapped (NICE, 2013) to simulate 10,000 pairs of incremental cost and QALY outcomes of the FOCUS intervention. This captures the relationship between costs and QALYs and look at how the pairs of net costs and QALYs are distributed on the cost effectiveness plane. Doing so will capture parameter uncertainty in our modelling. This will allow us to undertake cost-effectiveness acceptability analysis, which is recommended by NICE for health technology appraisals (NICE, 2013).

The ICER measures the cost per QALY gained by an intervention which then raises the question of whether the additional cost of a QALY is worth paying for. To help address this, the ICER can be compared to benchmark or threshold values of how much decision makers may be willing to pay to gain one additional QALY.This is analogous to placing a monetary value on one QALY. However in the UK there is no universally agreed cost-effectiveness threshold value. One commonly reported threshold is from the National Institute for Health and Care Excellence (NICE) in the UK of approximately £20,000 to £30,000 per QALY (NICE, 2015). Although some argue that this may have decreased in recent years as expenditure has been constrained (McCabe et al, 2008). A more relevant estimate of the threshold of £18,317 per QALY (taking into account expenditure breakdown and mortality) was produced in 2013, although this was noted to be variable according to other factors (e.g. according by disease category and primary care trust) (Claxton et al, 2013). Once again, in February 2015, this analysis was updated; this estimated a more relevant threshold would be around £13,000 per QALY (Claxton et al, 2015). Recognising this lack of consensus, the monetary value of our simulated QALYs will be varied from £0 to £30,000. These reflect a range of hypothetical willingness to pay thresholds (WTPT), from decision makers being willing to pay nothing for an additional QALY (i.e. they are only interested in the lowest cost option), to them being willing to pay £30,000 to gain 1 QALY.

Each of the net QALY estimates from the bootstrap simulation results can be revalued by multiplying it by a willingness to pay threshold. Using these revalued QALY estimates it is then possible to estimate the A net benefit statistic (NB) for each pair of simulated net costs and net outcomes as:

NB = (O * threshold) – C, where O = net outcome score and C = net cost.

This process is repeated for the WTPT values of interest to generate a cost effectiveness acceptability curve (CEAC). For the simulated net cost and QALY pairs, the CEAC shows the probability that the intervention is cost-effective for each WTPT value (i.e. provides a positive NB) – represents the overall probability that it is cost-effective (e.g. 7,500/10,000 = 75%). This probability will vary at different ICER threshold values. For example, if decision makers are willing to pay more for an additional QALY, the additional health benefits from an intervention would become more valuable. It is therefore likely that such an intervention would be cost-effective in a bigger proportion of the 10,000 results. A cost-effectiveness

acceptability curve will plot the proportion of bootstrapped simulations where the NB of an intervention is equal to or greater than zero for each WTPT value.

2.8 Sensitivity analysis

Sensitivity analysis will be used to test the impact of the study design on the ICER and results of the cost-effectiveness acceptability analysis.

Table 2 sensitivity analysis

Assumptions/ variables	**Changes**	**Rationale**
Measure of health benefits	• Positive and negative syndrome scale (PANSS) • The Process of Recovery Questionnaire (QPR)	Secondary analyses will explore the cost-effectiveness of FOCUS intervention using a problem-specific measure of effectiveness, rather than the generic QALY. For the PANSS measure the outcome will be cost per clinically relevant threshold for improvement (25% or 50% improvement) in line with the paper by Leucht et al (2005). The for QPR measure there are no currently defined thresholds for improvement, different scenarios for percentage improvement will be used to take this into account.
Utility value set to estimate QALYs	Alternative EQ-5D value sets (Devlin et al, 2016; van Hout et al, 2012)	Secondary analyses will explore the impact of using alternative value sets to calculate QALYs. The most recent set by Devlin et al will be used in the base case analysis. With the older crossover value set used to produce an alternative set of utility values from the EQ-5D data.
Time horizon	9 months	The trial time horizon is 21 months. A secondary analysis will consider the 9 month follow-up, to assess the impact of different follow-up periods on cost-effectiveness results.

2.9 Subgroup analysis

The potential for different cost-effectiveness results across different groups will be explored. The subgroups to be explored are:

- Duration of illness (or age of onset of psychotic symptoms)
- Dose of clozapine at baseline
- Number of anti-psychotics at baseline

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