**Prediction and management of cardiovascular risk for people with severe mental illnesses. A cluster randomised controlled trial in primary care (PRIMROSE)**

**Final statistical and economic analysis plan**

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Initial work recording the introduction, trial summary, measures 10/2013

**Introduction**

This analysis plan sets out the methods of analysing the predetermined primary and secondary outcomes of PRIMROSE and the health economics outcomes, which will be reported in the National Institute for Health Research report at the end of the trial and also in the main peer review paper to result from this randomised controlled trial.

The analysis of this cluster randomised trial will follow the CONSORT statement guidelines and the associated extension for cluster randomised trials1-3. It will also follow the appropriate standard operating procedures written by the Priment Clinical Trials Unit.

**Trial summary**

**Aims**

The aim of the study is to test the effectiveness and cost effectiveness of a primary care led intervention to reduce cardiovascular disease risk in patients with severe mental illnesses (SMI).

**Primary objective**

* To establish the effectiveness of the intervention in reducing total cholesterol over a 12 month period compared with standard care

**Secondary objectives**

* To determine the impact of the intervention on the following cardiovascular disease risk factors: HBA1c, blood pressure, BMI, waist circumference, total cholesterol/ HDL cholesterol ratio, HDL cholesterol, LDL cholesterol, 6 month smoking abstinence, cardiovascular disease risk scores.
* To determine whether the intervention leads to an increase in exercise, improved diet or reduced alcohol intake
* To determine whether the intervention improves uptake of statins, adherence to statins and attendance at appointments
* To establish the cost-effectiveness of the intervention considering the costs of the intervention itself and other direct health care costs alongside the outcomes
* To determine the effect of the intervention on the number of hospital admissions
* To assess the effect of the intervention on patient satisfaction with services and quality of life.
* To determine the effect of the intervention on mental health outcomes

**Study population**

*Inclusion criteria*

* GP patients on the mental health register with a computer diagnosis of severe mental illness, that is, schizophrenia, persistent delusional disorder, schizoaffective disorder, bipolar affective disorder, psychosis, psychotic depression or other psychotic disorder.
* Raised total cholesterol above 5 **OR** raised total cholesterol/ HDL cholesterol Ratio above 4 **AND** one or more of the following risk factors:
  + BMI >30 kg/m2
  + Current smoker
  + Blood pressure >140mmHg systolic and/ or >90mmHg diastolic on two or more consecutive occasions
  + HbA1c of 42-47mmol/mol (6.0–6.4%) or impaired fasting glucose (5.5-6.9 mmol/l)
  + Diagnosis of diabetes
  + Diagnosis of hypertension
* Aged 30-75 years old
* Able to give written informed consent
* Agreed to be contacted by a researcher

*Exclusion criteria*

* Too acutely unwell defined as under acute psychiatric care
* Primary diagnosis of an organic mental health problem and/ or severe cognitive impairment
* Life expectancy <6 months
* Pregnant at baseline
* Pre-existing cardiovascular disease
* Unable to give informed consent
* Personality disorder or depression/ anxiety without any psychotic features

For patients who already receive statins, if their total cholesterol or total cholesterol/ HDL ratio remains raised at the initial screening, they will not be explicitly excluded, since they still require monitoring and further risk reduction.

**Trial design**

This is a non-blinded cluster randomised trial, with GP practices being randomised to the intervention or treatment as usual.

The trial started in October 2013 and follow up to be complete by January 2017.

**Randomised treatments**

*Intervention*

Patients in the GP practices allocated to the intervention will be offeredthe cardiovascular disease risk reducing service over six months. There will be flexibility over the delivery of the service depending on each individual participant’s preferences and needs; however the intervention will include one or more of the following elements:

* Lifestyle advice and education on diet and exercise.
* Delivery of simple behaviour techniques to encourage patients to make healthy lifestyle changes
* Signposting participants to other services such as smoking cessation or physical activity programmes
* Statin prescriptions to participants whose cardiovascular risk or lipids exceed recommended thresholds.
* Prescription of other medications such as nicotine replacement therapy for smoking cessation or metformin for diabetes and weight loss.
* Involvement of carers and mental health key workers in monitoring adherence, encouraging attendance at appointments and encouraging a healthy lifestyle.

Progress with cardiovascular disease risk reduction will be reviewed at weekly or fortnightly appointments, decreasing to monthly monitoring if satisfactory progress is made with reducing cardiovascular disease risk.

*Treatment as usual*

Practice nurses will receive no additional training on cardiovascular disease risk reduction. Participants will be sent British Heart Foundation (BHF) leaflets. Practice staff will not be asked to review participants, to check adherence or arrange statin prescriptions.

**Sample size**

A total of 350 patients from 70 GP practices will be recruited into the study. In determining the size of the trial we considered 1. important effect sizes 2. size of clusters and 3. attrition.

*1. Effect size*

Our primary outcome is total cholesterol. Two community studies of UK adults with severe mental illness reveal mean total cholesterol levels of 5.4mmol/l (SD 1.3)4 and 5.7mmol/l (SD 1.4)5.

We consider an effect size of 0.4 standard deviations difference in cholesterol, between the two trial arms, to be the minimum clinically important difference. Statins usually have a far greater effect sizes, approaching two standard deviations6, however in this effectiveness trial we are comparing two different primary care strategies, so cannot expect effects as large as this. Based on a two sample t-test to detect a difference of 0.4 x (1.3mmol/l) requires 132 participants per arm, with 90% power and 5% significance level.

*2 and 3. Sample size inflation for clustering and attrition*

We have assumed that 5 participants will be recruited per practice. In previous cardiovascular disease work we recruited 74 people with severe mental illness from seven practices of variable size. Dropout rates in severe mental illness trials are <20% at 12 months7, 8. Using an intraclass correlation coefficient of 0.02 for trials in primary care6 and average cluster size of 4 patients per practice (after allowing for 20% attrition) gives 140 patients per arm. Inflating this figure for 20% attrition and rounding up result in a total of 350 participants and 70 practices for the trial.

**Randomisation**

GP practices will be randomised on a 1:1 basis to receive either the intervention or treatment as usual. Randomisation of GP practices will be carried out by the same independent statistician. The full randomisation procedure is set out in the randomisation protocol.

**Blinding**

This will be a non-blinded study. However, the primary outcome is total cholesterol level, which is objectively measured and other data will be collected by a research nurse who will be blind to allocation. The statisticians and health economists will be blind to allocation until the analyses have been agreed.

**Outcomes**

*Primary outcome*

Total cholesterol at 12 months. This reading is obtained through analysis of a blood sample in the laboratory, so is measured objectively and blind to allocation.

*Secondary outcomes*

10 year CVD risk score (new PRIMROSE risk tool, Framingham re-estimated to the UK population and QRISK2)10-12 in this order of preference.

BMI

Blood pressure (systolic and diastolic)

Total cholesterol/ HDL cholesterol ratio

HbA1c

Waist circumference

HDL cholesterol

Smoking status, operationalised as non-smoker (0), ex-smoker (1), current smoker (2)

Change in number of cigarettes smoked per day from baseline (12 months - baseline) as a continuous outcome. Those who are non-smokers or ex-smokers will be assigned 0 cigarettes smoked.

Exercise will be assessed using the International Physical Activity Questionnaire (IPAQ) short form13, 14. It is structured so that it gives separate scores in three domains: walking, moderate intensity activity and vigorous intensity activity. It is scored by multiplying the number of minutes the domain is carried out by the frequency per week. This can further by multiplied by the MET (metabolic equivalent of task) minutes to get the score in terms of MET minutes. There are standard MET minutes for each domain15: walking = 3.3 MET minutes, Moderate physical activity = 4.0 MET minutes and Vigorous physical activity = 8.0 MET minutes. From these a total score in terms of MET minutes will be calculated by the statistician.

Diet will be assessed using the Dietary Instrument for Nutrition Education (DINE)16. This asks a number of questions on foods within fat, fibre and unsaturated fats to give a score based on frequency each food group is eaten; these will be the outcomes analysed. The scores are calculated within the database. .

Alcohol use is measured using the Alcohol Use Disorders Identification Test (AUDIT)17. Participants will first complete the AUDIT-C. If they score five or more on AUDIT-C, they will be asked the additional questions in AUDIT to give their total score. If they score less than five on AUDIT-C, that will be their final score. There will be two analyses:

* Including all 10 questions of the AUDIT (AUDIT-C for those who scored less than 5)
* Including the first nine questions of the AUDIT (AUDIT-C for those who scored less than 5). The decision to do this was because the final question is “Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?” As a possible element of the Primrose intervention is reducing alcohol intake, there may be bias in that response by trial arm.

Adherence to the intervention - for the purposes of the analysis, this will be attending at least two appointments

Satisfaction with the services over the trial period using the Client Satisfaction Questionnaire (CSQ)18. This is an 18 item measure which each item is scored on a four point likert scale from 1 (lowest degree of satisfaction) to 4 (highest degree of satisfaction).

Psychiatric outcomes are measured using The Warwick-Edinburgh Mental Well-being Scale (WEMWBS)21. This is a 14 item scale, with five responses 1 (none of the time) to 5 (all of the time). Scores for each item are summed to give a score between 14 and 70 with a higher score indicating better mental wellbeing.

Adherence to medication will be measured using the Morisky Scale of Adherence (MMS)22. This will be asked twice on each administration, once concerning psychotropic medications and the other concerning statins, antihypertensives, metformin, stop-smoking medication and/ or diabetic medications. The scale contains eight questions; the first seven of which are yes/ no questions and the final one is a likert scale. The first seven questions are scored 1=yes, 0=no. The final question is scored 0 for never/ rarely and 1 for any other response. This gives a score between 0 and 8. A score of 0 is high adherence, 1 to 2 medium and more than 2 is low adherence.

*Health economics outcomes*

Incremental costs of the intervention, from the perspective of the NHS and PSS. Cost-effectiveness of the intervention, measured in terms of the primary and secondary outcome measures, plus quality-adjusted life years (QALYs), estimated at one year and lifetime. These will be explained further in the health economic analysis section of this analysis plan.

**Data collection**

*Baseline*

Clinical diagnoses of SMI

Length of psychiatric illness,

Date of birth, sex, marital status, employment and ethnicity

Postcode (to enable calculation of Townsend deprivation quintile)

CMHT, care worker details, CPA (yes/no),

The Warwick-Edinburgh Mental Well-being Scale (WEMWBS)21

Morisky Scale of Adherence (MMS)22 administered twice, once for psychiatric drugs and once for CVD related drugs

10 year CVD risk score (new PRIMROSE risk tool, Framingham re-estimated to the UK population and QRISK2)10-12

Additional risk score variables if risk score is not available

Blood pressure

Lipids (total cholesterol, HDL cholesterol, total:HDL, LDL cholesterol, and triglycerides)

Diabetes status

Smoking status

HbA1c

Weight

Height

Waist circumference

Exercise (IPAQ)13, 14

Diet (DINE)16

Alcohol use (AUDIT-C and AUDIT)17

Previous admissions over 1 year

Physical comorbid conditions

Current medications including antipsychotic dose and class

Previous CVD screening results

Previous (in the last 12 months) prescriptions of statins, anti-hypertensives and hypoglycaemics

EQ-5D-5L for quality of life19, 20

Client Service Receipt Inventory23

*6 and 12 months*

Blood pressure

Lipids (total cholesterol, HDL cholesterol, Total:HDL, LDL cholesterol, and triglycerides)

Additional risk score variables if risk score is not available

Diabetes status

Smoking status

HBA1c

Weight

Height

Waist circumference

Exercise (IPAQ)13, 14

Diet (DINE)16

Alcohol use (AUDIT-C and AUDIT)17

Current medications including antipsychotic dose and class

EQ-5D 5L for quality of life19, 20

Client Service Receipt Inventory23

Timing of interventions received

Morisky Scale of Adherence (MMS)22 administered twice, once for psychiatric drugs and once for CVD related drugs

*12 months*

10 year CVD risk score (new PRIMROSE risk tool, Framingham re-estimated to the UK population and QRISK2)10-12

Adverse events including side effects of statins and cessation of antipsychotics

Adherence to the intervention (attendance at appointments, attendance at CVD risk reducing services)

Client satisfaction using the Client Satisfaction Questionnaire – CSQ18

**Data entry**

Data will be entered using a web based system set up by Sealed Envelope24. This has been set up so that, it mirrors the data collection sheets in order. It also has range checks, consistency checks and for closed questions gives a number of options plus “other” where appropriate. Assessors who will be entering the data will have no access to the group allocation through this system.

With the checks in place, there should not be any issues with illegal values being entered or inconsistent data being entered so necessary cleaning should be minimal. However, data will be checked by the Statistician before analysis and any problems reported to the Trial Manager, who will rectify them as appropriate before data analysis. The statistician will not have access to postcodes; if any additional cleaning/ sorting are required, this will be done by another member of the study team or the Priment Database Developer.

The randomisation variable will be held separately to the main body of data. It will be given to the statisticians and health economists without labels so they remain blind to allocation when they are ready to analyse the data.

**Statistical analyses**

The CONSORT1-3 flow diagram will be constructed by/ in collaboration with the Trial Manager who will have logs of general practices and service users who were invited and did and did not agree to take part in the study. It will include number of service users in each arm of the trial, and the numbers who have follow up data available.

All analyses will be on an intention to treat basis.

Statistical analyses will be carried out using Stata25

*Descriptive statistics*

Initial analyses will look at summary statistics for all variables, both overall and by randomised group. Summary statistics for continuous variables will be mean or median, (with SD, or interquartile range) as appropriate. Summary statistics for categorical variables will be frequency and percentage within each category. No statistical significance tests for baseline characteristics by randomised group will be performed. However, large imbalances between randomised groups will be noted.

*Analysis of the primary outcome*

The primary outcome will be analysed using a marginal model (using generalised estimating equations) adjusting for the baseline cholesterol, whilst accounting for clustering (GP practice) with robust standard errors. Either exchangeable or independent correlation matrix will be specified. However, if the if the assumptions regarding missing data are violated or the marginal model fails to converge , then a linear random effects model will be used, with a random effect to account for clustering by GP practice. Results will be presented as mean difference between randomised arms with 95% confidence interval and P-value.

*Analysis of the secondary outcomes*

Appropriate marginal models will be used to analyse the secondary outcomes, unless the primary analysis uses random effects models; in which case the secondary outcomes will be analysed in a similar way. The results for the secondary outcomes will be presented as estimates with 95% CIs.

If random effects models are used, for both the primary and continuous secondary outcomes, the residuals will be checked for normality. If they are not Normally distributed, outcomes may be transformed. If it is necessary to categorise outcomes, it will be done with clinical input. We will only consider categorising secondary outcomes.

For smoking status, ordered logistic regression with robust standard errors will be employed unless the primary outcome does not converge, then ordered random effects modelling will be used. The ordering will be non-smoker, ex-smoker, current smoker.

*Missing data*

The extent and patterns of missing data will be investigated. Potential bias due to missing data will be investigated initially by comparing the baseline characteristics of the trial participants with complete follow-up measurements compared to those who have no outcome data. Further analyses will look at percentage missingness for all variables by randomised group. Logistic regression accounting for clustering by general practices will be used to identify predictors of missingness. If necessary the primary analyses will be adjusted for predictors of missingness associated with the outcome. If appropriate multiple imputation 27 will be used, for example if further information can be gained using the 6 month measurement data of the outcome for those with outcome missing at 12 months. If the ICC for general practice is less than 0.01, then the clustering by practice will not be considered in the imputation model. If data are imputed, analogous analyses, using Rubin’s Rules28, to the main analyses of the primary and secondary outcomes will be used as supportive analyses.

Complete case analyses will be the main analyses from this study.

*Supportive analyses*

Controlling for baseline predictors of missingness and/ or baseline imbalances between randomised group that may be related to the outcome (if any). These may be age, sex, statin prescription, weight, antipsychotic prescription or cardiovascular risk score. If any risk score is a predictor of missingness, it will be modelled separately to the other predictors of missingness.

If the proportion of non-exposure to the intervention is greater than 5%, an appropriate analysis accounting for non-adherence will be considered. Those in the treatment as usual practices will be assigned an adherence score equivalent to no adherence to the intervention. If it is appropriate to carry out this analysis, it will be done once the statistician has been unblinded to randomised group.

**Health Economics analysis**

**Aim**

The aim of the economic evaluation is to determine if the Primrose intervention is cost-effective compared to treatment as usual, for a range of values of willingness to pay for a quality adjusted life year (QALY) gained. The primary analysis will be from a healthcare cost perspective, however we will also perform analyses including societal costs.

**Outcomes**

* Health service use (community and acute services), primary CVD preventions services, employment, housing, out of pocket health care costs and leisure activities during one year follow-up period
* EQ-5D-5L at baseline, 6 and 12 months.
* Impact on carers.
* including attendance at services, appointments and medication
* Proportions accepting and continuing CVD risk reducing medications (for example, statins, nicotine replacement therapy, bupropion and interventions)
* Proportions accepting and continuing other primary prevention interventions such as stop smoking services, weight management and brief interventions for alcohol misuse.
* Timing of interventions received within the trial: for example, prescriptions, repeat blood tests, referrals to CVD risk management services
* All hospital admissions during the trial period
* Proportions accessing primary care and community mental health services
* Medications
* Quality of life measured using the EQ 5D 5L19. This is a five item, five level questionnaire, scored 1 (no problem) to 5(extreme problems). Value sets corresponding to the responses participants give to the items are available from the Euroqol website20.
* There is also a 100 point visual analogue scale, anchored at 0 with the worst health you can imagine and 100 with the best health you can imagine. Participants mark how they feel on the day they complete the measure.

**Analyses**

All analyses will follow the assumptions made in the previous section regarding missing data and loss to follow-up. In line with the statistical analysis, the primary economic evaluation will be a complete case analysis. Adjustment for predictors of missingness and the use of multiple imputation will follow the same principles as the statistical analysis plan above. Sensitivity analyses will be conducted accounting for loss to follow up and missing data as described below (Sensitivity analyses).

*Health service resource use*

Descriptive statistics for the percentage of patients and mean number of contacts for each type of health, social care, employment, housing and out of pocket health care resources will be reported for baseline, 6 and 12 months, including data completeness. Descriptive statistics on the impact on carers will also be reported.

*Cost of the intervention*

The mean cost per patient of the Primrose intervention will be calculated from training of staff members to administer the Primrose intervention, staffing costs of each appointment, consumables such as information sheets/ pamphlets, and costs of any tests such as blood tests that need to be performed.

*Cost of health and social care service use*

Acute and community health care service use for the Primrose intervention and treatment as usual group will be calculated from patient completed questionnaires and data collected from patient records at baseline, 6 months and 12 months. These will be costed for each patient using unit costs from the most recent Unit Costs of Health and Social Care published by the Personal Social Services Research Unit29 and reference costs30. Mean cost per patient for the Primrose intervention and treatment as usual groups will be reported by type of service use at 6 and 12 months. Total costs and 95% CIs will be adjusted by baseline service use. The cost of any medication prescribed as part of the Primrose intervention will be taken from the British National Formulary31. Carer costs will be costed using the human capital cost ie cost of time spent in caring activities multiplied by the average wage.

*QALYs*

We will calculate the mean cost per quality adjusted life year (QALY) gained of this nurse led intervention compared to treatment as usual over 12 months. QALYs will be calculated using the ED-5D-5L and the formula developed by EuroQol. We will calculate the mean area under the curve for each group from baseline to 12 months, controlling for any baseline differences using regression analysis including clustering for GP practices.

*Confidence intervals*

Confidence intervals for mean costs (calculated using regression analysis clustering for GP practices) and QALYs will be calculated using non-parametric bootstrap with replacement.

*Incremental cost-effectiveness ratio (ICER)*

The mean costs and QALYs calculated above will be used to calculate the mean incremental cost per QALY gained of Primrose intervention compared to treatment as usual.

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

The results of the non-parametric bootstrap will be presented on a CEP. A CEAC will also be constructed using the bootstrap data from a range of values of willingness to pay for a QALY gained. The probability that the Primrose intervention is cost-effective compared to treatment as usual at a willingness to pay for a QALY gained of 20,000 and 30,000 will be reported.

*Supportive analysis: Relationship between number of sessions, cost and outcomes*

The aim of this analysis is to examine if there are increasing or diminishing marginal returns for each unit of investment in the intervention. It will provide additional information to the statistical analysis of non-exposure to the intervention, described above. The analysis will provide information on if there is a specific number of appointments or costs that represent the most efficient input (staff labour) for output (QALYs or reduction in cholesterol).

To test this we will plot the relationship between the following inputs and the outputs (i) reduction in cholesterol and (ii) increase in QALYs, as a result of the intervention:

1. Number of sessions that each patient attended.
2. Total cost of intervention (number of sessions multiplied by cost of clinical staff delivering the intervention divided into health care assistant (HCA) and practice nurse).
3. Number of sessions plus other services accessed (e.g. smoking cessation, weight loss).

Once inputs and outputs have been plotted the most appropriate algorithm for identifying the point of diminishing returns will be selected and the results reported.

*Subgroup analysis*

Patients in the intervention group may have received the intervention from a practice nurse or a HCA. Descriptive statistics for the HCA versus practice nurse will be reported. We will conduct an analysis comparing the mean incremental cost per and outcome gained for HCA compared to practice nurse delivering the intervention. The net monetary benefit for a range of values of willingness to pay for an outcome gained will be reported for HCA, practice nurse and treatment as usual.

*Sensitivity analyses*

If any key assumptions become apparent during the analysis these will also be tested for as part of the sensitivity analyses. Costs will also be reported alongside other outcomes. A secondary analysis including costs from the societal perspective (adding employment, housing and out of pocket costs) will also be conducted. An additional analysis including carer costs will also be included. Results accounting for missing data using multiple imputation, as set out in the statistical analysis plan above, will also be reported.

*Long term modelling*

Results from the trial data will be fed into the 10 year Primrose cardiovascular disease economic model. Costs, QALYs, mortality and CVD related deaths for Primrose compared to TAU over 10 years will be reported. We will calculate the 10 year ICER for Primrose compared to TAU and report a CEAC and CEP generated using probabilistic sensitivity analysis

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