Statistical Analysis Plan

TRIAL FULL TITLE	The use of cardiac rehabilitation services to aid the recovery of colorectal cancer patients: A pilot randomised controlled trial (RCT) with embedded feasibility study
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TRIAL STATISTICIAN	Petra Rauchhaus
TRIAL CHIEF INVESTIGATOR	Dr. Gill Hubbard
SAP AUTHOR	Petra Rauchhaus

Name: Gill Hubbard

Signed: XXXX

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Abbreviations and Definitions

AE	Adverse Event
ANCOVA	Analysis of Co-Variance
CI	Confidence Interval
CRF	Case Report Form
EoI	End of Intervention
FACT-C	Functional Assessment of Cancer Therapy - For patients with Colorectal cancer
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
HADS	Hospital Anxiety and Depression Scale
NHS	National Health Service
RCT	Randomised Clinical Trial
SAP	Statistical Analysis Plan
SPAQ	Scottish Physical Activity Questionnaire

Introduction

Preface

The research question is: Is using an existing cardiac rehabilitation service delivered by a cardiac multi-disciplinary team (e.g. cardiac physiotherapist, cardiac nurse) with support from a cancer-exercise specialist, to mixed classes of cancer/cardiac patients (with some components tailored to meet cancer patients' needs and delivered by a cancer nurse), an acceptable model of rehabilitation to aid the recovery of colorectal cancer patients? Our ultimate aim was to conduct an RCT of the clinical and cost effectiveness of utilising an existing cardiac rehabilitation service versus usual care (no routine NHS rehabilitation provision) to aid the recovery of colorectal cancer patients. Given the uncertainties surrounding such an RCT, we proposed to conduct a pilot RCT with embedded feasibility study to inform the design and conduct of a larger scale trial for which separate funding would be required. In this proposed preliminary study, we were seeking to undertake a phased programme of work comprising of intervention testing and feasibility work (Phase 1) and a pilot trial with a process evaluation (Phase 2) within the context of planning a definitive large scale RCT. We also piloted an economic evaluation because interventions have a cost component that needs to be considered when evaluating the effectiveness of the intervention to reduce the burden of a disease.

Purpose of the analyses

This SAP describes the analysis of the pilot RCT Phase II data. It will compare intervention versus control. to provide data to the planning of a larger RCT, and will be included in the clinical study report.

Objectives and Endpoints

Study Objectives

- To determine eligibility, consent, recruitment and retention rates and speed of recruitment.
- To determine likely contamination across trial arms.
- To determine completion rates for proposed outcomes measurement tools at baseline and follow up.
- To provide data for sample size calculation for a definitive RCT.
- To test intervention fidelity according to study protocol.
- To assess the extent to which intervention and trial procedures can be integrated into routine clinical practice.

- To conduct a preliminary economic evaluation of the cancer rehabilitation programme.

Endpoints

Primary outcome: physical activity

Physical activity was assessed using the Actigraph GT1M accelerometer (Actigraph LLC, Pensacola, Florida). Participants were asked to wear an accelerometer for 7 days on 3 occasions (T0 - before patients are randomised to the intervention or control group; T1 - at the end of the intervention (data will be collected 12 weeks after baseline for patients in the control arm); and T2 - 3 months later). Physical activity was also assessed subjectively using the Scottish Physical Activity Questionnaire (SPAQ) to ascertain the types of activities participants engaged in.

Secondary outcomes

Quality of life: EQ-5D was used to measure quality of life.

Anxiety and depression: The Hospital Anxiety and Depression Scale (HADS), which consists of 14 questions, 7 for anxiety and 7 for depression, was used to measure anxiety and depression

Fatigue: The Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F), which is a 13-item fatigue FACT subscale, was used to measure cancer-related fatigue.

Cancer Specific Quality of Life was assessed using the Functional Assessment of Cancer Therapy – Colorectal (FACT-C) Questionnaire.

Physical activity self-efficacy, which is the belief that one can engage in, and meet physical activity goals, was also measured.

According to the behaviour motivation hypothesis, perceived risk is positively and directly related to health behaviour. Risk perception of suffering from diseases has been found to play an important role in the development of intentions to perform physical activity among older adults and in explaining cancer-related behaviours. Given the lack of agreement about quality of methods of measuring cancer risk perception, we included absolute (i.e. estimation of personal risk) and comparative measures (i.e. comparison of personal risk to other people's risk). We also included conditional (i.e. rating the probability that a certain event (e.g. cancer recurrence) will occur given their adaptive behaviour (e.g. increasing physical activity) is, or is not, performed) and unconditional (i.e. rating the probability that a certain event will occur without specifying the adaptive behaviour) measures.

Study Methods

General Study Design and Plan

The intervention was rehabilitation for colorectal cancer patients in a cardiac rehabilitation setting. An 8/12-week (number of weeks depending on research site) post-hospital rehabilitation programme was delivered by a member of the cardiac multi-disciplinary team (e.g. cardiac physiotherapist, cardiac nurse or dietician) to a mixed class of cancer/cardiac patients in a cardiac rehabilitation setting with some components specifically tailored for cancer patients and delivered by a cancer nurse. Rehabilitation classes were delivered twice weekly or once a week depending on research site. The rehabilitation programme comprised of 60/90 minutes (depending on research site) of exercise training (aerobic and muscle strengthening) delivered to a mixed class of cancer/cardiac patients by a cardiac physiotherapist.

Participants set individual physical activity goals with advice and support from the physiotherapist.

The exercise class was followed by 30/60 minutes (depending on research site) of education (e.g. stress management, diet, drug therapy, smoking cessation, benefits of exercise and relaxation). A colorectal cancer nurse delivered some educational sessions (e.g. cancer therapies) to cancer patients. These educational sessions were either be delivered to a group of cancer patients or one-to-one by telephone

Patients randomised to the control arm of the pilot received ‘Staying healthy after bowel cancer’ booklet by Bowel Cancer UK, which includes a section on ‘staying fit’.

Outcome and process measures were administered on three occasions: i) T0 - before patients were randomised to the intervention or control group, ii) T1 - at the end of the intervention (data was collected 12 weeks after baseline for patients in the control arm) and iii) T2 - 3 months later. Participants were asked to wear an accelerometer for 7 days on 3 occasions (T0 - before patients were randomised to the intervention or control group; T1 - at the end of the intervention (data was collected 12 weeks after baseline for patients in the control arm); and T2 – 3 months later.

Randomisation and Blinding

Patients were randomised to the intervention or control group after they consented to participating in the study and after baseline primary and secondary measures were collected. Randomisation with stratification by centre was conducted by Tayside Clinical Trials Unit. Due to the nature of the intervention, the trial was not blinded.

Sample Size

As this is a pilot RCT with embedded feasibility study, a formal power calculation is not appropriate; the study is not powered to detect a clinically meaningful difference in the primary outcome between the rehabilitation and usual care groups.

Rather the aim is to provide robust estimates of the likely rates of recruitment and retention, and to yield estimates of the variability of the primary and secondary outcomes to inform power calculations for a future large-scale trial. We will therefore use the pilot trial (Phase 2 of the proposed study) in order to provide a quantitative estimate of the intervention impact (relative to control) in order to inform the sample size estimation for a definitive trial.

For the pilot RCT (Phase 2), we believe that over 6 months across the 3 sites we will be able to approach 250 patients. From their responses we will be able to determine whether it is possible to recruit patients and also estimate eligibility, consent, participation and retention rates and speed of recruitment for a future large scale trial.

We have conservatively estimated that we will recruit approximately 66 patients. Cancer clinicians estimate that approximately one third will be ineligible (e.g. have advanced disease) and based on recruitment to a RCT about physical activity with cancer patients in Scotland (27% recruitment rate) and a trial involving colorectal cancer patients within 3 months of completing surgery conducted in Canada (35% recruitment rate) we estimate that about a third of eligible patients will consent. Thus, we estimate that in Site 2 and 3 26 patients in each site will be recruited (13 intervention group and 13 control group). In Site 1, we estimate that 14 patients will be recruited (7 intervention group and 7 control group). However, a recruitment rate of 71 per cent, which was achieved in a study of a personalised lifestyle programme for colorectal cancer survivors in Scotland would provide a total of 118 patients

General Considerations

Timing of Analyses

The final analysis will be performed after all data have been entered and the database has been locked.

Analysis Populations

Analysis population will be all available subjects on an intention-to-treat basis for the outcome measures.

Missing Data

This is an intention to treat study so all non compliers, withdrawn patients or missing data will be analysed by imputation. Missing data will be handled using multiple imputation methods, assuming that the assumption of data missing at random is met. We will also do a completed cases only analysis.

Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), number of missing records, mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by subject and treatment and where appropriate by visit number within subject.

All summary tables will be structured with a column for each treatment in the order (Intervention, Control) and an additional column for the total population relevant to that table/treatment, including any missing observations'

Demographic and Baseline Variables

Baseline characteristics for patients are: Age, gender, colorectal cancer diagnosis, treatment for colorectal cancer (Colon or rectal surgery; laparoscopic or open surgery; Temporary, permanent stoma or no stoma; Chemotherapy or no chemotherapy).

Efficacy Analyses

Scoring for outcomes follows the scoring instructions given for each questionnaire. Where no such instruction is present, the following approach will be taken:

If no more than 20% of questionnaire items are missing, the missing items will be replaced by the mean of the remaining items to build a sum score. Where more than 20% of the items are missing, the sum score will be set to missing.

Data for continuous outcome measures will be assessed for normality prior to analysis. Transformations of the outcome variables will be used where necessary if these are not normally distributed.

Outcomes will be analysed as baseline versus end of intervention (EoI) and baseline versus 3 months after intervention.

Continuous outcome will be using multiple linear regression (i.e. analysis of covariance, ANCOVA). Intervention effect differences will be reported with 95% confidence intervals (CIs) and p-values. The baseline characteristics will be explored for meaningful differences between trial arms. Where these are considered meaningful and important these variables will be entered into a stepwise selection procedure and the primary analysis will be adjusted for these variables if they are statistically selected (usual criteria $p < 0.05$).

Outcome measurements across multiple study visits (baseline, EoI, 3 months) will also be analysed using mixed effects (repeated measures) regression models. Models will include fixed effects for intervention group, time point, and their interaction, plus random effects for each subject to account for repeated measures, and will assume a general covariance structure. Each model will also include fixed effects for baseline values of the outcome, other covariates, in the same way as described above for ANCOVA models.

Ordinal and binary outcomes will be analysed as described above using logistic regression.

Primary Efficacy Analysis

The primary outcome is the change in physical activity recorded with accelerometers between baseline and EoI. The variables to be analysed are minutes spent each week on light moderate and vigorous exercise as well as minutes spent sedentary and will be analysed using multiple linear regression. The model will have outcome as the dependent variable with baseline values as a covariate along with intervention group (Intervention/Control), and hospital as fixed effects.

Confounding variables to be assessed for importance are: Cognitive risk perception, Affective risk perception, Physical Activity self-efficacy, age, sex, surgery type (Colon or rectal surgery), Surgical intervention (e.g. laparoscopic or open surgery); stoma (Temporary (a loop ileostomy), permanent stoma or no stoma) and medical intervention (Chemotherapy or no chemotherapy).

Secondary Efficacy Analyses

- SPAQ: All minutes of activity during the previous week will be summed up for analysis to provide a total minutes of activity in a week. In addition, the activities will be summed up separately for each week and analysed... Where no entries were made for a day, it will be assumed that there was no activity (0 minutes) in this category.

- FACT-C: The questionnaire consists of 5 subscales (Physical Well-being (PWB), Social/Family Well-being (SWB), Emotional Well-being (EWB), Functional Well-being (FWB), Additional Concerns (AC)). Composite scales are also calculated as described in the guidelines. As emotional well-being was not collected in this trial, composite scores including those questions were not created.

- FACIT-F: The questionnaire consists of 13 items and will be calculated as described in the guidelines.

- Activity Self-efficacy: If no more than 20% of the items are missing, a sum score will be created from all items in the questionnaire and used for analysis.

- EQ-5D: Physical domains will be analysed separately using logistic regression as described above. The health state will be analysed using ANCOVA as described above. In addition, the health utility score will be created and analysed.
- HADS: Two separate scores for anxiety and depression will be created and analysed.
- Risk perception: Three distinct scores will be created: Cognitive risk perception, affective risk perception and perceived severity as a sum of 2 questions each. Each score will only be created if both items are present. Scores will be analysed as described.
- Service use: This data will be analysed by the health economics team and is not part of this SAP.

Safety Analyses

Adverse Events

Adverse events (AE) will be coded with MedDRA 16.1. Where more than one diagnosis is present in the AE description, the AE will be split with all the descriptors kept the same for all diagnosis. Adverse events will be reported by primary System Organ Class (SOC) and Preferred Term (PT).

Subjects will be counted only once when calculating the incidence of AEs. An overview table will be created counting the number of adverse events by system organ class and preferred term.

Descriptors for Adverse events will be tabulated separately as described for categorical variables in section 8. The total number of AEs will be used as basis for tabulation.

Serious Adverse Events

Serious Adverse Events (SAE) will be reported with all other AEs as described in section 10.1. However, they will be reviewed for the trial report on a case by case basis by the PI.

Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

Technical Details

All analysis will be performed using SAS 9.3. All data, analysis programs and output will be kept on the Mackenzie Server and backed up according to the internal IT SOPs.

Analysis programs will be required to run without errors or warnings. The analysis programs for outcomes will be reviewed by a second statistician, and any irregularities within the programs will be investigated and fixed and date of finalised analysis programs will be signed and recorded.