CanACT Trial

Statistical Analysis Plan

1.0

Started: 6th December 2016
Edited: 4th July 2017

Version History Log

Version	Date Implemented	Details of change
0.1	13/12/2016	
0.2	30/01/2017	
0.3	07/04/2017	Implemented RO's comments.
0.4	27/04/2017	Implemented feedback from TMG.
0.5	06/06/2017	Implemented feedback from MS and MK
0.6	04/07/2017	Implementing final feedback from TMG.
1.0	04/07/2017	

Contents

1. Study Summary

For full details see the protocol (version 9.0 21.06.2016).

Title	CanACT: The feasibility of recruiting and undertaking a randomised controlled trial to help with coping using two talking interventions, ACT or a Talking Control for people receiving treatment to control their cancer symptoms"
Short title	CanACT Trial
Chief Investigator	Marc Serfaty
Statisticians	Senior statistician: Prof Rumana Omar Trial statistician: Ms Victoria Vickerstaff
Health economist	Dr Anna Gola
Design	A single blind, parallel group, exploratory 2 arm randomised controlled trial, nested qualitative study and economic evaluation.
Primary objective	a) To test the feasibility of recruitment to/and attrition in people with advanced cancer into a randomised controlled trial of TAU plus ACT compared to TAU plus TC b) To explore the feasibility of providing a therapist delivered intervention; individual ACT or TC c) To assess the usefulness and acceptability of a number of clinical and economic outcomes d) To determine whether data generated from outcomes in this trial support a larger RCT into the clinical effectiveness of ACT in advanced cancer patients
Primary Outcome Measure	Functional Assessment of Cancer Scale (FACT-G) at 3 months
Population	People aged >18 years with any cancer diagnosis screened using the Functional Assessment of Cancer Scale (FACT-G; Cella et al, 1994) with total scores below 81 (Brucker et al, 2004) will be assessed for eligibility.
Sample size	Numbers are chosen on pragmatic grounds as sufficient to demonstrate feasibility in terms of recruitment, acceptance of randomisation and attrition. We shall aim to recruit 54 patients, approximately 27 into each arm, and assuming 17% attrition anticipate that 45 patients complete the trial.
Randomisation	We shall randomise 54 patients to either TAU plus either TC (n=27) or TAU plus ACT (n=27).
Clinical Trials Gov	ISRCTN13841211

2. Analysis plan in protocol

Data analysis will be descriptive. Given this is a feasibility study, our main outcomes of interest are rate of recruitment, acceptability of randomisation, process of therapies, level of attrition from therapy and research, patients' experience of therapy and the function of the ACT manual. However, we shall also estimate differences (with confidence intervals) in our main clinical and social outcomes between the trial arms at 3 months, using linear regression adjusted for baseline values of the outcome or suitable alternatives in case of non-normally distributed data.

This will inform the sample size calculation for a large-scale RCT. We will also explore the possibility of including the 6-month clinical and social outcome data depending on the attrition levels in our analysis using regression models that can incorporate repeated measurements. We will investigate if attrition levels are similar across the trial arms and examine the characteristics of participants who drop out and reasons for attrition where available. This will help us to understand the pattern of missingness in the data and to make appropriate plans to handle missing data for the large-scale RCT.

3. Introduction

3.1. Purpose and scope of the statistical analysis plan

This document describes the main statistical analyses to be applied to the data from CanACT Trial.

3.2. Writing the Statistical analysis plan

This Statistical Analysis Plan was written by Victoria Vickerstaff and Rumana Omar. The plan was agreed by the Trial Management Group (To be sent to the TMG).

3.3. Analysis organisation

Unmasking of the data and the final analysis will be performed after the last patient has completed follow-up, all relevant data have been entered, checked and locked, the analysis plan has been finalised and approved, and the analysis programs prepared as much as possible.

The primary analysis will be performed independently by two statisticians (VV and RO) to ensure its accuracy.

3.4. Data checking

Before analysis, basic checks will be performed to check the quality of the data. Incomplete or inconsistent data include:

- Missing data
- Data outside expected range
- Other inconsistencies between variables e.g. in the dates the questionnaires were completed

If any inconsistencies are found, the corresponding values will be double checked with the researchers and corrected if necessary. All changes will be documented by the trial statistician.

4. Description of the trial

4.1. Duration of the treatment period and frequency of follow up

The trial duration per participant is 6 months. Participants complete all questionnaires at baseline, and 3 and 6 months after randomisation. The primary outcome measure is also completed at 1.5 and 4.5 months after randomisation.

5. Data collection

5.1. Primary outcome measures

The primary outcome measure is change in functioning in several areas of life (physical, social, emotions and general activity) as measured by the Functional Assessment of Cancer Scale, FACT-G (Version 4; Cella et al, 1993) at 3 months.

5.2. Secondary outcome measures (table 1)

The secondary outcome measures are:

a) Psychological wellbeing: Kessler-10 (K10; Kessler et al, 2003), a 10-item self-report global measure of psychological distress.

b) Physical function:

Two minute walking test: the distance, measured in meters, walked in 2 minutes (walking continuously, in a controlled space, at own speed, using an aid if necessary). One minute sit to stand test: number of times a person can stand up and sit down from a standardised chair over one minute. (Leung et al 2006, Oldervoll et al 2006)

c) Acceptance and Action Questionnaire II (AAQII; Bond et al, 2011): A 10 item scale measuring experiential avoidance that assesses willingness to accept undesirable thoughts and feelings, whilst acting in congruence with personal values and goals

d) Valued Living Questionnaire (VLQ; Wilson et al 2010) – 10 items representing different domains of living, in which each participant is asked to rate each domain for its importance to their own values, and how consistent their actions are with these values.

Other measures

a) Prescribed medications: dose and changes in prescribed medication (analgesics, antidepressants, anxiolytics and major tranquillisers).

b) Other psychological therapies. Any psychological intervention received during the trial (e.g. hypnotherapy, art therapy, counselling, CBT, spiritual healing, or relaxation).

c) Complementary therapies: any received during the trial (e.g. aromatherapy, massage, reiki, reflexology, herbal remedies).

d) Gym and physical therapies: referral for exercise may affect physical function.

e) Expectations of therapy at baseline: (Borkovec, Nau, 1972) Participants will predict on a 7 point Likert scale the degree to which they think they may or may not improve

f) Treatment preference at baseline: recorded on a 4 point Likert scale (Serfaty 2009).

g) Dropout from therapy and attrition: Reasons for not attending therapy sessions or loss to follow up (e.g. dislike of therapy, deteriorating health, death)

h) Patient satisfaction: a 5 point scale to record whether ACT seemed useful.

i) Experience of therapy: the 6 item Counselling Questionnaire (Corney, 1999) to rate experience of therapy.

j) Therapy components Checklist for ACT and TC. These checklists are collected at the end of each therapy session.

The measures are collected at the following times:

Table 1 Timing of data collection

Measures	Baseline	1 ½ months post baseline	Post-intervention (3 months)	4 ½ months post baseline	Follow-up (6 months)
Functional Assessment of Cancer Therapy - General	✓	✓	✓	✓	✓
Kessler Psychological Distress Scale	✓		✓		✓
2 minute walking test	✓		✓		✓
1 minute sit to stand test	✓		✓		✓
Acceptance and Action Questionnaire-II	✓		✓		✓
Value Living Questionnaire	✓		✓		✓
EQ5-D	✓		✓		✓
ICECAP supportive care measure	✓		✓		✓
Client Service Receipt Inventory	✓		✓		✓
Satisfaction with care			✓		
Counselling questionnaire			✓		
Expectation of therapy	✓				
Treatment preference	✓				
Assessment of blindness			✓		✓
Attrition			✓		✓
Other therapies used			✓		✓

The health economic measures EQ-5D, ICECAP-Supportive Care measure and Client Service Receipt Inventory will be analysed by the health economist, Anna Gola, as described in the section titled 'Health economics plan' below. (*To add the health economic plan)*

5.3. Visit windows

In the event that the scheduled visits are not precisely 1.5, 3, 4.5 and 6 months after baseline, we will accept completed CRFs that are within ± 3.25 weeks (23 days) of the due date. 3.25 weeks was chosen as this is the mid-point between the follow-ups.

6. Data analysis plan – Data description

6.1. Brief description of proposed analyses

For the primary analysis, we will analyse participants under the intention-to-treat assumptions (i.e. based on the initial treatment assignment and not on the treatment eventually received).

6.2. Recruitment and representativeness of recruited patients

A CONSORT flow chart will be constructed. This will include the number of patients approached and assessed for eligibility, number of patients agreeing to enter the trial, then by treatment arm: the

number continuing through the trial, the number withdrawing at each time point, the number lost to follow-up at each time-point and the numbers excluded/ analysed.

6.3. Baseline comparability of randomised groups

Summary measures for the baseline characteristics of the ACT and talking control groups will be presented as mean and standard deviation for continuous, symmetric variables; medians and inter-quartile ranges for continuous, skewed variables; and frequencies and percentages for categorical variables. These summaries will be based on observed observations only and the number of missing observations will be reported.

6.4. Adherence to allocated treatment and attrition

Some loss to follow-up is expected over 3 months. The proportion of participants missing each outcome will be summarised in each arm and at each time point.

Potential bias due to missing data will be investigated initially by comparing the baseline characteristics of the trial participants who have complete follow-up measurements with those who have incomplete follow-up or no outcome data.

If differences are observed in the participants' characteristics in this descriptive analysis, factors which are likely to be associated with the outcome will be included in a multilevel logistic regression analysis (with missing yes or no as outcome) to identify predictors of missing data.

Reasons for withdrawal from treatment will be summarised where available.

This will help us to understand the pattern of missing data and to make appropriate plans to both minimise and manage missing data on a large-scale RCT.

6.5. Adverse event reporting

Adverse events (AE), adverse reactions (AR), serious adverse events (SAE) and serious adverse reactions (SAR) will be summarised.

7. Data analysis plan

Data analysis will be descriptive. Given this is a feasibility study, our main outcomes of interest are rate of recruitment, acceptability of randomisation, process of therapies, level of attrition from therapy and research, patients' experience of therapy.

7.1. Analysis of primary outcome

We emphasise that this is exploratory in that we could not aim to test the effectiveness of the intervention in this small pilot trial. The primary outcome of the trial is the FACT-G measurement at 3 months. The main statistical analysis will estimate the difference in the FACT-G score between patients randomised to ACT and talking control by intention to treat at 3 months, using observed values only.

Regression methods (analysis of covariance) that adjust for randomisation factors (centre) and the baseline value of the outcome (FACT-G) will be used. In the case of non-normally distributed data,

suitable alternatives will be used. The estimated differences between the arms, with confidence intervals, will be presented.

Presentation of all findings will be in accordance with the latest CONSORT statement. These results will inform the sample size calculation for a large scale RCT.

7.2. Analysis of multiple time points

We will also explore the possibility of including the 6-month clinical outcome data depending on the attrition levels in our analysis using regression models that can incorporate repeated measurements.

If appropriate, we will use mixed effect models, using all patient outcome data over the 6-months, to investigate how the primary outcome changes over time. Such models allow analysis of repeated outcome measurements data (recorded every 1.5 months over 6 months) while taking into account the correlation between measurements from the same patient. By using interaction terms between randomisation group and time, we will also be able to investigate differences between groups over time.

7.3. Model checking

The model assumes that the residuals are normally distributed and homoscedastic. This will be checked using residuals plots. If substantial departures from normality occur, a transformation of the outcome variable will be considered. We will also investigate whether there are any outliers or observations with high leverage (if an observation has a particularly "extreme" covariates). Sensitivity analysis will be carried out if necessary.

7.4. Missing items in the scale

The scoring algorithm for the FACT-G instrument accounts for any missing items. For each subscale, the scoring algorithm prorates the scores, by averaging the available items. This is equivalent to using person mean imputation.

8. Other analyses

8.1. Sensitivity analysis

Depending on the number of dropouts and deaths over the 6 months, we will also explore the option of fitting a joint model using the primary outcome (FACT-G) and a survival outcome. If appropriate, we will also perform a joint model excluding the participants that dropped out.

We will also perform an analysis adjusting for the number of therapy sessions the participants received.

We will calculate the intra cluster correlation coefficient to describe the therapist clustering, if any.

8.2. Analysis of secondary outcomes

Similar analyses will be conducted for the secondary outcomes using appropriate models for the type of outcome. As for the primary analysis, we will check the model assumptions.

Results from all secondary analyses will be presented as estimates with confidence intervals. P-values will not be reported.

8.3. Missing items in scales and subscales of secondary outcomes

The number and percentage of complete data for the secondary outcomes will be reported. If there are missing values we will initially use any missing value guidance provided for the secondary outcome scales.

Otherwise, we will use individual imputation if 20% or fewer items are missing for an individual in a questionnaire (Gottschall et al. 2012, Shrive et al. 2006). For example, in a scale with 10 items, imputation will be applied to individuals with 1 or 2 items missing. The scale score will be calculated based on the complete values and these replacements. Depending on the proportion of patients with missing data, either a single imputation (person mean imputation) or multiple imputation will be used.

9. Software

The statisticians will download the data from the trial specific online database provided by Sealed Envelope into a format suitable for Stata. All the statistical analysis will be performed using Stata version 14 (or above).

10. General statistical considerations

All statistical tests and confidence intervals will be 2-sided. Confidence intervals will be at the 95% level.

11. References

Gottschall, Amanda C., Stephen G. West, and Craig K. Enders. "A comparison of item-level and scale-level multiple imputation for questionnaire batteries."Multivariate Behavioral Research 47.1 (2012): 1-25.

Shrive, Fiona M., et al. "Dealing with missing data in a multi-question depression scale: a comparison of imputation methods." BMC medical research methodology 6.1 (2006): 57.