DOI:
10.1186/s13063-025-08734-9

Document Version
Publisher's PDF, also known as Version of record

Trials

UPDATE

Open Access

Statistical analysis plan for a pragmatic randomised controlled trial comparing enhanced acceptance and commitment therapy plus (+) added to usual aftercare versus usual aftercare only, in patients living with or beyond cancer: SUrvivors' Rehabilitation Evaluation after CANcer (SURECAN) trial

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Abstract

Background The aim of the SURECAN trial is to evaluate a person-centred intervention, based on Acceptance and Commitment Therapy (ACT Plus (+)), for people who have completed treatment for cancer with curative intent, but are experiencing poor quality of life. We present the statistical analysis plan for assessing the effectiveness and cost-effectiveness of the intervention in improving quality of life 1 year post randomisation.

Methods and design SURECAN is a multi-centre, pragmatic, two-arm, partially clustered randomised controlled superiority trial comparing the effectiveness of ACT + added to usual care with usual aftercare. The target sample size is 344 (172 per arm), randomised centrally in a 1:1 ratio.

Results The primary outcome is the total score of the Functional Assessment of Cancer Therapy scale-General (FACT-G) at 52 weeks, analysed using a partially nested mixed-effects model with heteroskedastic error terms. Secondary outcomes include scores at 16 and 52 weeks: FACT-G subscales; Fear of Cancer Recurrence Inventory (FCR4); positive and negative Impact of Cancer scales (IOCv2); Hospital Anxiety and Depression scale (HADS); Chalder Fatigue Scale (CFQ); and physical activity, measured on a modified version of the Godin scale. Health economic analyses will determine the incremental cost-effectiveness ratio (ICER) in terms of quality-adjusted life years (QALYs) derived from the Euroqol 5-Dimension 5-Level (EQ-5D-5L) compared to usual care at 52 weeks.

Discussion This manuscript is the statistical analysis plan (SAP) and economic evaluation for the SURECAN trial. Any exploratory or post hoc analyses will be identified as such in the respective analysis report.

Trial registration The trial was prospectively registered. ISRCTN: ISRCTN67900293. Registered on 09 December 2019.

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Keywords Statistical analysis plan, Cancer survivor, Quality of life, Cost-effectiveness, Acceptance and commitment therapy, Pragmatic trial, Partially clustered design

Introduction

At the end of 2008, an estimated 2 million people in the UK were living with and beyond cancer, often referred to as cancer survivors [1] and cancer prevalence in the UK is projected to grow by 3% a year between 2010 and 2040 [2]. Those living with and beyond cancer face challenges related to their physical health, mental health, relationships, finances and employment which can all impact their quality of life (QoL). A national survey of adult cancer survivors in England evaluated QoL, identifying several areas of concern. These encompassed fears around cancer recurrence (reported by 57%), fatigue (43%), concerns regarding body image (31%) and low levels of physical activity (30% reporting doing no physical activity) [3]. Poor QoL has also been linked to unemployment amongst individuals of working age [4], with as many as one-third experiencing job loss following cancer diagnosis [3].

There is considerable variation in UK National Health Service (NHS) provision of post-treatment care [5, 6], and available interventions show only moderate effectiveness, often being inaccessible [6, 7]. Two significant policy documents have underscored the importance of addressing cancer survivorship. The National Cancer Survivorship Initiative aimed to decrease the number of individuals with unmet physical and psychological support needs whilst increasing the employment rate amongst cancer survivors [5]. The initiative recommended self-management strategies following appropriate assessment and treatment, alongside the implementation of physical activity programmes and vocational support [5]. Similarly, the Independent Cancer Taskforce, established by NHS England, advocated for every cancer patient to receive a personalised "recovery package" of aftercare, incorporating tailored pathways for follow-up care [8].

Acceptance and Commitment Therapy (ACT) lends itself to addressing the challenges faced by cancer survivors and has shown promise in other chronic conditions [9] as well as in a trial of patients receiving cancer treatment [10]. ACT combines mindfulness techniques with strategies to increase psychological flexibility despite challenging thoughts and emotions, encouraging individuals to accept the things that they cannot change (e.g. that the cancer may return) and take committed action towards things they can change (i.e. meeting their life goals, despite having had cancer) [11].

Our programme development grant examined 16 systematic reviews of non-pharmacological interventions targeting the improvement of quality of life in cancer survivors, with only exercise and cognitive behaviour therapy demonstrating consistent efficacy, albeit with modest effect sizes and limited long-term follow-up [7]. To date, there appear to have been no large randomised controlled trials of ACT therapy in cancer survivors, where the intervention is delivered to participants one to one by trained therapists [12].

An ACT intervention that additionally incorporates an exercise intervention [13] and work support [14] (for those who require it), is person-centred and applicable to patients with any cancer type would be an important contribution to the NHS. We define this intervention as ACT Plus (+). Our work around the development of this intervention has been published [15, 16].

The SURECAN trial is a multi-centre, pragmatic, two-arm, partially clustered, randomised controlled superiority trial comparing the effectiveness of ACT + added to usual care with usual aftercare care only on quality of life, as measured by the Functional Assessment of Cancer Therapy scale-General (FACT-G), at 52 weeks [15]. Follow-up of all participants will be completed in November 2024, with analysis completed by April 2025.

Here we present the statistical analysis plan (SAP) for the clinical effectiveness and cost-effectiveness of the SURECAN trial. Writing of the SAP follows the statistical analysis plan guidelines by Gamble et al. [17]. The SAP (version 1.0 dated 16/09/2024) was written in conjunction with the SURECAN protocol (version 5.0 date 02/10/2023) [15].

Methods and design

Study objectives

The primary objective is to evaluate the effectiveness of ACT + in improving quality of life at 1 year, as measured by the total score of the FACT-G scale [18], compared to usual care alone in patients living with and beyond cancer.

Secondary objectives include examining:

- The effectiveness of ACT + in improving FACT-G score at 16 weeks post randomisation (approximately end of treatment).
- The effectiveness of ACT + in improving secondary outcomes at 16 weeks (approximately end of treatment) and at 1 year (52 weeks).

- The effectiveness of ACT + in improving FACT-G total score at 52-week follow-up amongst those who received at least 4 ACT + sessions.
- Whether the effectiveness of ACT + varies according to age, gender, type of cancer, severity of depression, and the effects of loneliness and worry in relation to COVID-19 at baseline for the primary outcome of total score on the FACT-G. For the subsample of breast cancer participants, a subgroup analysis will be included based on cancer treatment received.
- To describe the safety of ACT + in addition to usual care compared to usual care alone.
- To descriptively explore clinical effects in the subsample of participants included up to 2 years.

Health economics objectives include the determination of:

- The incremental cost-effectiveness ratio (ICER) in terms of quality-adjusted life years (QALYs) compared to usual care at 52-week follow-up.
- The impact of ACT + on health and societal costs at 16- and 52-week follow-up.
- The cost-effectiveness of ACT + with usual care in terms of FACT-G total score compared to treatment as usual at 16 and 52 weeks.

Trial design

The protocol for the SURECAN trial has been published [15]. In brief, this is a pragmatic, parallel-group, two-arm, partially clustered, randomised controlled superiority trial, with an internal pilot, to determine whether ACT + in addition to usual aftercare versus usual aftercare only improves quality of life, as measured by the FACT-G, at 1-year follow-up in patients living with and beyond cancer. This is a partially clustered/nested design, whereby individuals randomised to treatment group are nested within therapist delivering the intervention, but no such nesting occurs in the control arm. Participants are followed up at 7 weeks (approximately mid-therapy), 16 weeks (end of therapy) and 52 weeks after randomisation. Additional outcome data will be collected at the 2-year mark for participants who will have reached 2 years from randomisation by the time the last recruited participant completes their 52-week follow-up.

The internal pilot is planned after a 6-month recruitment period. There is no planned formal interim analysis comparing outcome data between the intervention and control group. The final analysis will take place once all the follow-up data has been collected, the analysis plan is formally agreed, the data cleaned, and database locked.

Inclusion and exclusion criteria

Participants will be recruited from hospital clinics. Patients attending a follow-up cancer care and meeting the inclusion criteria (Table 1) are eligible for recruitment into SURECAN.

Intervention

Participants in the control arm receive usual aftercare. Usual aftercare varies considerably between hospitals and cancer groups. We previously conducted a survey of oncology health care practitioners which found that dietary advice, medical assessment, exercise advise, counselling and end of care assessments were offered to varying degrees within and between specialities and sites. Mindfulness, work support and cognitive behavioural therapy were rarely offered [6].

In the intervention arm, participants will receive ACT + and usual care. ACT is a psychological approach which aims to increase psychological flexibility via acceptance of things one cannot change (i.e. cancer recurrence) and enable participants to move towards a

Table 1 Inclusion and exclusion criteria for the SURECAN trial

Inclusion	Exclusion
1. Patients within 24 months of having completed cancer treatment of the index cancer (or nearing completion) with curative intent/long-term remission for breast cancer, lower gastrointestinal cancer, a urological cancer, a haematological cancer, head and neck cancer, or any other common cancer with good survival	1. Will not have completed their cancer treatment by the commencement of the trial (excepting those receiving long-term, ongoing maintenance treatment (e.g. androgen suppression treatment for prostate cancer))
2. Aged 18 years or over	2. Receiving care for symptom control alone
3. Ability to give informed consent	3. Currently receiving another psychological intervention (participants taking antidepressants or anxiolytic drugs remain eligible)
4. Sufficient fluency in spoken English to be able to participate in a talking-based therapy delivered in English	4. Other serious co-morbid condition which would make it difficult for the participant to receive a talking-based, one-to-one intervention
5. Score of 78 or less on the FACT-G at both screening and baseline measurement time points	5. Requiring urgent psychiatric or clinical psychology assessment

life that is valued. It encourages individuals to meet the demands of life, shifting perspectives when necessary whilst balancing competing interests. We integrated conversations about work/vocational activity as well as exercise, tailored to the desires of the participant, as work and exercise have been shown to be important in helping people recover [19]. Manuals were written for patients and therapists. The therapists were trained over 3 days in ACT + by an ACT trainer and the co-chief investigator (TC) as well as other members of the team. Supervision was provided and therapy integrity will be formally assessed by independent raters once all participants have completed therapy. Hourly sessions, weekly or fortnightly can be delivered on-line, via telephone or face to face.

Blinding

Version 1.0 (date 16/09/2024) of the SAP was written whilst trial statisticians had no access to unblinded trial data or emerging trial results. Trial statisticians will remain blind until all data has been collected and the SAP is formally finalised. Participants and the site trial teams were not blinded to their treatment allocation as this is impossible to do. The co-chief investigators remain blind until the final analysis is conducted.

Additional data items are collected in the intervention arm and therefore access to the full dataset will lead to unblinding, even if uninformative codes are used for the treatment arms, therefore the statistician performing the analysis will do so unblinded. Any potential deviations from the agreed SAP will be discussed with blinded senior or independent statistician to ensure decisions are not influenced by the data or emerging results. The primary analysis will be independently checked against the finalised SAP to ensure it has been carried out in accordance with it.

Randomisation

Individuals were randomly allocated to ACT + with usual aftercare or usual aftercare alone in a 1:1 allocation ratio using stratified randomisation using randomly permuted blocks of varying size. Block sizes were unknown to researchers. Stratification factors were (a) site (1 = Barts Health NHS Trust, 2 = Sheffield Teaching Hospitals NHS Foundation Trust, 3 = University College London Hospital NHS Foundation Trust, 4 = Barking, Havering and Redbridge NHS Trust, 5 = Homerton University Hospital NHS Foundation Trust, 6 = Kings College Hospital NHS Foundation Trust) and (b) cancer group (1 = breast, 2 = lower gastrointestinal, 3 = urological, 4 = haematological, 5 = head and neck).

Power and sample size

The initial sample size calculated for the trial, without adjustment for clustering or drop-outs, was 266 (133 per arm) to provide 90% power for detection of a minimally clinically important effect size (Cohen's *D*) of 0.4 assuming a 2-sided 5% significance level. The effect size is based on existing literature, determined previously as 0.42 and 0.46 for FACT-G [8, 9]. This effect size represents a difference of 6 points on FACT-G in a cancer population [10]. We assumed each therapist would see 10 participants, an intracluster correlation coefficient (ICC) of 0.01 and allowed for drop-out by 52 weeks of 15%. The estimated total sample size required was of 344 (172 per arm) patients.

Average estimates of therapist effects for clinical trials are typically around 0.08, but these figures vary across studies due to their reliance on outcome, research design and statistical analysis employed [20, 21]. ACT + employs a manualised approach with structured intervention sessions, with therapists undergoing training and receiving monthly supervision on its delivery. The treatment concludes at 16 weeks, whilst the primary outcome is measured at 52 weeks. These features are expected to minimise therapist effects to negligible levels by the time of primary outcome collection. However, to be cautious, we have accounted for the possibility of low levels of clustering, estimated at 0.01.

During the internal pilot, we aim to recruit 45 participants. Progression criteria to proceed to the main trial are described in Table 2.

Outcomes

Participants completed questionnaires related to the outcome measures at the following time points: baseline, 7 weeks (mid-therapy), 16 weeks (end of therapy) and 52 weeks after randomisation. For a subset of participants, additional outcome data will be collected at the 2-year mark. Table 3 summarises the primary and secondary outcomes.

The Godin-Shephard Leisure-Time Physical Activity Questionnaire is a short questionnaire that asks how many times strenuous, moderate or mild physical activities took place for more than 15 min during a typical 7-day period [22]. The example activities provided are grouped under the categories of strenuous, moderate and mild based upon their metabolic equivalent of task (MET) value. This MET value is a measure of the energy expended undertaking the task. Strenuous activities are defined as having a MET of 9, moderate activities 5 METS and mild activities 3 METS. An overall score is then calculated by multiplying the frequency of each activity category by their corresponding MET values

Table 2 Green and amber progression criteria

Objective	Green: Proceed to main trial	Amber: Some adjustments may be required before proceeding to main trial
Acceptability of the trial		
Ability of clinicians to identify patients that go on to become eligible with FACT-G score of 78 or less once screened by the study team	135 Patients	134-105 Patients
Participants randomised to ACT+ taking the offer up and receiving at least one session	75%	55-74%
Participants randomised to ACT+ receiving 3 or more sessions	50%	30-49%
Feasibility of a future trial		
Proportion of eligible participants recruited into the study	30%	20-29%
Proportion of trial participants completing the 7 week questionnaire	90%	85-89%

and summing. For the SURECAN trial, we modified the Godin scale to focus on adapting the questionnaire to provide the key metrics of self-reported frequency, intensity and duration of physical activity. We included the collection of data on how many minutes of activity was undertaken for each category of activity in the last 7 days. In addition, some of the example activities that were not applicable to a UK setting such as alpine skiing, snow-mobiling and horseshoe pitching were removed and some activities were also re-categorised based on their updated MET values, for example jogging was re-categorised from strenuous to moderate.

The primary economic evaluation will use QALYs derived from the Euroqol 5-Dimension 5-Level (EQ-5D-5L). Resource use and lost employment information will be measured using the Client Service Receipt Inventory (CSRI) [23]. Intervention costs will be calculated by costing staff time associated with the ACT + delivery. Therapist time will be costed using the unit costs for appropriate staff from the PSSRU (University of Kent) [24] and the NHS reference costs [25] (most recent year available).

Across all arms, the cost of the healthcare service use at baseline and 16- and 52-week follow-up will be calculated by combining the CSRI data with the most recent versions of the University of York and Kent unit costs for health and social care 2023 and NHS reference costs. Lost employment costs will be estimated using average UK wage rates from the Annual Survey of Hours and Earnings (most recent edition) [26].

EQ-5D-5L ratings will be converted to an EQ-5D-3L tariff using the established cross-walk method [27]. The tariff is anchored by 1 (representing full health) and 0 (representing death). The Manca et al. area under the curve method will be used to calculate QALYs over the period from baseline to 52 weeks post intervention whilst controlled for baseline utility (reference) [28].

We will assume that change in the EQ-5D-5L tariff score between any two adjacent time periods will be linear. A linear regression model will be used to estimate

Table 3 Outcome measures and collection time points

Domain	Measure	Number of items	Endpoint
Primary outcome			
Quality of life	FACT-G [18]	27	Total item score (range 0–108)
Secondary outcomes			
Physical well-being	FACT-G subscale	7	Total item score (range 0–28)
Social/family well-being	FACT-G subscale	7	Total item score (range 0–28)
Emotional well-being	FACT-G subscale	6	Total item score (range 0–24)
Functional well-being	FACT-G subscale	7	Total item score (range 0–28)
Fear of cancer recurrence[a]	FCR4 [29]	5	Total item score (range 5–25)
The positive and negative Impact of Cancer scales (IOC)[a]	Positive impact subscale IOCv2 [30]	17	Mean of items (range 1 to 5)
The positive and negative Impact of Cancer scales (IOC)[†]	Negative impact subscale IOCv2 [30]	20	Mean of items (range 1 to 5)
Fatigue[a]	Chalder Fatigue (CFQ) Scale [31]	11	Total item score (range 0–33)
Anxiety[a]	Hospital Anxiety and Depression (HADS) subscale [32]	14	Total item score (range 0–21)
Depression[a]	HADS subscale [32]	14	Total item score (range 0–21)
Physical activity	Modified Godin scale	NA	Total minutes of strenuous activities, mild activities, moderate activities, all physical activity (strenuous, moderate and mild) and strenuous and moderate activity Total frequency of strenuous activities, mild activities, moderate activities, all physical activity (strenuous, moderate and mild) and strenuous and moderate activity
Health economic outcomes			
Measurement of health and social care use and lost employment	Client Service Receipt Inventory (CSRI) [23]		
Quality of life	EQ-5D-5L [33]		

All measures were collected at baseline, week 7 (≥4 weeks and <11 weeks), week 16 (≥11 weeks and <34 weeks), week 52 (≥34 weeks and <78 weeks) and 2 years (≥78 weeks) where possible

[a] Lower scores on these questionnaires indicate improvement

utility gains with number of QALYs as the dependent variable and independent variables will be group identifiers and baseline utility.

The secondary evaluation question will use difference in mean FACT-G score at 16- and 52-week follow-up. Effect estimates will be taken from the main statistical analysis and combined with average costs for each arm to produce ICERs.

Statistical principles

All analyses will be conducted using Stata version 18 or later.

Continuous data will be summarised by mean (standard deviation) or median (interquartile range) depending upon its distribution and categorical variables presented as *n* (%).

Hypothesis tests will be two-sided and conducted under a superiority framework. Estimated treatment effects will be presented with corresponding 95% confidence interval. For all analyses, a significance level of 5% will be used. As the intervention arm includes therapist, clustering will be accounted for in all analyses in the intervention arm using therapists as the units of clustering. The control arm will be treated as independent data. No formal adjustment for multiple testing will be made. All secondary outcome results will be included in reports to ensure no selective reporting.

Estimand framework

Inference on the primary and secondary outcomes is complicated by the potential occurrence of intercurrent events. An intercurrent event is defined as an event that happens after randomisation which either affects the measurement, interpretation or existence of an outcome [34]. The intercurrent events identified a priori for SURECAN are treatment discontinuations/non-adherence, assigned treatment not received, use of non-trial treatments, cancer recurrence and death. Table 4 describes the treatment effect to be estimated for SURECAN using the five attributes of the estimand framework.

Table 4 Estimand framework summary for all outcomes in the SURECAN study

Aspect	Definition
Target population	Patients ≥ 18 with a FACT-G score of 78 or less who are within 24 months of having completed (or nearing completion) of cancer treatment with curative intent for common cancers with good survival
Variable/endpoint	Total score of the FACT-G questionnaire 52 weeks post randomisation
Treatment conditions	Intervention group—ACT Plus (+). Participants in the intervention arm receive usual aftercare in addition to ACT + therapy. The intervention takes the form of up to eight therapy sessions Control arm—participants in the control arm receive usual aftercare only Usual aftercare is as currently provided by the NHS and local services
Population level summary measure	Participant level difference in means (intervention versus control group) at 52 weeks post randomisation
Intercurrent events	**Strategy**
Treatment discontinuation/non-adherence	Treatment policy The data collected for the variable of interest are used regardless of whether or not the intercurrent event occurs
Assigned treatment not received	Treatment policy
Use of non-trial treatments: with/without continuing trial treatment Due to the pragmatic nature of the trial, participants are free to take up other treatments (which are requested to be documented in the CSRI). However, they must not be receiving a psychological treatment (or planning/referred to/for) at the point of recruitment	Treatment policy
Cancer recurrence	Treatment policy for primary analysis In sensitivity analyses of the primary outcome, we apply the principle stratum approach to estimate the effect of treatment in those who do not experience a recurrence
Death	Principle stratum approach where we estimate the treatment effect in the stratum that do not die

As a sensitivity analysis, we wish to determine the effect of ACT + in the subpopulations of those that do not experience the post-randomisation event of cancer recurrence. As this is a post randomisation characteristic, normal subgroup analyses are not appropriate here. Instead, this will be formulated as a principle stratum estimand [35, 36]. Participants who experience the intercurrent event of cancer recurrence will be excluded from the analysis population as to estimate the principal stratum effect. There are four principle stratum that can be defined (i) those who would not experience the intercurrent event if allocated to either treatment arm, (ii) those who would experience the intercurrent event in the treatment arm but not in control, (iii) those who would experience the intercurrent event on control but not on intervention and (iv) those that would experience the intercurrent event on either treatment arm. For our estimator to be unbiased, we have assumed that there are no participants who fall into stratums (ii) or (iii). It is plausible to assume that the occurrence of the intercurrent event is not affected by treatment allocation because the intervention is not designed to target cancer. This assumption will be partially tested by comparing the proportions experiencing cancer recurrence between the treatment groups [36].

Accounting for missing data

Scoring of questionnaires will be performed according to the questionnaire manual, or published recommendations, where questionnaire items are missing. In order to calculate a score, at least half of the items within a subscale should be non-missing for the FACT-G, HADS [37, 38] and IOCv2. For the FCR4 and CFQ, 75% non-missing is required.

The number (percentage) of missing demographic data and clinical outcomes at baseline and follow-up time points will be summarised.

For the analysis of the primary and secondary outcomes, we assume that the data are Missing At Random (MAR) in the sense that missingness is not systematically related to the missing value once we know the values of the other variables included in the analysis model. If the proportion of observations with missing data is greater than 5% [39], sensitivity analysis to the missing data assumption will be explored for the primary outcome by including the predictors of missingness in the primary analysis and additionally carrying out an analysis using multiple imputation (MI) so long as we have strong predictors of missingness and an imputation model that is predicting plausible values.

Under the MI approach, the missing data mechanism will be assumed to be MAR. Logistic regression will be used with missingness indicator as an outcome to determine which baseline variables are predictors of missingness. Variables which are statistically significant at 5% will indicate a strong predictor for missing data. Multiple Imputation by Chained Equations will be conducted using Stata's mi command. The number of imputations (and thus completed datasets generated) will mirror the proportion of participants with at least one missing value [40].

The imputation model will include variables identified to be predictors of the missing data mechanism; auxiliary variables correlated with outcome ($r > 0.40$); and all variables contained in the substantive model. For continuous outcomes, truncated regression will be used to ensure imputed data do not extend beyond the range of the questionnaire. Imputation will be performed separately for each treatment group, by including an interaction effect between treatment group and the missingness predictor. MI will be conducted using standard linear regression. This has been shown to likely produce valid results due to the expected ICC being very small. More complicated imputation methods are not implemented in standard statistical software and may not be appropriate when the number of clusters and cluster size is small, as in this study [41]. Individual analyses on each imputed dataset will be combined using Rubin's rules [42]. If attrition between control and intervention differs by more than 5%, pattern-mixture modelling (controlled MI) will be explored using a delta-based approach which moves the missing data assumptions towards Missing Not At Random.

Diagnostic checks will be performed on the imputation model to compare the distributions of imputed values with the non-missing values. These checks may be done graphically or via summary statistics.

For the economic evaluation, where partial CSRI data for a participant are missing we will (a) assume zero use if information is blank for that service across all time points, (b) assume a median number of contacts based on other users of the service if we know that service contacts did take place and (c) assume a median duration of service if based on other users of the service if we know that service contacts did take place.

Missing cost and EQ-5D-5L data will be imputed using multiple imputation methods on 1000 bootstrapped resamples. We will assume that data are MAR. The imputation will be conducted on each bootstrapped resample in turn and cost-effectiveness estimates made on each using chained equations and predictive mean matching based on the five nearest neighbours.

Statistical analysis

Analyses will be reported in accordance with the CONSORT statement, and its extension for the reporting of non-pharmacological interventions [43, 44] and the analysis follows the Sex and Gender Equity in Research (SAGER) guidelines [45]. In SURECAN, information was collected only on a participant self-reported gender. Sex, as a classification of male or female based on biological distinction, was not collected.

Participant flow

Participant flow through the trial will be summarised by a CONSORT flow diagram [46]. This will include the numbers: eligible and consented, randomised, allocated to each intervention, attending each visit and included in the primary analysis.

The number of participants attending each study time point (baseline, week 7, week 16, week 52 and 2 years) will be summarised by treatment allocation alongside the mean and standard deviation of the number of days since randomisation that the visit took place.

For the analysis of primary and secondary outcomes, the data collected will be assigned to a specific visit according to the following timing: week 7 (≥ 4 weeks and < 11 weeks), week 16 (≥ 11 weeks and < 34 weeks), week 52 (≥ 34 weeks and < 78 weeks) and 2 years (≥ 78 weeks). Sensitivity analyses will explore the primary analysis results under a smaller 2-week targeted timing, 52 weeks (52–54-week window).

The number of withdrawals, and the reason for withdrawal, from the trial, for both therapists and participants will be summarised by allocation arm.

In the case of participant withdrawals, the timing of withdrawal will be summarised by the number of days post randomisation, mean and standard deviation and categorised according to the time period in which the withdrawal took place, i.e. baseline to week 7, week 7 to week 16, week 16 to week 52 and beyond week 52. Data on enrolment, withdrawals and loss to follow-up will be presented separately by gender.

Baseline data

Demographic information (including age, gender, education, employment, living arrangements and caring responsibilities), cancer type and the baseline values of the clinical outcomes will be summarised by treatment group, with no formal hypothesis testing for group differences. Baseline characteristics of the therapists involved in the ACT + intervention will be summarised which include core profession, years of experience, gender, age and ethnicity.

Treatment adherence and engagement

Treatment adherence and engagement will be summarised in the ACT + allocation arm. A flow diagram will be produced that shows the number of participants attending each of the 8 therapy sessions and the point at which any withdrawals took place, alongside the reason.

The numbers attending each therapy session (*n*, %), the average number of sessions attended (mean, SD), the number of participants who attended all sessions (*n*, %) and the number of withdrawals from therapy (*n*, %) will be summarised for each of the 8 intervention delivery sites.

The information from the end of therapy review will be summarised which includes the number of sessions attended, reasons for not attending all 8 sessions, and ratings completed by the therapist as to how much the participant has changed since the start of the study (very much worse to very much better) and the degree to which the participant understood the model of therapy (not at all to completely).

Patients who have attended 4 or more ACT + sessions will be considered as having received/complied with the intervention.

The number and percentage of participants who have engaged with any new activities such as new job, hobbies or interests since the start of the SURECAN study will be summarised at 16 and 52 weeks by allocation arm, alongside a summary (*n*, %) of the regularity of the activity (daily, 2–3 times a week, weekly, monthly, other).

Service use

Tables will be produced for each trial arm by time point showing (a) the number and percentage of participants using services measured with the CSRI and (b) the mean number and standard deviation of contacts with services for those with at least one contact categorised by service type. We will not test any of the differences between trial arms for individual services for statistical significance.

Protocol deviations

Major protocol deviations detailed in file notes such as those randomised under the incorrect stratification factor, randomised in error, received incorrect dose, or received the incorrect allocation will be summarised by allocation group. For the purposes of primary analysis, participants will be analysed under the treatment group to which they were randomised. Those who were randomised under the incorrect stratification factor will be analysed using the true stratification value [47] and the primary analysis will include those who were randomised in error. Sensitivity of the primary outcome analysis to these assumptions will be explored through sensitivity analyses.

Primary and secondary analysis

The primary outcome is the FACT-G scale at 52-week follow-up. The primary outcome will be analysed using a partially nested mixed-effects model with heteroskedastic error terms with the Satterthwaite approximation for degrees of freedom to avoid upward bias of the type I error rate. In the intervention arm only, a random intercept will be specified to allow for the clustering by therapist; participants in the control arm will be treated as independent [48]. Randomisation stratification factors will be included as covariate in the model. The model will also adjust for FACT-G scores at baseline. The resulting model will produce a difference of FACT-G score in the intervention versus the control arm after adjustment for all the covariates. The model will be fitted using a restricted maximum likelihood procedure. Failure of convergence of the primary analysis model may be an indicator that the model specification is too complex to be properly supported by the data. We will explore alternative strategies in turn to reduce model complexity such as trying an alternative optimisation algorithm, alternative methods to account for clustering, i.e. treat participants in the control arm as clusters of size 1; remove covariates from the model; and analyse ignoring clustering.

All continuous secondary outcomes will be analysed similarly at 16 and 52 weeks separately. The secondary outcomes are total scores of the four subscales of the FACT-G, FCR4 total score, positive and negative IOCv2 mean scores, CFQ total score, the HADS scale (both subscales) total scores and frequency and intensity of physical activity as measured on the modified Godin scale. Observed ICCs for each outcome will be calculated using an ANOVA approach (using Stata's loneway command) with 95% confidence intervals calculated using Swiger's method [49].

The relationship between the number of ACT + sessions attended and the value of the FACT-G score at 52 weeks will be examined in the intervention arm only. This will be explored graphically with a plot that shows mean FACT-G score with associated 95% CI for each level of "dose", i.e. number of sessions attended.

The Complier Average Causal Effect (CACE) estimate is defined as the difference between the outcome in those participants who complied with the intervention and those participants who would have complied if assigned to treatment [50]. Compliance is observed in the treatment arm as those participants that attended at least 4 ACT + therapy sessions.

There are no known predictors of compliance in the literature. Therefore, data from the intervention arm will be used to identify relevant predictors of compliance amongst the baseline characteristics using logistic regression; variables significant at the 10% level will be included in the CACE analysis as predictors of compliance.

The CACE estimate will be calculated using a latent variable approach with structural equation modelling using the approach described by Troncoso [51]. We will use the following assumptions: random assignment (i.e. the characteristics that make participants in the intervention group comply would also make participants in the control group comply), monotonicity (i.e. there will be no "defiers", those that do the opposite of treatment assignment, and no "always-takers", those that take the intervention regardless of assignment), stable unit treatment values (i.e. the outcome for any participant is independent of the group assignment of other participants) and the exclusion restriction (i.e. the treatment has no effect on the outcome in those that did not comply with the intervention). We will adjust for primary outcome scores at baseline and stratification factors and this model will also include a random intercept in the intervention arm only for clustering by therapist.

Subgroup analyses

The trial has not been powered to detect subgroup effects; hence, these should be considered exploratory. To explore any differential treatment effects, the primary analysis will be repeated to include an interaction term between treatment and baseline subgroup variable. Interactions for quantitative factors (such as worry in relation to COVID_19) will be modelled as a linear main effect and an interaction with this linear effect.

The subgroups to be considered are:

- Age
- Gender (male, female, non-binary, other)
- Type of cancer (breast, lower GI, haematological, urological, head and neck)
- Severity of depression, as measured by the HADS depression subscale at baseline
- Loneliness (0–10 scale)
- Worry in relation to COVID-19 at baseline (I do not worry, I occasionally worry, I spend much of my time worrying, I spend most of my time worrying)

For the subsample of breast cancer participants, we will conduct an exploratory subgroup analysis for:

- Breast cancer treatment received (chemo/radio/endocrine/biological vs surgery (wide local excision; mastectomy without reconstruction; mastectomy with breast reconstruction and unilateral or bilateral))

The presence of an interaction will be tested using a likelihood ratio test comparing the subgroup analysis model, including the interaction effect, and the primary analysis model, not including the interaction term but including the main effect of the subgroup factor. All patients with complete outcome data will be included in the subgroup analysis. For each subgroup category, we will report summary statistics of the outcome by treatment arm, with treatment effect estimates and 95% confidence intervals. A p value for the interaction test will also be reported.

Sensitivity analyses

To assess the sensitivity of the primary analysis to assumptions around the missing data mechanism, the primary analysis will be repeated including predictors of missingness, and if greater than 5% of data is missing MI will be carried out.

To explore sensitivity to protocol deviations, the primary analysis will be repeated allowing for each protocol deviation in turn, and then all protocol deviations together as follows: (1) treatment analysed as that received rather than allocated, (2) removing those that received the incorrect dose of ACT + and (3) removing visits that occurred outside of scheduled visit window.

As a sensitivity analysis, we wish to determine the effect of ACT + in the subpopulations of those that do not experience the post-randomisation event of cancer recurrence. A principle stratum approach is being used to deal with the intercurrent event of cancer recurrence. Participants who experience the intercurrent event of cancer recurrence will be excluded from the analysis population as a way to estimate the principal stratum effect.

Health economic analysis

Sample means and standard deviation (SD) of intervention costs, healthcare costs and total costs (and SD) will be reported for each trial arm from a health and social care perspective. The sample mean productivity loss each group will also be reported to provide broader information on the economic benefits of each method.

Cost and QALY differences for ACT + in combination with usual care group compared to usual care will be estimated using linear regression models. If cost data are skewed, bootstrapping with 1000 resamples will be used to produce confidence intervals around cost and QALY differences.

ICERs will be calculated for cost per QALY and incremental cost per point improvement in FACT-G for the intervention group compared to usual care.

If outcomes are better for one group compared to the alternative groups, and costs are lower, the group would be dominant. If outcomes are better and costs are higher, an ICER will be generated.

Cost-effectiveness planes will be produced, using 1000 cost outcome pairs (from the aforementioned bootstrapped regression models) to present uncertainty around the ICER estimates in the main analysis. Cost-effectiveness acceptability curves will be produced using the bootstrapped results to present the proportion of bootstrapped replicates that are cost-effective at a range of threshold values. For QALYs, there are established threshold values (£20,000 and £30,000) by the National Institute for Health and Care Excellence.

Deterministic sensitivity analysis will be conducted by varying the most utilised service unit costs upwards and downwards by 10, 25 and 50%.

A Markov model will be developed to assess the long-term cost-effectiveness of the intervention (ACT + in combination with usual care) in comparison to usual care. Health states will be defined over the time based on the FACT-G. Costs and QALYs will be attached to the previously described health states. The costs and the probabilities of the model will be derived from published literature, the trial dataset and expert opinion.

Safety data

The number of adverse events and serious adverse events, their relation to the intervention, and whether they were expected or unexpected will be summarised by treatment group.

Further analyses

For the subset of participants who were followed up for 2 years, their baseline characteristics and clinical outcomes will be summarised by treatment group; no formal hypothesis testing will be conducted.

Further exploratory analyses will not be constrained by this analysis plan but will generally adhere to its principles. Any post hoc analyses, including those requested by journal reviewers, will be explicitly identified as such in the final trial report.

Discussion

The SURECAN trial will evaluate a person-centred intervention, based on ACT +, for people who have completed treatment for cancer with curative intent, but are experiencing poor quality of life.

The estimand of interest is the difference in means for the total score of the FACT-G at 52 weeks post randomisation between ACT + (in addition to usual care) versus usual care alone. The population is participants ≥ 18 with a FACT-G score of 78 or less who are within 24 months of having completed (or nearing completion) of cancer treatment with curative intent for common cancers with good survival. The analysis will follow ITT principles, i.e. participants will be analysed as randomised. The treatment policy strategy will be used to handle all intercurrent events, except for death, where the analysis will use a principle stratum approach. Sensitivity analyses will explore the missing data assumptions, protocol deviations and the treatment effect for the subgroup of participants that do not experience cancer recurrence during their involvement in the trial will (this is consistent with a principle stratum strategy).

This analysis plan describes the primary, secondary and health economic analyses for the SURECAN trial. Any exploratory, post hoc or unplanned analyses will be clearly identified as such in the respective study analysis report.

The SURECAN trial is individually randomised, and the intervention is delivered by therapists to multiple participants. Participant outcomes may be affected by the skill or enthusiasm of the therapist delivering the intervention; therefore, participant outcomes may be similar amongst those being seen by the same therapist and can no longer be treated as independent. The extent of correlation is measured by the ICC. This potential clustering of outcomes is only present in the intervention arm of SURECAN, referred to as a partially clustered or nested design. In the research literature, the clustering present in these designs has not always been recognised, or appropriately accounted for in the sample size calculations or analysis [52–54]. The analysis of clustered designs using methods that do not appropriately account for the clustering of observations will lead to confidence intervals that are too narrow and an increased type I error rate, meaning interventions could appear better than they truly are. Clustering of outcomes reduces the effective sample size and so this must be inflated at the design stage using an estimate of the ICC [55]. A barrier to researchers being able to appropriately power these designs is that observed ICCs are not often reported and therefore appropriate estimates to use in sample size calculations are difficult to find [54]. Our aim is that publication of this SAP will not only allow full transparency of the SURECAN analysis but will also raise awareness of the clustering present in these designs and encourage others to consider this and publish the ICCs observed in their trials.

Abbreviations

CSRI	Client Service Receipt Inventory
ITT	Intention-to-treat
IQR	Interquartile range
MAR	Missing At Random
MI	Multiple imputation
RCT	Randomised controlled trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
ICC	Intracluster correlation coefficient

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08734-9.

Supplementary Material 1.

Acknowledgements
We acknowledge Professor Richard Hooper's contribution as independent statistician in reviewing the statistical analysis plan.

Authors' contributions
CR and OQ drafted and finalised the statistical analysis plan. PM and EG drafted and finalised the health economic aspects, with review by ST, IK and TC. ST and TC are the co-chief investigators for this trial. CR is the senior statistician, IK is the trial co-ordinator and PM the senior health economist. All authors have read, commented on and reviewed the manuscript.

Funding
This study is funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research (PGfAR) (RP-PG-0616–20002). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The funder was not involved in the development of the statistical analysis plan or writing of this manuscript.

Data availability
Anonymous and pseudonymous research data will be available from the Pragmatic Clinical Trials Unit on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics committee approval was obtained in advance Research Ethics Committee (REC) South West—Cornwall & Plymouth Research Ethics Committee (REF: 19/SW/0214). All participants gave written informed consent prior to participation.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 27 December 2024 Accepted: 14 January 2025
Published online: 30 January 2025

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