BMJ Open

SafeFit Trial: Virtual clinics to deliver a multimodal intervention to improve psychological and physical wellbeing in people with cancer. Protocol of a COVID-19 targeted non-randomised phase III trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048175
Article Type:	Protocol
Date Submitted by the Author:	18-Dec-2020
Complete List of Authors:	Grimmett, Chloe; University of Southampton, School of Health Sciences Bates, Andrew; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre West, Malcolm; University of Southampton Faculty of Medicine, School of Cancer Sciences; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre Leggett, Samantha; University Hospital Southampton NHS Foundation Trust Varkonyi-Sepp, Judit; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre Campbell, Anna; Edinburgh Napier University, School of Applied Science Davis, June; Macmillan Cancer Support Wootton, Stephen; University of Southampton, School of Human Development and Health, Faculty of Medicine; NIHR Cancer and Nutrition Collaboration Shaw , Clare ; Royal Marsden NHS Foundation Trust, NIHR Biomedical Research Centre Barlow, Rachael; University Hospital of Wales, Cardiff and Vale University Health Board Ashcroft, Joanna; St George's University Hospitals NHS Foundation Trust Scott, Andrew ; University of Portsmouth, School of Sport, Health and Exercise Science Moyes, Helen; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre Hawkins, Lesley; University Hospital Southampton NHS Foundation Trust, Critical Care/Anaesthesia and Perioperative Medicine Research Unit Levett, Denny; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre; University of Southampton, School of Clinical and Experimental Sciences, Faculty of Medicine Grocott, Michael P. W.; University of Southampton, School of Clinical and Experimental Sciences, Faculty of Medicine; University Hospital Southampton NHS Foundation Trust, NIHR Biomedical Research Centre Williams, Fran; Wessex Cancer Alliance Jack, Sandy; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre

Keywords:	ONCOLOGY, Adult oncology < ONCOLOGY, PUBLIC HEALTH, REHABILITATION MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

SafeFit Trial: Virtual clinics to deliver a multimodal intervention to improve psychological and physical wellbeing in people with cancer. Protocol of a COVID-19 targeted non-randomised phase III trial.

Short title: SafeFit Trial: Multimodal intervention for people with cancer; a COVID-19 targeted trial.

Grimmett, C., Bates, A., West, M., Leggett, S., Varkonyi-Sepp, J., Campbell, A., Davis, J., Wootton, S., Shaw, C., Barlow, R., Ashcroft, J., Scott, A., Moyses, H., Hawkins, L., Levett, DZH., Williams, F., Grocott, MPW*., & Jack, S*.

* Joint senior authors

Corresponding author: Dr Chloe Grimmett, c.grimmett@soton.ac.uk

Affiliations:

Dr Chloe Grimmett, School of Health Sciences, University of Southampton, Southampton, SO17 1BJ, UK. orcid.org/0000-0002-7540-7206.

Andrew Bates, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK Orcid.org/ 0000-0002-3614-0270.

Mr Malcolm West, School of Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK; NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK. Orcid ID/0000-0002-0345-5356.

Samantha Leggett, National Institute for Health Research (NIHR) Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, SO16 6YD, UK. orcid.org/0000-0002-7400-8123.

Judit Varkonyi-Sepp, NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, SO166YD, orcid.org/0000-0002-7269-0261.

Prof Anna Campbell, School of Applied Science, Edinburgh Napier University, EH11 4BN, Scotland. Orcid: 0000-0003-3517-7335.

June Davis, Macmillan Cancer Support, 89, Albert Embankment, London, SE1 7UQ, UK orcid.org/0000-0002-1953-1632.

Dr Stephen Wootton, School of Human Development and Health, Faculty of Medicine, University of Southampton SO16 6YD, UK / NIHR Cancer and Nutrition Collaboration. orcid.org/0000-0002-9495-9719.

Dr Clare Shaw, National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London, UK. orchid.org/0000-0003-4169-9391.

Dr Rachael Barlow, Clinical Lead Prehabilitation Service, University Hospital of Wales, Cardiff and Vale University Health Board, Heath Park, Cardiff, CF14 4XL, Wales. orchid.org/0000-0001-9940-9209.

Dr Joanna Ashcroft, St George's University Hospital NHS Foundation Trust, SW17 0QT, UK.

Dr Andrew Scott, School of Sport, Health and Exercise Science, University of Portsmouth, Portsmouth, UK. orcid.org/0000-0003-1478-8962.

Helen Moyses, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK.

Lesley Hawkins, Critical Care/Anaesthesia and Perioperative Medicine Research Unit, University Hospital Southampton NHS Foundation Trust. UK. orcid.org/0000-0003-1304-6393.

Prof Denny Levett, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK; School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton SO16 6YD.

Anaesthesia and Critical Care Research Unit, University Hospital Southampton NHS Foundation Trust.

Prof Michael P W Grocott, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK; School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton SO16 6YD.

Fran Williams, Wessex Cancer Alliance, Oakley Road, Southampton, SO16 4GX.

Prof Sandy Jack, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK. Orcid.org/0000-0003-2763-7303.

Abstract

Introduction: The impact of the COVID-19 pandemic (caused by the SArS-CoV-2 virus), on individuals with cancer has been profound. It has led to increased anxiety, distress and deconditioning due to reduced physical activity. We aim to investigate whether SafeFit; a multi-modal intervention of physical activity, nutrition and psychological support delivered virtually by cancer exercise specialists (CES) can improve physical and emotional functioning during the COVID-19 pandemic.

Methods and analysis: A phase III non-randomised intervention trial, target recruitment of 1050 adults with suspected or confirmed diagnosis of cancer. All recruited participants will receive the multimodal intervention delivered by CES for six months. Sessions will be delivered 1-to-1 using telephone/video conferencing consultations. CES will work with each participant to devise a personalised programme of 1) physical activity, 2) basic dietary advice and 3) psychological support, all underpinned by a behaviour change intervention.

Primary outcome: Physical and emotional functioning as measured by the EORTC-QLQ-C30. Secondary outcomes: Overall quality of life measured by EORTC-QLQ-C30 and EQ-5D-5L, health economics, patient activation, self-efficacy to self-manage chronic disease, distress, Impact of Covid-19 on emotional functioning, self-reported physical activity, functional capacity and nutrition. Adherence to the intervention will also be measured and a process evaluation conducted.

Ethics and dissemination: Ethical approval was obtained from the Health Research Authority (reference number: 20/NW/0254). Results of this trial will be disseminated through publication of

peer reviewed articles, presentations at scientific conferences and to the public and people with cancer in collaboration with our patient and public involvement representatives and partners.

Trial registration: NCT04425616
Sponsor: University Hospital Southampton NHS Foundation Trust

Article summary – *Strengths and Limitations up to 5 short bullet points, no longer than on sentence each that relate specifically to the methods*

- The SafeFit Trial will evaluate a novel approach to delivering multimodal exercise, nutrition and psychological support to people with cancer safely during and beyond the COVID-19 pandemic.
- The intervention will be delivered by cancer exercise specialists who have been upskilled using a bespoke training package, including nutrition, psychological support and Healthy Conversation Skills.
- The intervention, underpinned by evidence-based behaviour change techniques, seeks to empower participants to develop new behaviours that can be sustained for the long-term.
- Limitations of the trial include absence of a control group and reliance on self-report measures to evaluate behaviour change.

Keywords: cancer, intervention, physical activity, nutrition, psychological support, multimodal, virtual

Introduction

The COVID-19 pandemic, caused by the SArS-CoV-2 virus, has led to re-prioritising of clinical care and the impact on individuals with a cancer diagnosis has been profound. Treatments and follow-up care have been severely disrupted affecting 650,000 people with cancer in the UK alone and many supportive services have also been postponed (1) (2). Moreover, once infected with SArS-CoV-2 people with cancer experience significantly worse clinical outcomes (3). Although not all people living with and beyond cancer are now advised to shield many remain fearful of leaving their homes due to the risks of contracting the virus and the consequences of COVID-19 (1).

For many people with cancer, the pandemic has resulted in deconditioning due to social isolation, reduced physical activity and changes to eating habits that limit their ability to consume sufficient energy and nutrients to meet their needs. Cancer is typically a disease of older adults who are at

particular risk of pulmonary complications as a result of COVID-19, which will likely be exacerbated by reduced cardiopulmonary fitness associated with such reductions in activity levels. Furthermore, smoking, poor nutrition and obesity are independent risk factors for developing cancer which concurrently increase vulnerability to severe COVID-19 (4).

Good nutrition and regular physical activity have proven to be effective at addressing a variety of disease and treatment-related consequences of cancer and optimising physical fitness is also likely to decrease morbidity and mortality associated with COVID-19 (5). Thus, supporting this population to maximise engagement in physical activity and improve nutritional status is imperative.

Supporting psychological well-being is also vital for people with cancer. Higher levels of anxiety and depression are associated with poor quality of life and physiological outcomes both early in the treatment pathway and in patients who have completed treatment (6-8). Many people with cancer will continue to experience distress, depression and anxiety months and years after cancer treatment completion. These issues are exacerbated by the COVID-19 pandemic through reduced access to informal social support networks and formal psychological support services. Macmillan Cancer Support reported in June 2020 that over 270,00 people with cancer in the UK have experienced panic or anxiety attacks because of the COVID-19 pandemic (9).

The SafeFit trial, as described in this paper, was conceived when our research team was forced to pause recruitment to the Wessex-Fit-4-Cancer Surgery Trial (10), a multimodal prehabilitation trial delivered in community settings. We wanted to develop a new programme to support patients throughout and beyond the COVID-19 pandemic. The multimodal structure of the intervention is informed by the recent Macmillan, Royal College of Anaesthetists and National Institute of Health Cancer and Nutrition Collaboration, Research Principles and Guidance for Prehabilitation within the Management and Support of People with Cancer (11). The guidance advocates for a multimodal approach encompassing exercise, nutrition and psychological support in order to optimise cancer patients prior to treatment increasing their resilience to withstand cancer therapies and hasten their recovery.

It is now accepted that people with cancer require 'end-to-end' pathway support, at the point of diagnosis, throughout treatment and recovery. The SafeFit Trial adopted the multimodal prehabilitation model for universal provision of support with patients recruited at any point in the treatment and recovery pathway. People with cancer are increasingly turning to remote support

services and distanced and home-based interventions have been shown to be effective in supporting dietary and physical activity behaviour change (12). However, evidence suggests that inclusion of a supervised component increases intervention adherence (13) and longer-term maintenance of physical activity behaviour change (14).

Considerable research has explored the most effective 'ingredients' of a behaviour change intervention in cancer populations to improve engagement and adherence to such interventions as well as promote longer-term behaviour change. A recent Cochrane review supports the use of goal setting, setting of graded tasks and instruction on how to perform behaviour to maximise intervention adherence (13). Additionally, action planning and social support are associated with maintenance of behaviour change (14). Furthermore, there is growing evidence of the role of self-efficacy – a person's belief in their ability to perform a given task – in supporting behaviour change with evidence that self-efficacy is a mediator of exercise behaviour in clinical populations and a predictor of exercise adherence (15). The SafeFit Trial is underpinned by behavioural science using evidence-based behaviour change techniques to optimise patient engagement and support self-management and long-term behaviour change.

The proposed trial explores the impact of SafeFit, a virtually delivered multimodal intervention, on the physical and emotional wellbeing of people with cancer.

Methods and analysis:

Trial design and setting:
The SafeFit Trial is a phase III non-randomised intervention with multimodal components of exercise, nutrition optimisation and psychological support delivered remotely by telephone and/or video conferencing.

Trial objectives and outcome measures:

Primary objective: To investigate the efficacy of SafeFit interventions to improve physical and emotional functioning as measured by change in the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC QLQ-C30) (16) over the 6-month intervention. Five items are answered using a Likert scale 1-4 are scored to provide a function score from 0-100. Higher scores represent higher functioning. This subscale has been used in previous

interventions in cancer populations and is sensitive to change over time.

The main secondary objectives are to investigate the impact of the SafeFit Trial on:

Quality of life and cost-effectiveness: Overall cancer-specific quality of life and global health status, cognitive and social function and nine symptom sub-scales as measured by the EORTC-QLQ-C30. Quality of life as measured by the EQ-5D-5L. A standardised instrument developed by the EuroQol Group for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, the EQ-5D-5L health questionnaire provides a simple descriptive profile and a single index value for health status (17). Resources used to deliver the SafeFit trial will be measured and valued and health economic analysis conducted using the EQ-5D-5L and the Patient Activation Measure (see below for details).

Self-efficacy and Patient Activation: Self-efficacy to self-manage chronic disease will be measured by the Self-Efficacy for Managing Chronic Disease Scale; a 6-item measure with higher scores indicating greater confidence to manage illness-related problems (18). Patient activation will be measured by the Patient Activation Measure (PAM) (19). The PAM is a validated self-report survey. Each survey response is scored and based on the total score between 1 and 100; responders are categorized to 4 activation levels.

Psychological distress will be measured using the Emotion Thermometers (20). A simple rapid modular visual analogue screening tool for detection and monitoring of emotional disorders in clinical practice. Four emotional domains (distress, anxiety, depression and anger) are measured using a visual analog scale (0-10) and one outcome domain – need for help (21). Impact of COVID-19 on psychological functioning will be measured by the Impact of Events Scale (22).

Behaviour change: Self-reported physical activity will be measured using the modified Godin Leisure Time Exercise Questionnaire (23). This is widely used in the exercise oncology literature and has been validated against objective activity monitoring and measures of physical fitness (24). Diet will be measured using the World Cancer Research Fund (WCRF) modified HealthCheck tool (25) which examines intake of fruits, vegetables, wholegrains, red and processed meats, processed foods high in fat and sugar, sugary drinks and alcoholic beverages.

Self-reported height (baseline only) weight, weight loss and changes in nutritional status will be measured by short form Patient Generated Subjective Global Assessment (26, 27). Functional capacity will be measured by the Duke Activity Status Index (DASI). The DASI also allows for the calculation of the individuals predicted peak oxygen consumption (28).

Finally, differences in response to the SafeFit Trial depending on COVID-19 status; confirmed COVID-19, suspected COVID-10, self-isolation, none will be explored.

The above outcomes (except for health economics) will be assessed at 6 months (primary endpoint), in addition to 3 months (mid intervention) and 12 months (post-intervention follow-up).

Exploratory outcomes: Overall survival (all-cause mortality) at 12 months.

Demographic and clinical data will be collected at baseline including age, sex, postcode, ethnicity, education, employment status, marital status, living arrangement (who they live with), household accommodation and car ownership. Self-reported clinical data will include date of diagnosis, cancer type and stage, cancer status, treatment/s (current and historical) and co-morbidities.

Inclusion/Exclusion criteria:
Adults (aged ≥18 years) with suspected or confirmed diagnosis of cancer. Individuals unable to give informed consent will not be eligible for this trial.

Recruitment and recruitment procedures:
Potential participants will be recruited via self-referral, with the SafeFit trial advertised through social media, via partner organisations include Macmillan Cancer Support, and through clinical teams and multidisciplinary team meetings.

Potential participants will visit the SafeFit Trial website and complete a Smart Survey to express their interest in the trial. A welcome email will be sent to potential participants together with a patient information sheet. A member of the trial team will then telephone potential participants to confirm eligibility. During this telephone call potential participants will complete the following screening to confirm suitability for the trial:

i. The Physical Activity Readiness Questionnaire PARQ+ (29) This tool screens participants presenting acute or uncontrolled long term conditions that would be exacerbated by exercise (30).

ii. COVID-19 status (confirmed COVID-19, suspected COVID-1, self-isolation, none)

iii. Nutritional state (problems eating or drinking and unintended weight loss), whether the individuals are receiving nutritional support and if they are under the care of a Registered Dietitian. Those assessed to be malnourished (BMI<18.5) or reporting specific Nutritional Impact Symptoms of dysphagia, diarrhoea or vomiting or receiving Artificial Nutritional Support will not receive the standard nutritional advice element of the trial. Appropriate referrals for nutritional support will be made for those identified as at risk of malnutrition.

iv. Psychological distress. Those scoring ≥8 on the distress thermometer are asked additional questions. Those at risk of self-harm will not be recruited to the trial and appropriate referrals for support will be made.

Participants will be eligible for inclusion to the trial providing they are safe to receive at least one of the three components. For example, a potential participant who is deemed unsafe to exercise would receive the nutritional and psychological components of the intervention. The exercise element would be introduced if/when it is safe to do so.

All eligible participants will then complete an online consent form and baseline questionnaires. Those not willing or able to complete questionnaires online will be posted paper copies with a return pre-paid envelope. Once baseline questionnaires are complete participants will be matched with a CES. Participants will have the opportunity to complete an electronic Holistic Needs Assessment (eHNA) prior to the telephone call with the trial team. See Figure 1 for trial flow.

Intervention:

The intervention duration will be 6 months. Participants will receive up to three one-to-one sessions per week for 1 month (weeks 1-4-), weekly for 2 months (week 5-12) and monthly for 3 months (Week 16, 20 and 24).

Exercise: Participants will be supported to engage in at least one and up to three exercise sessions per week including: (i) aerobic exercise at a rating of perceived exertion of 11-14 (6-20 scale) accumulating up to 30 minutes per session; (ii) resistance exercise of 8-10 different exercises each

for 2x 8-15 repetitions performed in a controlled manner and covering the whole body and range of motion. Resistance exercise should be performed through the full pain free range of motion covering the whole body with maintenance of good alignment for 10-30 seconds, with some movements held for a second set of 10-30 seconds if stiff. Engagement will involve a combination of supervised exercise sessions during the one-to-one sessions (if requested by the participant) and unsupervised home-based sessions.

Psychological support: The CES will provide psychological support as per levels 1 and 2 of the Improving Supportive and Palliative Care for Adults with Cancer (31). This includes recognising the psychological needs of patients, providing compassionate communication, general psychological support and simple, self-management focused signposting and problem solving.

Nutrition support: The CES will work with participants to review their diet and eating habits against World Cancer Research Fund recommendations using the modified 'HealthCheck' online tool to identify areas of change as appropriate (25). Participants will review their consumption of fruit and vegetables, wholegrains, red and processed meat, processed foods high in sugar and fat, processed meats, and alcohol intake with the aim to achieve WCRF recommendations for cancer survivors through incremental goal setting. The CES will regularly check for unintended weight loss or changes in gastrointestinal function and/or changes in the ability to eat/drink and report abnormalities immediately to the trial team.

Behaviour change support: The CES will receive training in Healthy Conversation Skills (32). This will enable them to deliver a client-centred, solution focused, empowering intervention informed by social cognitive theory. The intervention is aimed at increasing patients' self-efficacy and motivation to adopt behaviour change. The same skillset and delivery modality will be employed to support patients in engaging in the exercise and nutrition components of the intervention as well as adopting strategies to self-manage their psychological well-being. Participants will be provided with a SMARTER goal-planning sheet to assist with goal setting and action planning during consultations with their CES. The titrated support acts to increase participant's autonomy and support long-term engagement in these new behaviours. See Appendix A for list of Behaviour Change Techniques employed as per the taxonomy of Behaviour Change Techniques (33) and used flexibly within sessions as per the person-centred approach.

Training programme for Cancer Exercise Specialists:

All CES will have training in exercise referral and/or additional qualifications in Cancer and Exercise Rehabilitation and will deliver the SafeFit interventions. All CES will also receive a bespoke training package delivered online by the trial team, supported by the clinical team:

1) Health Conversation Skills - Online Healthy Conversation Skills training (eMECC Lite). This training is an online version of the Royal Society for Public Health-accredited MECC Lite Healthy Conversation Skills training. Consistent with the face-to-face training, the online version is highly interactive and experiential. The training equips trainees with skills to create and identify opportunities to hold conversations about health and wellbeing, to explore the individuals' barriers and facilitators to making change and taking control, to use active listening, and to support individuals to find their own solutions, plan for taking action to implement these solutions, monitor progress and adjust, plan and action as needed.

2) Nutrition – A webinar with accompanying support material will be delivered by an experienced dietitian [CS] to provide training in generic nutritional principles in line with the recommendations from the World Cancer Research Fund and British Dietetic Association and to identify deterioration in nutritional status. The webinar covers; the principles of healthy eating ('eat well' advice), weight management, symptom management, prehabilitation advice before treatment starts, rehabilitation advice during and after treatment. Links to trusted dietary resources provided on the internet will be made available.

3) Emotional support - A webinar with accompanying supportive materials will be delivered by an experienced clinical psychologist (JA) specialising in oncology. This will focus on communication skills, recognising emotions, active listening and questioning.

Safety during sessions: It will be the responsibility of the CES to complete a pre-session screening checklist to monitor condition, medical contacts, medication and COVID-19 status. If appropriate exercise will continue, be modified with observation or stopped and review sought from the treating medical team. In the case of an acute medical event during the exercise session, the CES will advise the participant to call their GP or 111. If concerned about collapse, the CES will call 999. The CES will ask the participant to repeat the distress thermometer before each session. If the participant scores 8 or above for 2 consecutive weeks they will be encouraged to contact Macmillan Cancer Support helpline and/or their GP. In the case of suicidal or self-harm ideation, the CES will advise contacting Samaritans, SHOUT, GP or 111. If concerned about immediate risk the CES will call 999. Participants who experience a marked deterioration in their nutritional state (e.g. stricture, swallow, inanition, weight loss) will be directed back to their cancer care team. Participants with a confirmed diagnosis,

or suspicion of, COVID-19 will have their exercise intervention paused for 14 days but, symptoms allowing, will be able to receive the other interventions. The exercise intervention will also be paused if anybody in their household is displaying COVID-19 symptoms. Acute events and changes in condition and/or treatment plan will be reported to the trial team. Cases of immediate physical or mental health concern will be raised with the Chief Investigator or senior clinician with delegated authority. All other cases will be discussed at a weekly multi-disciplinary clinical team review. In case of incomplete information or ongoing investigation, it will be the responsibility of the participant to gain clinical sign off before resuming trial activity. All adverse and series adverse events will be recorded.

Fidelity checks: Attendance at each scheduled session will be documented by the CES throughout the trial using session completion logs, these will be regularly reviewed by the trial team. The CES will be offered group supervisions once every two weeks to address any concerns during the trial. Approximately 20% of trainers will have two sessions (initial assessment and one follow-up call) observed (via recording of video or telephone call) and assessed against a bespoke implementation checklist to assess fidelity of intervention delivery, including assessment of competency for delivery of HCS.

See TiDiER checklist (Appendix B) for detailed description of intervention components, training procedures and links to additional resources.

Process evaluation:

A comprehensive process evaluation will enable identification of barriers and facilitators to the implementation of and participation in the SafeFit trial. It will afford an in-depth understanding of processes, relationships and communications that helped or hindered conduct of the trial.

The process evaluation will assess acceptability of the SafeFit Trial from the perspective of participants and professionals delivering the programme as well as identifying barriers and enablers to engagement with and adherence to the programme. We will also capture data to explain how the intervention worked, who it did and didn't work for and why, along with other issues with delivery of the intervention and participant receptivity. Qualitative in-depth semi-structured interviews will be conducted with participants enrolled in the trial and professionals involved in the delivery of the trial. This will include N=25 participants who will be purposively sampled to include a range of age, sex, disease type, time since diagnosis and adherence to scheduled calls. Interviews will focus on the

barriers and facilitators to participation in the trial and success (or not) of behaviour change. These data will provide explanatory insight into the findings of the trial.

Interviews will also be conducted with CES delivering the trial as well as administrative personnel coordinating the trial (N=15). The purpose of these interviews is to understand the barriers and facilitators to the delivery of the prescribed interventions as well as views of the usefulness of training received.

Normalisation Process Theory (NPT) will underpin the conceptual framework that will structure the process evaluation (i.e. the interview schedules, findings and their interpretation). NPT provides an explanatory framework to better understand the routine embedding of healthcare interventions in their social contexts, in particular *why some processes seem to lead to a practice becoming sustained over a long term while others do not.* The starting point of NPT are the dynamics associated with the embedding of a practice i.e. what people actually do and how they work together (34).

Patient and Public Involvement (PPI):

People with cancer were consulted at the outset of this trial. We worked closely with four research partners including individuals living with cancer (who were shielding), caring for someone with cancer and recovering from cancer. They provided suggestions of how potential participants might be reassured of the safety of the trial as well as support they might need to access the virtual intervention. They also reviewed trial questionnaires, patient facing documentation and piloted the self-referral process. Moreover, they agreed to be members of our steering group and will contribute to the oversight of the trial. In previous trials conducted by our research group, PPI representatives have been invited to speak at conferences and stakeholder events, providing powerful testimonies. We intend to continue this approach with the current trial. The research team will liaise the PPI involvement lead in University Hospital Southampton's Biomedical Research Centre to identify training and support needs of our research partners throughout the trial.

Statistical analysis plan and sample size calculation:

Preliminary data suggest that approximately 62% of patients will have a 'good' Physical Function score of >83 at baseline, and 43% of patients will have a 'good' Emotional Function score at baseline (>71) as determined by threshold for clinical importance for the EORTC-QLQ-C30 (35). In order to detect an 8% improvement in the proportion of patients with good physical/emotional function score with 90% power (alpha=0.05), 1050 patients will be required (allowing for 20% drop-out).

Descriptive statistics will be used to summarise baseline demographic and clinical variables. For continuous variables, the mean and standard deviation will be calculated for Normally distributed data. If the data are not Normally distributed, the median and interquartile range will be calculated. Categorical or binary variables will be summarised as frequency and percentage of total.

The primary endpoints are EORTC-QLQ-C30 physical function and emotional function scales measured at 6 months. The McNemar test will be used to investigate whether there is a difference in the proportion of patients with good physical function and emotional function score at the end of the intervention (6 months) compared to baseline. In order to account for multiple comparisons, the Holm procedure will be used to adjust p-values.

Repeated measures logistic regression will be used to investigate the change over all trial visits (baseline, 3, 6 and 12 months), and to adjust for clinically prognostic factors which will include age, gender, cancer type, tumour site, systemic anti-cancer treatment.

Subgroup analysis will also be performed. The proportion of patients with good physical function/emotional function score at 6 months (with confidence interval) will be calculated for each subgroup, and will be displayed on a forest plot, along with the p-value for interaction. COVID-19 status (confirmed COVID-19, suspected COVID-19, self-isolation, none), curative vs palliative, chemo/rad vs. not, surgery vs. not, adherent to intervention vs. not (adherence is defined as completing ≥70% of calls with CES), tumour site, baseline QoL (above 85 vs. 85 total EORTC-QLQ-C30 score).

Analysis of secondary endpoints (including but not limited to anxiety, depression, confidence to self-manage chronic disease, physical activity and dietary behaviour change, Duke activity status) will be performed using the appropriate statistical tests/regression models depending on the outcome data type (i.e. continuous, ordinal, binary), and taking into account the paired nature of the data (before and after intervention). This will be described in a detailed statistical analysis plan.

Exploratory analysis: The Cox proportional hazards model will be used to investigate the relationship between change in emotional and physical function and mortality within 1 year. The Kaplan-Meier plot will be used to illustrate the survival of different patient groups.

Anticipated dates of trial commencement and completion:

Recruitment commenced in June 2020 with estimated completion date for recruitment and follow-up assessments of August 2022.

Strengths and limitations:

The SafeFit trial provides a novel approach to deliver exercise, nutrition and emotional support to people with cancer. The virtual method of delivery allows access to this personalised and holistic support from individual's homes, mitigating any risk of exposure to COVID-19 as well as removing well-established barriers to in-person interventions including travel and ability to integrate programmes within other life commitments. Underpinned by evidence-based behaviour change techniques it aims to empower participants to establish new behaviours that will be embedded in their everyday lives for the long-term. The trial is limited by the lack of comparison group. Measures of behaviour change are self-report and thus may introduce bias.

Ethics and dissemination:

Health Research Authority (HRA) ethical approval has been received prior to the opening of the trial (reference: 20/NW/0254). Any protocol modifications will be approved by the HRA before being implemented. Any amendments will be reported on dissemination of the trial. The trial has been registered with ClinicalTrials.gov: NCT04425616. The University Hospital Southampton NHS Foundation Trust is the Sponsor of this trial. Monitoring and auditing will be conducted in accordance with the Sponsor's policies and procedures. An independent data monitoring committee will be convened and will have oversight of trial data management.

Trial results will be disseminated to academics, commissioners, policy makers and the public through several avenues. Journal articles and scientific conferences will be used to disseminate to academic audiences. We will also communicate results to the Cancer Alliances, charities and through recognised NHS communication systems and social media. The University Hospital Southampton NHS Foundation Trust press office will coordinate press releases of key findings. We will also work in collaboration with our PPI representatives and partners to ensure dissemination to people with cancer.

Authors contributions:

CG drafted the manuscript. CG, SJ, JD and MPWG designed the trial. JA provided clinical psychology expertise, SW, CS and RB provided nutrition and dietetic expertise, JVS provided expertise in Healthy Conversation Skills Training, AS and AC provided expertise in exercise oncology and methods of evaluation, DZHL provided clinical oversight and expertise, SL, MW and AB provided expertise in trial

process and management, HM provided statistical expertise and devised the analysis plan with CG, SJ and MG. All authors contributed critically to revising and final approval of the manuscript.

Funding Statement: Funding has been received from Macmillan Cancer Support, the Wessex Cancer Alliance, the National Lottery (DCMS) and the Clinical Research Network to support this trial.
This protocol includes independent work [CS] supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. MG is part funded by the NIHR Senior Investigator Scheme and the NIHR Southampton Biomedical Research Centre. SL is supported by the National Institute for Health Research through the NIHR Southampton Biomedical Research The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Data Statement: There are no data in this work.

Acknowledgements: With thanks to Lisa Young for providing clinical advice and support.

Competing Interest statement: No competing interests.

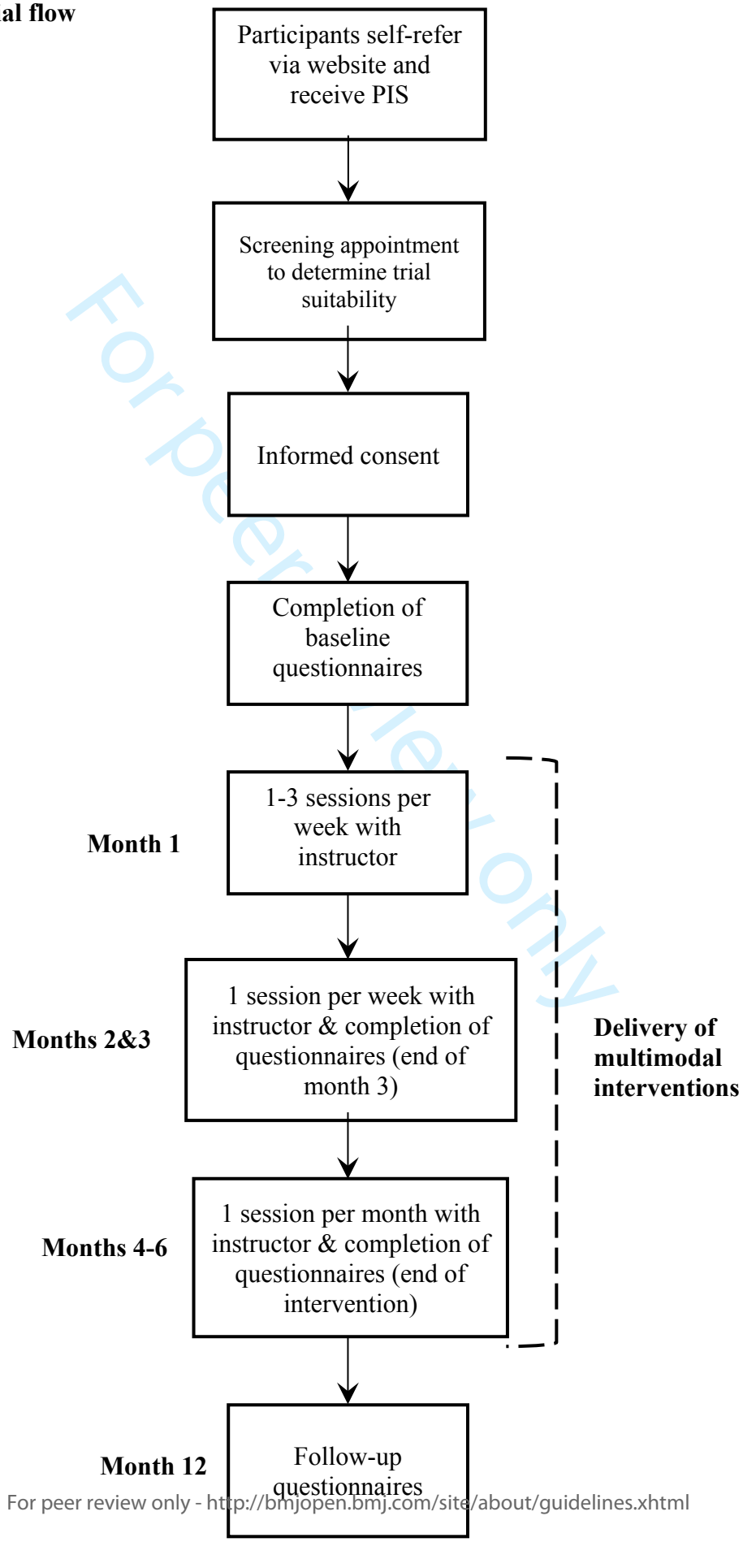
References

1. Macmillan Cancer Support; The forgotten 'C'? The impact of Covid-19 on cancer care. 2020.
2. Sud A, Jones ME, Broggio J, Loveday C, Torr B, Garrett A, et al. Collateral damage: the impact on cancer outcomes of the COVID-19 pandemic. medRxiv. 2020:2020.04.21.20073833.
3. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet. 2020;395(10241):1907-18.
4. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ. 2020;368:m1198.
5. Silver JK. Prehabilitation could save lives in a pandemic. Bmj. 2020;369:m1386.
6. Bruce J, Thornton AJ, Powell R, Johnston M, Wells M, Heys SD, et al. Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: a population-based cohort study. Pain. 2014;155(2):232-43.
7. Foster C, Haviland J, Winter J, Grimmett C, Chivers Seymour K, Batehup L, et al. Pre-Surgery Depression and Confidence to Manage Problems Predict Recovery Trajectories of Health and Wellbeing in the First Two Years following Colorectal Cancer: Results from the CREW Cohort Study. PLoS One. 2016;11(5):e0155434.
8. Mavros MN, Athanasiou S, Gkegkes ID, Polyzos KA, Peppas G, Falagas ME. Do psychological variables affect early surgical recovery? PLoS One. 2011;6(5):e20306.
9. Macmillan Cancer Support. Coronavirus: Half a million people with cancer are too scared to leave the house; 2020 [Available from: https://news.sky.com/story/coronavirus-half-a-million-people-with-cancer-are-too-scared-to-leave-the-house-research-shows-12017108.
10. Trials.gov. The Wessex Fit-4-Cancer Surgery Trial (WesFit) 2018 [Available from: https://clinicaltrials.gov/ct2/show/NCT03509428.
11. Macmillan Cancer Support, RCoA and NIHR. Principles and guidance for prehabilitation within the management and support of people with cancer. 2019 Jan 2019.
12. Goode AD, Lawler SP, Brakenridge CL, Reeves MM, Eakin EG. Telephone, print, and Web-based interventions for physical activity, diet, and weight control among cancer survivors: a systematic review. J Cancer Surviv. 2015;9(4):660-82.
13. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting habitual exercise in people living with and beyond cancer. Cochrane Database Syst Rev. 2018;9(9):Cd010192.
14. Grimmett C, Corbett T, Brunet J, Shepherd J, Pinto BM, May CR, et al. Systematic review and meta-analysis of maintenance of physical activity behaviour change in cancer survivors. International Journal of Behavioral Nutrition and Physical Activity. 2019;16(1):37.
15. McAuley E, Szabo A, Gothe N, Olson EA. Self-Efficacy: Implications for Physical Activity, Function, and Functional Limitations in Older Adults. American Journal of Lifestyle Medicine. 2011;5(4):361-9.
16. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
17. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

18. Lorig KR, Sobel DS, Stewart AL, Brown BW, Jr., Bandura A, Ritter P, et al. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. Med Care. 1999;37(1):5-14.
19. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. Health Serv Res. 2005;40(6 Pt 1):1918-30.
20. Mitchell AJ, Baker-Glenn EA, Granger L, Symonds P. Can the Distress Thermometer be improved by additional mood domains? Part I. Initial validation of the Emotion Thermometers tool. Psychooncology. 2010;19(2):125-33.
21. Mitchell AJ, Morgan JP, Petersen D, Fabbri S, Fayard C, Stoletniy L, et al. Validation of simple visual-analogue thermometer screen for mood complications of cardiovascular disease: the Emotion Thermometers. J Affect Disord. 2012;136(3):1257-63.
22. Weiss DS. The Impact of Event Scale: Revised. Cross-cultural assessment of psychological trauma and PTSD. International and cultural psychology. New York, NY, US: Springer Science + Business Media; 2007. p. 219-38.
23. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. BMC Med Res Methodol. 2015;15:60-.
24. Godin GSR. Godin leisure-time exercise questionnaire. . Medicine Science Sports and Exercise. 1997;26:S36-8.
25. World Cancer Research Fund. Cancer Health Check [Available from: https://www.wcrf-uk.org/uk/cancer-health-check.
26. Jager-Wittenaar H, de Bats HF, Welink-Lamberts BJ, Gort-van Dijk D, van der Laan B, Ottery FD, et al. Self-Completion of the Patient-Generated Subjective Global Assessment Short Form Is Feasible and Is Associated With Increased Awareness on Malnutrition Risk in Patients With Head and Neck Cancer. Nutr Clin Pract. 2020;35(2):353-62.
27. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.
28. Alonso J, Permanyer-Miralda G, Cascant P, Brotons C, Prieto L, Soler-Soler J. Measuring functional status of chronic coronary patients. Reliability, validity and responsiveness to clinical change of the reduced version of the Duke Activity Status Index (DASI). Eur Heart J. 1997;18(3):414-9.
29. Bredin SSD, Gledhill N, Jamnik VK, Warburton DER. PAR-Q+ and ePARmed-X+: new risk stratification and physical activity clearance strategy for physicians and patients alike. Can Fam Physician. 2013;59(3):273-7.
30. Warburton DER, Jamnik V, Bredin SSD, Shephard RJ, Gledhill N. The 2020 Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and electronic Physical Activity Readiness Medical Examination (ePARmed-X+): 2020 PAR-Q+. The Health & Fitness Journal of Canada. 2019;12(4):58-61.
31. National Institute for Healtha and Care Excleence. Improving supportive and palliative care for adults with cancer, Cancer service guideline [CSG4]. 2004.
32. Tinati T, Lawrence W, Ntani G, Black C, Cradock S, Jarman M, et al. Implementation of new Healthy Conversation Skills to support lifestyle changes - what helps and what hinders? Experiences of Sure Start Children's Centre staff. Health Soc Care Community. 2012;20(4):430-7.
33. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med. 2013;46(1):81-95.

34. May CR, Mair F, Finch T, MacFarlane A, Dowrick C, Treweek S, et al. Development of a theory of implementation and integration: Normalization Process Theory. Implementation Science. 2009;4(1):29.
35. Giesinger JM, Loth FLC, Aaronson NK, Arraras JI, Caocci G, Efficace F, et al. Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. J Clin Epidemiol. 2020;118:1-8.

Figure 1. Trial flow



Appendix A: Behaviour change techniques (BCT) coded to the BCT taxonomy (BCTT V1)

BCT label	BCT no. (BCTT v1)	Example Intervention component
Goal setting (behaviour)	1.1	Participants agree with the CES a goal for a specified period of time, for example walking for 30 minutes twice in the next week
Problem solving	1.2	CES use the SMARTER goal setting sheets to prompt the participant to analyse factors that might get in the way of them achieving a goal and how it can be overcome. For example, if it is raining the participant could perform an online exercise session rather than exercise outside.
Action planning	1.4	CES use SMARTER goal setting sheets to prompt detailed specification of goals include day of the week and time that they will perform a particular behaviour, for example I will have meat free dinners on Monday, Wednesday and Friday
Review behaviour goal(s)	1.5	During each 1-to-1 session the CES reviews behaviour goal(s) with the participants and modifies them collaborative as necessary, e.g. setting an easier goal if the previous goal was not achievable.
Discrepancy between current behaviour and goal	1.6	When reviewing dietary behaviour, the CES and participant will review current diet with the WCRF guidelines and identify areas for improvement
Feedback on behaviour	2.2	The CES and participant will reflect and discuss changes to behaviour made during the course of the intervention
Self-monitoring of behaviour	2.3	Participants have an activity diary which they are encouraged to complete throughout the intervention, noting goals set and whether they were achieved
Social support (unspecified)	3.1	The CES provides praise when participants perform a planned behaviour
Social support (practical)	3.2	The CES provides practical support to perform a behaviour, for example providing a live exercise class during the 1-to-1 consultations.
Social support (emotional)	3.3	The CES provides emotional support throughout the intervention and encourages the participant to seek that from others in their social network for continuation of support if necessary/appropriate.
Instruction on how to perform a behaviour	4.1	The CES may for example demonstrate specific exercises live during 1-to-1 video conferencing session
Demonstration of the behaviour	6.1	The CES may provide links to online videos of specific resistance exercises for example for participants to use independently
Behavioural practice/rehearsal	8.1	The participant may choose to use a relaxation app before bed each evening if they have difficulties with sleep and/or anxiety

Habit formation	8.3	The participant may plan to eat fruit every morning with breakfast to increase fruit and fibre intake.
Graded tasks	8.7	The CES works with the participant to start with easy to achieve goals, such as walking for 10 minutes 3 times a week, gradually increasing the difficulty overtime.
Credible source	9.1	The CES presents as a credible source with in-depth understanding of the benefits of the intervention components which are discussed with the participant.
Verbal persuasion about capability	15.1	If the participants express self-doubt about achieving a behaviour the CES will encourage the participant that they are capable of doing so, such as performing resistance exercises if a participant has a stoma.
Focus on past success	15.3	The CES will regularly review with the participant the improvements they have made over the course of the intervention

Appendix B TIDiER checklist

BRIEF NAME		PAGE
Provide the name or a phase that describes the intervention	Multimodal interventions including: Exercise, nutrition and psychological support, underpinned by behaviour change support.	
WHY		
Describe any rationale, theory or goal of the elements essential to the intervention	This trial is designed to support long-term health and well-being. To do so patients need to be supported to engage in exercise, consume a healthful diet based on current guidance and recommendations and address any psychological needs. Evidence suggests behaviour change interventions underpinned by theory are more successful than those without. Therefore, an evidence-based theoretically informed behavioural change support intervention is being embedded within the SafeFit Trial.	
WHAT		
Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide	<u>Participants</u> Goal setting sheet to record goals set and achievement (or not) SMARTER planning sheet to support goal setting Participants will be provided with links to the following dietary resources depending on individual needs/preference: The World Cancer Research Fund provides information for the general public on diet to reduce the risk of cancer https://www.wcrf-uk.org/ 'Eating well when you have cancer' from the Royal Marsden Hospital https://www.royalmarsden.nhs.uk/your-care/living-and-beyond-cancer/eating-well 'Eating well during cancer' from the World Cancer Research Fund https://www.wcrf-uk.org/uk/health-advice-and-support/eat-well-during-cancer Macmillan information on the Build Up diet: http://be.macmillan.org.uk/Downloads/beMacmillan%20PDFs/MAC13614_Buildingupdiet_lowres_E03_P08_20200206_KA.pdf	

information on where the materials can be accessed (e.g. online appendix, URL).	Eatwell guide (NHS): https://www.nhs.uk/live-well/eat-well/ Macmillan information and video: https://www.macmillan.org.uk/cancer-information-and-support/treatment/preparing-for-treatment/eating-well-and-keeping-active Resources for nutrition during exercise: https://www.royalmarsden.nhs.uk/your-care/living-and-beyond-cancer/eating-well-keep-fit and NHS: https://www.nhs.uk/live-well/eat-well/food-and-drinks-for-sport/ British Dietetic Association https://www.bda.uk.com/resource/sport-exercise-nutrition.html Non cancer specific diet https://www.bda.uk.com/food-health/food-facts/all-food-fact-sheets.html Participants will be provided with links to the following psychological support resources depending on individual needs/preference: Stress and anxiety: https://www.nhs.uk/conditions/stress-anxiety- depression/feel-better-and-happy/ Relaxation: https://www.mind.org.uk/information-support/tips-for-everyday- living/relaxation/relaxation-exercises/ Managing anxiety: https://www.nhs.uk/conditions/stress-anxiety- depression/moodzone-mental-wellbeing-audio-guides/ Relaxation techniques: https://www.cntw.nhs.uk/resource-library/relaxation- techniques/ Sleep https://www.sleepstation.org.uk/articles/ https://www.nhs.uk/live-well/sleep-and-tiredness/how-to-get-to-sleep/ https://www.nhs.uk/oneyou/every-mind-matters/sleep/ Mindfulness: http://www.velindrecc.wales.nhs.uk/mindfullness-app Tools for problem solving and letting go of worry: https://www.nhs.uk/apps- library/worrytree/	

Links to Macmillan Cancer Support online chat, online community https://community.macmillan.org.uk/ and telephone support line will also be available.

Cancer Exercise Specialists

Trainers will be provided with copies of all participant documents in addition to a training manual including:

- Escalation plans for any physical, metabolic or mental health concerns
- A webinar regarding psychological support is delivered by a clinical psychologist. Lasting 50mins, this covers use of open questions (when, whey how, what, who etc), reflection, elaboration, clarification, focus on feelings, questions to draw on personal skills and resources e.g. 'what has worked well in the past?', the Confided, Helped, I, Professional, Summaries (CHIP) model (ref) as well as communication tips to support remote communication. A supporting document is provided including key concepts covered.
- Similarly, a webinar providing dietary advice in accordance with the WCRF guidance, will be delivered by a consultant dietitian. This emphasises the purpose of the intervention to guide participants in dietary goal setting in accordance with guidance described by the World Cancer Research Fund and British Dietetic Association. Additional resources addressing nutrition and exercise, information on first line dietary advice for people experiencing side effects of treatment such as a poor appetite will also be provided.

- Healthy Conversation Skills: A highly interactive and experiential live online training session will be delivered by accredited Healthy Conversation Skills trainers in one session lasting 3 hours. The training is the online version of the Royal Society for Public Health accredited Healthy Conversation Skills eMECC Lite face-to-face training. It promotes an empowering, person-centred and solution-focused approach supporting people to change their behaviour. The training equips trainees with skills to create and identify opportunities to hold conversations about health and wellbeing, to explore individuals' barriers and facilitators to making change and taking control, to use active listening, and to support individuals to find their own solutions, plan for taking action to implement these solutions, monitor progress and adjust plan and action as needed.

- Covid-19 TopMed talks providing an overview of advice regarding exercise, nutrition and psychological support during covid-19 pandemic
  https://topmedtalk.libsyn.com/topmedtalk-macmillan-cancer-support-mental-well-being-for-the-patient-0
  https://topmedtalk.libsyn.com/topmedtalk-macmillan-cancer-support-healthy-eating-and-cancer-0
  https://topmedtalk.libsyn.com/topmedtalk-macmillan-cancer-support-get-active-and-feel-good

	All trainers also complete Introduction to Good Clinical Practice Training	
Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Participants receive a minimum of 1 and up to 3 one-to-one sessions with CES in the first month, delivered by telephone or video conferencing depending on participant preference. This reduces to 1 per week for the following 2 months and monthly for the following 3 months. Sessions will include live exercise training and/or discussion regarding previous and ongoing exercise completed by the participant. Participants will be supported to engage in at least one and up to 3 exercise sessions per week including: Aerobic exercise at a rating of perceived exertion of 11-14 (6-20 scale) accumulating 30 minutes per session, resistance exercise of 8-10 exercises for 2x 8-15 repetitions performed in a controlled manner and covering the whole body and range of motion exercise performed through pain free range of motion covering the whole body to be maintained in good alignment for 10-30 seconds, with some movements held for a second set of 10-30 seconds if stiff. These activities will be personalised and tracked in the session completion logs held by the CES. At the start of intervention CES will work through the WCRF health check to identify areas in the diet that would benefit from modification. This examines consumption of fruit and vegetables, wholegrains, red and processed meat, processed foods high in sugar and fat, processed meats, alcohol intake. Trainers support participants to set goals around diet modification throughout the intervention in order to achieve WCRF dietary recommendations. During each consultation CES will discuss any unintentional weight loss and change in nutrition impact symptoms that would require further specialist advice or prevent participants from taking part in exercise, for example, vomiting or diarrhoea. During each consultation CES will open a conversation around emotional wellbeing providing an opportunity for participants to share any concerns such as anxiety, low mood and distress. Core components of active listening, open questioning and empathy will be employed throughout to support emotional wellbeing. The CES will support participants to develop self-management skills, accessing resources and signposting to support services as appropriate. Possible suggested resources include mindfulness and relaxation exercises and Apps, information on anxiety management, problem solving and letting go of worry, available through NHS and Macmillan Cancer Support websites (as described above). The CES will employ healthy conversation skills during each session supporting goal setting and action planning for all three components of the intervention emphasising development of autonomy and self-efficacy to self-manage with the aim of enabling long-term adherence following completion of the intervention.	
WHO PROVIDED		

For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Intervention providers are personal trainers with additional training in exercise referral and/or additional qualifications in Cancer and Exercise Rehabilitation. All CES will have received the SafeFit training package and physical resources outlined above.	
HOW		
Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	All sessions will be delivered one-to-one by telephone or video conferencing.	
WHERE		
Describe the type(s) of location(s) where the intervention	Participants home or place of preference.	

occurred, including any necessary infrastructure or relevant features		
WHEN and HOW MUCH		
Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose	Sessions last approximately 1 hour with 1-3 sessions per week for 1 month, weekly sessions months 2-3, monthly sessions to 6 months. The content of each session will be personalised. Data on type, intensity and dose of exercise performed, and any nutrition and psychological support goals set will be collected in the session completion logs.	
TAILORING		
If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	This is a personalised intervention and all elements will be tailored to participant baseline characteristics, needs and preferences and adapted throughout.	

MODIFICATION		
If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	Trial ongoing	
HOW WELL		
Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Attendance at each scheduled session will be documented throughout the duration of the trial using session completion logs. CES will return session completion logs weekly during weeks 1-12 and monthly during weeks 16-24, documenting the content of each session. These logs will be regularly reviewed by the research team. Trainers will be offered group supervisions once every two weeks to address any concerns during the trial. Fidelity checks: approximately 20% of trainers will have 2 sessions (initial assessment and one follow-up call) assessed against a bespoke implementation checklist to assess fidelity of intervention delivery including assessment of competency for delivery of Healthy Conversation Skills.	
Actual: If intervention adherence or fidelity was assessed, describe the extent to which	Trial ongoing	

the intervention was delivered as planned		

BMJ Open

SafeFit Trial: Virtual clinics to deliver a multimodal intervention to improve psychological and physical wellbeing in people with cancer. Protocol of a COVID-19 targeted non-randomised phase III trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048175.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Jun-2021
Complete List of Authors:	Grimmett, Chloe; University of Southampton, School of Health Sciences Bates, Andrew; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre West, Malcolm; University of Southampton Faculty of Medicine, School of Cancer Sciences; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre Leggett, Samantha; University Hospital Southampton NHS Foundation Trust Varkonyi-Sepp, Judit; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre Campbell, Anna; Edinburgh Napier University, School of Applied Science Davis, June; Macmillan Cancer Support Wootton, Stephen; University of Southampton, School of Human Development and Health, Faculty of Medicine; NIHR Cancer and Nutrition Collaboration Shaw , Clare ; Royal Marsden NHS Foundation Trust, NIHR Biomedical Research Centre Barlow, Rachael; University Hospital of Wales, Cardiff and Vale University Health Board Ashcroft, Joanna; St George's University Hospitals NHS Foundation Trust Scott, Andrew ; University of Portsmouth, School of Sport, Health and Exercise Science Moyes, Helen; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre Hawkins, Lesley; University Hospital Southampton NHS Foundation Trust, Critical Care/Anaesthesia and Perioperative Medicine Research Unit Levett, Denny; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre; University of Southampton, School of Clinical and Experimental Sciences, Faculty of Medicine Williams, Fran; Wessex Cancer Alliance Grocott, Michael P. W.; University of Southampton, School of Clinical and Experimental Sciences, Faculty of Medicine; University Hospital Southampton NHS Foundation Trust, NIHR Biomedical Research Centre Jack, Sandy; University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre

Primary Subject Heading:	Oncology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	ONCOLOGY, Adult oncology < ONCOLOGY, PUBLIC HEALTH, REHABILITATION MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

SafeFit Trial: Virtual clinics to deliver a multimodal intervention to improve psychological and physical wellbeing in people with cancer. Protocol of a COVID-19 targeted non-randomised phase III trial.

Short title: SafeFit Trial: Multimodal intervention for people with cancer; a COVID-19 targeted trial.

Grimmett, C., Bates, A., West, M., Leggett, S., Varkonyi-Sepp, J., Campbell, A., Davis, J., Wootton, S., Shaw, C., Barlow, R., Ashcroft, J., Scott, A., Moyses, H., Hawkins, L., Levett, DZH., Williams, F., Grocott, MPW*., & Jack, S*.

* Joint senior authors

Corresponding author: Dr Chloe Grimmett, c.grimmett@soton.ac.uk

Affiliations:

Dr Chloe Grimmett, School of Health Sciences, University of Southampton, Southampton, SO17 1BJ, UK. orcid.org/0000-0002-7540-7206.

Andrew Bates, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK Orcid.org/ 0000-0002-3614-0270.

Mr Malcolm West, School of Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK; NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK. Orcid ID/0000-0002-0345-5356.

Samantha Leggett, National Institute for Health Research (NIHR) Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, SO16 6YD, UK. orcid.org/0000-0002-7400-8123.

Judit Varkonyi-Sepp, NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, SO166YD, orcid.org/0000-0002-7269-0261.

Prof Anna Campbell, School of Applied Science, Edinburgh Napier University, EH11 4BN, Scotland. Orcid: 0000-0003-3517-7335.

June Davis, Macmillan Cancer Support, 89, Albert Embankment, London, SE1 7UQ, UK orcid.org/0000-0002-1953-1632.

Dr Stephen Wootton, School of Human Development and Health, Faculty of Medicine, University of Southampton SO16 6YD, UK / NIHR Cancer and Nutrition Collaboration. orcid.org/0000-0002-9495-9719.

Dr Clare Shaw, National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London, UK. orchid.org/0000-0003-4169-9391.

Dr Rachael Barlow, Clinical Lead Prehabilitation Service, University Hospital of Wales, Cardiff and Vale University Health Board, Heath Park, Cardiff, CF14 4XL, Wales. orchid.org/0000-0001-9940-9209.

Dr Joanna Ashcroft, St George's University Hospital NHS Foundation Trust, SW17 0QT, UK.

Dr Andrew Scott, School of Sport, Health and Exercise Science, University of Portsmouth, Portsmouth, UK. orcid.org/0000-0003-1478-8962.

Helen Moyses, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK.

Lesley Hawkins, Critical Care/Anaesthesia and Perioperative Medicine Research Unit, University Hospital Southampton NHS Foundation Trust. UK. orcid.org/0000-0003-1304-6393.

Prof Denny Levett, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK; School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton SO16 6YD.
Anaesthesia and Critical Care Research Unit, University Hospital Southampton NHS Foundation Trust.

Fran Williams, Wessex Cancer Alliance, Oakley Road, Southampton, SO16 4GX.

Prof Michael P W Grocott, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK; School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton SO16 6YD.

Prof Sandy Jack, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK. Orcid.org/0000-0003-2763-7303.

Abstract

Introduction: The impact of the COVID-19 pandemic (caused by the SArS-CoV-2 virus), on individuals with cancer has been profound. It has led to increased anxiety, distress and deconditioning due to reduced physical activity. We aim to investigate whether SafeFit; a multi-modal intervention of physical activity, nutrition and psychological support delivered virtually by cancer exercise specialists (CES) can improve physical and emotional functioning during the COVID-19 pandemic.

Methods and analysis: A phase III non-randomised intervention trial, target recruitment of 1050 adults with suspected or confirmed diagnosis of cancer. All recruited participants will receive the multimodal intervention delivered by CES for six months. Sessions will be delivered 1-to-1 using telephone/video conferencing consultations. CES will work with each participant to devise a personalised programme of 1) physical activity, 2) basic dietary advice and 3) psychological support, all underpinned by a behaviour change intervention.

Primary outcome: Physical and emotional functioning as measured by the EORTC-QLQ-C30. Secondary outcomes: Overall quality of life measured by EORTC-QLQ-C30 and EQ-5D-5L, health economics, patient activation, self-efficacy to self-manage chronic disease, distress, Impact of Covid-19 on emotional functioning, self-reported physical activity, functional capacity and nutrition. Adherence to the intervention will also be measured and a process evaluation conducted.

Ethics and dissemination: Ethical approval was obtained from the Health Research Authority (reference number: 20/NW/0254). Results of this trial will be disseminated through publication of peer reviewed articles, presentations at scientific conferences and to the public and people with cancer in collaboration with our patient and public involvement representatives and partners.

Trial registration: NCT04425616

Sponsor: University Hospital Southampton NHS Foundation Trust

Article summary – *Strengths and Limitations up to 5 short bullet points, no longer than on sentence each that relate specifically to the methods*

- The SafeFit Trial will evaluate a novel approach to delivering multimodal exercise, nutrition and psychological support to people with cancer safely during and beyond the COVID-19 pandemic.
- The intervention will be delivered by cancer exercise specialists who have been upskilled using a bespoke training package, including nutrition, psychological support and Healthy Conversation Skills.
- The intervention, underpinned by evidence-based behaviour change techniques, seeks to empower participants to develop new behaviours that can be sustained for the long-term.
- Limitations of the trial include absence of a control group and reliance on self-report measures to evaluate behaviour change.

Keywords: cancer, intervention, physical activity, nutrition, psychological support, multimodal, virtual

Introduction

The COVID-19 pandemic, caused by the SArS-CoV-2 virus, has led to re-prioritising of clinical care and the impact on individuals with a cancer diagnosis has been profound. Treatments and follow-up care have been severely disrupted affecting 650,000 people with cancer in the UK alone and many supportive services have also been postponed (1) (2). Moreover, once infected with SArS-CoV-2 people with cancer experience significantly worse clinical outcomes (3). Although not all people living with and beyond cancer are now advised to shield many remain fearful of leaving their homes due to the risks of contracting the virus and the consequences of COVID-19 (1).

For many people with cancer, the pandemic has resulted in deconditioning due to social isolation, reduced physical activity and changes to eating habits that limit their ability to consume sufficient energy and nutrients to meet their needs. Cancer is typically a disease of older adults who are at particular risk of pulmonary complications as a result of COVID-19, which will likely be exacerbated by reduced cardiopulmonary fitness associated with such reductions in activity levels. Furthermore,

smoking, poor nutrition and obesity are independent risk factors for developing cancer which concurrently increase vulnerability to severe COVID-19 (4).

Good nutrition and regular physical activity have proven to be effective at addressing a variety of disease and treatment-related consequences of cancer and optimising physical fitness is also likely to decrease morbidity and mortality associated with COVID-19 (5). Thus, supporting this population to maximise engagement in physical activity and improve nutritional status is imperative.

Supporting psychological well-being is also vital for people with cancer. Higher levels of anxiety and depression are associated with poor quality of life and physiological outcomes both early in the treatment pathway and in patients who have completed treatment (6-8). Many people with cancer will continue to experience distress, depression and anxiety months and years after cancer treatment completion. These issues are exacerbated by the COVID-19 pandemic through reduced access to informal social support networks and formal psychological support services. Macmillan Cancer Support reported in June 2020 that over 270,00 people with cancer in the UK have experienced panic or anxiety attacks because of the COVID-19 pandemic (9).

The SafeFit trial, as described in this paper, was conceived when our research team was forced to pause recruitment to the Wessex-Fit-4-Cancer Surgery Trial (10), a multimodal prehabilitation trial delivered in community settings. We wanted to develop a new programme to support patients throughout and beyond the COVID-19 pandemic. The multimodal structure of the intervention is informed by the recent Macmillan, Royal College of Anaesthetists and National Institute of Health Cancer and Nutrition Collaboration, Research Principles and Guidance for Prehabilitation within the Management and Support of People with Cancer (11). The guidance advocates for a multimodal approach encompassing exercise, nutrition and psychological support in order to optimise cancer patients prior to treatment increasing their resilience to withstand cancer therapies and hasten their recovery.

It is now accepted that people with cancer require ‘end-to-end’ pathway support, at the point of diagnosis, throughout treatment and recovery. The SafeFit Trial adopted the multimodal prehabilitation model for universal provision of support with patients recruited at any point in the treatment and recovery pathway. People with cancer are increasingly turning to remote support services and distanced and home-based interventions have been shown to be effective in supporting dietary and physical activity behaviour change (12). However, evidence suggests that inclusion of a

supervised component increases intervention adherence (13) and longer-term maintenance of physical activity behaviour change (14).

Considerable research has explored the most effective 'ingredients' of a behaviour change intervention in cancer populations to improve engagement and adherence to such interventions as well as promote longer-term behaviour change. A recent Cochrane review supports the use of goal setting, setting of graded tasks and instruction on how to perform behaviour to maximise intervention adherence (13). Additionally, action planning and social support are associated with maintenance of behaviour change (14). Furthermore, there is growing evidence of the role of self-efficacy – a person's belief in their ability to perform a given task – in supporting behaviour change with evidence that self-efficacy is a mediator of exercise behaviour in clinical populations and a predictor of exercise adherence (15). The SafeFit Trial is underpinned by behavioural science using evidence-based behaviour change techniques to optimise patient engagement and support self-management and long-term behaviour change.

The proposed trial explores the impact of SafeFit, a virtually delivered multimodal intervention, on the physical and emotional wellbeing of people with cancer.

Methods and analysis:

Trial design and setting:

The SafeFit Trial is a phase III non-randomised intervention with multimodal components of exercise, nutrition optimisation and psychological support delivered remotely by telephone and/or video conferencing.

Trial objectives and outcome measures:

Primary objective: To investigate the efficacy of SafeFit interventions to improve physical and emotional functioning as measured by change in the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC QLQ-C30) (16) over the 6-month intervention. Five items for physical function and four for emotional function are answered using a Likert scale 1-4 are scored to provide a function score from 0-100. Higher scores represent higher functioning. This subscale has been used in previous interventions in cancer populations and is sensitive to change over time.

The main secondary objectives are to investigate the impact of the SafeFit Trial on:

Quality of life and cost-effectiveness: Overall cancer-specific quality of life and global health status, cognitive and social function and nine symptom sub-scales will be measured by the EORTC-QLQ-C30. Quality of life will also be measured by the EQ-5D-5L. A standardised instrument developed by the EuroQoI Group for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, the EQ-5D-5L health questionnaire provides a simple descriptive profile and a single index value for health status (17). Resources used to deliver the SafeFit trial will be measured and valued and health economic analysis conducted using the EQ-5D-5L and the Patient Activation Measure (see below for details).

Self-efficacy and Patient Activation: Self-efficacy to self-manage chronic disease will be measured by the Self-Efficacy for Managing Chronic Disease Scale; a 6-item measure with higher scores indicating greater confidence to manage illness-related problems (18). Patient activation will be measured by the Patient Activation Measure (PAM) (19). The PAM is a validated self-report survey. Each survey response is scored and based on the total score between 1 and 100; responders are categorized to 4 activation levels.

Psychological distress will be measured using the Emotion Thermometers (20). A simple rapid modular visual analogue screening tool for detection and monitoring of emotional disorders in clinical practice. Four emotional domains (distress, anxiety, depression and anger) are measured using a visual analog scale (0-10) and one outcome domain – need for help (21). Impact of COVID-19 on psychological functioning will be measured by the Impact of Events Scale (22). No validated measure is available to measure the impact of COVID-19 on physical function.

Behaviour change: Self-reported physical activity will be measured using the modified Godin Leisure Time Exercise Questionnaire (23). This is widely used in the exercise oncology literature and has been validated against objective activity monitoring and measures of physical fitness (24). Diet will be measured using the World Cancer Research Fund (WCRF) modified HealthCheck tool (25) which examines intake of fruits, vegetables, wholegrains, red and processed meats, processed foods high in fat and sugar, sugary drinks and alcoholic beverages.

Self-reported height (baseline only) weight, weight loss and changes in nutritional status will be measured by short form Patient Generated Subjective Global Assessment (26, 27). Functional capacity will be measured by the Duke Activity Status Index (DASI). The DASI also allows for the calculation of the individuals predicted peak oxygen consumption (28).

Finally, differences in response to the SafeFit Trial depending on COVID-19 status; confirmed COVID-19, suspected COVID-10, self-isolation, none will be explored.

The above outcomes (except for health economics) will be assessed at 6 months (primary endpoint), in addition to 3 months (mid intervention) and 12 months (post-intervention follow-up). A follow-up email/phone call will be made at each time point if necessary, to maximise data completion.

Exploratory outcomes: Overall survival (all-cause mortality) at 12 months.

Demographic and clinical data will be collected at baseline including age, sex, postcode, ethnicity, education, employment status, marital status, living arrangement (who they live with), household accommodation and car ownership. Self-reported clinical data will include date of diagnosis, cancer type and stage, cancer status, treatment/s (current and historical) and co-morbidities.

Inclusion/Exclusion criteria:
Adults (aged ≥18 years) with suspected or confirmed diagnosis of cancer. Individuals unable to give informed consent will not be eligible for this trial.

Recruitment and recruitment procedures:
Potential participants will be recruited via self-referral, with the SafeFit trial advertised through social media, via partner organisations include Macmillan Cancer Support, and through clinical teams and multidisciplinary team meetings.

Potential participants will visit the SafeFit Trial website and complete a Smart Survey to express their interest in the trial. A welcome email will be sent to potential participants together with a patient information sheet. A member of the trial team will then telephone potential participants to confirm eligibility. During this telephone call potential participants will complete the following screening to confirm suitability for the trial:

i. The Physical Activity Readiness Questionnaire PARQ+ (29) This tool screens participants presenting acute or uncontrolled long term conditions that would be exacerbated by exercise (30).

ii. COVID-19 status (confirmed COVID-19, suspected COVID-1, self-isolation, none)

iii. Nutritional state (problems eating or drinking and unintended weight loss), whether the individuals are receiving nutritional support and if they are under the care of a Registered Dietitian. Those assessed to be malnourished (BMI<18.5) or reporting specific Nutritional Impact Symptoms of dysphagia, diarrhoea or vomiting or receiving Artificial Nutritional Support will not receive the standard nutritional advice element of the trial. Appropriate referrals for nutritional support will be made for those identified as at risk of malnutrition.

iv. Psychological distress. Those scoring ≥8 on the distress thermometer are asked additional questions. Those at risk of self-harm will not be recruited to the trial and appropriate referrals for support will be made.

Participants will be eligible for inclusion to the trial providing they are safe to receive at least one of the three components. For example, a potential participant who is deemed unsafe to exercise would receive the nutritional and psychological components of the intervention. The exercise element would be introduced if/when it is safe to do so.

All eligible participants will then complete an online consent form and baseline questionnaires. Those not willing or able to complete questionnaires online will be posted paper copies with a return pre-paid envelope. Once baseline questionnaires are complete participants will be matched with a CES. Participants will have the opportunity to complete an electronic Holistic Needs Assessment (eHNA) prior to the telephone call with the trial team. See Figure 1 for trial flow.

Intervention:

The intervention duration will be 6 months. Participants will receive up to three one-to-one sessions per week for 1 month (weeks 1-4-), weekly for 2 months (week 5-12) and monthly for 3 months (Week 16, 20 and 24).

Exercise: Participants will be supported to engage in at least one and up to three exercise sessions per week including: (i) aerobic exercise at a rating of perceived exertion of 11-14 (6-20 scale) accumulating up to 30 minutes per session; (ii) resistance exercise of 8-10 different exercises each

for 2x 8-15 repetitions performed in a controlled manner and covering the whole body and range of motion. Resistance exercise should be performed through the full pain free range of motion covering the whole body with maintenance of good alignment for 10-30 seconds, with some movements held for a second set of 10-30 seconds if stiff. Engagement will involve a combination of supervised exercise sessions during the one-to-one sessions (if requested by the participant) and unsupervised home-based sessions.

Psychological support: The CES will provide psychological support as per levels 1 and 2 of the Improving Supportive and Palliative Care for Adults with Cancer (31). This includes recognising the psychological needs of patients, providing compassionate communication, general psychological support and simple, self-management focused signposting and problem solving.

Nutrition support: The CES will work with participants to review their diet and eating habits against World Cancer Research Fund recommendations using the modified 'HealthCheck' online tool to identify areas of change as appropriate (25). Participants will review their consumption of fruit and vegetables, wholegrains, red and processed meat, processed foods high in sugar and fat, processed meats, and alcohol intake with the aim to achieve WCRF recommendations for cancer survivors through incremental goal setting. The CES will regularly check for unintended weight loss or changes in gastrointestinal function and/or changes in the ability to eat/drink and report abnormalities immediately to the trial team.

Behaviour change support: The CES will receive training in Healthy Conversation Skills (32). This will enable them to deliver a client-centred, solution focused, empowering intervention informed by social cognitive theory. The intervention is aimed at increasing patients' self-efficacy and motivation to adopt behaviour change. The same skillset and delivery modality will be employed to support patients in engaging in the exercise and nutrition components of the intervention as well as adopting strategies to self-manage their psychological well-being. Participants will be provided with a SMARTER goal-planning sheet to assist with goal setting and action planning during consultations with their CES. The titrated support acts to increase participant's autonomy and support long-term engagement in these new behaviours. See Appendix A for list of Behaviour Change Techniques employed as per the taxonomy of Behaviour Change Techniques (33) and used flexibly within sessions as per the person-centred approach.

Training programme for Cancer Exercise Specialists:

All CES will have training in exercise referral and/or additional qualifications in Cancer and Exercise Rehabilitation and will deliver the SafeFit interventions. All CES will also receive a bespoke training package delivered online by the trial team, supported by the clinical team:

1) Health Conversation Skills - Online Healthy Conversation Skills training (eMECC Lite). This training is an online version of the Royal Society for Public Health-accredited MECC Lite Healthy Conversation Skills training. Consistent with the face-to-face training, the online version is highly interactive and experiential. The training equips trainees with skills to create and identify opportunities to hold conversations about health and wellbeing, to explore the individuals' barriers and facilitators to making change and taking control, to use active listening, and to support individuals to find their own solutions, plan for taking action to implement these solutions, monitor progress and adjust, plan and action as needed.

2) Nutrition – A webinar with accompanying support material will be delivered by an experienced dietitian [CS] to provide training in generic nutritional principles in line with the recommendations from the World Cancer Research Fund and British Dietetic Association and to identify deterioration in nutritional status. The webinar covers; the principles of healthy eating ('eat well' advice), weight management, symptom management, prehabilitation advice before treatment starts, rehabilitation advice during and after treatment. Links to trusted dietary resources provided on the internet will be made available.

3) Emotional support - A webinar with accompanying supportive materials will be delivered by an experienced clinical psychologist (JA) specialising in oncology. This will focus on communication skills, recognising emotions, active listening and questioning.

Safety during sessions: It will be the responsibility of the CES to complete a pre-session screening checklist to monitor condition, medical contacts, medication and COVID-19 status. If appropriate exercise will continue, be modified with observation or stopped and review sought from the treating medical team. In the case of an acute medical event during the exercise session, the CES will advise the participant to call their GP or 111. If concerned about collapse, the CES will call 999. The CES will ask the participant to repeat the distress thermometer before each session. If the participant scores 8 or above for 2 consecutive weeks they will be encouraged to contact Macmillan Cancer Support helpline and/or their GP. In the case of suicidal or self-harm ideation, the CES will advise contacting Samaritans, SHOUT, GP or 111. If concerned about immediate risk the CES will call 999. Participants who experience a marked deterioration in their nutritional state (e.g. stricture, swallow, inanition, weight loss) will be directed back to their cancer care team. Participants with a confirmed diagnosis,

or suspicion of, COVID-19 will have their exercise intervention paused for 14 days but, symptoms allowing, will be able to receive the other interventions. The exercise intervention will also be paused if anybody in their household is displaying COVID-19 symptoms. Acute events and changes in condition and/or treatment plan will be reported to the trial team. Cases of immediate physical or mental health concern will be raised with the Chief Investigator or senior clinician with delegated authority. All other cases will be discussed at a weekly multi-disciplinary clinical team review. In case of incomplete information or ongoing investigation, it will be the responsibility of the participant to gain clinical sign off before resuming trial activity. All adverse and series adverse events will be recorded.

Fidelity checks: Attendance at each scheduled session will be documented by the CES throughout the trial using session completion logs, these will be regularly reviewed by the trial team. The CES will be offered group supervisions once every two weeks to address any concerns during the trial. Approximately 20% of trainers will have two sessions (initial assessment and one follow-up call) observed (via recording of video or telephone call) and assessed against a bespoke implementation checklist to assess fidelity of intervention delivery, including assessment of competency for delivery of HCS.

See TiDiER checklist (Appendix B) for detailed description of intervention components, training procedures and links to additional resources.

Process evaluation:

A comprehensive process evaluation will enable identification of barriers and facilitators to the implementation of and participation in the SafeFit trial. It will afford an in-depth understanding of processes, relationships and communications that helped or hindered conduct of the trial.

The process evaluation will assess acceptability of the SafeFit Trial from the perspective of participants and professionals delivering the programme as well as identifying barriers and enablers to engagement with and adherence to the programme. We will also capture data to explain how the intervention worked, who it did and didn't work for and why, along with other issues with delivery of the intervention and participant receptivity. Qualitative in-depth semi-structured interviews will be conducted with participants enrolled in the trial and professionals involved in the delivery of the trial. This will include N=25 participants who will be purposively sampled to include a range of age, sex, disease type, time since diagnosis and adherence to scheduled calls. Interviews will focus on the

barriers and facilitators to participation in the trial and success (or not) of behaviour change. These data will provide explanatory insight into the findings of the trial.

Interviews will also be conducted with CES delivering the trial as well as administrative personnel coordinating the trial (N=15). The purpose of these interviews is to understand the barriers and facilitators to the delivery of the prescribed interventions as well as views of the usefulness of training received.

Normalisation Process Theory (NPT) will underpin the conceptual framework that will structure the process evaluation (i.e. the interview schedules, findings and their interpretation). NPT provides an explanatory framework to better understand the routine embedding of healthcare interventions in their social contexts, in particular *why some processes seem to lead to a practice becoming sustained over a long term while others do not.* The starting point of NPT are the dynamics associated with the embedding of a practice i.e. what people actually do and how they work together (34).

Patient and Public Involvement (PPI):

People with cancer were consulted at the outset of this trial. We worked closely with four research partners including individuals living with cancer (who were shielding), caring for someone with cancer and recovering from cancer. They provided suggestions of how potential participants might be reassured of the safety of the trial as well as support they might need to access the virtual intervention. They also reviewed trial questionnaires, patient facing documentation and piloted the self-referral process. Moreover, they agreed to be members of our steering group and will contribute to the oversight of the trial. In previous trials conducted by our research group, PPI representatives have been invited to speak at conferences and stakeholder events, providing powerful testimonies. We intend to continue this approach with the current trial. The research team will liaise the PPI involvement lead in University Hospital Southampton's Biomedical Research Centre to identify training and support needs of our research partners throughout the trial.

Statistical analysis plan and sample size calculation:

Preliminary data suggest that approximately 62% of patients will have a 'good' Physical Function score of >83 at baseline, and 43% of patients will have a 'good' Emotional Function score at baseline (>71) as determined by threshold for clinical importance for the EORTC-QLQ-C30 (35). In order to detect an 8% improvement in the proportion of patients with good physical/emotional function score with 90% power (alpha=0.05), 1050 patients will be required (allowing for 20% drop-out).

Descriptive statistics will be used to summarise baseline demographic and clinical variables. For continuous variables, the mean and standard deviation will be calculated for Normally distributed data. If the data are not Normally distributed, the median and interquartile range will be calculated. Categorical or binary variables will be summarised as frequency and percentage of total.

The primary endpoints are EORTC-QLQ-C30 physical function and emotional function scales measured at 6 months. The McNemar test will be used to investigate whether there is a difference in the proportion of patients with good physical function and emotional function score at the end of the intervention (6 months) compared to baseline. In order to account for multiple comparisons, the Holm procedure will be used to adjust p-values.

Repeated measures logistic regression will be used to investigate the change over all trial visits (baseline, 3, 6 and 12 months), and to adjust for clinically prognostic factors which will include age, gender, cancer type, tumour site, systemic anti-cancer treatment.

Subgroup analysis will also be performed. The proportion of patients with good physical function/emotional function score at 6 months (with confidence interval) will be calculated for each subgroup, and will be displayed on a forest plot, along with the p-value for interaction. COVID-19 status (confirmed COVID-19, suspected COVID-19, self-isolation, none), curative vs palliative, chemo/rad vs. not, surgery vs. not, adherent to intervention vs. not (adherence is defined as completing ≥70% of calls with CES), tumour site, baseline QoL (above 85 vs. 85 total EORTC-QLQ-C30 score).

Analysis of secondary endpoints (including but not limited to anxiety, depression, confidence to self-manage chronic disease, physical activity and dietary behaviour change, Duke activity status) will be performed using the appropriate statistical tests/regression models depending on the outcome data type (i.e. continuous, ordinal, binary), and taking into account the paired nature of the data (before and after intervention). This will be described in a detailed statistical analysis plan.

Exploratory analysis: The Cox proportional hazards model will be used to investigate the relationship between change in emotional and physical function and mortality within 1 year. The Kaplan-Meier plot will be used to illustrate the survival of different patient groups.

Anticipated dates of trial commencement and completion:

Recruitment commenced in June 2020 with estimated completion date for recruitment and follow-up assessments of August 2022.

Strengths and limitations:

The SafeFit trial provides a novel approach to deliver exercise, nutrition and emotional support to people with cancer. The virtual method of delivery allows access to this personalised and holistic support from individual's homes, mitigating any risk of exposure to COVID-19 as well as removing well-established barriers to in-person interventions including travel and ability to integrate programmes within other life commitments. Underpinned by evidence-based behaviour change techniques it aims to empower participants to establish new behaviours that will be embedded in their everyday lives for the long-term. The trial is limited by the lack of comparison group. Measures of behaviour change are self-report and thus may introduce bias.

Ethics and dissemination:

Health Research Authority (HRA) ethical approval was received 20th May 2020 (protocol V2 date: 13th May 2020), prior to the opening of the trial (reference: 20/NW/0254). Any protocol modifications will be approved by the HRA before being implemented. Any amendments will be reported on dissemination of the trial. The trial has been registered with ClinicalTrials.gov: NCT04425616. The University Hospital Southampton NHS Foundation Trust is the Sponsor of this trial. Monitoring and auditing will be conducted in accordance with the Sponsor's policies and procedures. An independent data monitoring committee will be convened and will have oversight of trial data management.

Trial results will be disseminated to academics, commissioners, policy makers and the public through several avenues. Journal articles and scientific conferences will be used to disseminate to academic audiences. We will also communicate results to the Cancer Alliances, charities and through recognised NHS communication systems and social media. The University Hospital Southampton NHS Foundation Trust press office will coordinate press releases of key findings. We will also work in collaboration with our PPI representatives and partners to ensure dissemination to people with cancer.

Data collection, quality and storage

Data will be collected and stored on password protected databases by trial personnel, who are trained in Good Clinical Practice (GCP) and General Data Protection Regulations (GDPR). Confidentiality will be ensured before, during and after the trial and all procedures for handling, storing, destroying and processing data will be compliant with the Data Protection Act 2018. Patient reported outcome

measures will be completed on paper or using the electronic case report form (ALEA™) depending on patient preference. Prior to any statistical analysis, all variables will be checked for the number of missing and impossible values. Impossible values will be defined by clinical opinion. The trial sponsor and Chief Investigators will have access to the final dataset.

Authors contributions:

CG drafted the manuscript. CG, SJ, JD and MPWG made substantial contributions to the conception and design of the trial. JA provided clinical psychology expertise, contributing to design of the psychological component of the intervention and providing critical intellectual content. SW, CS and RB provided nutrition and dietetic expertise, contributing to the design of the nutritional components of the intervention, providing critical intellectual content. JVS provided expertise in Healthy Conversation Skills Training, contributing to the design of the behaviour change components of the intervention, providing critical intellectual content. AS and AC provided expertise in exercise oncology and methods of evaluation, contributing to the design of the exercise components of the intervention, providing critical intellectual content. DZHL provided clinical oversight and expertise, SL, LH, FW, MW and AB provided expertise in trial process and management, HM provided statistical expertise and devised the analysis plan with CG, SJ and MG. All authors contributed critically to revising and final approval of the manuscript.

Funding Statement: Funding has been received from Macmillan Cancer Support (award/grant number is not applicable), the Wessex Cancer Alliance (award/grant number is not applicable), the National Lottery (Digital, Culture Media and Sport. Grant number: 20142065) and the Clinical Research Network (award/grant number is not applicable) to support this trial.
This protocol includes independent work [CS] supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. MG is part funded by the NIHR Senior Investigator Scheme and the NIHR Southampton Biomedical Research Centre. SL is supported by the National Institute for Health Research through the NIHR Southampton Biomedical Research The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Data Statement: There are no data in this work.

Acknowledgements: With thanks to Lisa Young for providing clinical advice and support.

Competing Interest statement: No competing interests.

Figure 1: Trial flow

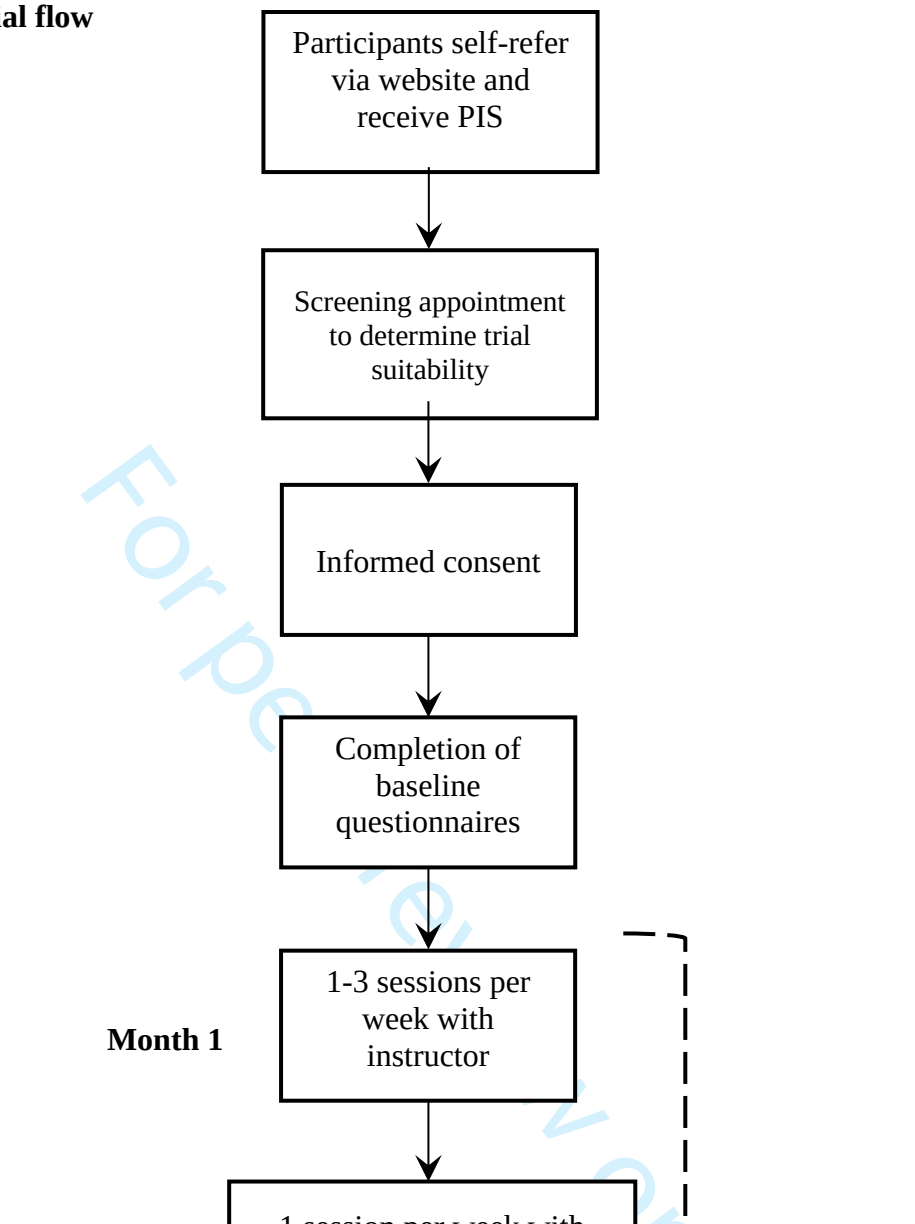
References

1. Macmillan Cancer Support; The forgotten 'C'? The impact of Covid-19 on cancer care. 2020.
2. Sud A, Jones ME, Broggio J, Loveday C, Torr B, Garrett A, et al. Collateral damage: the impact on cancer outcomes of the COVID-19 pandemic. medRxiv. 2020:2020.04.21.20073833.
3. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet. 2020;395(10241):1907-18.
4. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ. 2020;368:m1198.
5. Silver JK. Prehabilitation could save lives in a pandemic. Bmj. 2020;369:m1386.
6. Bruce J, Thornton AJ, Powell R, Johnston M, Wells M, Heys SD, et al. Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: a population-based cohort study. Pain. 2014;155(2):232-43.
7. Foster C, Haviland J, Winter J, Grimmett C, Chivers Seymour K, Batehup L, et al. Pre-Surgery Depression and Confidence to Manage Problems Predict Recovery Trajectories of Health and Wellbeing in the First Two Years following Colorectal Cancer: Results from the CREW Cohort Study. PLoS One. 2016;11(5):e0155434.
8. Mavros MN, Athanasiou S, Gkegkes ID, Polyzos KA, Peppas G, Falagas ME. Do psychological variables affect early surgical recovery? PLoS One. 2011;6(5):e20306.
9. Macmillan Cancer Support. Coronavirus: Half a million people with cancer are too scared to leave the house; 2020 [Available from: https://news.sky.com/story/coronavirus-half-a-million-people-with-cancer-are-too-scared-to-leave-the-house-research-shows-12017108.
10. Trials.gov. The Wessex Fit-4-Cancer Surgery Trial (WesFit) 2018 [Available from: https://clinicaltrials.gov/ct2/show/NCT03509428.
11. Macmillan Cancer Support, RCoA and NIHR. Principles and guidance for prehabilitation within the management and support of people with cancer. 2019 Jan 2019.
12. Goode AD, Lawler SP, Brakenridge CL, Reeves MM, Eakin EG. Telephone, print, and Web-based interventions for physical activity, diet, and weight control among cancer survivors: a systematic review. J Cancer Surviv. 2015;9(4):660-82.
13. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting habitual exercise in people living with and beyond cancer. Cochrane Database Syst Rev. 2018;9(9):Cd010192.
14. Grimmett C, Corbett T, Brunet J, Shepherd J, Pinto BM, May CR, et al. Systematic review and meta-analysis of maintenance of physical activity behaviour change in cancer survivors. International Journal of Behavioral Nutrition and Physical Activity. 2019;16(1):37.
15. McAuley E, Szabo A, Gothe N, Olson EA. Self-Efficacy: Implications for Physical Activity, Function, and Functional Limitations in Older Adults. American Journal of Lifestyle Medicine. 2011;5(4):361-9.
16. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
17. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

18. Lorig KR, Sobel DS, Stewart AL, Brown BW, Jr., Bandura A, Ritter P, et al. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. Med Care. 1999;37(1):5-14.
19. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. Health Serv Res. 2005;40(6 Pt 1):1918-30.
20. Mitchell AJ, Baker-Glenn EA, Granger L, Symonds P. Can the Distress Thermometer be improved by additional mood domains? Part I. Initial validation of the Emotion Thermometers tool. Psychooncology. 2010;19(2):125-33.
21. Mitchell AJ, Morgan JP, Petersen D, Fabbri S, Fayard C, Stoletniy L, et al. Validation of simple visual-analogue thermometer screen for mood complications of cardiovascular disease: the Emotion Thermometers. J Affect Disord. 2012;136(3):1257-63.
22. Weiss DS. The Impact of Event Scale: Revised. Cross-cultural assessment of psychological trauma and PTSD. International and cultural psychology. New York, NY, US: Springer Science + Business Media; 2007. p. 219-38.
23. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. BMC Med Res Methodol. 2015;15:60-.
24. Godin GSR. Godin leisure-time exercise questionnaire. . Medicine Science Sports and Exercise. 1997;26:S36-8.
25. World Cancer Research Fund. Cancer Health Check [Available from: https://www.wcrf-uk.org/uk/cancer-health-check.
26. Jager-Wittenaar H, de Bats HF, Welink-Lamberts BJ, Gort-van Dijk D, van der Laan B, Ottery FD, et al. Self-Completion of the Patient-Generated Subjective Global Assessment Short Form Is Feasible and Is Associated With Increased Awareness on Malnutrition Risk in Patients With Head and Neck Cancer. Nutr Clin Pract. 2020;35(2):353-62.
27. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.
28. Alonso J, Permanyer-Miralda G, Cascant P, Brotons C, Prieto L, Soler-Soler J. Measuring functional status of chronic coronary patients. Reliability, validity and responsiveness to clinical change of the reduced version of the Duke Activity Status Index (DASI). Eur Heart J. 1997;18(3):414-9.
29. Bredin SSD, Gledhill N, Jamnik VK, Warburton DER. PAR-Q+ and ePARmed-X+: new risk stratification and physical activity clearance strategy for physicians and patients alike. Can Fam Physician. 2013;59(3):273-7.
30. Warburton DER, Jamnik V, Bredin SSD, Shephard RJ, Gledhill N. The 2020 Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and electronic Physical Activity Readiness Medical Examination (ePARmed-X+): 2020 PAR-Q+. The Health & Fitness Journal of Canada. 2019;12(4):58-61.
31. National Institute for Healtha and Care Excleence. Improving supportive and palliative care for adults with cancer, Cancer service guideline [CSG4]. 2004.
32. Tinati T, Lawrence W, Ntani G, Black C, Cradock S, Jarman M, et al. Implementation of new Healthy Conversation Skills to support lifestyle changes - what helps and what hinders? Experiences of Sure Start Children's Centre staff. Health Soc Care Community. 2012;20(4):430-7.
33. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med. 2013;46(1):81-95.

34. May CR, Mair F, Finch T, MacFarlane A, Dowrick C, Treweek S, et al. Development of a theory of implementation and integration: Normalization Process Theory. Implementation Science. 2009;4(1):29.
35. Giesinger JM, Loth FLC, Aaronson NK, Arraras JI, Caocci G, Efficace F, et al. Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. J Clin Epidemiol. 2020;118:1-8.

Figure 1. Trial flow



Appendix A: Behaviour change techniques (BCT) coded to the BCT taxonomy (BCTT V1)

BCT label	BCT no. (BCTT v1)	Example Intervention component
Goal setting (behaviour)	1.1	Participants agree with the CES a goal for a specified period of time, for example walking for 30 minutes twice in the next week
Problem solving	1.2	CES use the SMARTER goal setting sheets to prompt the participant to analyse factors that might get in the way of them achieving a goal and how it can be overcome. For example, if it is raining the participant could perform an online exercise session rather than exercise outside.
Action planning	1.4	CES use SMARTER goal setting sheets to prompt detailed specification of goals include day of the week and time that they will perform a particular behaviour, for example I will have meat free dinners on Monday, Wednesday and Friday
Review behaviour goal(s)	1.5	During each 1-to-1 session the CES reviews behaviour goal(s) with the participants and modifies them collaborative as necessary, e.g. setting an easier goal if the previous goal was not achievable.
Discrepancy between current behaviour and goal	1.6	When reviewing dietary behaviour, the CES and participant will review current diet with the WCRF guidelines and identify areas for improvement
Feedback on behaviour	2.2	The CES and participant will reflect and discuss changes to behaviour made during the course of the intervention
Self-monitoring of behaviour	2.3	Participants have an activity diary which they are encouraged to complete throughout the intervention, noting goals set and whether they were achieved
Social support (unspecified)	3.1	The CES provides praise when participants perform a planned behaviour
Social support (practical)	3.2	The CES provides practical support to perform a behaviour, for example providing a live exercise class during the 1-to-1 consultations.
Social support (emotional)	3.3	The CES provides emotional support throughout the intervention and encourages the participant to seek that from others in their social network for continuation of support if necessary/appropriate.
Instruction on how to perform a behaviour	4.1	The CES may for example demonstrate specific exercises live during 1-to-1 video conferencing session
Demonstration of the behaviour	6.1	The CES may provide links to online videos of specific resistance exercises for example for participants to use independently
Behavioural practice/rehearsal	8.1	The participant may choose to use a relaxation app before bed each evening if they have difficulties with sleep and/or anxiety

Habit formation	8.3	The participant may plan to eat fruit every morning with breakfast to increase fruit and fibre intake.
Graded tasks	8.7	The CES works with the participant to start with easy to achieve goals, such as walking for 10 minutes 3 times a week, gradually increasing the difficulty overtime.
Credible source	9.1	The CES presents as a credible source with in-depth understanding of the benefits of the intervention components which are discussed with the participant.
Verbal persuasion about capability	15.1	If the participants express self-doubt about achieving a behaviour the CES will encourage the participant that they are capable of doing so, such as performing resistance exercises if a participant has a stoma.
Focus on past success	15.3	The CES will regularly review with the participant the improvements they have made over the course of the intervention

Appendix B TIDiER checklist

BRIEF NAME	
Provide the name or a phase that describes the intervention	Multimodal interventions including: Exercise, nutrition and psychological support, underpinned by behaviour change support.
WHY	
Describe any rationale, theory or goal of the elements essential to the intervention	This trial is designed to support long-term health and well-being. To do so patients need to be supported to engage in exercise, consume a healthful diet based on current guidance and recommendations and address any psychological needs. Evidence suggests behaviour change interventions underpinned by theory are more successful than those without. Therefore, an evidence-based theoretically informed behavioural change support intervention is being embedded within the SafeFit Trial.
WHAT	
Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide	<u>Participants</u> Goal setting sheet to record goals set and achievement (or not) SMARTER planning sheet to support goal setting Participants will be provided with links to the following dietary resources depending on individual needs/preference: The World Cancer Research Fund provides information for the general public on diet to reduce the risk of cancer https://www.wcrf-uk.org/ 'Eating well when you have cancer' from the Royal Marsden Hospital https://www.royalmarsden.nhs.uk/your-care/living-and-beyond-cancer/eating-well 'Eating well during cancer' from the World Cancer Research Fund https://www.wcrf-uk.org/uk/health-advice-and-support/eat-well-during-cancer Macmillan information on the Build Up diet: http://be.macmillan.org.uk/Downloads/beMacmillan%20PDFs/MAC13614_Buildingupdiet_lowres_E03_P08_20200206_KA.pdf

information on where the materials can be accessed (e.g. online appendix, URL).	Eatwell guide (NHS): https://www.nhs.uk/live-well/eat-well/ Macmillan information and video: https://www.macmillan.org.uk/cancer-information-and-support/treatment/preparing-for-treatment/eating-well-and-keeping-active Resources for nutrition during exercise: https://www.royalmarsden.nhs.uk/your-care/living-and-beyond-cancer/eating-well-keep-fit and NHS: https://www.nhs.uk/live-well/eat-well/food-and-drinks-for-sport/ British Dietetic Association https://www.bda.uk.com/resource/sport-exercise-nutrition.html Non cancer specific diet https://www.bda.uk.com/food-health/food-facts/all-food-fact-sheets.html Participants will be provided with links to the following psychological support resources depending on individual needs/preference: Stress and anxiety: https://www.nhs.uk/conditions/stress-anxiety- depression/feel-better-and-happy/ Relaxation: https://www.mind.org.uk/information-support/tips-for-everyday- living/relaxation/relaxation-exercises/ Managing anxiety: https://www.nhs.uk/conditions/stress-anxiety- depression/moodzone-mental-wellbeing-audio-guides/ Relaxation techniques: https://www.cntw.nhs.uk/resource-library/relaxation- techniques/ Sleep https://www.sleepstation.org.uk/articles/ https://www.nhs.uk/live-well/sleep-and-tiredness/how-to-get-to-sleep/ https://www.nhs.uk/oneyou/every-mind-matters/sleep/ Mindfulness: http://www.velindrecc.wales.nhs.uk/mindfullness-app Tools for problem solving and letting go of worry: https://www.nhs.uk/apps- library/worrytree/

Links to Macmillan Cancer Support online chat, online community https://community.macmillan.org.uk/ and telephone support line will also be available.

Cancer Exercise Specialists

Trainers will be provided with copies of all participant documents in addition to a training manual including:

- Escalation plans for any physical, metabolic or mental health concerns
- A webinar regarding psychological support is delivered by a clinical psychologist. Lasting 50mins, this covers use of open questions (when, whey how, what, who etc), reflection, elaboration, clarification, focus on feelings, questions to draw on personal skills and resources e.g. 'what has worked well in the past?', the Confided, Helped, I, Professional, Summaries (CHIP) model (ref) as well as communication tips to support remote communication. A supporting document is provided including key concepts covered.
- Similarly, a webinar providing dietary advice in accordance with the WCRF guidance, will be delivered by a consultant dietitian. This emphasises the purpose of the intervention to guide participants in dietary goal setting in accordance with guidance described by the World Cancer Research Fund and British Dietetic Association. Additional resources addressing nutrition and exercise, information on first line dietary advice for people experiencing side effects of treatment such as a poor appetite will also be provided.

- Healthy Conversation Skills: A highly interactive and experiential live online training session will be delivered by accredited Healthy Conversation Skills trainers in one session lasting 3 hours. The training is the online version of the Royal Society for Public Health accredited Healthy Conversation Skills eMECC Lite face-to-face training. It promotes an empowering, person-centred and solution-focused approach supporting people to change their behaviour. The training equips trainees with skills to create and identify opportunities to hold conversations about health and wellbeing, to explore individuals' barriers and facilitators to making change and taking control, to use active listening, and to support individuals to find their own solutions, plan for taking action to implement these solutions, monitor progress and adjust plan and action as needed.

- Covid-19 TopMed talks providing an overview of advice regarding exercise, nutrition and psychological support during covid-19 pandemic
  https://topmedtalk.libsyn.com/topmedtalk-macmillan-cancer-support-mental-well-being-for-the-patient-0
  https://topmedtalk.libsyn.com/topmedtalk-macmillan-cancer-support-healthy-eating-and-cancer-0
  https://topmedtalk.libsyn.com/topmedtalk-macmillan-cancer-support-get-active-and-feel-good

	All trainers also complete Introduction to Good Clinical Practice Training
Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Participants receive a minimum of 1 and up to 3 one-to-one sessions with CES in the first month, delivered by telephone or video conferencing depending on participant preference. This reduces to 1 per week for the following 2 months and monthly for the following 3 months. Sessions will include live exercise training and/or discussion regarding previous and ongoing exercise completed by the participant. Participants will be supported to engage in at least one and up to 3 exercise sessions per week including: Aerobic exercise at a rating of perceived exertion of 11-14 (6-20 scale) accumulating 30 minutes per session, resistance exercise of 8-10 exercises for 2x 8-15 repetitions performed in a controlled manner and covering the whole body and range of motion exercise performed through pain free range of motion covering the whole body to be maintained in good alignment for 10-30 seconds, with some movements held for a second set of 10-30 seconds if stiff. These activities will be personalised and tracked in the session completion logs held by the CES. At the start of intervention CES will work through the WCRF health check to identify areas in the diet that would benefit from modification. This examines consumption of fruit and vegetables, wholegrains, red and processed meat, processed foods high in sugar and fat, processed meats, alcohol intake. Trainers support participants to set goals around diet modification throughout the intervention in order to achieve WCRF dietary recommendations. During each consultation CES will discuss any unintentional weight loss and change in nutrition impact symptoms that would require further specialist advice or prevent participants from taking part in exercise, for example, vomiting or diarrhoea. During each consultation CES will open a conversation around emotional wellbeing providing an opportunity for participants to share any concerns such as anxiety, low mood and distress. Core components of active listening, open questioning and empathy will be employed throughout to support emotional wellbeing. The CES will support participants to develop self-management skills, accessing resources and signposting to support services as appropriate. Possible suggested resources include mindfulness and relaxation exercises and Apps, information on anxiety management, problem solving and letting go of worry, available through NHS and Macmillan Cancer Support websites (as described above). The CES will employ healthy conversation skills during each session supporting goal setting and action planning for all three components of the intervention emphasising development of autonomy and self-efficacy to self-manage with the aim of enabling long-term adherence following completion of the intervention.
WHO PROVIDED	

For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Intervention providers are personal trainers with additional training in exercise referral and/or additional qualifications in Cancer and Exercise Rehabilitation. All CES will have received the SafeFit training package and physical resources outlined above.
HOW	
Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	All sessions will be delivered one-to-one by telephone or video conferencing.
WHERE	
Describe the type(s) of location(s) where the intervention	Participants home or place of preference.

occurred, including any necessary infrastructure or relevant features	
WHEN and HOW MUCH	
Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose	Sessions last approximately 1 hour with 1-3 sessions per week for 1 month, weekly sessions months 2-3, monthly sessions to 6 months. The content of each session will be personalised. Data on type, intensity and dose of exercise performed, and any nutrition and psychological support goals set will be collected in the session completion logs.
TAILORING	
If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	This is a personalised intervention and all elements will be tailored to participant baseline characteristics, needs and preferences and adapted throughout.

MODIFICATION	
If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	Trial ongoing
HOW WELL	
Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Attendance at each scheduled session will be documented throughout the duration of the trial using session completion logs. CES will return session completion logs weekly during weeks 1-12 and monthly during weeks 16-24, documenting the content of each session. These logs will be regularly reviewed by the research team. Trainers will be offered group supervisions once every two weeks to address any concerns during the trial. Fidelity checks: approximately 20% of trainers will have 2 sessions (initial assessment and one follow-up call) assessed against a bespoke implementation checklist to assess fidelity of intervention delivery including assessment of competency for delivery of Healthy Conversation Skills.
Actual: If intervention adherence or fidelity was assessed, describe the extent to which	Trial ongoing

the intervention was delivered as planned	

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___4_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____NA_____
Protocol version	3	Date and version identifier	_____15_____
Funding	4	Sources and types of financial, material, and other support	_____16_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1_____
	5b	Name and contact information for the trial sponsor	_____15_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____N/A_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____15____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9-11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10 and appendix A & B
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	consent provided
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.