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A Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors: a Pilot Randomized Controlled Trial Protocol (the T-CRF Trial)

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ABSTRACT.

Introduction. Cancer-related fatigue (CRF) is one of the most common and debilitating adverse effects of cancer and its treatment reported by cancer survivors. Physical activity, psychological interventions, and management of concurrent symptoms have been shown to be effective in alleviating CRF. This pilot randomized controlled trial (RCT) will determine the feasibility of a telehealth CRF clinic intervention (T-CRF) to implement evidence-based strategies and assess the impact of the intervention on CRF and other clinical factors in comparison to usual care.

Methods and analysis. A parallel-arm (intervention vs. usual care) pilot RCT will be conducted at the Princess Alexandra Hospital in Queensland, Australia. Sixty cancer survivors aged 18 years and over, who report moderate or severe fatigue on the Brief Fatigue Inventory and meet other study criteria will be recruited. Participants will be randomized (1:1) to receive the T-CRF intervention or usual care (i.e., specialist-led care, with a fatigue information booklet). The intervention is a 24-week program of three telehealth nurse-led consultations and a personalized CRF management plan. Clinical and resource use outcomes include cancer survivor fatigue, symptom burden, level of physical activity, productivity loss, hospital resource utilization, and carer's fatigue and productivity loss. Descriptive statistics will be used to report on feasibility and process-related elements additional to clinical and resource outcomes.

Ethics and dissemination. This trial is prospectively registered (ACTRN12620001334998). The study protocol has been approved by the Metro South Health and Hospital Services Human Research Ethics Committee (MSHHS HREC/2020/QMS/63495). Findings will be disseminated through peer-reviewed publications, national and international conferences, and seminars or workshops.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first RCT to assess a 'telehealth cancer-related fatigue clinic' (T-CRF) intervention embedded in the community setting.
- The study will provide novel insights into the impact of an evidence-based systematic intervention for fatigue on health resource utilization and health service use in a clinical setting.
- This study will explore the experiences and outcomes for caregivers of cancer survivors involved in the telehealth cancer-related fatigue intervention.
- Due to the nature of the intervention, blinding of the participants and treatment providers (cancer nurses and intervention physiotherapist) will not be possible.

INTRODUCTION

Background

Cancer-related fatigue (CRF) is reported by cancer survivors as one of the most common and debilitating adverse effects during and after cancer treatment (1, 2), with two in three cancer survivors having experienced some form of fatigue, and one in three cases assessed as severe (2). CRF differs to 'normal' fatigue as it cannot not be relieved through rest and sleep, and is defined as "*a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning*" (1). While the exact mechanisms of CRF are unknown, its effect on cancer survivors' quality of life and functioning is well established. CRF has long lasting negative impacts on the physical, mental, emotional, and social wellbeing of cancer survivors (3-9), and can result in general weakness, diminished concentration or attention, emotional instability and decreased motivation or interest to engage in usual activities (1, 10). CRF can also adversely affect the ability to return to work and engage in meaningful social relationships and leisure activities; negatively affecting cancer survivors' mental health and quality of life (11, 12). Moreover, CRF can influence a cancer survivor's willingness to commence or continue with their cancer treatment, or their willingness and ability to attend follow-up appointments, potentially influencing treatment outcomes and survival (10). While the prevalence of CRF is high during active treatment, many cancer survivors continue to report moderate to severe fatigue at 12 months post-diagnosis and for several years after treatment completion (13). Additionally, caregivers of cancer survivors can also face significant emotional, physical, psychosocial and spiritual fatigue burden that affects their productivity, particularly while those they are caring for receive active treatment (11, 14-17).

Many studies have investigated strategies for reducing CRF (13). Despite their frequent use in the past, pharmacological treatments (e.g., modafinil, erythropoietin, methylphenidate) are largely ineffective for CRF, and may be potentially harmful to its users (18,19). Several guidelines, including the *'National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for CRF'*, now recommend nonpharmacological interventions including physical activity (i.e., aerobic exercise, resistance exercise, yoga), psychological interventions (i.e., cognitive behavioral therapy, psycho-educational therapy), physical therapies (i.e., massage, acupuncture), and energy conservation techniques (1, 10). A meta-analysis including 113 randomized clinical trials (n=11,525), identified that exercise (weighted effect size (WES): 0.30; 95% CI: 0.25-0.36; P< .001), psychological (WES: 0.27; 95% CI:0.21-0.33; P< .001) or combined (WES: 0.26; 95% CI:0.13-0.38; P< .001) interventions are the most effective strategies for reducing CRF during and after cancer treatment when compared to pharmacologic interventions and other therapies (21). In addition to the above, there is also randomized controlled trial (RCT) evidence suggesting the benefits of management of concurrent symptoms for improving CRF (22).

Despite high-quality evidence of effective management strategies for CRF, it remains an unmet need for most cancer survivors, suggesting that current management strategies are not well implemented in clinical practice (1, 2). A recent scoping review on the implementation of CRF management strategies into clinical practice identified a lack of high-quality studies, highlighting the disconnect between effective CRF interventions and routine clinical care (23). As a key implementation strategy, the concept of a 'CRF clinic' has been shown to be a successful method for systematic assessment and management of CRF in cancer survivors (24, 25). These clinics are often physician-led, provided in well-resourced centres of excellence, and require patients to attend face-to-face appointments at the cancer centre (24, 25). With CRF being one of the most common unmet needs reported by cancer survivors, it is key to develop and test more accessible methods for delivering such CRF clinics. *First*, with the increasing use of telehealth, especially in the post-COVID era, it is extremely important to determine if a CRF clinic can be sufficiently delivered using telehealth (26-28). *Second*, trained cancer nurses (29) are *already* managing a myriad of cancer symptoms and delivering psychological and physical activity interventions in their practice (30), which are key evidence-based strategies for managing CRF. Utilizing nurses, the largest cancer care workforce, as the key workforce to lead CRF clinics is the next logical step to enhance service accessibility, ultimately facilitating implementation of evidence-based care and improving CRF outcomes in cancer survivors.

Therefore, our pilot RCT seeks to determine the feasibility of a nurse-led, telehealth cancer-related fatigue (T-CRF) intervention and assess the preliminary efficacy of the intervention on CRF and other clinical factors in comparison to usual care for cancer survivors and carers. Specifically, this trial will evaluate the feasibility of implementing the T-CRF intervention into routine care by assessing recruitment, attrition, functionality, acceptability, satisfaction with care, adherence among participants, and intervention fidelity among program administrators. This trial will also evaluate the preliminary efficacy of the T-CRF intervention according to clinical and resource outcomes including cancer survivor fatigue, symptom burden, physical activity, productivity loss, hospital resource utilization, and carer fatigue and productivity loss.

METHODS AND ANALYSIS

Study Design

A parallel-group, pilot RCT (1:1, intervention vs. usual care) study design will be used to determine the feasibility and evaluate the preliminary efficacy of the T-CRF intervention. The study design will incorporate individualized treatment flexibility in a real-world setting to provide realistic estimates of effects when implemented in a fully powered RCT (31). The study protocol (v1.1) has been prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (32).

Study Setting

Cancer survivors and their carers will be recruited through outpatient clinics of the Division of Cancer Services at the Princess Alexandra Hospital (PAH), a tertiary hospital located in Brisbane, Queensland, Australia.

Participants

Eligibility criteria

Cancer survivors experiencing moderate to severe fatigue (i.e., Brief Fatigue Inventory (BFI) score of 4 or greater (33)), and who are receiving cancer treatment at the PAH will be approached for recruitment. Eligible participants will be over 18 years of age and be at least six weeks post completion of primary cancer treatment (i.e., surgery, radiotherapy, chemotherapy) OR have completed at least 3-months of maintenance treatment (i.e., hormone therapy, immunotherapy, chemotherapy). One informal carer of recruited cancer survivors will also be invited to participate if they are over 18 years of age. Further details of eligibility criteria for carers and cancer survivors are provided in Table 1.

Table 1: Study Eligibility Criteria

Cancer Survivor Inclusion Criteria	Cancer Survivor Exclusion Criteria	Carer Inclusion Criteria	Withdrawal criteria (if applicable)
≥ 18 years of age Have a definitive diagnosis of solid tumor or hematological cancer Receive care at the Princess Alexandra Hospital (PAH) outpatient clinics	Presence of severe mental, cognitive, or physical conditions that would limit the person's ability to participate. This ensures patients have the capacity to provide informed consent, and participation in the study will not pose unethical burden on the person.	≥ 18 years of age Self-endorsing or identified by cancer survivors as "a relative, friend, or partner who you have a close relationship with and who assists you with medical care on a regular basis and who may or may not live in the same residence as you and who is not paid for their help".	Altered mental capacity resulting in inability to provide continuing informed consent. Death
Be 6-weeks post completion of primary cancer treatment (i.e., surgery, radiotherapy, chemotherapy) OR have completed at least 3-months of maintenance treatment (i.e., hormone therapy, immunotherapy chemotherapy)	Known prognosis of <6 months at the discretion of the treating clinician. This ensures participation in this study will not pose unethical burden on cancer survivors nearing end of life.	The caregiver's care recipient must be participating in the study.	Unforeseeable circumstances where participation in this study may pose unethical burden on the cancer survivor and/ or carer or hinder their ability to provide informed consent.
≥ 4 on the global fatigue score of the Brief Fatigue Inventory (BFI) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 Not currently receiving specialist palliative care Have access to a telephone/ mobile device **OR** a computer and internet connection. Agrees and has the capacity to upload wearable device data	Medical conditions or circumstances (e.g., active infections) where participation in this study may pose unethical burden on the cancer survivor or hinder their ability to provide informed consent or participate.		

Recruitment and Consent

Potentially eligible cancer survivors will be identified and approached by their treating clinicians who will gauge their interest in the study, provide a study brochure and gain verbal consent to being approached by the research team. Cancer survivors will be contacted by a research team member, screened for eligibility, and provided with study information. After a time of reflection (at least 24 hours), cancer survivors will be invited to sign a consent form to indicate their willingness to participate. At the time of consent, cancer survivor participants will be asked for their consent to contact their primary informal carer. Informal carers (individuals self-endorsed or identified by cancer survivors as a relative, friend, or partner they have a close relationship with and who assists them with care) will be contacted by the research team, provided with study information and after a time of reflection (at least 24 hours), they will be invited to sign a consent form to indicate willingness to participate in the trial.

Trial procedures

Sample size

Sixty cancer survivors experiencing moderate or severe fatigue (n=30 per arm) will be recruited. This study is not hypothesis testing; thus, power level is not the consideration underpinning sample size. Our chosen sample size for this study falls within the range of recommendations for preliminary studies of this nature (34, 35). PAH service data for indicates a throughput of more than 30 cancer survivors per week. Of these, approximately 30-50% will report moderate-to-severe cancer-related fatigue (2). As our research team is embedded within the clinical care team at the PAH, we anticipate a high referral rate (~10 per week) and a recruitment rate of ~5 per week following full eligibility screening. All consented cancer survivors will be invited to refer their informal carer to participate in the trial. The sample size for informal carers is expected to be approximately 30, as we anticipate 50% of the carers referred by recruited cancer survivors will agree to participate in the study.

Randomization and allocation

Randomization occurs at the level of the cancer survivor participant. Carer participants are assigned to the same group as their cancer survivor. Computer-generated random numbers will be used to allocate cancer survivor participants in a 1:1 ratio by a researcher not involved in recruitment, intervention implementation, or data collection. Allocation numbers will be sealed in opaque envelopes prepared by an independent researcher. Randomization will be blocked using random permuted blocks of four and six to ensure that the groups are balanced periodically within stratification groups. To ensure equal distribution of participants with different levels of fatigue, participants will be stratified by their fatigue severity (moderate: 4-6 or severe 7-10 on the BFI scale) at baseline.

Blinding

Outcome assessors and data analysts will be blinded to group allocation. Participants will be advised not to reveal their group allocation to the outcome assessor. Due to the nature of intervention, trial participants and intervention administrators will not be blinded to group allocation.

Intervention

All participants will be provided with a written 3-page booklet on "Fatigue and Cancer" published by Cancer Council Australia (36), regardless of arm assignment.

Arm 1: The T-CRF Clinic (Intervention)

The overarching aim of the intervention is to systematically implement evidence-based strategies including, but not limited to the promotion of physical activities/exercise intervention; delivery of psychological interventions; management of concurrent symptoms; and general coping. The design of the T-CRF clinic is informed by the NCCN CRF guidelines (1) and incorporates CRF assessment, the development of management strategies, and the provision of referral pathways. Specific components of the T-CRF clinic intervention are listed in Supplementary Material 1.

Briefly, after cancer survivor participant enrolment, nurses working at the non-government organization Cancer Council Queensland (CCQ) will receive a referral from the research team indicating cancer survivor medical and treatment histories; fatigue severity; physical activity behaviors; nutritional status; any contraindications to unsupervised exercise recommendations; and a recommended clinic schedule at weeks 0-2, week 12-14 and week 24-26 post-baseline (see Figure 1). The CCQ nurse will contact cancer survivor participants directly to arrange three telehealth clinic appointments and four booster phone calls, two between each clinic appointment. During clinic consultations, nurses will: 1) conduct a CRF assessment; 2) provide verbal education on fatigue management addressing: physical activity, current symptoms and/or general coping; 3) co-develop a CRF Management Plan including up to three Specific, Measurable, Achievable, Relevant, and Time bound (SMART) goals that address physical activity, current symptoms, and/or general coping; and 4) facilitate referrals. During consultations, CCQ nurses will be guided by a nurse clinic checklist that details the required components of each clinic session. Where referral pathways at PAH are not available or appropriate, CCQ nurses will refer cancer survivors to community organizations or to their primary care provider to coordinate community referrals. Cancer survivor participants will be emailed or posted a copy of their CRF Management Plan developed by the research team (see Supplementary 2).

- ENTER FIGURE 1 HERE -

CCQ nurses will make general recommendations for exercise intensity levels and supervision based on an adapted clinical pathway triage algorithm developed by Stout and colleagues (37) (Figure 2). This decision-making support tool enables personalized condition assessment, risk stratification, and referral

to optimal settings for exercise promotion in cancer survivors – in this regard, to address CRF. Participants who require exercise supervision will be referred to the cancer physiotherapist of the PAH, who will offer face-to-face or telehealth group exercise sessions over 12 weeks (once weekly) or 6 weeks (twice weekly), or one-on-one exercise sessions including aerobic, resistance, flexibility, and balance activities depending on individual need and available equipment. Face-to-face group exercise allows for eight participants supervised by two physiotherapists, and telehealth group exercise allows for five participants supervised by one physiotherapist. Attendance at supervised exercise sessions or referrals to community exercise programs will be recorded as a measure of adherence to the intervention. Between the first and second T-CRF clinics, CCQ nurses will provide two 10-20 min follow-up booster phone calls to participants to monitor progress towards meeting SMART goals and offer support. Adherence to the intervention will be monitored using clinic and phone review checklists.

- ENTER FIGURE 2 HERE -

Intervention training and adverse events

CCQ nurses have extensive experience in caring for cancer survivors. Intervention physiotherapists are nationally accredited by the Australian Physiotherapy Association and have extensive experience caring for cancer survivors. CCQ nurses will receive additional training with regards to all components of the T-CRF intervention. Briefly, training will comprise of a written manual with information on how to deliver the intervention, and material on communication, motivational interviewing, and cognitive behavioral techniques; and a one-day workshop incorporating a mix of written mock intervention case studies and motivational interviewing role play activities.

Participants requiring supervised exercise require medical clearance from their treating oncology team and will undergo a comprehensive initial assessment with vital signs monitored pre- and post- exercise by the intervention physiotherapist to ensure safety. Procedural guidelines are in place to deal with unexpected exercise-related adverse events as clinically indicated. Existing incident reporting structures at the PAH will be followed and the participant's treating clinician, cancer nurse coordinator, and CCQ intervention nurses will be informed. A detailed review of cancer survivor participant assessment forms and exercise history will be undertaken by an independent oncologist. For participants who experience any emotional distress during CCQ intervention nurse consults will be referred to the CCQ counselling service consisting of nurse counsellors and psychologists for evaluation and clinical management.

Intervention Fidelity

In addition to the use of clinic and phone booster checklists, Participants and CCQ nurses will be asked to consent to the audio recording of all nurse-led clinics for quality assurance and to re-check any data or information. Fidelity of the intervention will be assessed using the framework for behavioral interventions recommended by the National Institutes of Health (NIH) (38, 39) as outlined in Table 2. It is expected that some of these strategies will be refined through the conduct of the pilot trial.

Table 2: Intervention Fidelity Strategies

Study Design	Study design procedures have been designed to ensure that the study can adequately test its hypotheses in relation to underlying theory and clinical practices.

Training Providers	Standardized provider training includes procedures to ensure that interventionists have been satisfactorily trained to deliver the intervention to cancer survivor participants. This training will involve:
	• Provision of a study manual to all staff which includes:
	  ○ Generic study related information: study overview, reporting/documentation guidelines, communication flowchart, rationale for the study treatment, self-management goal setting, motivational interviewing, and health coaching.
	  ○ Intervener-specific information: Job description, intervention protocol, quality assurance and monitoring
	• The Trained Registered Nurse responsible for the intervention will have approximately 4-hours of pre-reading modules developed by the chief investigators and approximately 4-hours of practical training. This will include:
	  ○ Clinical management of CRF
	  ○ NCCN CRF Guidelines
	  ○ Exercise and physical activity advice
	  ○ Provision of self-management support (including collaborative goal setting and motivational interviewing, sleep hygiene and energy conservation)
	  ○ Education about referral pathways for services within Princess Alexandra Hospital referral flow charts and contact details for community services
	• The data collector will have necessary pre-reading and training. This will include:
	  ○ Data collection tools and procedures to be used
	  ○ NCCN CRF Guidelines for the screening and assessment of CRF

Delivery of Treatment	Intervention procedures will be monitored to improve delivery of intervention and comparison of conditions, and ensure that the intervention is delivered as intended, through: • The nurse-led clinics will be audio and/ or video recorded and checked for quality assurance. • The intervention fidelity will be closely monitored and discussed during the monthly meeting for the first 3 months of the trial between the intervention nurses, intervention physiotherapist, RA, and/or CIAs. • Omissions and/or protocol deviations will be reviewed on an individual basis. • Intervention checklist completed at the end of each intervention to allow protocol deviation tracking across interveners and conditions. • Minimizing contamination between conditions by training interventionists to address cancer survivor participant questions about randomization and their assigned condition using non-biased explanations.
Receipt of Treatment	Treatment receipt focuses on the cancer survivor participant and includes procedures to assure that the treatment was both received and understood. This goal will be achieved by: • Ensuring participants understand the information provided for each intervention, by checking through use of active questions and behavioral observations
Enactment of Treatment Skills	Enactment of treatment skills includes processes to monitor and improve cancer survivor participant ability to perform treatment-related behavioral skills and cognitive strategies in relevant real-life settings as intended. This goal will be achieved by: • ensuring participants are aware of the follow up schedules and responsibilities of all health professionals. • ensuring participants will have a copy of the completed self-management care plan including all care responsibilities and goals set for the individual

Arm 2: Control (Usual Care)

The control arm consists of usual follow-up care plus a written 3-page booklet on "Fatigue and Cancer" published by Cancer Council Australia (36). Follow-up arrangements at the PAH will vary primarily according to cancer type, and is determined by the treating surgeon, medical oncologist, or radiation oncologist through a specialist-led model.

Baseline and follow-up procedures

Study schedules for data collection and a schematic of the trial design are shown in Table 3 and Figure 1 respectively. Clinical characteristics and demographics (i.e., age, gender, ethnicity, highest level of education, living arrangements, marital status, employment) will be collected directly from participants and medical records by outcome assessors at baseline (T1). All participant-reported outcomes will be collected at baseline (T1), 12-14 weeks (T2), 24-26 weeks (T3), and 48 weeks (T4) post-baseline. Instruments will be self-administered via online surveys using REDCap (Research Electronic Data Capture) or interviewer-administered by blinded outcome assessors via telephone. Participants and healthcare providers will be invited to opt into a semi-structured interview at T4 either face-to-face, by telephone, or through videoconferencing as per interviewee preference. Semi-structured interviews will be utilized to collect data on intervention functionality, acceptability, and satisfaction that will be guided by the Consolidated Framework for Implementation Research (see Supplementary Material 3 for the interview guide).

Table 3: Study Schedule for Data Collection

PROCESS	EST TIME (MIN)	CONSENT	BASELINE (T1)	WEEK 2$^{\Delta}$	WEEK 13±1$^{\Delta}$ (T2)	WEEK 25±1$^{\Delta}$ (T3)	WEEK 49±1 (T4)
Self-Report Data Collection - Cancer Survivor Participant							
Garmin Education	5	X					
PG-SGA SF (10 items)	5	X					
BFI (10 items)	3		X		X	X	X
MSAS (32 items)	5		X		X	X	X
AAS and fruit and vegetable intake (8 items)	5		X		X	X	X
AES-S (18 items)	5		X		X	X	X
Productivity (3 items)	2		X		X	X	X
Interview	15						X
Medical Record Data Collection - Cancer Survivor Participant							
Participant Characteristics			X				
Garmin Data			X		X	X	X
Health resource data					X	X	X
Process outcomes data					X	X	X

Referral to services*				**O**	**O**	**O**	
Self-Report Data Collection - Carer							
BFI (10 items)	5		**X**		**X**	**X**	**X**
iVICQ (14 items)	10		**X**		**X**	**X**	**X**
Interview*	15						**X**

X = conducted by research assistant
O = conducted by intervention nurse
$^{\Delta}$ Data collection will occur as close as practically possible to the timepoint.
*Only completed for participants in the T-CRF intervention group
T: time point; PG-SGA SF: Patient-Generated Subjective Global Assessment Short Form; BFI: Brief Fatigue Inventory; MSAS: Memorial Symptom Assessment Scale; AAS: The Active Australia Survey; AES-S: Self-reported apathy; iVICQ: institute for Medical Technology Assessment Valuation of Informal Care Questionnaire.

Outcomes

Primary outcomes include measurements relevant to the feasibility of conducting large-scale RCT. Secondary outcomes involve measurements of clinical efficacy intended for use in the full-scale trial.

Trial feasibility

Feasibility of the T-CRF trial is the primary outcome of this pilot RCT and will be assessed using the following process outcomes: recruitment and uptake, attrition, adherence, fidelity, apathy, functionality, acceptability, and satisfaction with the intervention (see Table 4).

Table 4: Study Outcome measures

Outcome Domain	Specific Measurement	Metric and method of aggregation	Time-point of interest
PROCESS MEASURES			
Apathy	Self-Reported Apathy Evaluation Scale (AES-S) (40)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Adherence and fidelity among program administrators: Completion of clinic records	Completion of items on the nurse clinic checklist and booster phone checklist.		12 weeks, 24 weeks, and 48 weeks
Adherence and fidelity: Referrals to allied health and community services	Number and type of allied health and community service referrals raised and number actioned and attended as reported by research assistant, intervention nurse or cancer survivor participant and verified with electronic hospital medical records		12 weeks, 24 weeks, and 48 weeks
Treatment fidelity among program administrators: Intervention delivery	Audio and video recording of telehealth sessions.		12 weeks, 24 weeks, and 48 weeks

Intervention functionality, acceptability & satisfaction.	Semi-structured interviews with stakeholders (i.e., cancer survivor participants, carer participants, CCQ nurses, other health care providers) to discuss acceptability, and barriers and facilitators to implementing of T-CRF intervention.		48 weeks
Recruitment and Attrition	Information from research assistant records and hospital records.		Baseline, 48 weeks.
OUTCOME MEASURES			
Fatigue	Brief Fatigue Inventory (BFI) (33)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Symptom Distress	Memorial Symptom Assessment Scale (MSAS) (45)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Physical Activity (Subjective)	Active Australia Survey (AAS)(46) International Physical Activity Questionnaire short-form (IPAQ-S) (47)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Physical Activity (Objective)	Number of steps per day, number of stairs climbed per day, total hours doing moderate intensity exercise per day, and total hours slept per day as measured by Garmin wrist-worn activity tracker (VívoSmart 4, Garmin Australasia Pty Ltd, NSW, Australia)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Productivity Loss	Incidence and severity of financial distress and employment interference as measured by a 3-item survey developed by the research team (48, 49).	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Hospital resource utilisation	Electronic hospital medical records	Number of hospital admissions and emergency presentations	Baseline, 12 weeks, 24 weeks, and 48 weeks
Carer's Fatigue	Brief Fatigue Inventory (33)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Carer's Productivity Loss	Modified version of the Institute for Medical Technology Assessment Valuation of Informal Care Questionnaire (iVICQ) (50).	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
CANCER SURVIVOR PARTICIPANT CHARACTERISTCS			
Demographics	Participant Interview	Collection of age, gender, ethnicity, education, living arrangements, marital status, and employment	Baseline
Clinical Characteristics	Participant interview Malnutrition Screening Tool (MST) (51)	Past and current medical conditions and syndromes, current medications and supplements, cancer diagnosis, previous cancer treatment, current cancer treatment, and fatigue history using participant interview, and nutrition risk	Baseline

Recruitment, intervention uptake and attrition will be assessed using screening logs and online REDCap survey data. Intervention adherence and fidelity of intervention nurses will be evaluated through assessing the number of items completed on the nurse-clinic checklist during consultations and booster phone calls. Apathy will be measured using the Self-Reported Apathy Evaluation Scale (AES-S) (40). Intervention functionality, acceptability, and satisfaction will be evaluated using a cancer survivor satisfaction survey as well as stakeholder semi-structured interviews. Semi-structured interviews will be conducted with intervention nurses and other health care providers involved in providing care for cancer survivor participants. Cancer survivors and carers allocated to the T-CRF trial arm will be invited to participate in an interview at the 12-month time point. Guiding questions (Appendix 1) and analysis of the interviews will be guided by the Consolidated Framework for Implementation Research (*CFIR).*

Clinical outcomes

A secondary goal is to assess the efficacy of the T-CRF intervention on cancer survivor's fatigue, symptom burden, productivity loss, hospital resource utilization, level of physical activity, as well as carer's fatigue, and carer's productivity loss. These outcomes will be assessed using validated self-report measures and medical record data as described in Table 3. Additionally, participants will be required to wear a Garmin wrist-worn activity monitoring device at no additional cost. This will measure physical activity (pedometer: number of steps per day, altimeter: number of stairs climbed, total hours doing moderate intensity exercise based on heart rate per day, and total hours slept per day).

Withdrawal and Study Termination

Any participant can withdraw from the study at any time and for any reason without prejudice. If a cancer survivor or carer participant is withdrawn because of an adverse event (AE), the investigator will arrange for appropriate follow-up care until the AE is resolved or has stabilized. Unresolved AEs will be followed until the last scheduled follow-up visit or until no longer indicated, per investigator discretion. In addition to AEs, other reasons for removal of participants from the study might include, but are not limited to, withdrawal of consent, administrative decision by the principal investigator or responsible organization, or protocol deviation. If a participant asks or decides to withdraw, all efforts will be made to complete and report the observations, especially primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. The primary reason for withdrawal (where known) will be identified and recorded on a case report form, along with the date of withdrawal. Withdrawal criteria are listed in Table 1.

STATISTICAL ANALYSIS

Descriptive statistics will be used to report on feasibility and process-related outcomes (e.g., recruitment rate, retention and attrition rates, adherence) as well as clinical and resource-use outcomes (e.g., fatigue, physical activity, hospital resource utilization). Preliminary effect size estimates for cancer survivor and resource use outcomes will be calculated following intention-to-treat principles using linear mixed

models to account for repeated measures and missing data. Models will include group, time and their interaction and be adjusted by fatigue severity and current cancer treatment. Balance of demographic variables between the usual care and intervention group will be examined and adjusted for potential confounders. Assumptions of all models (normality, linearity, homoscedasticity) will be examined using the residuals of the model and will be described using mean, median, skewness, kurtosis and plots such as histograms and QQ-plots. If assumptions are violated, models will be either bootstrapped or log transformed, as appropriate. Missing data will be explored using descriptive statistics. Generalized linear models will be used to provide estimates for categorical outcomes such as adherence, with appropriate link models used based on the outcome distribution. All statistical analysis will be undertaken by an independent statistician blinded to treatment allocation. Semi-structured interviews will be audio or video recorded and will be transcribed verbatim for thematic analysis; a method for systematically identifying, organising, and offering insight into, patterns of meaning (themes) across a dataset (41).

DATA MANAGEMENT

Data Management and Confidentiality

All data will be recorded in electronic case report forms. Participants will only be identified by a unique participant study number on the case report forms and other documents. A secure system for online and offline data capture will be used for direct data entry by both participants and research staff. Case report forms will be accessed by the project manager for data checking. Data queries will be generated and sent to the relevant research team member for response before the database is locked and released for statistical analysis. Other study-related documents (e.g., signed informed PICF) will be kept in strict confidence by the Chief Investigator.

Data Checking

Data will be directly entered into REDCap by members of the research team using a tablet or desktop computer. All research team members will receive training regarding data collection from the Project Manager. To maximize data integrity and completeness, the project manager will undertake routine audits with data validation performed via REDCap. Any discrepancies and missing data will be alerted and resolved with the relevant research team member(s) as soon as practical. All electronic case report forms will be maintained on the system with details of any changes logged accordingly.

Data Protection

Participants will be informed that data will be archived at PAH and that these data may be viewed by staff including the project manager and by external auditors on behalf of PAH and appropriate regulatory authorities including Metro South Health Human Research Ethics Committee (MSH HREC) and PAH Research Governance. Participants will be informed that a study report will be submitted to

regulatory authorities and for publication and conference presentation. However, participants will be de-identified in such reports with only their study identification number, gender, and age used for recording or linkage purposes.

Data Retention

Audio and video recordings of the telehealth intervention will be stored electronically at Queensland University of Technology in a secure repository and will be securely destroyed after analysis is conducted. All other source data, clinical records and laboratory data relating to the study will be archived at PAH for at least 15 years after study completion and remain available for retrospective review or audit. The investigator and study staff will be responsible for maintaining a comprehensive filing system of all essential study-related documentation. All essential documentation will be retained by PAH as per the requirements of the responsible organization for the same period required for medical records retention. No study document will be destroyed without written agreement between the PAH and the principal investigator. If the principal investigator wishes to assign the study records to another party or move them to another location, they will notify the responsible organization in writing of the new responsible person or the new location.

PATIENT AND PUBLIC INVOLVEMENT

To ensure cancer survivor perspectives were represented and accommodated in the intervention design and implementation, the patient support and advocacy group at CCQ were invited, have provided input into the study. Consumers were invited to provide comments and critical appraisal of the study protocol. They will also assist with raising the profile of the study through their consumer and clinical networks. CCQ will also be providing the intervention cancer nurses who will deliver the T-CRF clinics.

ETHICS AND DISSEMINATION

Prior to the commencement of the study, written approval was acquired by MSH HREC (ID: HREC/2020/QMS/63495), with Research Governance approval provided by the PAH Research Governance Office. This study will be conducted in accordance with the principles of the Declaration of Helsinki (42), Good Clinical Practice (CPMP/ICH/135/95) (43) and the National Health and Medical Research Council National Statement on Ethical Conduct in Research Involving Humans (44).

Archiving and regulatory inspection

In accordance with the guidance on Good Clinical Practice (GCP), this study may be selected for audit. Inspection of site facilities and review of study-related records may occur by a representative of the responsible organization or regulatory authority to evaluate the study conduct and compliance with the protocol, GCP, and applicable regulatory requirements. All study-related documents and records will be retained for a minimum of 15 years after trial completion. Written agreement from the responsible organization will precede destruction of the same.

Dissemination

Publication and reporting of results and outcomes of this trial will be accurate and honest, undertaken with integrity and transparency. Trial results will be disseminated to all participants with a summary sheet that will outline the trial findings in lay language. It is intended that the findings from this trial will be disseminated at academic, clinical and professional conferences, and published in high-quality, international peer-reviewed journals.

Protocol amendments and deviation

Neither the principal investigator nor the PAH will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the MSH HREC for approval before implementation. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter. Should any protocol deviation occur, it will be reported to the study project manager as soon as is reasonably practical. The deviation and the reason for its occurrence will be included in the study report.

TRIAL STATUS

This protocol (Version 1.1) was approved and registered on the Australian New Zealand Clinical Trial Registry (ANZCTR) on the 10th of December 2020 (ID: ACTRN12620001334998). The study started recruitment on 17th February 2021, and as of 1st November 2021, 40 cancer survivor participants and 16 carers have been enrolled. Data collection is anticipated to conclude in January 2023 (48 weeks following the final participant enrolled). Data analysis and manuscript preparation is anticipated to occur over six months, concluding in July 2023.

Acknowledgements

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Author Contributions: The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. RJC and RL conceptualized the study. OA, EPP and NHH led the design and writing of the pilot RCT protocol. All authors contributed important intellectual content to the trial design and written protocol and reviewed and approved the final version for publication.

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role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Data Sharing Statement: There are no limitations on investigator access to the trial dataset. However, the datasets generated and analyzed during this study will not be publicly available, though will be made available from the corresponding author on reasonable request.

Competing Interests: None Declared

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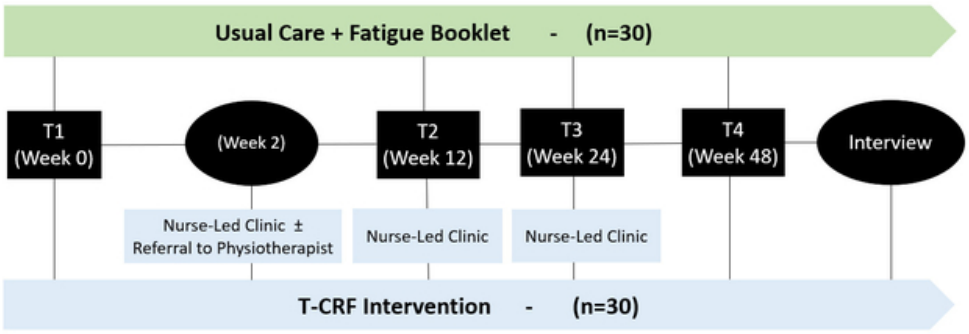
Figure Legend

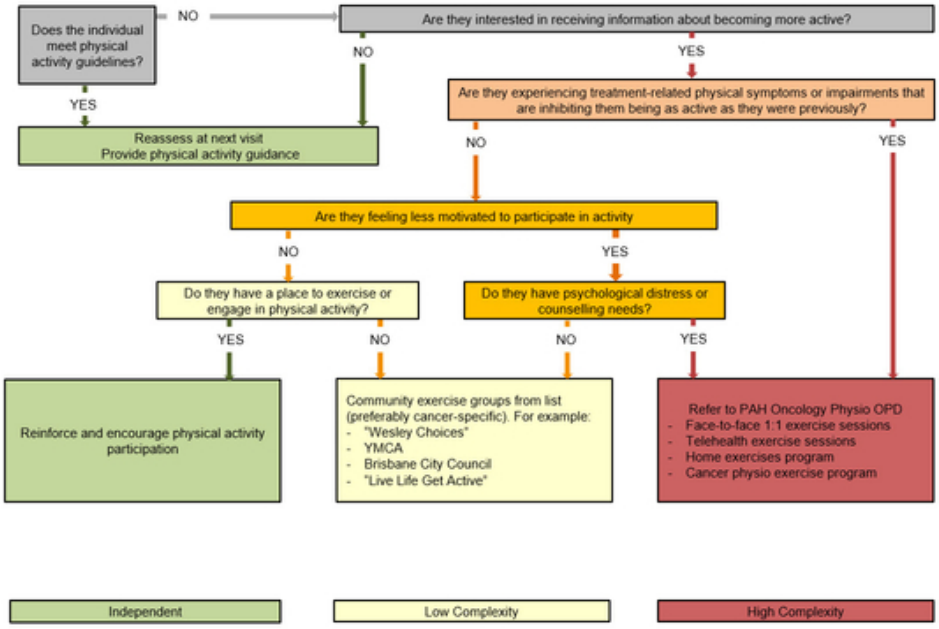
Figure 1: The Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors Follow-up. Schematic of the trial design. T1: baseline; T2: 12-14 weeks post-baseline; T2: 24-26 weeks post-baseline; T4: 48 weeks post-baseline

Figure 2: Algorithm for determining exercise intensity and levels of supervision. The pathway is intended to stratify individuals to higher (red), intermediate (yellow), or lower (green) condition complexity, which provides insight into the level of supervision and guidance that individuals may need to successfully engage in exercise and informs referrals. PAH – Princess Alexandra Hospital; OPD – outpatient department.



The Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors Follow-up. Schematic of the trial design. T1: baseline; T2: 12-14 weeks post-baseline; T2: 24-26 weeks post-baseline; T4: 48 weeks post-baseline

54x19mm (300 x 300 DPI)



Algorithm for determining exercise intensity and levels of supervision. The pathway is intended to stratify individuals to higher (red), intermediate (yellow), or lower (green) condition complexity, which provides insight into the level of supervision and guidance that individuals may need to successfully engage in exercise and informs referrals. PAH – Princess Alexandra Hospital; OPD – outpatient department.

48x33mm (300 x 300 DPI)

Supplementary Material 1. T-CRF Intervention as guided by the NCCN Fatigue Guidelines

Active Ingredient	Personnel Involved	Specific Activities	Time allocated
Pre-Clinic Referral Form			
Referral form (completed prior to 1st nurse-led clinic)	Research Team involved in participants' routine care at PAH and the participant	Once participants have consented to be part of the trial and been randomized to the T-CRF intervention group, the intervention nurse will request completion of the Clinic Referral Form from the Research Team prior to their 1st nurse-led clinic appointment. Data will be compiled from electronic medical records and discussions with treating clinicians (where applicable) to complete this referral. All information required for this referral form should have been collected as part of usual care and the participant will only be involved in the completion of this form if required information has not been gathered during usual care. This referral form will provide the information necessary for the comprehensive CRF assessment as per NCCN Guidelines. The referral form will include information such as the below: • Clinical characteristics (disease stage (recurrence or progression), type and length of treatment, patient's response to treatment). • Current medications and recent medication changes (prescribed, over the counter, herbal, vitamins, other supplements). • Fatigue assessment (onset, pattern, duration, change over time, associated or elevated factors, and interference with function as well as current management strategies). • Assessment of coping and support network (social, emotional, functional, financial support). • Identification of symptoms and symptom clusters (pain, emotional distress, sleep disturbance, poor sleep hygiene, anemia, nutrition impacting symptoms, activity level, medication side effects, alcohol abuse, substance abuse, and/or comorbidities/cancer treatment sequelae). • Assessment of functional status (e.g., exercise or activity patterns, ability to accomplish normal daily or enjoyable activities, participation in exercise programs).	
Nurse-led Clinic Appointment (≤1 hour) – where possible the same nurse will deliver all three clinics appointment to maximize continuity of care			
Assessment of CRF	Intervention Nurse and participant	Clinic 1: The intervention nurse will familiarize themselves with the participant's Clinic Referral form (i.e., CRF assessment) and confirm details with the participant Clinics 2-3: The Intervention nurse will evaluate progress towards reaching goals set in earlier clinics, as well as any relevant changes to their CRF assessment	10-minutes
Education on CRF	Intervention Nurse and participant	• Education on CRF pathophysiology and associated factors • Answer participant questions and correct misconceptions • Fatigue-related education regarding the three priority areas: physical activity, symptoms and coping strategies.	10-minutes

Management strategies for CRF as per NCCN Guidelines	Intervention Nurse and participant	Participants will set three SMART goals, which will encompass the following three priority areas as appropriate: 1. Physical activity (basic information on physical activity guidelines accompanied by a referral to cancer exercise program). 2. Symptoms (e.g., pain management, sleep hygiene, energy conservation techniques) 3. Coping (e.g., emotional, and psychological support) Personalized strategies will be discussed and developed between the intervention nurse and participant using motivational interviewing and goal setting, and a CRF management plan will be developed.	35-minutes
Referral to other services	Intervention Nurse and participant	• Referrals to other health professionals, where deemed appropriate and useful to meet patient goals, and according to existing referral pathways at Princess Alexandra Hospital or within the community (e.g., pharmacist, dietitian, social work, physiotherapist, occupational therapist, psychologist, psychiatrist, palliative care, GP for blood tests). • Where referral pathways at Princess Alexandra Hospital are not available/not appropriate, participants will be referred to community organizations or to their GP to coordinate community referrals (e.g., chronic disease management plan referral to access community dietitian).	5-minutes
Completion of documentation	Intervention Nurse. Participant not involved.	• Completion of nurse-led clinic checklist to ensure clinic guideline adherence. • Completion of participant CRF management plan, and a copy emailed to participant. • Completion and actioning of referrals, if necessary.	10-minutes
Physiotherapy Physical Activity and Exercise Prescription			
Framework for clinical decision making (Figure 1)	Intervention Physiotherapist and participant	Refer to Figure 1. Stepped process of review of current levels of physical activity, motivation to exercise, side effects of treatment, environment, and physical function to guide the type of physical activity/exercise recommended and supervision required. Programming will be guided by the Frequency, Intensity, Time and Type model as recommended by the American College of Sports Medicine Exercise Guidelines for Cancer Survivors.	150 minutes*

CRF: Cancer-related fatigue; PAH: Princess Alexandra Hospital; NCCN: National Comprehensive Cancer Network. *Aiming to meet physical activity guidelines of 150 mins of moderate intensity activity per week over a 12-week period.

Supplementary Material 2. EXAMPLE FATIGUE MANAGEMENT PLAN

FATIGUE MANAGEMENT PLAN

Clinic Number	Clinic Date		CCQ Nurse	

CONTACT INFORMATION

Name		Phone	
Address		Email	

FATIGUE ASSESSMENT

Onset of fatigue

Details:

Duration of Fatigue

Details:

Alleviating factors *Details:*

Frequency of fatigue

Details:

Pattern of fatigue

Details:

Interference with function *Details:*

CLINICAL NOTES

Physical Activity

- *Current exercise (Type, duration, frequency)*
- *Perceived barriers to physical activity*

Details:

Meeting guidelines? Yes No

Further Information: | Pages:

Contributing Symptoms

- *Pain*
- *Feeling sad*
- *Worrying*
- *Difficulty sleeping*
- *Anaemia*
- *Nutritional deficits*
- *Co-morbidities & medication*

Details:

Further Information: | Pages:

Coping

- *Current strategies (e.g., pacing)*
- *Social support*

Details:

Further Information: | Pages:

SMART GOALS

SMART GOAL 1	
Strategies	

SMART GOAL 2	
Strategies	

SMART GOAL 3	
Strategies	

REFERRALS		
Physical Activity		
	Details:	
Other Referrals	Details:	

SCHEDULE		
Clinic 2	date:	| time:
Phone check-in 1	date:	| time:
Phone check-in 2	date:	| time:
Clinic 3	date:	| time:
Phone check-in 3	date:	| time:
Phone check-in 4	date:	| time:

Supplementary Material 3. INTERVIEW GUIDE FOR T-CRF INTERVENTION GROUP ONLY

For participants

1. Describe your experiences with participating in the T-CRF Trial.
2. How did the trial meet your expectations?
3. What aspects of the trial were valuable to you?
4. What aspects of the trial were valuable to others? (carers, loved ones, health professionals)
5. (If applicable) Describe the impacts you saw from the intervention on your ability to work.
6. Describe any aspects of the trial that were challenging for you.
7. What kinds of changes or alterations do you think should be made to the trial?
8. Are there parts of the trial that shouldn't be changed?
9. Is there anything else about the trial you would like to share?

For carers of participants

1. Describe your experiences with the T-CRF Trial.
2. How did the trial meet your expectations?
3. What aspects of the trial were valuable to you?
4. What aspects of the trial were valuable to others? (the person you care for, loved ones, health professionals)
5. (If applicable) Describe the impacts you saw from the intervention on your ability to work.
6. Describe any aspects of the trial that were challenging for you.
7. What kinds of changes or alterations do you think should be made to the trial?
8. Are there parts of the trial that shouldn't be changed?
9. Is there anything else about the trial you would like to share?

For Health Care Professionals of participants

1. Describe your experiences with the T-CRF Trial.
2. How did the trial meet your expectations?
3. What aspects of the trial were valuable to you?
4. What aspects of the trial were valuable to others? (your patient/s, patient/s carers, other health care professionals)
5. Describe any aspects of the trial that were challenging for you.
6. Describe any aspects of the trial that you thought were challenging for your patient/s.
7. How does the trial compare to other alternatives that may have been considered or that you know about?
8. What kinds of changes or alterations do you think need to be made to the trial so it will work effectively in your setting?
9. Are there parts of the trial that shouldn't be changed?
10. Is there anything else about the trial you would like to share?

SPIRIT GUIDELINES REPORTING CHECKLIST

		Reporting Item	Page Number/Section
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Included in trial registration
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contribution	#5a	Names, affiliations, and roles of protocol contributors	1, 14
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	14
Roles and responsibilities: committees	#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)	14
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	3

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5,7
Objectives	#7	Specific objectives or hypotheses	4
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, non-inferiority, exploratory)	4
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	4
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)	Table 1
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5,6,7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving / worsening disease)	6,7
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return; laboratory tests)	Table 2
Interventions: concomitant care	#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	7,8, Table 3

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 & Table 4
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	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
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	5
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	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A. Participants not blinded to group allocation.
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors)	8, Table 4

		and a description of study instruments (e.g., 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	
Data collection plan: retention	#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	10
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	9
Statistics: outcomes	#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	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#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)	10
Methods: Monitoring			
Data monitoring: formal committee	#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	NA Pilot study does not have a DMC
Data monitoring: interim analysis	#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. Pilot study does not require interim analyses

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	6,7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7, Table 2
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10
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)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A. No ancillary studies
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	9
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
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. No ancillary studies

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	10
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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. No biological specimens collected

BMJ Open

A Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors: a Pilot Randomized Controlled Trial Protocol (the T-CRF Trial)

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A Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors: a Pilot Randomized Controlled Trial Protocol (the T-CRF Trial)

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ABSTRACT.

Introduction. Cancer-related fatigue (CRF) is one of the most common and debilitating adverse effects of cancer and its treatment reported by cancer survivors. Physical activity, psychological interventions, and management of concurrent symptoms have been shown to be effective in alleviating CRF. This pilot randomized controlled trial (RCT) will determine the feasibility of a telehealth CRF clinic intervention (T-CRF) to implement evidence-based strategies and assess the impact of the intervention on CRF and other clinical factors in comparison to usual care.

Methods and analysis. A parallel-arm (intervention vs. usual care) pilot RCT will be conducted at the Princess Alexandra Hospital in Queensland, Australia. Sixty cancer survivors aged 18 years and over, who report moderate or severe fatigue on the Brief Fatigue Inventory and meet other study criteria will be recruited. Participants will be randomized (1:1) to receive the T-CRF intervention or usual care (i.e., specialist-led care, with a fatigue information booklet). The intervention is a 24-week program of three telehealth nurse-led consultations and a personalized CRF management plan. The primary objective of this pilot RCT is to determine intervention feasibility, with a secondary objective to determine preliminary clinical efficacy. Feasibility outcomes include the identification of recruitment methods; recruitment rate and uptake; attrition; adherence; fidelity; apathy; and intervention functionality, acceptability, and satisfaction. Clinical and resource use outcomes include cancer survivor fatigue, symptom burden, level of physical activity, productivity loss, hospital resource utilization, and carer's fatigue and productivity loss. Descriptive statistics will be used to report on feasibility and process-related elements additional to clinical and resource outcomes.

Ethics and dissemination. This trial is prospectively registered (ACTRN12620001334998). The study protocol has been approved by the Metro South Health and Hospital Services Human Research Ethics Committee (MSHHS HREC/2020/QMS/63495). Findings will be disseminated through peer-reviewed publications, national and international conferences, and seminars or workshops.

ARTICLE SUMMARY

Strengths and limitations of this study

- This RCT assesses a 'telehealth cancer-related fatigue clinic' (T-CRF) intervention embedded in the community setting as distinct from the clinical setting.
- This feasibility pilot RCT study will provide data for an adequately powered effectiveness trial.
- This study design will enable individualized treatment flexibility and compare interventions in a real-world community setting to realistically inform clinical and community practice directly.
- This study is not powered to examine intervention efficacy and does not assess regionality.
- Due to the nature of the intervention, blinding of the participants and treatment providers (cancer nurses and intervention physiotherapist) will not be possible.

INTRODUCTION

Background

Cancer-related fatigue (CRF) is one of the most common and debilitating adverse effects experienced by cancer survivors during and after cancer treatment (1, 2), with two in three cancer survivors reporting some level of fatigue, and one in three cases assessed as severe (2). CRF differs to 'normal' fatigue as it cannot not be relieved through rest and sleep, and is defined as "*a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning*" (1). While the exact mechanisms of CRF are unknown, its influence on the quality of life and functional capacity of cancer survivors is well established. CRF has long lasting negative impacts on the physical, mental, emotional, and social wellbeing of people with cancer (3-9), often resulting in general weakness, diminished concentration or attention, emotional instability and decreased motivation or interest to engage in usual activities (1, 10). CRF can also adversely affect the ability to return to work and engage in meaningful social relationships and leisure activities; negatively affecting cancer survivors' mental health and quality of life (11, 12). Moreover, CRF can influence a cancer survivor's willingness to commence or continue with their cancer treatment, or their willingness and ability to attend follow-up appointments, potentially influencing treatment outcomes and survival (10). While the prevalence of CRF is high during active treatment, many cancer survivors also continue to report moderate to severe fatigue at 12 months post-diagnosis and for several years after treatment completion (13). Additionally, caregivers of cancer survivors can also face significant emotional, physical, psychosocial and spiritual fatigue burden that affects their productivity, particularly while those they are caring for receive active treatment (11, 14-17).

Many studies have assessed pharmacological and non-pharmacological strategies to reduce CRF (13). Despite their prior use, pharmacological treatments (e.g., modafinil, erythropoietin, methylphenidate) are largely ineffective for CRF, and may be potentially harmful to its users (18-20). Several guidelines, including the *'National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for CRF'*, now recommend non-pharmacological treatments including physical activity (i.e., aerobic exercise, resistance exercise, yoga), psychological interventions (i.e., cognitive behavioral therapy, psycho-educational therapy), physical therapies (i.e., massage, acupuncture), and energy conservation techniques (1, 10). A meta-analysis including 113 randomised clinical trials that involved 11,525 cancer survivors identified that exercise (weighted effect size (WES): 0.30; 95% CI: 0.25-0.36; P< .001), psychological (WES: 0.27; 95% CI:0.21-0.33; P< .001) or combined (WES: 0.26; 95% CI:0.13-0.38; P< .001) interventions as the most effective strategies for reducing CRF during and after cancer treatment when compared to pharmacologic interventions and other therapies (21). In addition, there is also recent evidence suggesting that the of management of concurrent symptoms also improves CRF (22).

Despite high-quality evidence of effective management strategies for CRF, it remains an unmet need for most cancer survivors, suggesting that current management strategies are not well implemented in clinical practice (1, 2). A recent scoping review on the implementation of CRF management strategies into clinical practice identified a lack of high-quality studies in the literature which also highlights the disconnect between effective CRF interventions and routine clinical care (23). As a key implementation strategy, the concept of a 'CRF clinic' is one successful method to facilitate the systematic assessment and management of CRF in cancer survivors (24, 25). These clinics are often physician-led, provided in well-resourced centres, and require cancer survivors to attend face-to-face appointments at the cancer centre (24, 25). With CRF being one of the most common unmet needs reported by cancer survivors, it is key to develop and test more accessible and sustainable methods for delivering such CRF clinics. *First*, with the increasing use of telehealth, especially in the post-COVID era, it is extremely important to determine if a CRF clinic can be sufficiently delivered using telehealth (26, 27). *Second*, trained cancer nurses (28) are *already* managing a myriad of cancer symptoms and delivering psychological and physical activity interventions in their practice (29), which are key evidence-based strategies for managing CRF. Nurses in partnership with allied health practitioners, key members of multidisciplinary cancer care, are the ideal workforce to lead CRF clinics and enhance service accessibility, ultimately facilitating implementation of evidence-based care and improving CRF outcomes in cancer survivors.

Our pilot RCT seeks to determine the feasibility of a community-based and cancer nurse-led, telehealth cancer-related fatigue (T-CRF) intervention and assess the preliminary efficacy of the intervention on CRF and other clinical factors in comparison to usual care for cancer survivors and carers. Specifically, this trial will evaluate the feasibility of implementing the T-CRF intervention within the community setting into routine care by assessing recruitment, attrition, functionality, acceptability, satisfaction with care, adherence among participants, and intervention fidelity among program administrators. This trial will also evaluate the preliminary efficacy of the T-CRF intervention according to clinical and resource outcomes including cancer survivor fatigue, symptom burden, physical activity, productivity loss, hospital resource utilisation, and carer fatigue and productivity loss. Preliminary efficacy data will be used to determine appropriate effect sizes and other statistical data that can be used in future statistical models to estimate sample sizes required to run the definitive clinical effectiveness trials.

METHODS AND ANALYSIS

Study Design

A parallel-group, pilot RCT (1:1, intervention vs. usual care) study design will be used to determine the feasibility and evaluate the preliminary efficacy of the T-CRF intervention. More specifically, this pilot RCT will provide feasibility and process data to inform the design of a fully powered RCT that will compare the effects of a novel clinic model of care verses usual care on the severity of CRF and related symptom outcomes. The pilot study design will incorporate individualized treatment flexibility in a

real-world setting to provide realistic estimates of effects when implemented in the definitive RCT (30).

The study protocol (v1.1) has been prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (31).

Cancer Survivor Inclusion Criteria	Cancer Survivor Exclusion Criteria	Carer Inclusion Criteria	Withdrawal criteria (if applicable)
≥ 18 years of age Have a definitive diagnosis of solid tumor or hematological cancer Receive care at the Princess Alexandra Hospital (PAH) outpatient clinics	Presence of severe mental, cognitive, or physical conditions that would limit the person's ability to participate. This ensures patients have the capacity to provide informed consent, and participation in the study will not pose unethical burden on the person.	≥ 18 years of age Self-endorsing or identified by cancer survivors as "a relative, friend, or partner who you have a close relationship with and who assists you with medical care on a regular basis and who may or may not live in the same residence as you and who is not paid for their help".	Altered mental capacity resulting in inability to provide continuing informed consent. Death
Be 6-weeks post completion of primary cancer treatment (i.e., surgery, radiotherapy, chemotherapy) OR have completed at least 3-months of maintenance treatment (i.e., hormone therapy, immunotherapy chemotherapy) ≥ 4 on the global fatigue	Known prognosis of <6 months at the discretion of the treating clinician. This ensures participation in this study will not pose unethical burden on cancer survivors nearing end of life. Medical conditions or	The caregiver's care recipient must be participating in the study.	Unforeseeable circumstances where participation in this study may pose unethical burden on the cancer survivor and/ or carer or hinder their ability to provide informed consent.

Study Setting

Cancer survivors and their carers will be recruited through outpatient clinics of the Division of Cancer Services at the Princess Alexandra Hospital (PAH), a tertiary hospital located in Brisbane, Queensland, Australia.

Participants

Eligibility criteria

Cancer survivors experiencing moderate to severe fatigue (i.e., Brief Fatigue Inventory (BFI) score of 4 or greater (32)), and who are receiving cancer treatment at the PAH will be approached for recruitment. Eligible participants will be over 18 years of age and be at least six weeks post completion of primary cancer treatment (i.e., surgery, radiotherapy, chemotherapy) OR have completed at least 3-months of maintenance treatment (i.e., hormone therapy, immunotherapy, chemotherapy). One informal carer of recruited cancer survivors will also be invited to participate if they are over 18 years of age. Further details of eligibility criteria for carers and cancer survivors are provided in Table 1.

score of the Brief Fatigue Inventory (BFI) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 Not currently receiving specialist palliative care Have access to a telephone/ mobile device **OR** a computer and internet connection. Agrees and has the capacity to upload wearable device data	circumstances (e.g., active infections) where participation in this study may pose unethical burden on the cancer survivor or hinder their ability to provide informed consent or participate.

Table 1: Study Eligibility Criteria

Recruitment and Consent

Potentially eligible cancer survivors will be identified and approached by their treating clinicians who will gauge their interest in the study, provide a study brochure and gain verbal consent to being approached by the research team. Cancer survivors will be contacted by a research team member, screened for eligibility, and provided with study information. After a time of reflection (at least 24 hours), cancer survivors will be invited to sign a consent form (Supplementary Material 1) to indicate their willingness to participate. At the time of consent, cancer survivor participants will be asked for their consent to contact their primary informal carer. Informal carers (individuals self-endorsed or identified by cancer survivors as a relative, friend, or partner they have a close relationship with and who assists them with care) will be contacted by the research team, provided with study information and after a time of reflection (at least 24 hours), they will be invited to sign a consent form (Supplementary Material 2) to indicate willingness to participate in the trial.

Trial procedures

Sample size

Sixty cancer survivors experiencing moderate or severe fatigue (n=30 per arm) will be recruited. This study is not hypothesis testing; thus, power level is not the consideration underpinning sample size. Our chosen sample size for this study falls within the range of recommendations for preliminary studies of this nature (33, 34). PAH service data for indicates a throughput of more than 30 cancer survivors per week. Of these, approximately 30-50% will report moderate-to-severe cancer-related fatigue (2). As our research team is embedded within the clinical care team at the PAH, we anticipate a high referral rate (~10 per week) and a recruitment rate of ~5 per week following full eligibility screening. All consented cancer survivors will be invited to refer their informal carer to participate in the trial. The sample size for informal carers is expected to be approximately 30, as we anticipate 50% of the carers referred by recruited cancer survivors will agree to participate in the study.

Randomization and allocation

Randomization occurs at the level of the cancer survivor participant. Carer participants are assigned to the same group as their cancer survivor. Computer-generated random numbers will be used to allocate cancer survivor participants in a 1:1 ratio by a researcher not involved in recruitment, intervention implementation, or data collection. Allocation numbers will be sealed in opaque envelopes prepared by an independent researcher. Randomization will be blocked using random permuted blocks of four and six to ensure that the groups are balanced periodically within stratification groups. To ensure equal distribution of participants with different levels of fatigue, participants will be stratified by their fatigue severity (moderate: 4-6 or severe 7-10 on the BFI scale) at baseline.

Blinding

Outcome assessors and data analysts will be blinded to group allocation. Participants will be advised not to reveal their group allocation to the outcome assessor. Due to the nature of intervention, trial participants and intervention administrators will not be blinded to group allocation.

Intervention

All participants will be provided with a written 3-page booklet on "Fatigue and Cancer" published by Cancer Council Australia (35), regardless of arm assignment.

Arm 1: The T-CRF Clinic (Intervention)

The overarching aim of the intervention is to systematically implement evidence-based strategies including, but not limited to the promotion of physical activities/exercise intervention; delivery of psychological interventions; management of concurrent symptoms; and general coping. The design of the T-CRF clinic is informed by the NCCN CRF guidelines (1) and incorporates CRF assessment, the development of management strategies, and the provision of referral pathways. Specific components of the T-CRF clinic intervention are listed in Supplementary Material 3.

Briefly, after cancer survivor participant enrolment, nurses working at the non-government organization Cancer Council Queensland (CCQ) will receive a referral from the research team indicating cancer survivor medical and treatment histories; fatigue severity; physical activity behaviors; nutritional status; any contraindications to unsupervised exercise recommendations; and a recommended clinic schedule at weeks 0-2, week 12-14 and week 24-26 post-baseline (see Figure 1). The CCQ nurse will contact cancer survivor participants directly to arrange three telehealth clinic appointments and four booster phone calls, two between each clinic appointment. During clinic consultations, nurses will: 1) conduct a CRF assessment; 2) provide verbal education on fatigue management addressing: physical activity, current symptoms and/or general coping; 3) co-develop a CRF Management Plan including up to three Specific, Measurable, Achievable, Relevant, and Time bound (SMART) goals that address physical activity, current symptoms, and/or general coping; and 4) facilitate referrals. During consultations, CCQ nurses will be guided by a nurse clinic checklist that details the required components of each clinic session. Where referral pathways at PAH are not available or appropriate, CCQ nurses will refer cancer survivors to community organizations or to their primary care provider to coordinate community referrals. Cancer survivor participants will be emailed or posted a copy of their CRF Management Plan developed by the research team (see Supplementary 4).

- ENTER FIGURE 1 HERE -

CCQ nurses will make general recommendations for exercise intensity levels and supervision based on an adapted clinical pathway triage algorithm developed by Stout and colleagues (36) (Figure 2). This decision-making support tool enables personalized condition assessment, risk stratification, and referral

to optimal settings for exercise promotion in cancer survivors – in this regard, to address CRF. Participants who require exercise supervision will be referred to the cancer physiotherapist of the PAH, who will offer face-to-face or telehealth group exercise sessions over 12 weeks (once weekly) or 6 weeks (twice weekly), or one-on-one exercise sessions including aerobic, resistance, flexibility, and balance activities depending on individual need and available equipment. Face-to-face group exercise allows for eight participants supervised by two physiotherapists, and telehealth group exercise allows for five participants supervised by one physiotherapist. Attendance at supervised exercise sessions or referrals to community exercise programs will be recorded as a measure of adherence to the intervention. Between the first and second T-CRF clinics, CCQ nurses will provide two 10-20 min follow-up booster phone calls to participants to monitor progress towards meeting SMART goals and offer support. Adherence to the intervention will be monitored using clinic and phone review checklists.

- ENTER FIGURE 2 HERE -

Intervention training and adverse events

CCQ nurses have extensive experience in caring for cancer survivors. Intervention physiotherapists are nationally accredited by the Australian Physiotherapy Association and have extensive experience caring for cancer survivors. CCQ nurses will receive additional training with regards to all components of the T-CRF intervention. Briefly, training will comprise of a written manual with information on how to deliver the intervention, and material on communication, motivational interviewing, and cognitive behavioral techniques; and a one-day workshop incorporating a mix of written mock intervention case studies and motivational interviewing role play activities.

Participants requiring supervised exercise require medical clearance from their treating oncology team and will undergo a comprehensive initial assessment with vital signs monitored pre- and post- exercise by the intervention physiotherapist to ensure safety. Procedural guidelines are in place to deal with unexpected exercise-related adverse events as clinically indicated. Existing incident reporting structures at the PAH will be followed and the participant's treating clinician, cancer nurse coordinator, and CCQ intervention nurses will be informed. A detailed review of cancer survivor participant assessment forms and exercise history will be undertaken by an independent oncologist. For participants who experience any emotional distress during CCQ intervention nurse consults will be referred to the CCQ counselling service consisting of nurse counsellors and psychologists for evaluation and clinical management.

Intervention Fidelity

In addition to the use of clinic and phone booster checklists, Participants and CCQ nurses will be asked to consent to the audio recording of all nurse-led clinics for quality assurance and to re-check any data or information. Fidelity of the intervention will be assessed using the framework for behavioral interventions recommended by the National Institutes of Health (NIH) (37, 38) as outlined in Table 2. It is expected that some of these strategies will be refined through the conduct of the pilot trial.

Table 2: Intervention Fidelity Strategies

Study Design	Study design procedures have been designed to ensure that the study can adequately test its hypotheses in relation to underlying theory and clinical practices.

Training Providers	Standardized provider training includes procedures to ensure that interventionists have been satisfactorily trained to deliver the intervention to cancer survivor participants. This training will involve:
	• Provision of a study manual to all staff which includes:
	  ○ Generic study related information: study overview, reporting/documentation guidelines, communication flowchart, rationale for the study treatment, self-management goal setting, motivational interviewing, and health coaching.
	  ○ Intervener-specific information: Job description, intervention protocol, quality assurance and monitoring
	• The Trained Registered Nurse responsible for the intervention will have approximately 4-hours of pre-reading modules developed by the chief investigators and approximately 4-hours of practical training. This will include:
	  ○ Clinical management of CRF
	  ○ NCCN CRF Guidelines
	  ○ Exercise and physical activity advice
	  ○ Provision of self-management support (including collaborative goal setting and motivational interviewing, sleep hygiene and energy conservation)
	  ○ Education about referral pathways for services within Princess Alexandra Hospital referral flow charts and contact details for community services
	• The data collector will have necessary pre-reading and training. This will include:
	  ○ Data collection tools and procedures to be used
	  ○ NCCN CRF Guidelines for the screening and assessment of CRF

Delivery of Treatment	Intervention procedures will be monitored to improve delivery of intervention and comparison of conditions, and ensure that the intervention is delivered as intended, through: • The nurse-led clinics will be audio and/ or video recorded and checked for quality assurance. • The intervention fidelity will be closely monitored and discussed during the monthly meeting for the first 3 months of the trial between the intervention nurses, intervention physiotherapist, RA, and/or CIAs. • Omissions and/or protocol deviations will be reviewed on an individual basis. • Intervention checklist completed at the end of each intervention to allow protocol deviation tracking across interveners and conditions. • Minimizing contamination between conditions by training interventionists to address cancer survivor participant questions about randomization and their assigned condition using non-biased explanations.
Receipt of Treatment	Treatment receipt focuses on the cancer survivor participant and includes procedures to assure that the treatment was both received and understood. This goal will be achieved by: • Ensuring participants understand the information provided for each intervention, by checking through use of active questions and behavioral observations
Enactment of Treatment Skills	Enactment of treatment skills includes processes to monitor and improve cancer survivor participant ability to perform treatment-related behavioral skills and cognitive strategies in relevant real-life settings as intended. This goal will be achieved by: • ensuring participants are aware of the follow up schedules and responsibilities of all health professionals. • ensuring participants will have a copy of the completed self-management care plan including all care responsibilities and goals set for the individual

Arm 2: Control (Usual Care)

The control arm consists of usual follow-up care plus a written 3-page booklet on "Fatigue and Cancer" published by Cancer Council Australia (35). Follow-up arrangements at the PAH will vary primarily according to cancer type, and is determined by the treating surgeon, medical oncologist, or radiation oncologist through a specialist-led model.

Baseline and follow-up procedures

Study schedules for data collection and a schematic of the trial design are shown in Table 3 and Figure 1 respectively. Clinical characteristics and demographics (i.e., age, gender, ethnicity, highest level of education, living arrangements, marital status, employment) will be collected directly from participants and medical records by outcome assessors at baseline (T1). All participant-reported outcomes will be collected at baseline (T1), 12-14 weeks (T2), 24-26 weeks (T3), and 48 weeks (T4) post-baseline. Instruments will be self-administered via online surveys using REDCap (Research Electronic Data Capture) or interviewer-administered by blinded outcome assessors via telephone. Participants and healthcare providers will be invited to opt into a semi-structured interview at T4 either face-to-face, by telephone, or through videoconferencing as per interviewee preference. Semi-structured interviews will be utilized to collect data on intervention functionality, acceptability, and satisfaction that will be guided by the Consolidated Framework for Implementation Research (see Supplementary Material 5 for the interview guide).

Table 3: Study Schedule for Data Collection

PROCESS	EST TIME (MIN)	CONSENT	BASELINE (T1)	WEEK 2$^{\Delta}$	WEEK 13±1$^{\Delta}$ (T2)	WEEK 25±1$^{\Delta}$ (T3)	WEEK 49±1 (T4)
Self-Report Data Collection - Cancer Survivor Participant							
Garmin Education	5	X					
PG-SGA SF (10 items)	5	X					
BFI (10 items)	3		X		X	X	X
MSAS (32 items)	5		X		X	X	X
AAS and fruit and vegetable intake (8 items)	5		X		X	X	X
AES-S (18 items)	5		X		X	X	X
Productivity (3 items)	2		X		X	X	X
Interview	15						X
Medical Record Data Collection - Cancer Survivor Participant							
Participant Characteristics			X				
Garmin Data			X		X	X	X
Health resource data					X	X	X
Process outcomes data					X	X	X

Referral to services*				O	O	O	
Self-Report Data Collection - Carer							
BFI (10 items)	5		X		X	X	X
iVICQ (14 items)	10		X		X	X	X
Interview*	15						X

X = conducted by research assistant
O = conducted by intervention nurse
$^{\Delta}$ Data collection will occur as close as practically possible to the timepoint.
*Only completed for participants in the T-CRF intervention group
T: time point; PG-SGA SF: Patient-Generated Subjective Global Assessment Short Form; BFI: Brief Fatigue Inventory; MSAS: Memorial Symptom Assessment Scale; AAS: The Active Australia Survey; AES-S: Self-reported apathy; iVICQ: institute for Medical Technology Assessment Valuation of Informal Care Questionnaire.

Outcomes

Primary outcomes include measurements relevant to the feasibility of conducting large-scale RCT. Secondary outcomes involve measurements of preliminary clinical efficacy intended for use in the full-scale trial.

Trial feasibility

Feasibility of the T-CRF trial is the primary outcome of this pilot RCT and will be assessed using the following process outcomes: recruitment and uptake, attrition, adherence, fidelity, apathy, functionality, acceptability, and satisfaction with the intervention (see Table 4).

Table 4: Study Outcome measures

Outcome Domain	Specific Measurement	Metric and method of aggregation	Time-point of interest
PROCESS MEASURES			
Apathy	Self-Reported Apathy Evaluation Scale (AES-S) (39)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Adherence and fidelity among program administrators: Completion of clinic records	Completion of items on the nurse clinic checklist and booster phone checklist.		12 weeks, 24 weeks, and 48 weeks
Adherence and fidelity: Referrals to allied health and community services	Number and type of allied health and community service referrals raised and number actioned and attended as reported by research assistant, intervention nurse or cancer survivor participant and verified with electronic hospital medical records		12 weeks, 24 weeks, and 48 weeks
Treatment fidelity among program administrators: Intervention delivery	Audio and video recording of telehealth sessions.		12 weeks, 24 weeks, and 48 weeks

Intervention functionality, acceptability & satisfaction.	Semi-structured interviews with stakeholders (i.e., cancer survivor participants, carer participants, CCQ nurses, other health care providers) to discuss acceptability, and barriers and facilitators to implementing of T-CRF intervention.		48 weeks
Recruitment and Attrition	Information from research assistant records and hospital records.		Baseline, 48 weeks.
CLINICAL OUTCOME MEASURES			
Fatigue	Brief Fatigue Inventory (BFI) (32)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Symptom Distress	Memorial Symptom Assessment Scale (MSAS) (40)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Physical Activity (Subjective)	Active Australia Survey (AAS)(41) International Physical Activity Questionnaire short-form (IPAQ-S) (42)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Physical Activity (Objective)	Number of steps per day, number of stairs climbed per day, total hours doing moderate intensity exercise per day, and total hours slept per day as measured by Garmin wrist-worn activity tracker (VívoSmart 4, Garmin Australasia Pty Ltd, NSW, Australia)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Productivity Loss	Incidence and severity of financial distress and employment interference as measured by a 3-item survey developed by the research team (43, 44).	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Hospital resource utilisation	Electronic hospital medical records	Number of hospital admissions and emergency presentations	Baseline, 12 weeks, 24 weeks, and 48 weeks
Carer's Fatigue	Brief Fatigue Inventory (32)	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
Carer's Productivity Loss	Modified version of the Institute for Medical Technology Assessment Valuation of Informal Care Questionnaire (iVICQ) (45).	Effect of time on mean change score between groups	Baseline, 12 weeks, 24 weeks, and 48 weeks
CANCER SURVIVOR PARTICIPANT CHARACTERISTCS			
Demographics	Participant Interview	Collection of age, gender, ethnicity, education, living arrangements, marital status, and employment	Baseline
Clinical Characteristics	Participant interview Malnutrition Screening Tool (MST) (46)	Past and current medical conditions and syndromes, current medications and supplements, cancer diagnosis, previous cancer treatment, current cancer treatment, and fatigue history using participant interview, and nutrition risk	Baseline

Recruitment, intervention uptake and attrition will be assessed using screening logs and online REDCap survey data. Intervention adherence and fidelity of intervention nurses will be evaluated through assessing the number of items completed on the nurse-clinic checklist during consultations and booster phone calls. Apathy will be measured using the Self-Reported Apathy Evaluation Scale (AES-S) (39). Intervention functionality, acceptability, and satisfaction will be evaluated using a cancer survivor satisfaction survey as well as stakeholder semi-structured interviews. Semi-structured interviews will be conducted with intervention nurses and other health care providers involved in providing care for cancer survivor participants. Cancer survivors and carers allocated to the T-CRF trial arm will be invited to participate in an interview at the 12-month time point. Guiding questions (Appendix 1) and analysis of the interviews will be guided by the Consolidated Framework for Implementation Research (*CFIR).*

Clinical outcomes

A secondary goal is to assess the preliminary efficacy of the T-CRF intervention on cancer survivor's fatigue, symptom burden, productivity loss, hospital resource utilization, level of physical activity, as well as carer's fatigue, and carer's productivity loss. These outcomes will be assessed using validated self-report measures and medical record data as described in Table 3. Additionally, participants will be required to wear a Garmin wrist-worn activity monitoring device at no additional cost. This will measure physical activity (pedometer: number of steps per day, altimeter: number of stairs climbed, total hours doing moderate intensity exercise based on heart rate per day, and total hours slept per day).

Withdrawal and Study Termination

Any participant can withdraw from the study at any time and for any reason without prejudice. If a cancer survivor or carer participant is withdrawn because of an adverse event (AE), the investigator will arrange for appropriate follow-up care until the AE is resolved or has stabilized. Unresolved AEs will be followed until the last scheduled follow-up visit or until no longer indicated, per investigator discretion. In addition to AEs, other reasons for removal of participants from the study might include, but are not limited to, withdrawal of consent, administrative decision by the principal investigator or responsible organization, or protocol deviation. If a participant asks or decides to withdraw, all efforts will be made to complete and report the observations, especially primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. The primary reason for withdrawal (where known) will be identified and recorded on a case report form, along with the date of withdrawal. Withdrawal criteria are listed in Table 1.

STATISTICAL ANALYSIS

Descriptive statistics will be used to report on feasibility and process-related outcomes (e.g., recruitment rate, retention and attrition rates, adherence) as well as clinical and resource-use outcomes (e.g., fatigue, physical activity, hospital resource utilization). Preliminary effect size estimates for cancer survivor and resource use outcomes will be calculated following intention-to-treat principles using linear mixed

models to account for repeated measures and missing data. Effect sizes will be reported as estimates with a 95% confidence interval, and without p-values due to the underpowered nature of the study. Models will include group, time and their interaction and be adjusted by fatigue severity and current cancer treatment. Balance of demographic variables between the usual care and intervention group will be examined and adjusted for potential confounders. Assumptions of all models (normality, linearity, homoscedasticity) will be examined using the residuals of the model and will be described using mean, median, skewness, kurtosis and plots such as histograms and QQ-plots. If assumptions are violated, models will be either bootstrapped or log transformed, as appropriate. Missing data will be explored using descriptive statistics. Generalized linear models will be used to provide estimates for categorical outcomes such as adherence, with appropriate link models used based on the outcome distribution. All statistical analysis will be undertaken by an independent statistician blinded to treatment allocation. Semi-structured interviews will be audio or video recorded and will be transcribed verbatim for thematic analysis; a method for systematically identifying, organising, and offering insight into, patterns of meaning (themes) across a dataset (47).

DATA MANAGEMENT

Data Management and Confidentiality

All data will be recorded in electronic case report forms. Participants will only be identified by a unique participant study number on the case report forms and other documents. A secure system for online and offline data capture will be used for direct data entry by both participants and research staff. Case report forms will be accessed by the project manager for data checking. Data queries will be generated and sent to the relevant research team member for response before the database is locked and released for statistical analysis. Other study-related documents (e.g., signed informed PICF) will be kept in strict confidence by the Chief Investigator.

Data Checking

Data will be directly entered into REDCap by members of the research team using a tablet or desktop computer. All research team members will receive training regarding data collection from the Project Manager. To maximize data integrity and completeness, the project manager will undertake routine audits with data validation performed via REDCap. Any discrepancies and missing data will be alerted and resolved with the relevant research team member(s) as soon as practical. All electronic case report forms will be maintained on the system with details of any changes logged accordingly.

Data Protection

Participants will be informed that data will be archived at PAH and that these data may be viewed by staff including the project manager and by external auditors on behalf of PAH and appropriate regulatory authorities including Metro South Health Human Research Ethics Committee (MSH HREC)

and PAH Research Governance. Participants will be informed that a study report will be submitted to regulatory authorities and for publication and conference presentation. However, participants will be de-identified in such reports with only their study identification number, gender, and age used for recording or linkage purposes.

Data Retention

Audio and video recordings of the telehealth intervention will be stored electronically at Queensland University of Technology in a secure repository and will be securely destroyed after analysis is conducted. All other source data, clinical records and laboratory data relating to the study will be archived at PAH for at least 15 years after study completion and remain available for retrospective review or audit. The investigator and study staff will be responsible for maintaining a comprehensive filing system of all essential study-related documentation. All essential documentation will be retained by PAH as per the requirements of the responsible organization for the same period required for medical records retention. No study document will be destroyed without written agreement between the PAH and the principal investigator. If the principal investigator wishes to assign the study records to another party or move them to another location, they will notify the responsible organization in writing of the new responsible person or the new location.

PATIENT AND PUBLIC INVOLVEMENT

To ensure cancer survivor perspectives were represented and accommodated in the intervention design and implementation, the patient support and advocacy group at CCQ were invited, have provided input into the study. Consumers were invited to provide comments and critical appraisal of the study protocol. They will also assist with raising the profile of the study through their consumer and clinical networks. CCQ will also be providing the intervention cancer nurses who will deliver the T-CRF clinics.

ETHICS AND DISSEMINATION

Prior to the commencement of the study, written approval was acquired by MSH HREC (ID: HREC/2020/QMS/63495), with Research Governance approval provided by the PAH Research Governance Office. This study will be conducted in accordance with the principles of the Declaration of Helsinki (48), Good Clinical Practice (CPMP/ICH/135/95) (49) and the National Health and Medical Research Council National Statement on Ethical Conduct in Research Involving Humans (50).

Archiving and regulatory inspection

In accordance with the guidance on Good Clinical Practice (GCP), this study may be selected for audit. Inspection of site facilities and review of study-related records may occur by a representative of the responsible organization or regulatory authority to evaluate the study conduct and compliance with the protocol, GCP, and applicable regulatory requirements. All study-related documents and records will

be retained for a minimum of 15 years after trial completion. Written agreement from the responsible organization will precede destruction of the same.

Dissemination

Publication and reporting of results and outcomes of this trial will be accurate and honest, undertaken with integrity and transparency. Trial results will be disseminated to all participants with a summary sheet that will outline the trial findings in lay language. It is intended that the findings from this trial will be disseminated at academic, clinical and professional conferences, and published in high-quality, international peer-reviewed journals.

Protocol amendments and deviation

Neither the principal investigator nor the PAH will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the MSH HREC for approval before implementation. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter. Should any protocol deviation occur, it will be reported to the study project manager as soon as is practical. The deviation and the reason for its occurrence will be included in the study report.

TRIAL STATUS

This protocol (Version 1.1) was approved and registered on the Australian New Zealand Clinical Trial Registry (ANZCTR) on the 10th of December 2020 (ID: ACTRN12620001334998). The study started recruitment on 17th February 2021, and as of 1st November 2021, 40 cancer survivor participants and 16 carers have been enrolled. Data collection is anticipated to conclude in January 2023 (48 weeks following the final participant enrolled). Data analysis and manuscript preparation is anticipated to occur over six months, concluding in July 2023.

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Author Contributions: The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. RJC and RL conceptualized the study. RJC, RL, PY, SMM, CPE, JFA MBP, BH, GL acquired and received the funding. JT, BH, JFA provided input on motivational interviewing, counselling techniques, and resources for the nurse-led intervention. OAA, EPP, JN, LT, FCW and NHH led the design, development, and writing of the pilot RCT protocol. LJ provided data and statistical analysis methods. All authors contributed important intellectual content to the trial design and written protocol and reviewed and approved the final version for publication.

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Data Sharing Statement: There are no limitations on investigator access to the trial dataset. However, the datasets generated and analyzed during this study will not be publicly available, though will be made available from the corresponding author on reasonable request.

Competing Interests: None Declared

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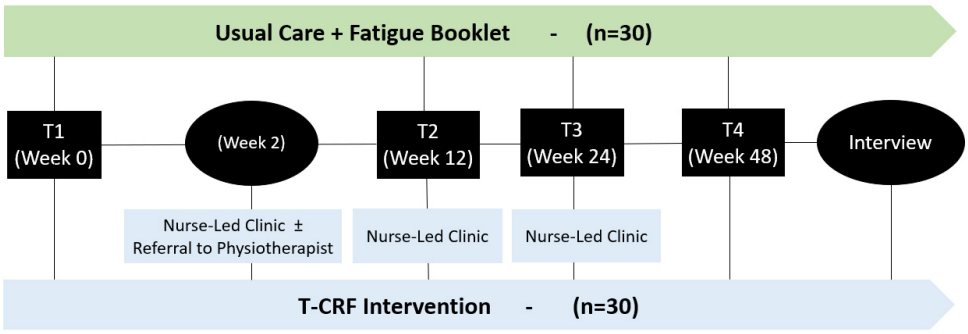
Figure Legend

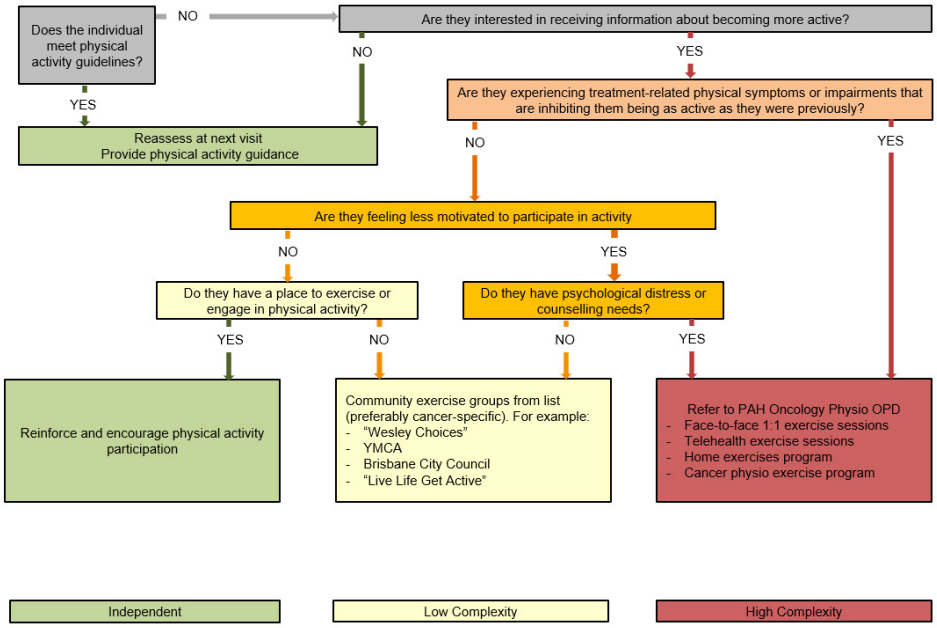
Figure 1: The Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors Follow-up. Schematic of the trial design. T1: baseline; T2: 12-14 weeks post-baseline; T2: 24-26 weeks post-baseline; T4: 48 weeks post-baseline

Figure 2: Algorithm for determining exercise intensity and levels of supervision. The pathway is intended to stratify individuals to higher (red), intermediate (yellow), or lower (green) condition complexity, which provides insight into the level of supervision and guidance that individuals may need to successfully engage in exercise and informs referrals. PAH – Princess Alexandra Hospital; OPD – outpatient department.



The Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors Follow-up. Schematic of the trial design. T1: baseline; T2: 12-14 weeks post-baseline; T2: 24-26 weeks post-baseline; T4: 48 weeks post-baseline

54x19mm (600 x 600 DPI)



Algorithm for determining exercise intensity and levels of supervision. The pathway is intended to stratify individuals to higher (red), intermediate (yellow), or lower (green) condition complexity, which provides insight into the level of supervision and guidance that individuals may need to successfully engage in exercise and informs referrals. PAH – Princess Alexandra Hospital; OPD – outpatient department.

48x33mm (600 x 600 DPI)

Supplementary Material 1. Patient Consent Form

Consent form – *Participant (Patient)*

Title	A Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors: A Pilot Randomised Controlled Trial (The T-CRF Trial)	
Short title	The T-CRF Trial	
Responsible Organisation	Princess Alexandra Hospital, Metro South Health	
Principal investigators	Dr Rahul Ladwa, Prof Raymond Chan, Elizabeth Pinkham, Lee Jones, Dr Bena Brown, Jodie Nixon, Prof Steve McPhail, Distinguished Prof Patsy Yates.	
Research team contacts	Insert Research Assistant name and contact	Telephone: Email:

Declaration by participant

- I have read, or have had read to me, and I understand the participant information and consent form.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I freely agree to participate in this clinical trial as described and understand that I am free to withdraw at any time during the study without affecting my future health care.
- I understand the purposes, procedures and risks of the research described in the trial.
- I understand that during the course of this research records held by Princess Alexandra Hospital may be accessed by my health care providers, Human Research Ethics Committee, research team, and Research Governance Officers to determine my eligibility for participation in this clinical trial and for the purposes of conducting and monitoring the clinical trial and verifying results.
- I give permission for my doctors, other health professionals, hospitals, laboratories or ambulances to release information held in my medical and health records to PAH concerning my disease and treatment for the purposes of this trial. I understand that such information will remain confidential.
- I understand that my information collected as part of this study may be used for secondary analysis for another research purpose. When this occurs, the researchers will seek appropriate ethics clearance and ensure the maintenance of my privacy.
- I consent to my treating doctor/s being notified of my participation in this study and any clinically relevant information noted by the trial nurse in the conduct of the trial.
- I understand that if I have any queries related to the study treatment including adverse events I should contact XXXX by mobile telephone XXXX, or via email at XXXX [replaced by research nurse once recruited]
- I understand if I have any queries I can contact XXXX by mobile XXXX or via email at XXXX [replaced by research nurse once recruited]
- I understand that I will be given a signed copy of this document to keep. We may like to ask you to participate in a future related study, or to obtain additional information or clarification related to your participation in this study. Please indicate below whether you are willing to be contacted about any future research studies.

(Continued over)

Consent form - *Participant*

Title	A Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors: A Pilot Randomised Controlled Trial (The T-CRF Trial)	
Short title	The T-CRF Trial	
Responsible Organisation	Princess Alexandra Hospital, Metro South Health	
Principal investigators	Dr Rahul Ladwa, Prof Raymond Chan, Elizabeth Pinkham, Lee Jones, Dr Bena Brown, Jodie Nixon, Prof Steve McPhail, Distinguished Prof Patsy Yates.	
Research team contact	Insert Research Assistant name and contact	Insert Research Assistant name and contact

(Continued from previous page)

Participating in an interview (optional)

☐ Yes, I agree to be contacted about participating in an interview.

☐ No, I do not want to be contacted about participating in an interview.

Permission to contact informal carer to participate in research (optional)

☐ Yes, I agree for you to contact my carer about participating in this research.

Carer Name: _____

Contact: _____

☐ No, I do not want you to contact my carer.

☐ Not applicable, I do not have a carer.

Future Studies (optional)

☐ Yes, I agree to be contacted about future research studies.

☐ No, I do not want to be contacted about future research studies.

Study Results (optional)

☐ Yes, I would like a copy of the study results.

☐ No, I do not want a copy of the study results.

Participant Signature _____ Date _____

Participant name _____ Time _____

Researcher Signature _____ Date _____

Researcher name _____ Time _____

Note: All parties signing the consent section must date and time their own signature.

Supplementary Material 2. Informal Carer Consent Form

Consent form – *Informal Carer*

Title	A Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors: A Pilot Randomised Controlled Trial (The T-CRF Trial)	
Short title	The T-CRF Trial	
Responsible Organisation	Princess Alexandra Hospital, Metro South Health	
Principal investigators	Dr Rahul Ladwa, Prof Raymond Chan, Elizabeth Pinkham, Lee Jones, Dr Bena Brown, Jodie Nixon, Prof Steve McPhail, Distinguished Prof Patsy Yates.	
Research team contacts	Insert Research Assistant name and contact	Telephone: Email:

Declaration by participant

- I have read, or have had read to me, and I understand the participant information and consent form.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I freely agree to participate in this clinical trial as described and understand that I am free to withdraw at any time during the study without affecting my future health care.
- I understand the purposes, procedures and risks of the research described in the trial.
- I understand that all information collected will remain confidential.
- I understand that my information collected as part of this study may be used for secondary analysis for another research purpose. When this occurs, the researchers will seek appropriate ethics clearance and ensure the maintenance of my privacy.
- I understand that if I have any queries related to the study I should contact XXXX by mobile telephone XXXX, or via email at XXXX [replaced by research nurse once recruited]
- I understand if I have any queries I can contact XXXX by mobile XXXX or via email at XXXX [replaced by research nurse once recruited]
- I understand that I will be given a signed copy of this document to keep. We may like to ask you to participate in a future related study, or to obtain additional information or clarification related to your participation in this study. Please indicate below whether you are willing to be contacted about any future research studies.

(Continued over)

Consent form – *Informal Carer*

Title	A Telehealth Cancer-Related Fatigue Clinic Model for Cancer Survivors: A Pilot Randomised Controlled Trial (The T-CRF Trial)	
Short title	The T-CRF Trial	
Responsible Organisation	Princess Alexandra Hospital, Metro South Health	
Principal investigators	Dr Rahul Ladwa, Prof Raymond Chan, Elizabeth Pinkham, Lee Jones, Dr Bena Brown, Jodie Nixon, Prof Steve McPhail, Distinguished Prof Patsy Yates.	
Research team contact	Insert Research Assistant name and contact	Insert Research Assistant name and contact

(Continued from previous page)

Participating in an interview

☐ Yes, I agree to be contacted about participating in an interview.

☐ No, I do not want to be contacted about participating in an interview.

Future Studies

☐ Yes, I agree to be contacted about future research studies.

☐ No, I do not want to be contacted about future research studies.

Study Results

☐ Yes, I would like a copy of the study results.

☐ No, I do not want a copy of the study results.

Participant Signature _____ Date _____

Participant name _____ Time _____

Researcher Signature _____ Date _____

Researcher name _____ Time _____

Note: All parties signing the consent section must date and time their own signature.

Supplementary Material 3. T-CRF Intervention as guided by the NCCN Fatigue Guidelines

Active Ingredient	Personnel Involved	Specific Activities	Time allocated
Pre-Clinic Referral Form			
Referral form (completed prior to 1st nurse-led clinic)	Research Team involved in participants' routine care at PAH and the participant	Once participants have consented to be part of the trial and been randomized to the T-CRF intervention group, the intervention nurse will request completion of the Clinic Referral Form from the Research Team prior to their 1st nurse-led clinic appointment. Data will be compiled from electronic medical records and discussions with treating clinicians (where applicable) to complete this referral. All information required for this referral form should have been collected as part of usual care and the participant will only be involved in the completion of this form if required information has not been gathered during usual care. This referral form will provide the information necessary for the comprehensive CRF assessment as per NCCN Guidelines. The referral form will include information such as the below: • Clinical characteristics (disease stage (recurrence or progression), type and length of treatment, patient's response to treatment). • Current medications and recent medication changes (prescribed, over the counter, herbal, vitamins, other supplements). • Fatigue assessment (onset, pattern, duration, change over time, associated or elevated factors, and interference with function as well as current management strategies). • Assessment of coping and support network (social, emotional, functional, financial support). • Identification of symptoms and symptom clusters (pain, emotional distress, sleep disturbance, poor sleep hygiene, anemia, nutrition impacting symptoms, activity level, medication side effects, alcohol abuse, substance abuse, and/or comorbidities/cancer treatment sequelae). • Assessment of functional status (e.g., exercise or activity patterns, ability to accomplish normal daily or enjoyable activities, participation in exercise programs).	
Nurse-led Clinic Appointment (≤1 hour) – where possible the same nurse will deliver all three clinics appointment to maximize continuity of care			
Assessment of CRF	Intervention Nurse and participant	Clinic 1: The intervention nurse will familiarize themselves with the participant's Clinic Referral form (i.e., CRF assessment) and confirm details with the participant Clinics 2-3: The Intervention nurse will evaluate progress towards reaching goals set in earlier clinics, as well as any relevant changes to their CRF assessment	10-minutes

Education on CRF	Intervention Nurse and participant	• Education on CRF pathophysiology and associated factors • Answer participant questions and correct misconceptions • Fatigue-related education regarding the three priority areas: physical activity, symptoms and coping strategies.	10-minutes
Management strategies for CRF as per NCCN Guidelines	Intervention Nurse and participant	Participants will set three SMART goals, which will encompass the following three priority areas as appropriate: 1. Physical activity (basic information on physical activity guidelines accompanied by a referral to cancer exercise program). 2. Symptoms (e.g., pain management, sleep hygiene, energy conservation techniques) 3. Coping (e.g., emotional, and psychological support) Personalized strategies will be discussed and developed between the intervention nurse and participant using motivational interviewing and goal setting, and a CRF management plan will be developed.	35-minutes
Referral to other services	Intervention Nurse and participant	• Referrals to other health professionals, where deemed appropriate and useful to meet patient goals, and according to existing referral pathways at Princess Alexandra Hospital or within the community (e.g., pharmacist, dietitian, social work, physiotherapist, occupational therapist, psychologist, psychiatrist, palliative care, GP for blood tests). • Where referral pathways at Princess Alexandra Hospital are not available/not appropriate, participants will be referred to community organizations or to their GP to coordinate community referrals (e.g., chronic disease management plan referral to access community dietitian).	5-minutes
Completion of documentation	Intervention Nurse. Participant not involved.	• Completion of nurse-led clinic checklist to ensure clinic guideline adherence. • Completion of participant CRF management plan, and a copy emailed to participant. • Completion and actioning of referrals, if necessary.	10-minutes
Physiotherapy Physical Activity and Exercise Prescription			
Framework for clinical decision making (Figure 1)	Intervention Physiotherapist and participant	Refer to Figure 1. Stepped process of review of current levels of physical activity, motivation to exercise, side effects of treatment, environment, and physical function to guide the type of physical activity/exercise recommended and supervision required. Programming will be guided by the Frequency, Intensity, Time and Type model as recommended by the American College of Sports Medicine Exercise Guidelines for Cancer Survivors.	150 minutes*

CRF: Cancer-related fatigue; PAH: Princess Alexandra Hospital; NCCN: National Comprehensive Cancer Network. *Aiming to meet physical activity guidelines of 150 mins of moderate intensity activity per week over a 12-week period.

Supplementary Material 4. EXAMPLE FATIGUE MANAGEMENT PLAN

FATIGUE MANAGEMENT PLAN

Clinic Number	Clinic Date		CCQ Nurse	

CONTACT INFORMATION

Name		Phone	
Address		Email	

FATIGUE ASSESSMENT

Onset of fatigue

Details:

Duration of Fatigue

Details:

Alleviating factors *Details:*

Frequency of fatigue

Details:

Pattern of fatigue

Details:

Interference with function *Details:*

CLINICAL NOTES

Physical Activity Details:

- *Current exercise (Type, duration, frequency)*
- *Perceived barriers to physical activity*

Meetin ; guid lines? Yes No

Further Infor nation: | Pages:

Contributing Symptoms Details:

- *Pain*
- *Feeling sad*
- *Worrying*
- *Difficulty sleeping*
- *Anaemia*
- *Nutritional deficits*
- *Co-morbidities & medication*

| Pages:

Further Information:

Coping Details:

- *Current strategies (e.g., pacing)*

Further Information: | Pages:

- *Social support*

SMART GOALS		
SMART GOAL 1		
Strategies		

SMART GOAL 2		
Strategies		

SMART GOAL 3		
Strategies		

REFERRALS		
Physical Activity		
	Details:	
Other Referrals	Details:	

SCHEDULE				
Clinic 2	date:		| time:	
Phone check-in 1	date:		| time:	
Phone check-in 2	date:		| time:	
Clinic 3	date:		| time:	
Phone check-in 3	date:		| time:	
Phone check-in 4	date:		| time:	

Supplementary Material 5. INTERVIEW GUIDE FOR T-CRF INTERVENTION GROUP

For participants

1. Describe your experiences with participating in the T-CRF Trial.
2. How did the trial meet your expectations?
3. What aspects of the trial were valuable to you?
4. What aspects of the trial were valuable to others? (carers, loved ones, health professionals) 5. (If applicable) Describe the impacts you saw from the intervention on your ability to work.
6. Describe any aspects of the trial that were challenging for you.
7. What kinds of changes or alterations do you think should be made to the trial?
8. Are there parts of the trial that shouldn't be changed?
9. Is there anything else about the trial you would like to share?

For carers of participants

1. Describe your experiences with the T-CRF Trial.
2. How did the trial meet your expectations?
3. What aspects of the trial were valuable to you?
4. What aspects of the trial were valuable to others? (the person you care for, loved ones, health professionals)
5. (If applicable) Describe the impacts you saw from the intervention on your ability to work.
6. Describe any aspects of the trial that were challenging for you.
7. What kinds of changes or alterations do you think should be made to the trial?
8. Are there parts of the trial that shouldn't be changed?
9. Is there anything else about the trial you would like to share?

For Health Care Professionals of participants

1. Describe your experiences with the T-CRF Trial.
2. How did the trial meet your expectations?
3. What aspects of the trial were valuable to you?
4. What aspects of the trial were valuable to others? (your patient/s, patient/s carers, other health care professionals)
5. Describe any aspects of the trial that were challenging for you.
6. Describe any aspects of the trial that you thought were challenging for your patient/s.
7. How does the trial compare to other alternatives that may have been considered or that you know about?
8. What kinds of changes or alterations do you think need to be made to the trial so it will work effectively in your setting?
9. Are there parts of the trial that shouldn't be changed?
10. Is there anything else about the trial you would like to share?

SPIRIT GUIDELINES REPORTING CHECKLIST

		Reporting Item	Page Number/Section
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Included in trial registration
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contribution	#5a	Names, affiliations, and roles of protocol contributors	1, 14
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	14
Roles and responsibilities: committees	#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)	14
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	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5,7
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	Table 1
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5,6,7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving / worsening disease)	6,7
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return; laboratory tests)	Table 2
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A No concomitant interventions committed or prohibited
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8, Table 3
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 & Table 4
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	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes),	5

		describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A. Participants not blinded to group allocation.
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., 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	8, Table 4
Data collection plan: retention	#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	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistics: outcomes	#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	8
Statistics: additional analyses	#20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	10
Methods: Monitoring			
Data monitoring: formal committee	#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	NA Pilot study does not have a DMC
Data monitoring: interim analysis	#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. Pilot study does not require interim analyses

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	6,7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7, Table 2
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10
Protocol amendments	#25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A. No ancillary studies
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	9
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
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. No ancillary studies
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	10
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material 1 & 2

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. No biological specimens collected