Activity as medicine in oncology for head and neck

The ACTIOHN Study

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STUDY SUMMARY

We aim to increase head and neck cancer (HaNC) patients' engagement in physical exercise. There are many proven benefits of engaging in exercise before, during, and following cancer treatment. These include reducing treatment-related toxicities, aiding recovery, reducing the risk of cancer returning, and improving physical and psychological well-being and quality of life (QOL). However, the vast majority of HaNC patients have low levels of physical activity both pre- and post-treatment. There are multiple reasons for this: 1) HaNC treatment is often aggressive with severe side-effects such as profoundly dry mouth, breathing through a hole in the neck, shoulder dysfunction, and trouble swallowing make it difficult to exercise; 2) apprehension about participating in groups due to altered facial appearance; 3) many patients are from low socio-economic areas, with high-risk smoking and alcohol behaviours and other health problems; and 4) HaNC services are regional, requiring long journeys to access specialist support. Our survey of 430 HaNC patients found a desire to participate in an exercise programme, however, individual preferences and perceived barriers to engagement were varied. Another issue is that HaNC patients' symptoms and circumstances change over time, thus exercise programmes should ideally have built-in flexibility to reduce the risk of these changes becoming barriers to exercise. We will develop personalised, collaborative, and flexible patient-centred exercise programmes, with tools to support HaNC-specific barriers to exercise, and test whether this is feasible and acceptable.

We will recruit 70 HaNC patients, pre-treatment and up to 2 months post-treatment, across two large HaNC units in NW and NE England. In consultation with HaNC physiotherapists, patients will work remotely with a cancer exercise specialist to devise a personalised exercise programme (including options for time, frequency, intensity, type, and location), using support tools to overcome HaNC-specific barriers, with weekly virtual support, delivered over 8-weeks. We will assess rates of uptake, retention and exercise adherence, patient reported symptoms and QOL, and physical fitness. We will interview patients and healthcare professionals to understand how acceptable they found the programme and explore any issues with integrating it into HaNC care.

Our study will determine whether further research into personalised exercise programmes is feasible and worthwhile for HaNC patients.

KEYWORDS

Head and neck cancer, physical exercise, feasibility

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1| BACKGROUND AND RATIONALE

Head and neck cancer (HaNC) represents malignancies arising from the mouth, pharynx and larynx and globally constitutes the sixth most common cancer (1). The UK incidence is rising and is expected to increase by 55% from 2011 to 2025, with 11,748 new cases per year projected for 2025 (2,3). This increase has been attributed in part to human papillomavirus-associated oropharyngeal cancer, where patients are younger at diagnosis with improved survival outcomes, hence a large number of patients are living longer with chronic treatment side effects. Traditional HaNC cohorts present at an older age, have considerable co-morbidities due to significant smoking and alcohol consumption, with low socio-economic status associated with poor health literacy making them hard to reach for rehabilitation engagement (2,4). HaNC treatment is often aggressive and multi-modal, resulting in a wide range of adverse effects on activities of daily living, appearance, wellbeing, and quality-of-life. Cancer survivorship research demonstrates that exercise has many benefits, however, HaNC patients are a severely underrepresented group in these studies (5). The ability to generalise findings is problematic due to HaNC patients differing considerably from survivors of other cancers, having lower levels of physical activity pre-treatment, and presenting with significant symptom-burden (6,7). Our preliminary research found that some of these symptoms, e.g., pain and major depression, are common to other cancers but tend to be higher in HaNC patients (7). Unique HaNC symptoms and treatment side effects include alterations to the airway (e.g., breathing through a hole in the neck), head and neck lymphoedema, neck pain, severe dry mouth, and swallowing problems that make it difficult to drink without coughing or choking (7). Some patients are dependent on a feeding tube through the nose or stomach (7). These issues pose substantial barriers to exercise participation. Our previous research (8,9) and PPI found many HaNC patients are motivated to participate in an exercise programme, were it available, although there was no clear consensus as to their preferred timing and mode of exercise. However, exercise programmes are not currently part of HaNC standard care and are excluded from NICE HaNC guidelines (10).

Centralisation of HaNC services has resulted in regional units serving large geographical areas with a complex care pathway, involving multiple healthcare professionals. Centralised service-based cancer exercise programmes are unlikely to be a good approach to supporting the uptake and adherence to programmes due to the negative impact of travel distance, cost, and the competing demands of HaNC patients at the time of scheduled facility-based exercise classes.

There has been low uptake of generic cancer exercise programmes in HaNC. A more personalised, collaborative, and flexible patient-centred approach that includes remote delivery is likely to better serve the needs of these patients. However, we do not know how or when to introduce exercise programmes to the pathway. The actual uptake and adherence to exercise by HaNC patients in the UK is unquantified and there are no bespoke HaNC resources to facilitate compliance. The delivery of an exercise intervention requires appropriate knowledge, training, and experience to address the unique challenges of life during and after HaNC. The many biopsychosocial issues that are unique to, or more severe in HaNC cohorts represent a major challenge for optimising the design, delivery, and adherence to an exercise programme.

2| STUDY AIMS AND OBJECTIVES

2.1 Aim

To investigate the delivery of personalised, flexible, and collaborative exercise programmes in HaNC patients, including uptake, adherence, and fidelity.

2.2 Objectives

1. To determine HaNC patients' eligibility, recruitment, adherence, and retention rates.
2. To report feasibility of delivery, including time point of uptake, integration into the care pathway, intervention components, and fidelity.
3. To determine the frequency, intensity, time, type, and location of exercise prescribed based on individual needs and preferences.
4. To obtain the views of HaNC patients and professionals on acceptability of the intervention, study processes, and integration to usual care.
5. To test candidate outcome measures and determine the required sample size for a full definitive study.

3| STUDY DESIGN

This is a multi-centre (Liverpool and Sunderland Head and Neck Cancer Centres) feasibility and acceptability study. The MRC framework for Developing Complex Interventions has informed the methods. It is a prospective, single armed, unblinded, mixed methods design.

4| OUTCOME MEASURES

4.1 Primary end point / outcomes

1. Exercise uptake: percentage of eligible patients that agreed to participate. Reasons for refusal also will be sought.

2. Exercise adherence:

    a. Exercise programme adherence: Percentage of the total prescribed exercise sessions completed.
    b. Permanent treatment discontinuation: permanent discontinuation of the exercise programme before the end of week 8;
    c. Treatment interruption: percentage of participants that missed at least three continuous scheduled training sessions;
    d. Dose modification: number of exercise sessions where the prescribed exercise was reduced by the participant, or reduced according to the exercise regressions embedded in each participant's exercise programme; and
    e. Early session termination: number of sessions terminated early by the participant.

4.2 Secondary end points / outcomes

4.2.1 Pre- and post-intervention measures of physical fitness:

- Aerobic endurance (6-Minute Walk Test),

- Lower body muscular strength and endurance (30-Second Chair Stand Test)
- Upper body muscular strength and endurance (Arm Curl Test)
- Agility and dynamic balance (8-Foot Up-and-Go Test)
- Shoulder and neck range of motion (goniometric measurements)

4.2.2 Pre- and post-intervention patient-reported measures

- Fatigue (Multidimensional Fatigue Symptom Inventory - Short Form)
- Quality of life (SF-36)
- Physical activity levels (International Physical Activity Questionnaire - Short Form)

4.2.3 Qualitative sub-study

5| ELIGIBILITY CRITERIA

Participants are eligible for the study if they meet the following criteria:

Inclusion criteria

1. ≥ 16-year-old.

2. Able to provide informed consent.

3. Diagnosed with HaNC for treatment with curative intent.

4. Between time of diagnosis and up to 8 weeks post-treatment.

5. Classified as low-medium risk according to an exercise risk stratification tool.

Exclusion criteria

1. Treated with palliative intent.

2. Classified as high risk according to an exercise risk stratification tool, or has any other unstable or uncontrolled medical condition associated with increased risk during exercise.

3. Unable to provide informed consent.

6| SETTING

This study will take place in two HaNC treatment centres in England (Liverpool and Sunderland). Patients will be approached about the study via their clinical appointment. Recruitment will take place over 13 months with follow up completed by month 20.

7| SAMPLE

Sample size has been determined pragmatically using feasibility study conduct guidance that recommends a sample size of between 24 and 50. The HaNC exercise literature suggests a sample size of 40 sufficient to estimate effect size for a full trial. Rates of attrition are reported to be between 12-40%. This study will identify 70 eligible patients, estimating a conservative retention rate of 60%, this will provide us with a minimum of 42 patients on study completion, and allows an estimation of the retention rate with an accuracy of 11.5%. For the recruitment period, for each month our target is: 1.5 patients per site, months 0-3 (n=9); 2.5 per site months 4-7 (n=20), 4 per site months 8-12 (40). The annual referral rate of newly diagnosed HaNC patients is approximately Liverpool n=800 and Sunderland n=220.

8| PROCEDURES

8.1 Recruitment

8.1.1 Patient identification and pre-screening

Potentially eligible participants will be identified by staff with delegated responsibility following the head and neck multidisciplinary team discussion. Patients will be approached about the study when attending standard of care pre-treatment appointments. All patients who are potentially eligible will be given a Patient Information Sheet (Appendix i and ii) to read and consider in their own time.

8.1.2 Screening and Consent

Potential participants will be screened against the eligibility criteria using the weekly speciality head and neck multidisciplinary team meeting lists, clinic lists, and patient medical notes. This will be completed either by the HaNC Research Nurse or the treating clinician (HaNC Surgeon or Oncologist). All patients who were deemed as potentially eligible for the study will be given a Patient Information Sheet (for the main study and qualitative sub-study) by the research practitioners/treating clinician at their next appropriate clinic visit .

Informed consent discussions will be undertaken by a delegated person (as per the delegation log, including GCP-trained members of the HaNC MDT and Research Nurses) with the opportunity for the patient to ask any questions and discuss the study in more detail. All patients will be given adequate time after receiving the Patient Information Sheet to decide whether or not they would like to take part (normally this would be 24 hours, however individual patients will be open to guide this minimum period). They will be contacted by telephone or at a subsequent clinical appointment by a GCP-trained member of the HaNC MDT or a Research Nurses to ascertain whether they are interested in participating.

With their permission, patients who initially express reservations will be offered opportunities to consider the study at two further time points (at the closest routine clinical appointments that coincide with the start of treatment and immediately after finishing treatment). For such patients we will always confirm with them that they would be willing to reconsider the study at the above specified time points. Patients will only be approached to reconsider their involvement if appropriate to do so (e.g., their reservations are due to timing), and with prior expression of willingness to reflect on their initial decision.

After eligibility has been confirmed, full written informed consent will be provided by signing, dating and initialling the consent form (Appendix iv and v), which will be witnessed by a person with delegated responsibility to do so. The original signed consent forms will be retained in the Investigator Site File (ISF), with a copy filed in the clinical notes and a copy provided to the patient. A letter to the patient's GP will be sent, informing them of their participation in the study (see Appendix vii)

8.1.3 Qualitative sub-study

8.1.3.1 Patient Interviews

During the study consent discussion, patients will be asked if they are willing to be contacted about a semi-structured interview for the qualitative sub-study. This is an option available to patients who consent, including those who withdraw or drop out early from the exercise programme as well as those who complete. A small sub-group of patients who decline taking part in the exercise programme will also be interviewed to explore their perspectives on exercise and what might make the programme more appealing to them.

All eligible patients will be given an Interview Patient Information Sheet to take away with them for consideration, at the same time as being provided with the main study information sheet. Approximately 20 survivor participants who consent to be contacted will be interviewed. The participants will be selectively sampled to cover a range of possible experiences based on gender, age, socio-demographics, location, type of cancer treatment and where possible, those that declined to participate. They will be selected and contacted at different time points (during and after the programme) and span patients with full to limited programme compliance. The focus will be on acceptability of the intervention, study processes and applicability of outcome measures.

The Research Associate will periodically telephone the clinical teams to collect contact details of patients who agree to contact. The Research Associate will contact the patient by telephone or text message and arrange a convenient time and date to conduct the interview. Patients will be offered the choice of being interviewed via telephone or video call. At the start of the next call from the Research Associate, there will be a discussion with the patient about the interview and verbal re-consent will be taken, including consent to audio-record the interview. The audio-recorder will be switched on and the researcher will go through the consent form and answer any questions over the telephone/video call. To ensure the consent recording is kept separate to the main interview the recorder will then be stopped and restarted before the interview is commenced. Patient interview guides are shown in Appendix viii.

8.1.3.2 Staff Interviews

Interviews with up to 20 staff (healthcare professionals, Cancer Exercise Specialist) will take place throughout the study, and may be done either face to face or over the telephone/teleconference. The interviews will be discussed with staff at the Site Initiation Visits, attended by the Research Associate. Staff will be given a Participant Information Sheet by the Research Nurse, who will obtain verbal consent to pass on their relevant contact details to the Research Associate. The interview will focus on assessments and programme delivery, usability of the study materials and intervention tools, and acceptability of the mode and timing of the intervention delivery.

For all telephone interviews, the same process regarding obtaining verbal consent will be followed as for the patient interviews. Written informed consent will be obtained for all face-to-face staff interviews. The staff interview guides are shown in Appendix ix.

8.2 Study Data and Assessments

8.2.1 Demographics and characteristics

- Age, gender, height, body mass, body mass index, SES, ethnicity
- Lifestyle – smoking and alcohol history, and current level of physical activity
- Tumour site and stage, HPV status, treatment type
- Co-morbidity (ACE-27)

8.2.2 Feasibility outcomes

- Number of patients screened
- Number of eligible/ineligible patients and reasons for ineligibility
- Number of patients agreed to participate and time point
- Reasons for refusal (where provided).
- Number of patients retained
- Reasons for and timepoint of withdrawal from study
- Adverse events

Outcomes will be recorded in the study log book by delegated research team member at site.

8.2.3 Exercise uptake and adherence outcomes

- Exercise uptake: percentage of eligible survivors that agreed to participate in the exercise programme. Reasons for refusal will be documented.
- Exercise adherence [57]:
    - Exercise programme adherence: percentage of the total prescribed exercise sessions completed;
    - Permanent treatment discontinuation: permanent discontinuation of the exercise programme before the end of week 8;
    - Treatment interruption: percentage of participants missing at least three continuous scheduled training sessions;
    - Dose modification: number of exercise sessions where the exercise volume was modified; and
    - Early session termination: number of sessions terminated early by the participant.

There will be a tick box in the patients' daily logs for them to state whether there was dose modification or early session termination, and a space to provide the reason(s) for this. Exercise programme adherence, permanent treatment discontinuation, and treatment interruption will be identified by the research team by scrutiny of the participants' logs.

8.2.4 Quantitative assessments

Assessments will be conducted to coincide with routine standard of care visits immediately before and after the 8-week intervention and will consist of patient-reported outcome measures via questionnaires and objective measures (Table 1). The fitness tests undertaken by the oncology specialist physiotherapists will follow a defined order and process, using a written test protocol, to ensure all tests are conducted consistently according to published standardised guidelines.

Table 1. Measurement properties of outcome measures. Assessments of physical fitness will be performed in the order shown in the table.

Outcome	Measurement Tool	Attributes
Fatigue	Multidimensional Fatigue Symptom Inventory - Short Form (MFSI-SF)	Comprises 30 statements or questions with a 5-point Likert-scale scoring response that assesses fatigue across five domains: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigour [51].
Health-related quality of life	Short-Form 36 Health Survey Questionnaire (SF-36)	Comprises 36 questions that cover eight domains of health: 1) Limitations in physical activities because of health problems; 2) Limitations in social activities because of physical or emotional problems; 3) Limitations in usual role activities because of physical health problems; 4) Bodily pain; 5) General mental health; 6) Limitations in usual role activities because of emotional problems; 7) Vitality (energy and fatigue); and 8) General health perceptions [52].
Subjective measure of physical activity levels	International Physical Activity Questionnaire (IPAQ)	27-item self-reported measure of different physical activity domains: job-related; transportation; housework, house maintenance, and caring for family; and recreation, sport, and leisure-time. Also assesses time spent sitting [53].

Objective measure of physical activity levels	Fitbit activity tracker	Wrist worn device with built-in triaxial accelerometer that measures movement of accelerations and has been shown to have a median wear-time adherence over 24-weeks of 100% in cancer survivors [54].
Upper body muscular strength and endurance	30-Second Chair Stand Test	Number of times within 30 s that an individual can rise to a full stand from a seated position without pushing off with the arms [55]. ICC = 0.89 [56].
Upper body muscular strength and endurance	30-Second Arm Curl Test	Maximum number of times a hand weight can be curled through a full range of motion in 30 s. Hand weight is 5 lb for women and 8 lb for men [55]. ICC = 0.81 [56].
Shoulder and cervical range of motion	Goniometer	Measurement of shoulder ROM in degrees and Cervical ROM in degrees
Agility and dynamic balance	8-Foot Up-and-Go Test	The shortest time taken to rise from a seated position on a chair, walk 8 feet around a cone, and sit back down on the chair [55]. ICC = 0.95 [56].
Aerobic endurance	6-Minute Walk Test	The maximum distance that can be walked along a 30 m course in 6 min Test [57]. ICC = 0.94 [56].

ICC = test-retest intraclass correlation coefficient.

8.2.5 Qualitative interviews

Interviews with patients and staff will be conducted by the Research Associate with experience in qualitative research and skills in interviewing vulnerable populations around sensitive topics. A topic guide has been developed from discussions with the wider team, including the patient panel and from literature around exercise participation (see Appendix viii). The topic guide will be used in the interviews but interviewees will be encouraged to speak freely about any other issues relating to the feasibility and acceptability of the study. The guide will be revised as new issues emerge in each interview. Each interview is expected to last between 40 and 60 minutes.

8.3 Data collection time points

8.3.1 Baseline

Demographics, patient characteristics, MFSI-SF; SF-36; IPAQ-SF; Fitbit accelerometer outcomes; 30-Second Chair Stand Test; 30-Second Arm Curl Test; goniometric measurements of shoulder and neck function; 8-Foot Up-and-Go Test; 6-Minute Walk Test.

8.3.2 During intervention

Patients will complete a simple exercise log sheet for every day during the 8-week exercise programme that they exercise. The log sheets will allow the determination of the frequency, intensity, duration, and type of exercise, and the different measures of exercise adherence. Any adverse events and reactions also will be recorded by patients in their log sheets.

8.3.3 End of intervention

MFSI-SF; SF-36; IPAQ; Fitbit accelerometer outcomes; 30-Second Chair Stand Test; 30-Second Arm Curl Test; goniometric measurements of shoulder and neck function; 8-Foot Up-and-Go Test; 6-Minute Walk Test; Adverse events.

8.4 Withdrawals and Drop Outs

Participants have the right to withdraw from the study at any time without having to give a reason. Investigator sites should try to ascertain the reason for withdrawal and document this reason within the Case Report Form and participant's medical notes. The PI may discontinue a participant from the study at any time if they consider it necessary for any reason including:

- Any change in medical status that results in the patient having a contraindication to exercise
- Participant withdrawal of consent
- Investigator's discretion that it is in the best interest of the participant to withdraw
- An adverse event that requires discontinuation of the intervention
- Termination of the study by the sponsor

Separate consent will be gained for interview participation therefore participants have the right to refuse to participate in the interview when contacted and those who choose to participate have the right to withdraw from or stop the interview at any time without having to give a reason.

8.5 End of study

The study will be considered as closed at 4 weeks after Last Patient Last Contact to allow for all completed assessment tools to be returned and collated, and the completion of the qualitative interviews.

9| STUDY INTERVENTION

9.1 Overview

The intervention is a personalised, collaborative, and flexible 8-week exercise programme, previously piloted with seven post-treatment HNC survivors and will be delivered remotely by a cancer exercise specialist to address the issue of regional cancer units serving large geographical areas. The step-by -step process is as follows:

1. The cancer exercise specialist will receive the following information from the oncology specialist physiotherapists regarding each participant:
    - Current clinical status and medications
    - Pre-intervention assessment results (see section 8 for details)
    - Any exercises, modifications, or precautions that should be incorporated into the exercise programme to address any musculoskeletal or other clinical issues, such as the patient having a percutaneous endoscopic gastrostomy tube.

    The information will be anonymised by using patient study identification codes and emailed to the cancer exercise specialist. Each patient's name, contact details, and study identification code will be given to the cancer exercise specialist by telephone so the cancer exercise specialist can then contact the patient to arrange their first meeting.
2. Development of an exercise programme that will be co-designed by the participant and the cancer exercise specialist, at their first meeting, based on a comprehensive individual needs analyses that considers information obtained from the oncology specialist physiotherapists and the participant's exercise history, exercise preferences, perceived barriers to exercise, and personal goals.
3. During the 8-week exercise programme, participants will complete a daily log that includes details of the intensity, duration, and type of exercise, including the resistance and number of sets and repetitions where resistance training has been prescribed. Patients also will log reasons for any non-adherence such as not initiating, modifying, or early termination of an exercise session.
4. The cancer exercise specialist will undertake a weekly individual consultation by video (or telephone call if necessary) with each participant during the 8-wk programme. Consultations will provide patient education, resolution of perceived exercise barriers, ask about and promote exercise adherence based on behaviour change theory, and encourage timely and accurate completion of daily logs.
5. The cancer exercise specialist will send two texts per week to each participant to further encourage timely and accurate completion of daily logs and provide a motivational message to promote programme adherence.
6. Patient behaviour change support will include 'top tips' information and 'exercise stories' of how to best manage specific HNC symptoms and overcome exercise barriers, developed through collaboration between clinicians and the CHANGE patient and public involvement group. In addition, the CancerFit website (http://www.cancerfit.me/site/), the Macmillan website (https://www.macmillan.org.uk/cancer-information-and-support/treatment/preparing-for-treatment/eating-well-and-keeping-active), and our Twitter feed will provide online resource support.
7. Patients will hand in their daily logs during their next routine clinical appointment.
8. After post-intervention assessments with the oncology specialist physiotherapist (see section 6), the participant will meet with the cancer exercise specialist for a final time to develop and agree a personalised exit strategy from the exercise intervention to facilitate transition to independent long-term exercise. This will involve discussing and formalising the patients' goals over the next 12 months, how the current exercise programme can be progressed, and a list and explanation of appropriate behaviour change techniques that the participant can apply.

9.2 Exercise programme design

Exercise programmes will be prescribed within the framework of current physical activity guidelines for cancer survivors, which state that survivors should engage in aerobic, resistance, and flexibility training. Neuromotor exercise also will be encouraged for any participants that present with balance issues during their initial assessments. However, patient needs and preferences will take precedence if these are not congruent with physical activity recommendations. This is in accordance with the

premise that the best exercise is the one the person will actually do. Details of the exercise programme design process will be recorded in the Cancer Exercise Specialist's notes as part of the needs analysis documentation.

Personalisation of exercise programmes will include appropriate manipulation of acute training variables (frequency, intensity, time, type, volume, and progression of exercise), and the location of the exercise. This will be based on the clinical status, physical activity history, exercise preferences, perceived barriers to exercise, and personal goals of each participant. A menu of no-cost, convenient, locally available, or virtual exercise options, partly informed by our previous research, will be used to help survivors choose their preferred exercise mode and location. The menu will initially be created by members of the research team and expanded by the cancer exercise specialist via his or her own experiences. However, participants will be encouraged to suggest alternatives based on preferences and any past successes at adhering to exercise and these will be added to the menu where appropriate as the study progresses. Participants will have the option to perform the exercise programme within their homes, in outside spaces, in other locations, or a combination of locations, exercising alone or with other people, depending on preference and perceived barriers. Advice on social distancing during exercise relating to Covid-19 will be given if applicable. Resistance bands will be given to participants for performing resistance exercises where appropriate. Resistance bands have been shown to be a versatile and effective method for developing muscular strength and endurance compared to the use of conventional resistance training equipment such as free weights and resistance training machines.

Flexibility will be embedded and formally written into each participant's exercise programme in the form of alternative exercise options, so participants can immediately respond to foreseeable emerging exercise barriers, such as indoor exercise for when outdoor exercise proves to be a barrier due to poor weather. This embedded flexibility is expected to improve participants' exercise barriers self-efficacy and exercise adherence.

9.3 Exercise progression and regression

Exercise programmes will be progressed towards meeting the minimum recommended amount of physical activity for cancer survivors. The focus, however, will be on avoiding inactivity and promoting exercise adherence rather than meeting the physical activity guidelines as a primary outcome goal. Exercise programmes will be progressed by manipulating only one acute training variable at a time. Where appropriate, the duration of aerobic exercise bouts will be increased by 5-10 min every 1-2 weeks until the participant can perform 30 min of continuous exercise at a particular intensity, after which exercise intensity will be progressively increased. Aerobic exercise intensity will be progressed by moving through the exercise intensity domains for ratings of perceived exertion proposed by the American College of Sports Medicine. Resistance training will be progressed using the double progressive method. This involves increasing the number of repetitions within the target repetition range and then changing to the resistance band with the next highest resistance when the upper value of the target repetition range can be performed with good form in all sets for a given exercise.

Flexibility will be embedded and formally written into each participant's exercise programme so that they can regress the exercise sessions in response to changes in adverse symptoms such as fatigue. This type of day-to-day 'autoregulation' will include manipulation of the programme's acute training variables such as completing only 50% of the training volume in a session where the participant perceives the full prescribed training volume is not achievable on that particular day.

9.4 Safety

Videos via a commercially available app (Physitrack, UK) will be used to show participants how to perform exercises safely and effectively. Where participants do not have access to apps, paper copies of exercise instructions printed from Physitrack will be supplied. Although all exercise will be performed by participants unsupervised, the cancer exercise specialist will check on resistance training and stretching technique during weekly telephone or video consultations. Each participant will be given a 'physiotherapy advice and information sheet' that provides safety information. This includes circumstances when not to start exercising, recognising adverse symptoms during exercise for which exercise should be immediately terminated, and information on what the participant should do if he or she experiences any of these symptoms. The physiotherapists will be the main contact for participants to report adverse symptoms, however, out-of-office hours contact details also will be provided. A traffic light system will be used by clinicians to flag any deterioration of participants during the exercise programme that may necessitate extra precautions, or temporary or complete cessation of exercise. This information will be communicated to the cancer exercise specialist.

9.5 Cancer Exercise Specialist

A certified cancer exercise specialist is an advanced fitness instructor with a level 4 vocational qualification in designing and delivering exercise oncology programmes. Cancer exercise specialists typically possess other fitness qualifications such as level 3 diplomas in personal training and exercise referral, and often have other level 4 specialist fitness qualifications such as in cardiovascular disease, diabetes and obesity, and pulmonary disease. The study will involve one cancer exercise specialist that will have the main direct responsibility for writing and supervising exercise programmes, and delivering behaviour change techniques. This person is highly likely to be self-employed and will have personal professional indemnity insurance, to a sufficient level that satisfies the Sponsor's requirements. A copy of their indemnity will be reviewed and retained, ensuring coverage for the lifespan of the project.

9.6 Training and support for cancer exercise specialist

The cancer exercise specialist will receive training from a chartered psychologist (AL) in motivational interviewing techniques that is underpinned by Self-determination Theory. The training will involve two, 2-hour remotely delivered workshops and include a bespoke workbook that contains content from workshop presentation slides, practical activities, scenario-based learning activities, action and coping planning sheets, and self-reflective diary sheets. The workbook also will include a matrix of behavioural change techniques that can be applied for different circumstances at different times over the 8-weeks. The cancer exercise specialist also will meet with AL for 1-hour during the second and sixth week after starting to work with the first participant to obtain further support on applying the motivational interviewing and other behaviour change techniques.

The design and delivery of all exercise programmes will be undertaken with the guidance and supervision (including fidelity checks) of a certified exercise physiologist (AM) who also holds many vocational fitness qualifications, including Cancer Exercise Specialist (Cancer Exercise Training Institute) and Cancer Rehabilitation (Wright Foundation CIC).

As part of their induction, the cancer exercise specialist will be given guidance and training on all aspects of data storage and participant confidentiality by the CI, Research Assistant, and Statistician before any exposure to patients recruited to the study.

Supervision will be via remote fortnightly meetings between AM and the cancer exercise specialist, including a review of all exercise programmes that have been administered and any issues that have arisen. The cancer exercise specialist also will have contact details for AM to contact him at any time with any queries.

9.7 Intervention fidelity

Participant fidelity will be determined by scrutiny of the participant log books after exercise programme completion (see section 8.2.3 for the different measures of exercise adherence). Completion of log books by the participants will be promoted and documented by the cancer exercise specialist during weekly meetings with participants. The percentage of pre- and post-intervention assessments that were completed by participants also will be determined. Cancer exercise specialist fidelity will be determined by a log book that details the times and dates that the cancer exercise specialist had meetings with the participants and when texts were sent to participants. The exercise physiologist (AM) will determine the extent to which the cancer exercise specialist has developed exercise programmes within the exercise prescription framework written for the study

10| SAFETY REPORTING

10.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject. Potential AEs identified for the physical exercise intervention include:

- Musculoskeletal injuries, including muscle strains, ligamental sprains, and joint injuries
- Injuries relate to falls
- Unexplained weakness or loss of sensation in a limb or face
- Cardiovascular event (rare)
- Breathing difficulties
- Hypoglycaemia/hyperglycaemia
- Confusion or disorientation
- Loss of vision
- Syncope (rare)
- Seizure
- Severe delayed onset muscle soreness
- Dislodged feeding tube (gastrostomy or nasogastric tube)
- Gastrostomy tube leak

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the intervention under study.
Adverse Reaction (AR)	An untoward or unintended response in a participant to which is related to the intervention under study i.e., that a causal relationship between the study intervention and an AE is at least a reasonable possibility and the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the intervention qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening*

	• Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the intervention, based upon the information provided.
Unexpected Serious Adverse Reaction (USAR)	A serious adverse reaction, the nature and severity of which is not consistent with the known information about the intervention under study.

10.2 Recording and reporting AEs and SAEs

AEs: All AEs that occur from baseline until seven days following the end of participation in the intervention must be recorded on the CRFs and in the patient medical notes. The study site PI is responsible for managing AEs at site according to the protocol. Seriousness and relation of the AE to the intervention should be assessed by the Investigator at site. The RA will maintain a detailed central record of all AEs that occur. There is no requirement to inform sponsor of individual AEs.

SAEs: All SAEs that occur from baseline up until the last follow-up must be reported to the CI and Sponsor immediately but no later than 24 hours of the site learning of its occurrence. The initial report will be made by the site Investigator completing the agreed SAE form which is sent via secure system to the CI.
For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the PI
- Whether the event is considered expected or unexpected.

10.3 Recording and reporting USARs

All USARs occurring from baseline up until seven days following the end of participation in the intervention must be reported to the NHS REC. The sponsor will perform this reporting. The assessment of expectedness will be performed by the CI against the known information for the study.

USARs must be reported no later than 15 calendar days after the sponsor has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

As soon as a site suspects that a SAR may be a USAR they must contact the CI, sponsor with a minimum set of information:

- Sponsor reference and study name (sponsor reference)

- Patient study number and date of birth
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., PI)

This information must be provided by email. The site is expected to fully cooperate with the sponsor in order that a full and detailed report can be submitted to the NHS REC within the required timelines.

11| STATISTICS AND ANALYSIS PLAN

11.1 Quantitative data

The primary outcome of the study is to report the retention rate of participants enrolled into the study. This will be done using counts and percentages along with 95% confidence interval. This will allow the retention rate to be estimated to a degree of precision (estimated to be 11.5%, if minimum sample size achieved). As this is a feasibility study no formal hypothesis tests will be undertaken. Both primary and secondary outcomes will be reported using standard summary statistics, means, medians, percentages etc., along with corresponding 95% confidence intervals at both baseline and follow up time points. Demographic information will also be reported using standard summary statistics. Estimates of variability in the primary outcome measure, along with a clinical estimate of the minimum clinically significant effect size will be used to determine the sample size for the full trial. All analysis will be undertaken using STATA software package.

11.2 Qualitative data

Thematic analysis will draw on the Framework approach. Data will be analysed by the Research Associate and Team members (JP, AL, VB, BY), and conducted iteratively throughout the project. The developing analysis will be regularly discussed at project meetings and where appropriate, inform changes to study processes. HaNC patient and staff transcripts will initially be analysed separately. The enquiry will focus on the feasibility and acceptability of introducing exercise using a personalised approach, at a range of time points, including the exit plan and exercise maintenance. The analysis team will discuss and agree emerging codes and themes. The analysis framework will then be constructed, informed by Normalization Process Theory, covering four key areas; how people make sense of a new practice (coherence); the willingness of people to sign up and commit to the new practice (cognitive participation); their ability to take on the work required of the practice (collective action); and activity undertaken to monitor and review the practice (reflexive monitoring). The analysis will remain open to relevant issues that may not be captured within the framework and novel issues arising in transcripts incorporated into a revised framework. Standard approaches to the rigorous analysis of qualitative data (including constant comparison, deviant case analysis, and member checking for accuracy) will be used.

11.3 Triangulation

Quantitative and qualitative data on patients' and healthcare professionals' engagement with the intervention, will be regularly discussed and triangulated at project management groups meetings to identify ways to refine the intervention and study processes while the study is ongoing. The impact of these refinements will then be examined both qualitatively and quantitatively.

Procedurally, the "following a thread" framework for triangulation and integrative analysis of qualitative and quantitative data will be adopted. There is no assumption over the primacy of either data type and will look for both convergences and divergences between them and aim to produce categories and themes that accommodate both types of data. Attention to exploring any divergences between the qualitative and quantitative data will be given, as these can often provide important insights. This will generate insights about ways of personalising the intervention to the needs and preferences of different patient groups, understanding variation in engagement and outcomes of interventions, and providing insights on the mechanisms by which interventions have an impact.

12| DATA HANDLING

Data will be stored on a password protected computer at the University of Liverpool, both the statistician and the primary investigator will retain a copy of the data on separate computers. Quantitative data will be pseudo-randomised prior to being sent to statistician with the participants name and other personal identifying data removed and replaced by a study number.

12.1 Data collection tools and source document identification

Data including the number of patients screened, approached and interested in taking part will be collected via a log completed by staff conducting screening. No patient identifiable data will leave the site.

Study data for an individual patient will be collected by each PI or their delegated person and recorded in the case report form (CRF) for the study. Patient identification on the CRF will be through a unique study identifier number. A record linking the patient's name to the unique study identifier number will be held only in a locked room at the study site, and is the responsibility of the PI. As such, patients cannot be identified from CRFs. The CI or delegated person will monitor completeness and quality of data recording in CRFs and will correspond regularly with site PIs (or their delegated team member) with the aim of capturing any missing data where possible, and ensuring continuous high quality of data.

Patients will complete the paper assessment tools as required. The tools will also only be identified using the unique patient identifier number. Data will be entered at sites onto a secure online system, with the paper originals remaining at site.

Interview recordings will be encrypted and password protected and sent to the University of Liverpool for transcribing.

12.2 Data handling and record keeping

Overall responsibility for data collection lies with the CI. Data collected on paper assessment tools will be entered onto a secure validated clinical data management system at sites by a delegated person. A unique study identifier will be used to identify participants on all paper data collection forms. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable data will leave the study site. Written consent forms will be kept securely according to the REC's requirements i.e., filed in the study site file. The study site file will be held in a locked security coded research office. The quality and retention of study data will be the responsibility

of the CI. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

Audio-recordings of interviews will be transcribed verbatim by a professional transcription agency with a secure up upload facility. Once transcripts have been received these will checked for accuracy and edited to remove identifying information to ensure anonymity of respondent. Each participant will be assigned a code which will give assurance that they cannot be identified. This will be stored with the scanned consent form/consent recording in the event that a volunteer wishes to withdraw from the study. The transcript will be held securely on the password-protected encrypted server at University of Liverpool. The recording will be deleted once the research team are happy that they will not need to revisit the raw data. Thus, apart from the consent form/recording no link to patient identifiable data will be present. Data will be managed using NVivo software. The analysis will be theoretically-informed by Normalization Process Theory and will be conducted according to the standard procedures of rigorous qualitative analysis including open and focused coding, constant comparison, deviant case analysis and mapping. There will be independent coding and cross checking and a proportion of data will be analysed collectively in data meetings where the research team share and exchange interpretations of key issues identified from the data analysis.

12.3 Access to data

Staff involved in the conduct of the study, including the PIs, the Working Group and NHS staff involved in screening and intervention will have access to the site files.

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities or the REC. Secure anonymised electronic data may however be released to the study statistician for analysis. The PI and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13| REGULATORY ISSUES

13.1 Ethics approval

The Chief Investigator will obtain approval Research Ethics Committee and Health Research Authority (HRA) approval. The study will be submitted to the research sites for Confirmation of Capacity and Capability. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

13.2 Indemnity

The University of Liverpool holds Indemnity and insurance cover with Marsh UK LTD, which apply to this study. The cancer exercise specialist has personal indemnity insurance up to £5m, inclusive of clinical research activities.

13.3 Sponsor

The University of Liverpool will act as Sponsor for this study. It is recognised that as an employee of the University the Chief Investigator has been delegated specific duties, as detailed in the Sponsorship Approval letter.

13.4 Audit

The study may be subject to inspection and audit by the University of Liverpool under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research (v3.2 10th October 2017).

14| PUBLICATION AND DISSEMINATION OF RESULTS

The study will be written up and submitted for peer review publication. Results will be made available to those involved in HaNC patient care and relevant patient forums.

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