COVERPAGE

Official Study Title:

Feasibility of a Co-designed PRe-radiotherapy Exercise Programme for People with Stage I-III Non-small Cell Lung cAnCEr: A Single-centre, Single Arm Pilot Study

Protocol Version:

V1.12 – 16/10/2025

Protocol Date:

16th October 2025

Sponsor / Institution:

Queens University Belfast

ClinicalTrials.gov Identifier (NCT Number):

Not yet assigned

PREFACE Study Protocol

Feasibility of a co-designed **PRe**-radiotherapy exercise programme for people with Stage I-III non-small cell lung c**A**n**CE**r: A single-arm pilot study

A single-centre, single arm pilot study

Protocol version and date:	V1.12 (16/10/2025)
IRAS Project ID	350051
Intervention:	Performing supervised exercise training immediately before radiotherapy
Sponsor:	Queen's University, Belfast
Funder:	Department for Economy

Protocol Summary

Study design	Single centre, single-arm, multimethod feasibility study Phase 1: Feasibility testing Phase 2: Qualitative Interviews
Primary objective	To assess the feasibility, and acceptability of delivering a co-designed, supervised pre-radiotherapy, exercise programme for people with stage I-III NSCLC, receiving radiotherapy with curative intent.
Secondary objectives	To assess the impact of the intervention on quality of life, functional ability, and other patient-reported outcome measures, such as symptom burden. To assess the accessibility, acceptability, and experience of the PA programme for patients and health care professionals (HCP). This will be achieved through conducting post-intervention, semi-structured, qualitative interviews
Target sample size	Phase 1: *n* = 30 Phase 2: *n* = 15
Enrolment criteria	• Patients with clinically or histologically confirmed NSCLC stages 1-3 • Planned to receive treatment with curative intention radiation as primary treatment. • ECOG performance status 0-2. • At least 18 years of age. • Can understand and communicate in English • Deemed safe to participate in moderate-intensity exercise and for ECG monitored, maximal exercise testing through the completion of a medical clearance form by their treating physician
Intervention	A Supervised, pre-radiotherapy exercise programme will be facilitated by the PhD Candidate concurrently with conventionally fractionated radiotherapy. The pre-radiotherapy exercise programme will consist of a 20-minute exercise session consisting of aerobic exercise at low, moderate, and high intensities, as tolerated. Exercise sessions will be conducted five days per week for 4 weeks in alignment with their radiotherapy treatment plan. Participants will be invited to the radiotherapy department 30 minutes before their scheduled appointment time to complete the exercise intervention. Participants will additionally be offered general advice on how to maintain physical activity based upon the latest cancer exercise guidelines (Campbell *et al.,*2019) The exercise programme used within this study has been adapted from Egegaard *et al.*, (2019) pre-radiotherapy exercise study for people with lung cancer. Adaptions were made through a series of two co-design workshops, where the research team collaborated with people who

	have been impacted by lung cancer through patient and public involvement.
Primary endpoint	Feasibility as assessed by recruitment, adherence, and retention to exercise duration and intensity, in addition to the occurrence of any adverse events assessed by CTCAEv5 criteria
Secondary endpoints	Questionnaires to measure quality of life and experience of symptoms burden, such as fatigue and breathlessness. These include the; International Physical Activity Questionnaire – Short Form (IPAQ-SF); European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30 with LC13); Pain score (Likert 1-10), Fatigue score (Likert 1-10) MRC dyspnoea scale; Rockwood Frailty Score; Distress thermometer. Physical function assessed will be assessed by 6-minute walk testing (6MWT) and the 30-second sit-to-stand test. Anthropological Measurements will include height & weight; Malnutritional Universal Screening Tool (MUST) score; resting blood pressure; resting heart rate. Finally, a qualitative evaluation, consisting of semi-structured interviews with participants, family members, and healthcare professionals, will be performed.
Other evaluations	Barriers and facilitators: Within the data collection sheet, barriers and facilitators encountered by each participant will be documented in the data collection sheet. Questionnaires: International Physical Activity Questionnaire – Short Form (IPAQ-SF), EORTC QLQ-30 with LC13, Pain score (Likert 1-10), Fatigue score (Likert 1-10) MRC dyspnoea scale.
Rationale for participant numbers	This is a single centre study, recruiting patients from the Northern Ireland Cancer Centre (NICC), Belfast City Hospital Phase 1: Sample size calculations are not required for feasibility studies. However, a sample size of 30 participants is recommended as per standard practice (Totton et al.,2023). Therefore, 30 participants identified over six months should be sufficient to determine feasibility. Phase 2: Based upon Braun and Clarke (2019) approach, 5 interviewees per group should be practical and sufficient to capture perceptions and experiences to achieve data saturation. These groups include: - Phase 1 participants who completed the programme. - Phase 1 participants who withdrew. - Phase 1 nominated persons (friends and family) - Healthcare professionals exposed to the programme
Analysis plan for primary and secondary endpoints	Phase 1: Feasibility outcomes will be collected on all patients screened. The number screened (those eligible and ineligible), those accrued and those not willing to participate with reasons for ineligibility and non-participation will be recorded and documented. This data will be examined and descriptive

	analysis carried out to identify any differences between participants and non-participants. Patient compliance, utilisation and satisfaction with the intervention will be assessed. Attendance and adherence to the planned exercise sessions will be recorded alongside and analysed using descriptive statistics. thematic analysis will also be used to identify themes within the information gained from the semi-structured qualitative interviews. The quantitative data will be analysed for mean change from baseline using paired samples t-tests. Due to the relatively small numbers, it is unlikely that statistically significant differences will be identified. However, it may be possible to identify clinically meaningful change. Regarding quality of life and symptom burden, change scores for the IPAQ-SF, EORTC QLQ-30 with LC-13, and MRC Dyspnoea can be calculated for each participant and categorised according to pre-established minimally important differences (MIDs).
Duration of patient participation and duration of study	All participants will be followed for 12 weeks following completion of baseline assessment. Study duration will be determined by the speed of recruitment, anticipated 6 months. Recruitment will last for 0.5 years with the remaining six months focused on completing data collection and analysis, and for those who enrol in the study toward the end.
Chief Investigator	Dr Gillian Prue School of Nursing and Midwifery Queen's University, Belfast
Principal Investigator	Dr Cathryn Crockett Consultant Clinical Oncologist based at Northern Ireland Cancer Centre, Belfast City Hospital, Belfast
Study Co-ordinator	PhD Candidate Matthew Beggs School of Nursing and Midwifery Queen's University, Belfast
Funding	The PREFACE Study is funded by the Department of Economy PhD Scholarship

Protocol Content

Figures

Tables

1. Introduction

1.1 Background information

1.1.1 Lung Cancer

Lung cancer (LC) is the leading cause of cancer mortality globally (World Health Organisation, 2023) and is responsible for 1032 annual deaths within Northern Ireland (NI), equating to 22% of all cancer deaths, with a 14% five-year survival rate (Northern Ireland Cancer Registry (NICAN), 2024; Northern Ireland Cancer Registry, 2023).

In addition to poor survival, people with LC can experience a highly burdensome array of debilitating symptoms which can reduce treatment outcomes, and quality of life (QoL), such as severe breathlessness, anxiety, depression and fatigue (Peddle-McIntyre et al., 2019). Therefore, leading UK healthcare societies, charities, and organisations encourage the development of innovative services and programmes to improve the quality of LC care (UKLCC, 2024; National Lung Cancer Audit, 2023; Bradley et al.,2021).

1.1.2 Radiotherapy resistance, tumour hypoxia and lung cancer

Radiotherapy (RT) is one of the main treatment methods throughout all stages of LC (Vinod & Hau, 2020; Delaney & Barton, 2015). Evidence-based guidelines estimate that approximately 4 out of 5 people with LC (77%) should receive a minimum administration of one fraction of RT as part of an optimal treatment plan for both curative and palliative intent (Vinod & Hau, 2020; Atun et al., 2015; Delaney & Barton,2015).

RT is an effective treatment modality which can utilised as either neo-adjuvant, adjuvant, or primary treatment (National Institute for Health and Care Excellence (NICE), 2024; Suveg et al., 2022). However, one issue which challenges the impact of Rxt on solid tumours is tumour hypoxia (TH) (Wu, et al., 2023; Barker et al., 2015).

Tumour hypoxia (TH) is a contributing factor of radiotherapy resistance (RR) (Wu et al., 2023) and is estimated to be present in up to 80% of non-small cell lung cancer (NSCLC) tumours (Nisar *et al.,* 2023). TH occurs when a tumour outgrows its available blood supply, creating areas of low oxygen (hypoxia) (Ortmann, 2024). Under hypoxic conditions, cancer cells can be 2-3 times more resistant to RT (Chen et al., 2024; Yoshimura et al., 2013). Consequentially, TH is directly correlated with poor patient survival outcomes, cancer progression, and resistance to cancer treatments (Ortmann, 2024; Ziolkowska-Suchanek, 2021; Muz et al.,2015). Therefore, developing innovative strategies to overcome TH remains a significant challenge for clinical research (Ortmann, 2024; Ziolkowska-Suchanek, 2021; Sia et al., 2020).

1.1.3 Exercise, cancer treatment, and tumour hypoxia

Since the publication of the first international roundtable discussion on exercise guidelines for cancer survivors (Schmitz et al., 2010), the evidence for exercise oncology research has significantly increased, creating a stronger rationale supporting the integration of exercise into cancer care (Coletta et al., 2022; Campbell et al., 2019). This led to the publication of the first international exercise guidelines for cancer survivors in 2019 (Campbell et al., 2019).

According to these guidelines, it is recommended that people diagnosed with cancer should avoid inactivity and should aim to achieve 150 minutes/week of aerobic exercise, in addition to strength training 2x/week, to avail of the benefits of exercise (Campbell et al., 2019). These include:

- Reduce cancer-related fatigue
- Improve health-related quality of life
- Improve physical functioning
- Improve sleep and reduce anxiety and depression
- Improve lymphoedema
- Improve bone health.

The American Society of Clinical Oncology published exercise guidelines for people with cancer during treatment (Ligibel et al., 2022). Ligibel et al., (2022) systemic review provided strong evidence to support the recommendation of oncology providers to recommend both aerobic and resistance exercise to people with cancer whilst receiving treatment with curative intent. However, due to the large variability in exercise programme design, recommendations of specific guidance for exercise duration and intensity during treatment cannot be determined.

In addition, pre-clinical research suggests that the effects of TH could be mitigated through the acute and chronic effects of exercise, therefore increasing the effectiveness of cancer treatments, such as radiotherapy (Brown et al., 2022; Avancini et al., 2020). For example, McCullough's (2014) pre-clinical research demonstrated an approximate 200% increase in tumour blood flow during exercise than when at rest, and a significant increase in patent blood vessels, decreasing TH. Furthermore, Dufresne *et al.,* (2020) pre-clinical research demonstrated that exercise in combination with radiotherapy had a greater effect on tumour shrinkage compared to radiotherapy alone. However, exercise alone did not cause this effect.

This increasing accumulation of evidence supports the hypothesis that cancer treatment could be more effective when supplemented with exercise (Esteves *et al.,* 2021; Cormie *et al.,* 2017). However, there is a lack of evidence in human studies to support this hypothesis in lung cancer (Seet-Lee et al.,2022). This is partly due to the challenges with measuring the effects of exercise on TH (Piraux et al., 2020). In addition, difficulties with TH measurement are compounded by the significant heterogenicity in exercise protocol design in pre-clinical research (ligibel *et al.,*2022;

Seet-Lee *et al.,* 2022), therefore understanding the minimally effective exercise prescription for adults to reduce TH in LC is currently a gap in research.

Egegaard *et al.,* (2019) conducted the only study to investigate the feasibility of delivering a pre-radiotherapy exercise programme for people receiving chemoradiotherapy treatment for stage III NSCLC. However, due to a low recruitment rate of 44.1%, study results were underpowered and were therefore described as explorative only. However, Egegaard *et al.,* (2019) results demonstrated a 90% attendance rate and 88.1% adherence rate to a pre-radiotherapy exercise prescription.

In summary, Egegaard et al., (2019) research provides proof of concept that a pre-radiotherapy exercise programme for people with LC can be performed safely, and is well tolerated, due to the low reporting of adverse events, and high attendance and adherence rates. However, Egegaard et al., (2019) research has been the only study to conduct pre-radiotherapy exercise research for people with LC. Typically, the conduct of only one feasibility study may not be sufficient to determine feasibility (Pearson *et al.,* 2020). Rather, the conduct of multiple feasibility studies, can provide a more comprehensive understanding on a research topic, due to the involvement of various methodological approached and research variabilities (Morgan *et al.,* 2021). Furthermore, this study contained only a small number of participants (n=14) and was conducted in only one country. This is relevant, as populations attitude towards physical activity, and prevalence of sedentary behaviour varies considerably between countries (Nikitara *et al.,* 2021; World Health Organisation, 2018). Therefore, acceptability of the programme may vary between countries based on the general public's attitude towards physical activity.

1.2 Study Rationale

As previously discussed, there is emerging evidence which supports the introduction of a pre-radiotherapy exercise programme for people with lung cancer, with its potential to improve treatment outcomes and patient quality of life (Ligibel et al., 2022; Brown et al., 2022; Dufresne et al., 2020; Egegaard et al., 2019; McCullough *et al.,* 2014). However, considering this is a new, understudied area of research, it is first necessary to understand the feasibility of delivering such an intervention within the operations of a radiotherapy department within the National Health Service (NHS), and alongside standardised radiotherapy treatment pathways.

In conclusion, the conduct of this feasibility study may strengthen Egegaard's *et al.,* (2019) 'proof of concept' conclusion that introducing a pre-radiotherapy exercise programme for people with lung cancer can be safely tolerated. Furthermore, it may provide additional insights into alternative methodological approaches which may improve future study conduct and design and enable larger clinical trials to be performed.

2.0 Aims and Objectives

2.1 Overall Aim

To assess the feasibility, and acceptability of delivering a co-designed, supervised pre-radiotherapy, exercise programme for people with stage I-III NSCLC, receiving radiotherapy with curative intent.

2.1.1 Primary Objective

To determine feasibility outcomes by measuring:

- Eligibility rates presented as the percentage of eligible participants identified and approached through participant screening.
- Recruitment rate presented as the total number of potential participants who were approached and who agreed to participate as a percentage of the total number who were approached.
- Exercise programme attendance by calculating the total number of attended sessions by the total number advised.
- Adherence to the pre-radiotherapy exercise programme through monitoring the participants ability to complete the advised duration and intensity of exercise during each session (adherence is accepted if completed 75% of duration without intensity modification)
- Participant retention rates calculated as the number of participants available to provide outcomes at the post-intervention assessment as a percentage of the total number recruited.
- To assess the tolerability and safety of the intervention, via recording of intervention-associated adverse events using the Common Terminology Criteria for Adverse Events v5 (National Institute of Health, 2021) (Appendix 1-4)

2.1.2 Secondary Objective

As this is a small-scale, unpowered, feasibility study with no comparison group, secondary outcomes will be exploratory. Secondary outcomes include:

- Initial exploration of/gathering preliminary evidence of the impact of the pre-radiotherapy exercise programme on the participants quality of life and symptom burden via patient reported outcome measures.
- To assess the accessibility, acceptability and experience of the exercise programme for patients and health care professionals (HCP). This will be achieved through conducting a post-intervention, exercise satisfaction questionnaire, and semi-structured, qualitative interviews with phase 1 participants (who have completed or withdrew from the programme), a nominated person (friends and family), and HCPs involved. This will be used to optimise the exercise programme for future effectiveness studies.

3.0 Research Design: Overview

This research will be conducted in accordance with the Medical Research Council's (MRC) framework (Skivington et al., 2021) for developing and evaluating complex interventions. The MRC Framework, is not designed as a research methodology to determine an interventions effect (Skirvington *et al.,* 2021), rather, this framework was developed to answer research questions beyond effect, such as understanding the acceptability, cost effectiveness, scalability, and transferability of interventions across different contexts (such as location, groups, populations etc). Therefore, adopting the MRC Framework allows the research team flexibility to explore the acceptability of delivering a new, complex intervention such as a pre-radiotherapy exercise programme, within the context of an NHS radiotherapy department.

This study will consist of two phases and will utilise a sequential, multi-method design. Phase 1 will involve a single-centre, single-arm feasibility study, phase 2 will involve a qualitative evaluation through the conduct of semi-structured, qualitative interviews with study participants, nominated family members, and HCPs directly, or in-directly involved in the research.

3.1 Phase One: Feasibility

The feasibility phase consists of delivering a supervised, pre-radiotherapy exercise programme for people diagnosed with stage I-III LC with behavioural change support. Additionally, participants must be receiving conventionally fractionated RxT, with curative intent. Participants receiving alternative treatment plans, such as stereotactic ablative therapy or 60-66Gy in 30-33 fractions over 6-6.5 weeks will be excluded from this study. This was based on recommendations from the lung cancer multi-disciplinary team (Dr Crockett, Dr McAleese, lung cancer clinical nurse specialists, and specialist radiographer).

Participants will be recruited from the NICC. Assessments will be taken at baseline immediately before each exercise session, and at the end of the exercise programme. The intervention will involve 4 weeks of supervised exercise training, conducted within radiotherapy department immediately before their scheduled treatment appointment (Monday to Friday). Supervised sessions will be facilitated by the PhD candidate who is a registered nurse with 6 years' experience (and is currently working) in cancer care, holds a valid Good Clinical Practice certificate, and the level 4 CanRehab specialist instructor course qualification. The level 4 CanRehab specialist instructor course is an accredited and assessed course available to exercise specialists and physiotherapists which provides them with the skills and competencies to provide exercise to people living with cancer.

3.2 Phase two: Qualitative evaluation

Following feasibility, phase 1 participants (including those who withdrew), will be invited for semi-structured interviews to understand the feasibility and acceptability of the programme through exploring experiences and satisfaction, perceived barriers and facilitators to the programme's delivery, and potential methods of optimisation/recommended changes. In addition, phase 1 participants will be asked to nominate a trusted friend or family member who has been present with the individual for a minimum of three days per week throughout the exercise programme, for qualitative interview. Finally, HCP exposed to the exercise programme will be invited for qualitative interview.

***Figure 1**: Study timeline*

Stage One

Participant eligibility initially screened by consultants at the new patient appointment. The Oncologist will discuss PREFACE participation and provide the Patient information sheet with an infographic.

Patients will be asked to wait the next 24 hours before consenting and will have 7 days to respond.

Phase 1

Stage Two

Once consented by PhD Candidate to the pre-radiotherapy exercise programme, the following will be conducted between treatment planning and start:

- Baseline assessments (Physical function tests, frailty scores, quality of life questionnaires,
- Maximal exercise stress testing
- Exercise support session and general physical activity advice

Phase 1

Stage Three

Preface pre-radiotherapy exercise progam mebegins on Day 1 of radiotherapy, which will consist of 20 minutes of aerobic exercise, immediately before their treatment, 5 days/week for duration of treatment (4 weeks). Participants will complete the PREFACE exercise programme arrive to radiotherapy department 30 minutes before their scheduled appointment to complete assessments and physical activity.

Phase 1

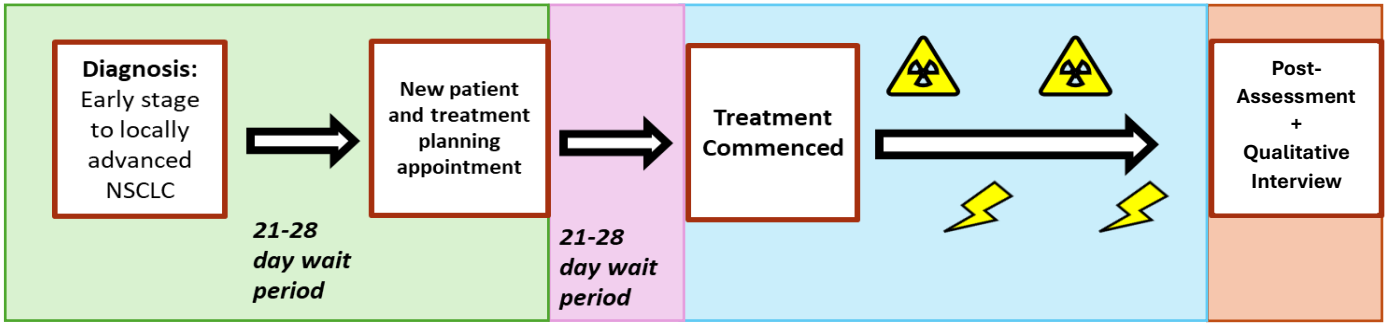
Stage Four

Following treatment completion, participants will be invited for post-intervention assessments and qualitative interviews.

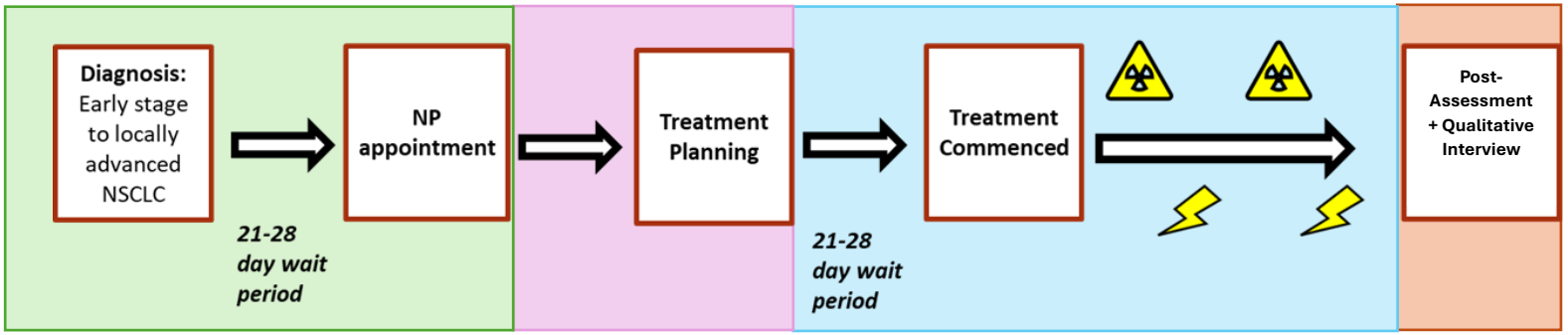
Post-intervention assessment will be completed on last day of treatment, and Qualitative interview will be optional. Participants will then be signposted for further resources and support with physical activity

Phase 2

Screening and recruitment Pathway #1



Screening and recruitment Pathway #2



4.0 Phase 1: Feasibility

4.1 Study Setting

Consent, pre and post assessment, and all pre-radiotherapy exercise sessions will be conducted within a designated area within the radiotherapy department in regional Northern Ireland Cancer Centre (NICC) in Belfast. This area has been discussed, agreed and allocated by the radiotherapy department manager within the NICC (Joanne McCarthy). Furthermore, the exercise equipment used within this study will be provided by the BCH main physiotherapy gym, and permission for this has been granted by Sarah Taggart (Band 8 Physiotherapist) prior to protocol submission.

4.2 Study Participants

Study participants will have been diagnosed with stage I-III NSCLC and prescribed conventionally fractionated radiotherapy only (55Gy in 20 fractions over 4 weeks) as their primary treatment. All study participants must also be treated within the radiotherapy department within the regional Northern Ireland Cancer Centre.

4.2.1 Inclusion Criteria

- Patients with clinically or histologically confirmed NSCLC stages 1-3.
- Planned to receive treatment with curative intention radiation as primary treatment.
- ECOG performance status 0-2.
- At least 18 years of age.
- Can understand and communicate in English.
- Deemed safe to participate in moderate-intensity exercise and for ECG monitored maximal fitness test through the completion of a medical clearance form by their treating physician.
- Able to provide written and informed consent.

** Participants may nominate a friend or family member to optionally attend assessment visits and PA sessions.*

4.2.2 Exclusion Criteria

Co-morbidities or symptoms which may contraindicate exercise including, but not limited to:

- Unstable or new angina (diagnosed within the previous month).
- Unstable or acute heart failure, cardiomyopathy, or other uncontrolled cardiac disease (as evidenced by symptomatic fluid retention, excessive breathlessness, rapid weight gain, swollen ankles or pitting oedema) within the previous 3 months.
- Presence of new or uncontrolled cardiac arrhythmias.
- Confirmed or suspected spinal cord compression.

- Uncontrolled diabetes (e.g. medication changed within 1 month, has had episodes of hypoglycaemia during the previous 2 weeks, or hyperglycaemia which does not decrease with exercise during the previous 2 weeks).
- Is receiving combination treatment with chemotherapy or immunotherapy.
- Current active secondary malignancy other than non-melanoma skin cancer.
- Has had orthopaedic surgery within the previous 3 months on weight-bearing bones.
- Chest pain while undertaking exercise or physical activity.
- No > Grade 2 peripheral neuropathy.
- Metastatic disease beyond localised metastatic involvement (e.g. bone or brain).
- Has discovered any abnormalities shown on the ECG monitored maximal fitness test which warrant early termination or contraindicate physical activity.
- People with living with a physical disability which would limit their ability to exercise safely on the stationary exercise bike used within this study.
- People who are non-English speakers.
- People who are pregnant.

* *Patient participation in other clinical research* – As an additional consideration, patients will be excluded if they are currently enrolled in an alternative exercise or physical activity study, as this may impact outcomes in both studies. However, if they have been involved in research prior to this or are currently involved in research in an unrelated area we will not immediately exclude them from trial participation. Instead, the PhD candidate, Chief investigator, and Principal investigator will discuss their involvement to determine safe and appropriate enrolment.

* *Physical disability* - it is with regret that we will be limited in our capacity to offer alternative exercises to accommodate people with a physical disability. To elaborate, the BCH main gym is willing to lend a stationary exercise bike to the research team in support of this study. However, due to limitations on equipment availability in the trust, and limited funding/resources to purchase equipment, people who have a physical disability which limits their capacity to exercise safely on the stationary bike will be excluded from this study. In an ideal scenario, we would also have a recumbent stationary bike to support more people with physical disability get involved within this research.

4.2.3 Sample Size

As this will be a feasibility study, sample size calculations are not required. However, a sample size of 30 participants is recommended as standard practice for feasibility studies (Totton *et al.,*2023). Therefore, it is estimated that 30 participants identified over approximately six months should be sufficient to determine the feasibility of the pre-radiotherapy exercise programme.

4.2.4 Screening, Recruitment and Withdrawal Procedures

Meetings with several HCPs working as part of the lung cancer multidisciplinary team have been undertaken to discuss the screening and recruitment process of this study. These HCPs include: two lung cancer consultants (Dr Crockett and Dr McAleese), two lung cancer specialist nurses (Chloe Givin & Stephanie Todd), a lung cancer specialist radiographer (Linda Young), and two research and development radiographers (Diane Holland & Norma Higgins).

Within the NICC, there are four consultants who prescribe conventionally fractionated radiotherapy for people with stage I-III NSCLC. However, there are two treatment pathways which require accommodation, as two consultants will receive their patients from the Belfast trust MDT discussion, and two consultants from the Northern Trust MDT discussion.

Therefore, the following two screening pathways have been agreed with the HCP's as listed above.

Figure 2: Screening and Recruitment Pathway 1

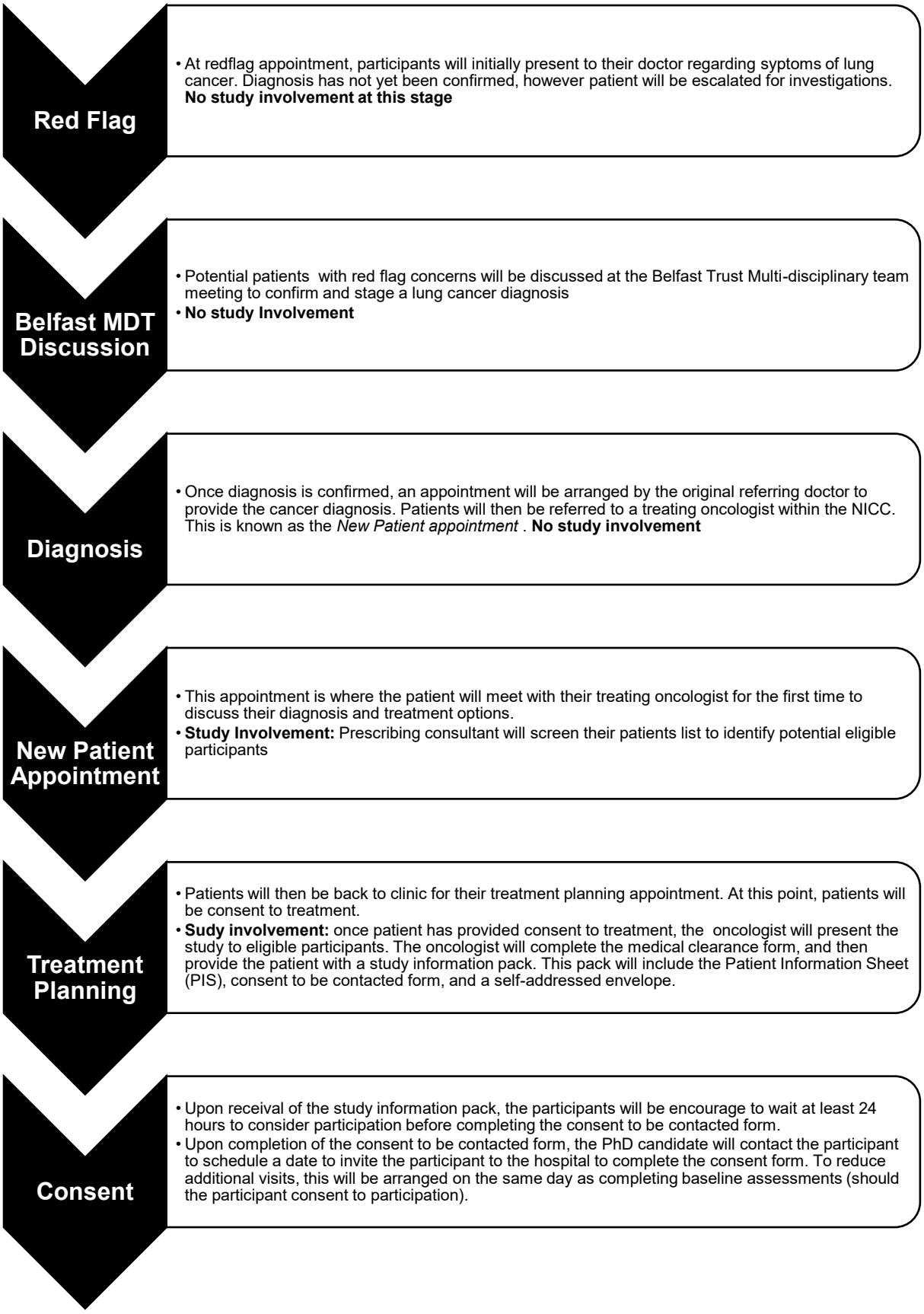
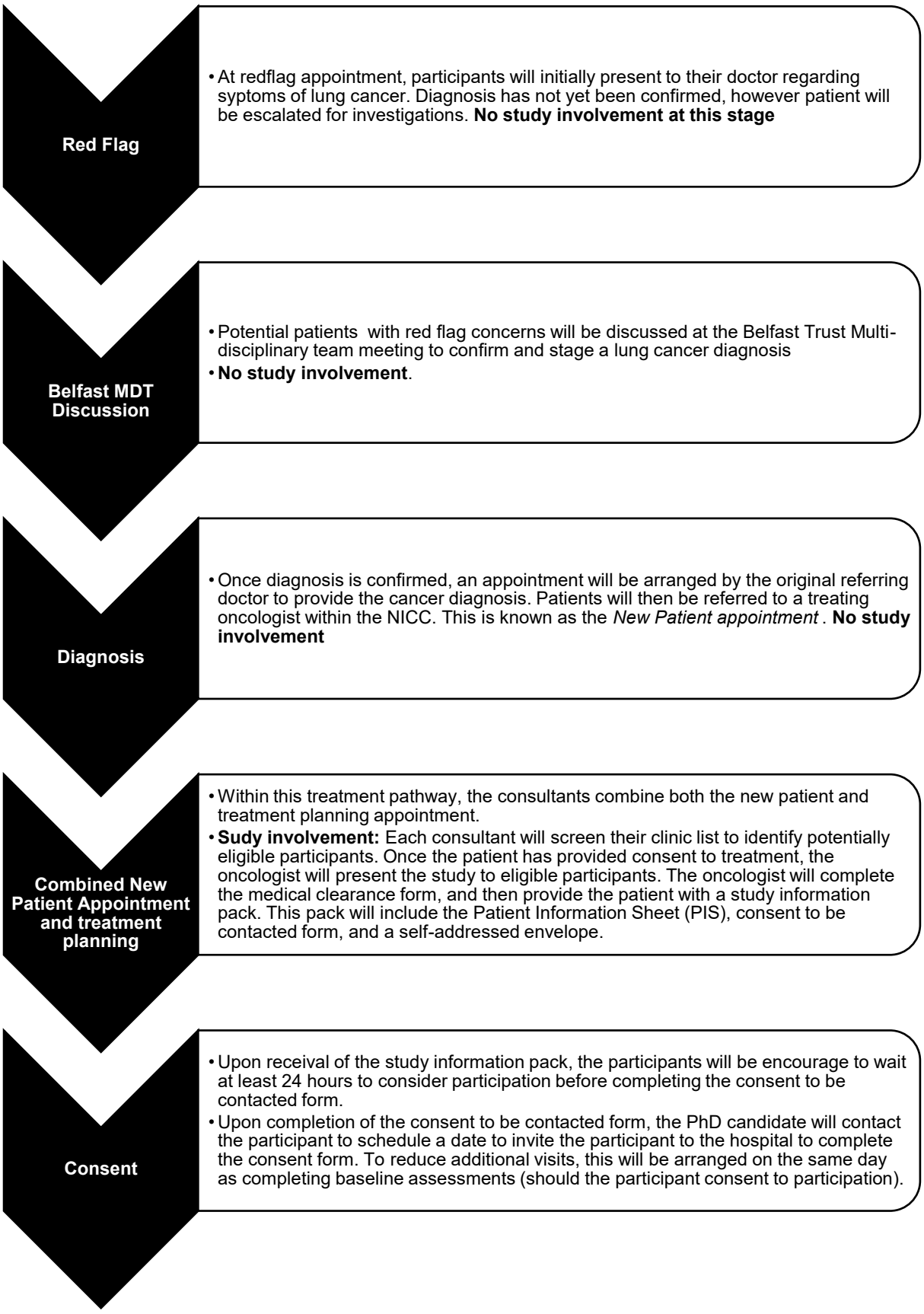


Figure 3: Screening and Recruitment Pathway 2



4.2.4.1 - Process of Screening & Eligibility

Each of the four lung cancer consultants will screen their patient list against the inclusion and exclusion criteria to determine potentially eligible participants. This is standard practice within the trust for clinical trials.

Each consultant will be assigned their own ‘screening code’ which will be pre-determined and labelled by Matthew Beggs. Each consultant will then be responsible for generating the patient's anonymous study ID. This will be achieved in the following stages:

1. On a shared OneDrive account with QUB, each consultant will be sent the following document:

    a. A screening and eligibility form (appendix 8)

**** Additionally, each consultant will be provided with a participant ID generating sheet (appendix 9). This document will be e-mailed separately, and each consultant will be asked to download this document, and to save it on their own trust OneDrive account. This document will not be shared with the research team. This is because completion of this document will contain patient details which the research team will not have permission to access before patient consent. Therefore, taking this step ensures that the research team won’t have access to any patient details before permission***.

2. When consultants screen their new patient appointment list (clinic), the consultant will complete the following steps:
    a. Document the total number of patients on the screening list.
    b. For potentially eligible participants, the consultant will be asked to input the details into the participant ID generating log (stored on trust One Drive account, not accessible by the research team. Data includes name, HSC number, and study ID). Obtaining this information is relevant as it allows the consultant to identify potential participants to approach in upcoming interviews.
    c. Finally, the consultant will be asked to complete the ‘New patient appointment’ section within the screening and eligibility form.
    d. A participant inclusion and exclusion criteria form will be provided to each consultant to accommodate screening (Appendix 56)

****Criteria for Potentially eligible participants include:***

- Person has received a diagnosis of stage 1-3 NSCLC; AND

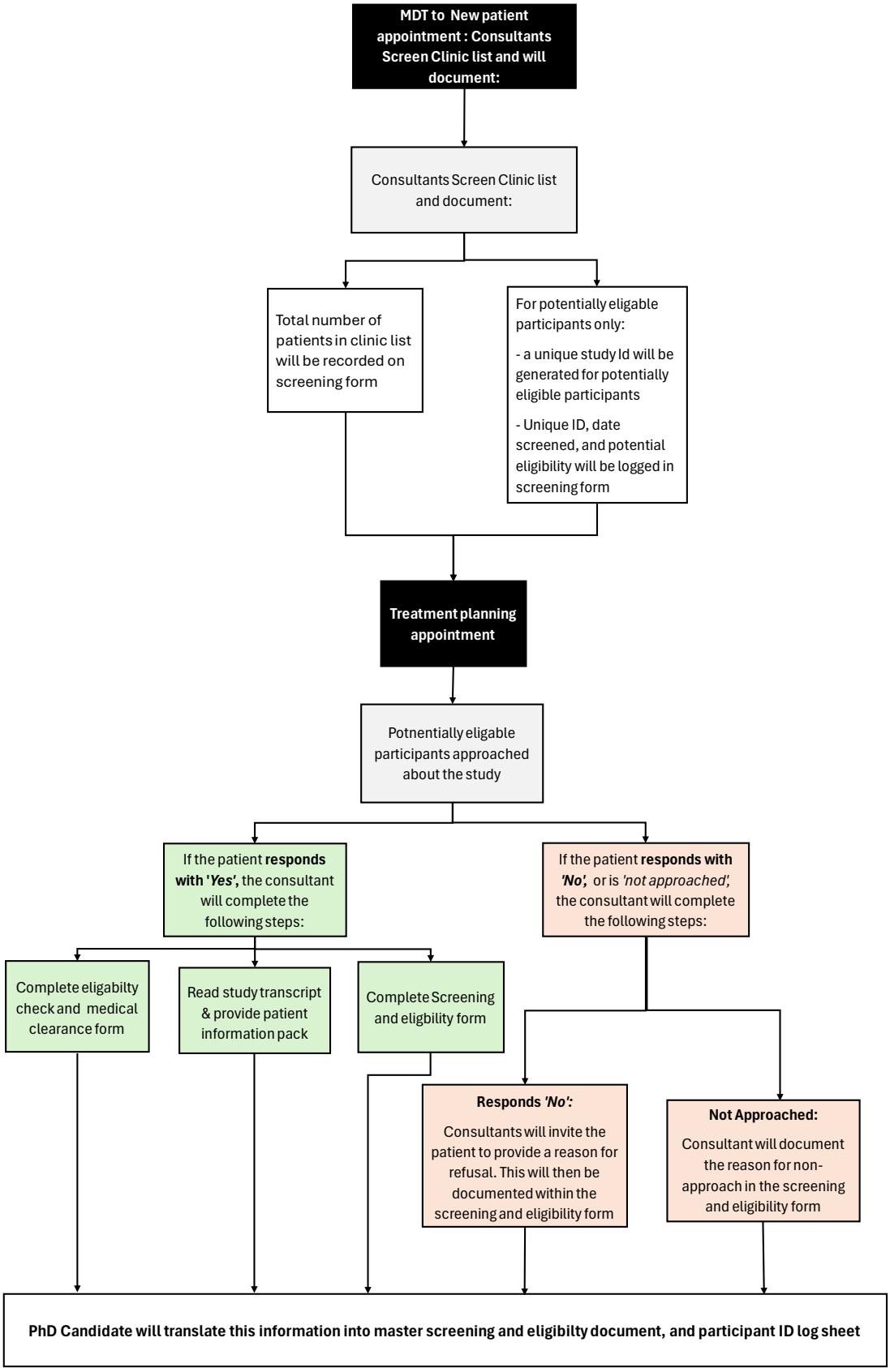
- Is planned to receive treatment with curative intention radiation as primary treatment.

3. At the treatment planning appointment, the consultant will then approach the participant regarding study involvement. If the patient says ‘Yes’, then the following process will be completed:
    a. Complete eligibility check
    b. Complete Medical clearance form for low-moderate intensity exercise and baseline testing
    c. Read study transcript.
    d. Provide patient information pack (containing patient information sheet, an infographic summarising the benefits of physical activity, a consent to be contacted form, a participant reference manual, and pre-paid envelope. This pack will be pre-prepared by the research team. Furthermore, the addition of the reference manual (Appendix 54) provides participants with more specific details regarding the trial.
    e. Update the Screening and eligibility form.
4. If the participant is ‘Not approached’ then the consultant will be asked to document the reason for non-approach in the screening and eligibility form (Patient distressed, deemed inappropriate based on patient conversations etc.)
5. If the participant ‘Is approached’ but they decline, then the consultants will be asked to invite the patient to provide a reason for why they declined (reiterating that they are under no obligation to provide a reason for their decision). This will then be documented within the screening and eligibility form.

**Recording this information is required to establish an unbiased study population and for reporting*

This process is demonstrated in the following diagram:

Figure 4: Screening and Eligibility Management Plan



4.2.1.2 - Master Screening and eligibility form for documentation within the Case Report File

From these documents, the researcher (Matthew Beggs) will translate this information into a master document which will be reported within the case report file (appendix 10). There will additionally be a master ID log sheet (appendix 37) which will be completed by the researcher (Matthew Beggs), documenting all of the participants unique codes, such as screening and enrolment codes.

This plan has been agreed has been agreed with the LC oncologists within the Belfast Trust (Dr Crockett, Dr McAleese).

4.2.5 Informed Consent

Should a participant decide to participate in the study, they first must complete the consent-to-be-contacted form (appendix 12). This will be provided within the information pack when the oncologists provide the study information pack. This additionally include a short study infographic (appendix 53) summarising five benefits of physical activity. This was implemented as a suggestion from the co-design workshops.

The consent-to-contact form may then be completed online via a QR code linked to a Microsoft form. The online Microsoft Form has been created within the security of the PhD candidates QUB Microsoft account and is QUB's preferred survey tool as it is part of the University supported Office 365 suite. This assures that the forms are covered under QUB purchased Microsoft security licenses, and QUB cyber protection policies. Furthermore, access can to response views can be restricted to only allocated members of the research team. Alternatively, participants can manually complete the consent-to-be-contacted form contained within the PIS (appendix 18) and post the form using the self-addressed envelope to the School of Nursing and Midwifery reception desk, at Queens University MBC building. From here, the PhD candidate will retrieve the sealed letter.

Participants completing the consent-to-be-contacted form, are agreeing for a nominated member of the research team to contact the potential participant to discuss enrolment, and to review their medical records to determine eligibility criteria.

Once the participant has completed the consent-to-be-contacted, the PhD candidate will contact the participant to further discuss study involvement, and to arrange a date and time to complete the consent process.

The PhD candidate taking informed consent is GCP trained, and suitably qualified and experienced. Potential participants will be given a minimum of 24 hours to consider study entry and provided with the opportunity to ask questions with the research team before informed consent (appendix 14) is obtained.

Where potential participants require further clarification about the benefits and risks of study participation this will be provided by either the research team or an independent senior physician. No study procedures will be conducted before consent. Participant information sheets have been co-designed within the PPI co-design workshops (As discussed in sections 7 and 10).

4.3 INTERVENTION

4.3.1 Study timeline

- Week 0 - Clinic visit at standard treatment planning appointment: Eligibility determined, and consent sought by treating oncologist: Participants will be provided with study information pack by their treating oncologist and advised to wait at least 24 hours to consider enrolment before contact. Should participants be interested, then they will complete the provided consent-to-be contacted form. Once completed, the PhD candidate will contact the potential participant to further discuss study participation and arrange a date to complete baseline assessments. Baseline assessments will be completed within a designated area at the radiotherapy department in the Northern Ireland Cancer Centre (NICC)
- Visit 1 – Consent, baseline assessment and physical activity support session (appendix 23) (week 0): The potential participants will meet with the PhD Candidate who will first complete the process of gaining consent. Once complete, the participant will complete baseline assessments and the physical activity support session with the PhD candidate. A full description of baseline assessments is illustrated in schedule of events figure (Table 1). During this process, the pre-radiotherapy exercise programme will be further explained, allowing the individual time to ask any question. In addition, participants will be offered general advice on how to enhance their general physical activity levels based upon the most up-to-date, evidence-based cancer exercise guidelines (Campbell et al.,2019). This will be achieved through a general discussion, and the provision of an information leaflet (appendix 25). Two additional leaflets will be provided: Fatigue management (appendix 25) and Nutritional support (appendix 26)
- Weeks 4-8 – Radiotherapy treatment commences, and the pre-radiotherapy exercise programme begins: Participants engage in a personalised, exercise programme completed immediately before each session of radiotherapy from day 1 of treatment until completion (full description provided below). On day one of treatment, participants will be invited to attend the radiotherapy centre 60 minutes before their scheduled appointment, where they will meet the PhD candidate. This is to accommodate additional time for the radiotherapy team to complete their pre-radiotherapy discussions and allow the participant additional time to ask any questions regarding the exercise programme. The participant will then be requested to attend the radiotherapy department 30 minutes before all subsequent treatments. The additional ten minutes is to accommodate extra time to discuss weekly goals and to complete a pre-exercise safety checklist (appendix 27). Participants will then proceed with a prescribed twenty-minutes of exercise, which will be coordinated with the treating radiographer to be completed as close to ‘beam on’ as possible. Participants will then proceed to their radiotherapy treatment as per standard operating procedures. Once complete, the participant will meet PhD candidate again for a de-brief and to discuss the following days’ activity. In total, each

participant will participate in 20 supervised exercise sessions with the PhD candidate over the four weeks of their radiotherapy treatment (5 sessions per week).

- ***Week 8*** – At the beginning of week 7, participants will be asked to consider taking part in a semi-structured qualitative interview (Phase 2 of the study). A participant information sheet (appendix 19) will be provided should they express interest and recommended to wait at a minimum of 24 hours before responding. Furthermore, on the last day of radiotherapy, participants will be invited to complete their post-intervention assessments. After completing their treatment, they will be provided with a voucher for the Belfast City Hospital canteen to refuel and rehydrate before completing the post-intervention assessment. After 1 hour, participants will be asked to return to the study area within the radiotherapy department to complete the post-intervention assessment **At this stage, phase 1 is now complete.*
- Week 8-14 – Participants who have completed the programme and have agreed to the qualitative interview, will be advised to wait a minimum of 4 weeks after their radiotherapy treatment completion before arranging the interview. This is to allow the participant sufficient time to recover from radiotherapy treatment. After 4 weeks, interviews can be arranged at a time or location which suits them, or at their 6–8-week post-treatment follow-up appointment (as standard practice). See section 5 for more details on Phase 2.

4.3.2 Physical activity Support Session

At the baseline assessment appointment, each participant will receive a physical activity support session delivered by the PhD candidate. This will be based on the Capability, Opportunity, and Motivation- Behaviour theory (COM-B) (Michie *et al.,* 2011), the Macmillan Physical Activity Behaviour Change (MPABC) Care Pathway (Appendix 28), and the four core principles of motivational interviewing; Expressing empathy; Understanding an individual's current behaviour and goals; identifying barriers; and self-efficacy promotion (Pinto & Ciccolo, 2011). The MPABC pathway is an evidenced-based model based on the NHS PA care pathway (Department of Health, 2012) and NICE public health guidance for behaviour change (NICE, 2014), tailored for use within cancer care (Moreton et al., 2018). As per best practice guidance, the PhD candidate will have achieved qualifications in level 4 Cancer Rehabilitation training and motivational interview training.

Details regarding the physical activity support session will be documented within the participants data collection sheet (appendix 29)

In addition, the PhD candidate will provide advice on how to remain physically active throughout their cancer journey. This will include discussing how the individual could work towards achieving the most recent recommended physical activity guidelines for people living with cancer. At the time of writing this protocol, these guidelines have been determined by the American College of Sports Medicine (ACSM), which are:

- 150 minutes of moderate intensity exercise per week

- 75 minutes of vigorous aerobic activity per week

- A combination of both moderate and vigorous activity

- Resistance training at least twice per week

- Stretching exercise before and after each session

- * If at risk of falling, co-ordination and balance exercises at least twice per week, such as tai chi or yoga

(Macmillan, 2023; Campbell *et al.,* 2019)

Recommendations will be personalised to the individual to help accommodate physical activity goals and objectives discussed within the physical activity support session.

4.3.3 The Pre-radiotherapy Exercise (PReFACe) Programme

A similar pre-radiotherapy exercise programme has been previously trialled for people with stage 3 LC receiving chemoradiotherapy (Egegaard et al., 2019). This exercise programme was adapted based on discussions within two co-design workshops with stakeholders, and an expert advisory group to create the PReFACe pre-radiotherapy exercise programme used within this study. For example, one of the main adaptions was the inclusion of different levels of intensity as opposed to one standard recommendation. This was raised and implemented to ensure that the exercise programme can be more inclusive to participants with variable baseline fitness.

PReFACe is a 4-week pre-radiotherapy exercise programme consisting of 20 exercise sessions, five days per week, performed within the BHSCT radiotherapy department immediately before treatment. All sessions will be supervised by the PhD Candidate. Participants will be invited to attend the radiotherapy department 30 minutes before their scheduled appointment to complete a pre-exercise safety screening form (10 minutes) (appendix 27). If safe to continue, participants will then engage in a 20-minute exercise session. The exercise session will consist of cycling on a stationary bike at various intensities.

The exercise programme consists of four levels of intensity ranging from the lowest intensity (level 1) to the highest intensity (level 4). Following the ECG monitored maximal fitness test (appendix 58), all participants will initially be recommended to start at the highest level of intensity based upon their baseline 6MWT (Casano et al., 2023) and frailty score (appendix 30):

Baseline Fitness parameters		**Starting level recommendations**
6MWT results	**Frailty score (Rockwood)**	
<250m	6-9	Level 1
250-400m	4-5	Level 2
>400m	0-3	Level 3 or 4

However, the participants preference will additionally be considered. For example, if a participant would like to start at a lower intensity due to low confidence, this will be accommodated. Participants can then either progress or regress through the levels of intensity based on performance and preference.

4.3.3.1 Calculating Intensity

The individuals %Heart Rate Reserve will be used to calculate intensity for each participant. This ensures that the prescribed exercise intensity will be personalised to the individuals baseline performance and capabilities.

There are three steps to calculate exercise intensity:

Step 1: Measure resting heart rate.

Step 2: Measure maximal heart rate through the ECG monitored maximal fitness test

Step 3: Use the Karvonen (Karvonen et al.,1957) formula to determine exercise intensity based upon %HRR (Heart Rate Reserve)

For example:

Resting HR = 80

Max HR of ECG monitored maximal fitness test = 160

Karvonen Calculation

'*%HRR = [HRmax – HRrest) x % required) + HR rest*'

Exercise Intensity	**%HRR**
Light	20-39%
Moderate	40-59%
Vigorous	60-84%

4.3.3.2 Monitoring Exercise Intensity

To monitor intensity, the heart rate reserve (%HRR) (Tran et al., 2022; Norton et al., 2010; Karvonen et al.,1957) and the 1-10 Modified Borg Scale (mBorg – Appendix 32) (Williams, 2017).

%HRR is a calculation used to determine exercise intensity based upon calculating the difference between your maximal and resting heart rate. %HRR can be calculated through applying a person's resting and maximal heart rate (calculated using estimate calculations, or more accurately through the results of a maximal

exercise test (ACPIR, 2023) to the Karvonen formula (Karvonen et al.,1957) to determine the target heart rate (BPM) necessary to maintain the desired exercise intensity (low-high). %HRR has been used to prescribe exercise intensities in exercise research in cancer (Viamonte *et al.,* 2023; Kirkham *et al.,* 2013) and other long term-conditions (Beale *et al.,* 2010).

Therefore, each participant will wear a heart rate monitoring device (polar hl-9 chest strap or watch equivalent) throughout all exercise sessions to monitor heart rate. This additional monitoring will ensure that the participant is exercising at the correct intensity. This will be monitored by the PhD candidate.

The MBS scale is a valid and reliable measurement tool in both healthy participants and those with co-morbidities, which provides an easily accessible method of prescribing and monitoring exercise intensities to monitor participants rate or perceived exertion (RPE) (Penko et al.,2017; Cleland et al., 2016). The advantage of the mBorg scale is that it requires no to minimal equipment and allows the individual to subjectively rate their level of exertion during exercise.

Combing mBorg with %HRR is a more accurate method to monitor exercise intensity as compared to mBorg alone as it provides additional objective parameters to monitor (BPM). Furthermore, it ensures that exercise intensities prescribed will be personalised to each individual participant.

Individuals may progress or regress from the different levels of exercise intensity based upon personal preference (if perceiving PA programme to be too easy or challenging), or on discretion from the PhD Candidate if the participant consistently fails to reach 75% adherence of the prescribed PA (failure twice per week). Attendance and adherence to the advised exercise session will be recorded within the participants data collection sheet (appendix 29) which will be retained by the PhD candidate and will document the following information:

- Weekly goals and objectives
- Weekly height, weight, and MUST score.
- Weekly Assessments including the Patient distress thermometer and Modified MRC Breathlessness-score.
- Weekly physical activity record table including:
    - Date and time of session
    - Attendance
    - Advised activity level (1,2,3 or 4)
    - Duration (start, stop, total)
    - Adherence (Achieved or modified)
    - Total distance cycled (km)
    - Comments on how the participant felt before and after the exercise session.
    - Participants comments summarising achieved weekly physical activity.
- Barriers and facilitators encountered.
- Exercise-related adverse events.

Recording information, such as total distance cycled, and weekly goals, was adopted as a motivational strategy as suggested by stakeholders within the co-design workshops.

In the event that a participant either does not attend or does not adhere to exercise, a non-attendance/adherence form (Appendix 36) will be completed with the participant by the PhD candidate. This document will record:

- Reasons for non-attendance (if applicable)
- Reasons for non-adherence (if applicable)
- Any session modifications made.
- Any other comments stated by the participant.

***Table 1**: Exercise Intensity levels*

Exercise Intensity Levels		Intensity	
		%HRR	mBorg
Level 1	1st - 10 warm-up and light intensity continuous cycling	20-39%	mBorg 2
	2nd - 10 minutes moderate intensity as continuous cycling	40-59%	mBorg 3-5
Level 2	1st – 5 warm-up and light intensity continuous cycling	20-39%	mBorg 2
	2nd - 15 minutes moderate intensity as continuous cycling	40-59%	mBorg 3-5
Level 3	1st - 5-minute warm-up as continuous cycling	20-39%	mBorg 2
	2nd - 10 minutes moderate intensity as continuous cycling	40-59%	mBorg 3-5
	3rd - 5 minutes high intensity as 30-second intervals	60-84%	mBorg 4-5

Level 4	1st - 5-minute warm-up as continuous cycling	20-39%	mBorg 2
	2nd - 5 minutes high intensity as 30-second intervals	60-84%	mBorg 4-5
	3rd - 5-minute moderate intensity as continuous cycling	40-59%	mBorg 3-5
	4th - 5 minutes high intensity as 30-second intervals	60-84%	mBorg 4-5

4.3.4 Screening and assessment to approve exercise intensity.

Each participant will be screened by their treating oncologist for medical clearance using a medical clearance form (Appendix 6). To achieve this, the consultants will screen for the following:

1. The patient is deemed medically clear to participate in light-to-moderate intensity exercise as detailed in the pre-radiotherapy exercise program and undergo pre/post fitness testing (6MWT, 30-second sit to stand).
2. The patient is suitable to undergo pre-intervention exercise stress testing to determine suitability for short-duration, high-intensity exercise as documented within the exercise program.
3. Exercise stress testing has been completed and reviewed, and the participant is deemed medically clear to undergo short-duration, high intensity exercise as detailed within the pre-radiotherapy exercise program.
4. The patient has completed all pre-radiotherapy pulmonary, and haematological assessments (as per standard care pathway) and is deemed suitable to proceed with conventionally fractionated radiotherapy.

4.3.4.1 ECG Monitored Maximal Fitness test.

The maximal exercise test, incorporating continuous ECG monitoring, will be conducted within the Northern Ireland Cancer Research Facility (NICRF) at Belfast City Hospital (BCH). All procedures will be performed and interpreted by trained staff under direct medical supervision.

The testing protocol is based on the original methodology described by Andersen *et al.* (1995) and is modified in alignment with protocols validated in previous studies involving individuals with non-small cell lung cancer (NSCLC) and other clinical populations (Egegaard et al., 2019; Moller et al., 2015; Løppenthin et al., 2014).

Participants will complete an incremental maximal test on a stationary cycle ergometer, with a total expected duration of 5–8 minutes. Each session commences with estimation of maximal heart rate (HRmax) (Fox *et al.,*1971), followed by a four-minute pre-test warm-up to determine the initial cycling workload (20–80 watts) and incremental load increases (5–20 watts per minute). After an initial rest period (1-2 minutes), the test begins with cycling intensity escalating in one minute increments until one of the termination criteria are met (Appendix). Throughout, heart rate (HR), blood pressure (BP), rate of perceived exertion (RPE), and ECG are monitored and recorded every minute.

Upon test completion, participants follow a five-minute, structured recovery phase with ECG, BP, HR, RPE, and relevant symptom monitoring. This procedure is consistent with published protocols (Egegaard et al., 2019; Moller et al., 2015; Løppenthin et al., 2014) and complies with current guidelines for maximal exercise testing, including recommendations from the American College of Sports Medicine (ACSM, 2025) and the Society for Cardiac Science and Technology (SCST, 2023) (see Appendix).

A qualified exercise physiologist will provide real-time ECG monitoring; any evidence of contraindication will result in participant study exclusion and referral to their treating oncologist for further assessment. Gas analysis will not be performed, as these outcomes do not align with the study aims and would increase participant burden unnecessarily. Test results will be used to objectively determine maximal heart rate for individualised exercise prescription and to identify any contraindications to high-intensity physical activity.

The protocol for this test is provided as an in appendix (58)

4.4 Data collection and management

4.4.1 Feasibility Measures

The primary outcome of this study is to determine the feasibility of delivering the pre-radiotherapy exercise programme. This will be achieved by measuring recruitment rates including decision statements documented within the master screening log (Appendix 37). Throughout the programme attendance will be calculated through recording the number of attended sessions by the total number advised. Adherence will be calculated through monitoring the participants ability to complete the advised exercise duration and intensity of each session. Acceptable adherence will be determined as completing 75% of the exercise session. Retention will be measured by calculating the total number of participants available to provide outcomes at the intervention end. This information will be recorded on a data collection form (Appendix 29).

Finally, the occurrence of adverse events will be monitored using CTCAE v5.0 (National Institute Health, 2017) (Appendix 1) to determine intervention safety.

CTCAE v5 will be used to monitor any skeletal-related events, pain, and other undesirable symptoms as a direct result of the intervention each PA session.

4.4.2 Secondary Measures

Secondary outcome measures will be assessed for the principal reason of testing the ability to undertake and complete measures, and not to detect differences from baseline or determine effect. This is due the small and unpowered sample size. However, secondary outcomes will be analysed identify any initial signals of efficacy, however, these outcomes will be defined as exploratory.

Baseline characteristics such as age, gender, diagnosis, co-morbidities, and previous exercise experience will be collected. Furthermore, reasons for inclusion will be documented in the screening log (Appendix 38). This information will be analysed to identify any potential factors which may contribute towards study participation and retention. Additional secondary outcomes will include quality of life (QoL) scales, physical fitness and activity levels, anthropometric measurements, and symptom monitoring. The schedule for enrolment, administration of interventions and assessment of outcomes (including those for phase 2 and 3) can be seen in Fig. 1.

A full explanation of secondary measures is provided below.

Physical fitness

Physical fitness will be assessed at baseline and week 14 using the 30-second sit-to-stand test (30 STS) (Appendix 11) and 6-minute walking test (6MWT) (Casano *et al.,* 2023). The number of repetitions will be recorded during the sit-to-stand test, while the distance covered in the six-minute walking test will determine aerobic fitness. Both the 6MWT and 30 STS are validated, standardised tests used to measure physical function in people living with chronic conditions (Harlod *et al.,* 2023; Balachandran *et al.,* 2021).

In addition, the participant's frailty score will be calculated using the Clinical Frailty Scale (CFS) (Rockwood et al., 2005 (Appendix 30). The CFS is used as a valid assessment tool for screening frailty in older adults (Moreno-Arino et al., 2020; Rockwood et al., 2005), although its validity for use in assessing frailty in cancer patients remains an active area of research, despite its frequent use in cancer care in countries such as Canada and the United Kingdom (Church et al.,2020; Tivey et al., 2020). However, within the context of this study, the CFS will be used alongside the 6MWT results, as a method of prescribing the participant with appropriate exercise intensities.

Physical Activity levels

The International Physical Activity Questionnaire – Short Form (IPAQ-SF) (Craig *et al.,* 2003) (Appendix 39) will be used as a self-report measure of physical activity to estimate physical activity levels both at baseline and post-exercise. However, the IPAQ-SF has been criticised for providing and over-estimation of physical activity when compared to objective measures, such as an accelerometer (Lee *et al.,* 2011). To improve the reliability of interpreting physical activity, it is recommended to

combine patient-reported outcome measures (such as IPAQ-SF) with objective monitoring, such as an accelerometer, for seven days (Lee et al., 2011). However, considering the timeframe of this study, due to the nature of radiotherapy scheduling, collecting objective measurements before baseline assessments will not be feasible. It is expected that individuals will receive a date to commence their treatment within 21-28 days after their treatment planning appointment, however this time may vary. It is important to this study that baseline assessments are completed before treatment commences, which will be within the variable 21-28 day waiting period. Therefore, delaying baseline assessment for 1-week may increase the risk of interfering with standard care. Therefore, in this instance, combining the IPAQ-SF with one week accelerometer would not be appropriate. Therefore, data from the IPAQ-SF will be used to explore the influence of the pre-radiotherapy exercise programme on the participant's weekly physical activity levels pre- and post-study.

Additionally, the Huffman's Exercise Satisfactions Scale (Huffman *et al.,* 2021) (Appendix 42) will be completed at baseline, week 8 and week 14 to understand the potential changes in the participants enjoyment and satisfaction of their current physical activity levels throughout the programme. The Huffman Exercise Satisfaction Scale was developed with stakeholders as a novel approach to measure older adults (aged ≥55 years) satisfaction with their physical activity levels. Although this scale has not yet been validated for use in cancer care, there is evidence which suggests it's suitability for use amongst adults aged ≥55 years (Huffman *et al.,* 2021). According to the Northern Ireland Cancer Registry (NICR), the most recent statistics (2018-2022) suggest the median age for a lung cancer diagnosis is 73 years, with 5.6% of patients being diagnosed aged ≤54 years (NICR, 2024). Therefore, the Huffman exercise satisfaction scale will be a sufficient measurement scale for the majority of participants eligible for this study.

Anthropological Measurements

Participant's height and weight will be measured to calculate the participants Malnutrition Universal Screening Tool (MUST) score (Appendix 33). MUST scores will be calculated at the baseline assessment, at weekly intervals throughout the exercise programme, and at the 14-week post-intervention assessment. This will be taken as a safety measure to ensure the participant does not lose excess weight throughout the PA programme. Excess weight loss will be determined by MUST as <5%, 5-10%, and >10% unplanned weight loss.

In the instance that a participant is experiencing greater than 5% unplanned weight loss over the 4 weeks of the pre-radiotherapy exercise programme, then participation will be stopped, and the participant will be immediately referred to their lung cancer specialist radiographer for assessment. The participant will only be allowed to continue with the exercise session when approved by either the lung cancer specialist radiographer, dietician, or by their treating oncologist.

Furthermore, the participants' resting blood pressure and resting heart rate will be recorded at baseline, before each exercise session, and at 14-week post-intervention follow-up.

Quality of Life

At baseline (week 0) and immediately post-intervention follow-up (week 8), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30 with LC13) (Aaronson *et al.,* 1993) questionnaire will be completed. EORTC QLQ-30 (Appendix 40) with LC13 (Appendix 41) is a reliable and validated, multidimensional quality-of-life questionnaire which is widely used in research for people with lung cancer (Hirckock *et al.,* 2024; Koller *et al.,* 2022).

Furthermore, participants will complete the National Comprehensive Cancer Network (NCCN) Distress thermometer (Riba, 2023) (Appendix 35) at baseline (week 0), weekly throughout the PReFACe pre-radiotherapy exercise programme (Weeks 4-8) and at post-intervention follow-up (week 14). The distress thermometer is a valid, and accurate screening tool used to quickly monitor for patient's distress with advanced cancer (Graham-Wisner *et al.,* 2021). In the event that the participant shows signs of worsening distress, they will be referred to their lung cancer specialist nurse for further support. In the instance that a participant experiences extreme distress (≤ 8), then the PhD candidate will stop the exercise session and immediately escalate to either the lung cancer specialist radiographer, their registrar, or on-call registrar (depending on who's available. The distress thermometer will be monitored as part of the daily and weekly, PReFACe data collection sheet (Appendix 29)

Symptoms

At week one, weekly throughout the pre-radiotherapy exercise programme (weeks 4-8), and at the post-intervention assessment (week 14), the modified Medical Research Council dyspnoea score (Appendix 34), pain score (1-10 Likert) (Appendix 31), and fatigue (1-10 Likert) (Appendix 31), will be monitored. All information will be documented within the daily and weekly, PReFACe data collection sheet (Appendix 29)

The schedule for enrolment, administration of interventions and assessment of outcomes (including those for phase 2 can be seen in Fig 2 and 3).

4.5 Data Analysis

4.5.1 Primary Outcome

Feasibility outcomes will be collected on all participants screened and enrolled onto the study. This will include:

- The number of potentially eligible participants screened,
- Those approached and enrolled into the study.
- Those who declined participation with reasons for non-participation.

This data will be recorded and documented on screening logs (Appendix 38). This data will be examined and descriptive analysis carried out to identify any differences between participants and non-participants.

Attendance, adherence, and retention rates for planned PA sessions will be recorded within the participant data collection sheet (appendix 29). These records will undergo descriptive analysis.

4.5.2 Secondary Outcomes

Due to the relatively small numbers and a lack of power calculation, statistically significance cannot be determined. However, it may be possible to identify meaningful changes which would warrant further investigation in future studies to confirm findings in powered samples. Therefore, quantitative data will be analysed using descriptive statistics including, measures of central tendency (mean, median, mode), variability (range and standard deviation) and frequency and percentages for categorical measures. This data will be analysed using the Statistical Package for the Social Sciences (SPSS v 24). Regarding the QOL measures, the change scores for the EORTC QLQ-30 (Appendix 40) with LC-13 (Appendix 41) questionnaire can be calculated for each participant and categorised according to pre-established minimally important differences (MIDs).

5.0 Phase 2: Qualitative Evaluation

5.1 Objectives

1. To explore the perceptions and experience of phase 1 participants taking part in the pre-radiotherapy exercise programme.
2. To explore the perceptions and experience of a nominated person (friend or family) of phase 1 participants who completed the pre-radiotherapy exercise programme.
3. To explore the perceptions of people who withdrew from the pre-radiotherapy exercise programme.
4. To explore the perceptions and experiences of clinicians, other healthcare professionals exposed to the intervention.

5.2 Eligibility

Phase 1 participants, a nominated person (participants friend of family member), participants who decided to withdraw from the programme, and HCPs who had exposure to the PReFACe intervention will be eligible and invited to participate in Phase 2 qualitative interviews. Additionally, those who declined participation will be invited to provide a statement for non-participation.

5.2.1 Phase 1 Participant Eligibility

Eligibility criteria for participants include:

- Can provide written informed consent and complete an interview conducted in English.
- Has either completed or partially participated in Phase 1

5.2.2 Nominated Person Eligibility

Eligibility criteria for nominated person include:

- Aged 18 and over
- Can provide written informed consent and complete an interview conducted in English.
- Is a nominated person by Phase 1 participant (friend or family) who has completed the Pre-radiotherapy exercise programme.
- Has spent time with phase 1 participant for a minimum of twice per week throughout the duration of the PReFACe pre-radiotherapy exercise programme. For example, the person has spent time with them in person either at home, in the community, or attending radiotherapy appointments.

5.2.3 HCP Eligibility

Eligibility criteria for HCP's include:

- Can provide written informed consent and complete an interview conducted in English.
- A member of the lung multidisciplinary healthcare team (including but not limited: to nurses, healthcare support workers, doctors, dietitians, social workers and counsellors) who:
    - Has had exposure to the intervention.
    - Has worked within either within radiotherapy department, or has been involved in the prescription, management, or administration of conventionally fractionated radiotherapy for people with stage 1-3 lung cancer for more than 2 months.

5.3 Recruitment and Consent

All participants will be recruited through methods of convenience sampling (Bruce *et al.,* 2024). The PhD candidate will approach all participants in phase 2 with the exception of nominated persons (further details provided below). All participants will be consented and interviews conducted by the PhD candidate.

5.3.1 Phase 1 Participants

The PhD candidate will approach phase 1 participants who have completed or withdrawn from Phase 1. Participants will be approached at the beginning of their final week of the pre-radiotherapy exercise programme (week 8). Participants who withdraw will be approached and invited by the PhD candidate at the time of withdrawal.

The PhD candidate will discuss involvement through the reading of a standardised script (Appendix 44). The participants will then be given a PIS (Appendix 19) providing further details on the qualitative interview process and contact details for the research team. The participant will then be asked to consider involvement for a minimum of 24 hours before agreeing to participate. The participant can then either

speak with the PhD candidate to confirm or decline Phase 2 participation either in person at one of the PReFACe exercise sessions, or via the contact details provided in the PIS.

If the participant agrees to Phase 2, a time, date, and location will be discussed which is most convenient for the participant. All participants will be encouraged to wait for a minimum of 4 weeks after their final session or radiotherapy before conducting the qualitative interview to allow sufficient time to recover from treatment.

Consent (Appendix 15) will then be obtained by the PhD candidate immediately before the qualitative interview takes place. The participant will not be asked any questions in relation to the interview until consent has been signed.

5.3.2 Nominated Person

Phase 1 participants will be approached by the PhD candidate at the beginning of their third week of the pre-radiotherapy exercise programme (week 7). Phase 1 participants will be asked to consider inviting a nominated person (friend or family member) for qualitative interview. If in agreement, then the phase 1 will be provided with a nominated persons form (Appendix 45), which explains the inclusion criteria. The phase 1 participant will also be provided with PIS (Appendix 21), consent to be contacted form (Appendix 13), and a self-addressed envelope to give to their nominated person. Within the PIS, the nominated person will be advised to consider involvement for a minimum of 24 hours before agreeing to participate.

Should the nominated person be interested, they can complete the consent-to-be contacted form provided (process as detailed in section 3.3.3). If the nominated person agrees to Phase 2, a time, date, and location will be discussed with the PhD candidate at a time which is most convenient for them. Qualitative interviews with nominated persons can be conducted at any point (weeks 9-14) after the phase 1 participant has completed their radiotherapy treatment.

Consent (Appendix 16) will then be obtained by the PhD candidate immediately before the qualitative interview takes place. The nominated person will not be asked any questions in relation to the interview until consent has been signed.

5.3.3 HCP

HCP who meet the eligibility criteria (Section 4.2.4) will be approached by the PhD candidate. The PhD candidate will first ask if the HCP would be interested in completing a qualitative interview. If in agreement, the PhD candidate provide the HCP with an information pack containing a PIS (Appendix 22), consent-to-be-contacted form (Appendix 13), and a self-addressed envelope. The HCP will be advised to read through the PIS and to consider involvement for a minimum of 24 hours before contacting the research team. The HCP can either approach the PhD candidate in person (if working within the radiotherapy department) or complete the consent-to-be-contacted form (as detailed in section 3.3.3).

If the HCP agrees to Phase 2, a time, date, and location will be discussed with the PhD candidate at a time which is most convenient for them. Qualitative interviews with HCP can be conducted at any point providing that they meet the eligibility criteria (Section 4.2.4).

Consent (Appendix 17) will then be obtained by the PhD candidate immediately before the qualitative interview takes place. The HCP will not be asked any questions in relation to the interview until consent has been signed.

5.4 Data Collection

All qualitative interviews will be semi-structured. Based upon Braun and Clarke (2019) approach to determining sample size for qualitative interviews, 5 interviewees per group (phase 1 participants, nominated persons, and HCP) should be a practical and sufficient to capture perceptions and experiences an achieve data saturation (*n=15).* This additionally is inconsideration of the time and resource constraints of the research team, and the total sample size of the feasibility study.

All interviews can either be conducted either face-to-face at a convenient time and location of the participants choosing, or online via a video call (Microsoft Teams) depending on the individual's preferences and personal circumstances. The interview will be guided by interview schedules specifically tailored to each group (Appendix 46). All questions will be open-ended to explore and understand the experience and acceptability of the PReFACe programme from the unique perspective of the group. To elaborate:

- Interview schedules for Phase 1 participants will focus on the perspective of participating within programme and the appropriateness of the assessments used.
- Interview schedule for nominate person(s) will focus on the perspective of observing the Phase 1 participant engaging in PReFACe programme.
- Interview schedules for HCP's will focus on the perspective of how they feel their patients managed the programme, and how the exercise programme was incorporated within the radiotherapy department.

Furthermore, all participants will be asked open-ended questions regarding the potential utility of the programme and to suggest any areas of modification to improve the participants experience and study design.

All interview schedules were formulated using Kallio *et al.,* (2016) five-step framework for developing qualitative semi-structured interview guides. In accordance with this framework, the PhD candidate drafted each topic guide based the candidate's previous knowledge and experience of the topic, and the aims and objectives of phase 2 qualitative research. Each schedule consists of two levels of questions:

1, Main themes – open-ended questions which encourage the individual to talk freely about their perception and experience on a subject

2, Follow-up questions – either pre-determined or improvised questions to help the research direct the conversation towards the study subject. Creating follow-up questions ensure that the researcher maintains interview flow and ensure that optimal information is extracted from the interview, without it becoming too precise.

Once initially drafted, the PhD candidate conducted an internal pilot testing with appropriate members of the researcher steering group to refine and improve the interview schedule. This stage was conducted to ensure questions are coherent and relevant to ensure high-quality data is extracted. Final refinements then made up the interview schedules used within Phase 2: Qualitative interviews (Appendices 46)

Regarding all interviews (or any other study procedures), if an interviewee becomes upset or distressed, a distress protocol will be followed (Appendix 47). Furthermore, the PhD candidate will adhere to a lone worker policy in the instances of domiciliary interviews (Appendix 48).

5.5 Data Analysis

Data from interviews will be audio-recorded and transcribed verbatim. Transcriptions of audio recorded interviews will be analysed using reflexive thematic analysis (RTA) (Braun & Clarke, 2020). Braun and Clarke (2020) provide a 6-step process to data analysis, which includes Data familiarization; code generation; theme searching; themes review; defining themes; report production (Bryne, 2021; Braun & Clarke, 2020). Although this process is reported as a logical sequence, data analysis is not a sequential process (Bryne, 2022; Braun & Clarke, 2020). Instead, RTA is described as a flexible, iterative process, where the researcher will move back and forth between each step to revise and regroup codes and themes to answer the research question. Data will be uploaded to Nvivo 12 software (Lumivero, 2024) to assist with data coding and management, and provide an audit trail. Data interpretations will then be verified with the researcher’s supervisory team.

5.6 Rigor

To ensure rigor in the conduct and analysis of qualitative interviews, the researcher will engage in reflexivity. This will be achieved through documentation of key decisions throughout data collection and analysis, and reflection upon interview performance and presentation, acknowledging their conduct may influence participant disclosure.

Additionally, the researcher will retain and update a field diary throughout the interview conduct. Within the field diary, verbal and non-verbal observations will be recorded immediately post-interview to document subtleties that may not be picked up via audio recorder e.g. mood, emotion, body language. This field diary will be used to aid data interpretation and analysis.

6.0 Schedule of events

6.1 Phase 1

A pre- and post- enrolment phase will be incorporated into the study period. This stage will include the process of eligibility screening, recruitment and consent, and will take place during the process screening and recruitment (Section 3.3).

Week 0 beings the week after participants have received their treatment planning appointment and begin the 21-28 day wait to start radiotherapy. Within this 21–28-day waiting period (weeks 0-3), participants will be consented to the study, complete their baseline assessments, and complete their physical activity support session.

Week 4 begins on the first day of the participants radiotherapy treatment. On this day participants will receive their first pre-radiotherapy exercise session as part of the PReFACe study. All exercise sessions as part of PReFACe will align with the participants radiotherapy treatment schedule i.e. 5 days a week for 4 weeks. Therefore, each participant will receive a total of 20 exercise sessions (5 days per week for 4 weeks) and will only be performed on days when the individual receives radiotherapy. This constitutes weeks 4-8 of the study period.

On the last day of their radiotherapy treatment (end of week 8), participants will additionally complete their post-intervention assessments. After radiotherapy, participants will be provided with a canteen voucher and allocated 1 hour to refuel and rehydrate before completing post-intervention assessments. After completion of the post-intervention assessment, this concludes phase 1.

6.2 Phase 2

Phase 2 will initiate at different time points depending on the individual being interviews. A full description is provided in section 5 and is illustrated in table 1.

Table 2: *Schedule of Events*

	Study Period						
			Phase 1 - Exercise Trial			**Phase 2 Qualitative Evaluation**	**End of Study**
TIMEPOINT**	**Pre-Enrolment**	**Post- Enrolment**	**Baseline assessment (Week 0-4)**	***PReFACe* Programme and radiotherapy begins (Week 4-8) [1]**	***PReFace* and radiotherapy Programme ends and post-intervention assessment (Week 8) [2]**	**6-8 week follow-up period (week 8-14) [3]**	**Close Out**
ENROLMENT							
Eligibility screen	X						
Informed consent [4]	X						
GP Letter		X					
INTERVENTIONS							
Four-week PReFACe Exercise Programme				←	→		
Physical activity support session			X				
Signpost to additional services						X	
ASSESSMENTS							
Baseline Characteristics: *Age, gender, diagnosis, co-morbidities*		X					
ECOG Performance Status		X			X		
Medical Clearance to exercise		X					
ECG maximal exercise Test		X					
PHASE 1: PReFACe pre-radiotherapy exercise Programme							

Recruitment rates		X					
Attendance rate				←	→		
Adherence rates				←	→		
Anthropological Measurements: *Height, weight, resting blood pressure, resting heart rate* [5]			X	←	→		
MUST Score			X	←	→		
Six minute walking test			X		X		
30 second sit-to-stand			X		X		
MRC Dyspnoea			X	←	→		
Rockwood Frailty			X		X		
NCCN Distress Thermometer			X	←	→		
International Physical Activity Questionnaire (Short form)			X		X		
EORTC QLQ-30 with LC13			X		X		
Fatigue (Likert 1-10)			X	←	→		
Pain score (Likert 1-10)			X	←	→		
Huffman exercise satisfaction score			X		X		
Adverse Event Report							
Baseline adverse event recording			X				
Intervention-associated adverse events assessments				←	→		
Phase 2: Qualitative Research							
Statement for non-participation	X						
Semi-structured qualitative interview with phase1 participants [6]					←	→	

Semi-structured qualitative interview with nominated person [7]							
Semi-structured qualitative interview with HCP [8]							
Semi-structured qualitative interview with phase 1 participants who withdrew[9]							

1, On the last day of radiotherapy, participants will received a 6-8 week break. Participants will then be followed up by their oncologist to ensure that they are recovering well from treatment.
2-3, The PReFACe exercise programme will align with the participants radiotherapy treatment schedule i.e. five days a week for 4 weeks. The PA programme will only be performed on days where the individual is receiving radiotherapy.
4, Participants will be screened for eligibility by their treating consultant or Lung cancer Nurse specialist at MDT. The if eligible, the consultants will read a standardised script regarding study participation, and provide the individual with an information pack. Within the pack will include the patient information sheet, a consent to be contacted form, and a self-addressed envelope. Should participants agree to contact, the research team will contact the participant and invite them to the radiotherapy center to complete consent and baseline assessment on the same day. Informed consent and baseline assessment will be completed within 1 week of the participants first contact.
5, Anthropological Measurements will be performed at baseline assessment, weekly throughout the PReFACe PA programme, and at post-intervention assessment.
6, Semi-structured interviews will be performed during the 6-8 week follow-up period either in person at the 6-8week routine post-treatment follow-up assessment; on a separate occasion at a time/place more suitable for the participant (in-person); or online via Microsoft team (if convenient). Participants will be advised to wait a minimum of 4 weeks after the final date of treatment before scheduling the interview.
7, Semi-structured interviews will be completed by a nominated friend or family member. Separate written consent from the friend/family member will be completed before the interview. The interview will be conducted on a separate occasion at a time/place more suitable for the participant (in-person); or online via Microsoft team (if convenient)
8, Semi-structured interview with HCP will be performed at any convenient point after 3 months from the study opening. HCP will be eligible if they are involved in the administration, management, organisation, or facilitation of the participants radiotherapy treatment. A separate consent form will be completed. The interview will be conducted within the radiotherapy center at the Northern Ireland Cancer Centre.
9, Interviews will be conducted when available. The interview will be conducted on a separate occasion at a time/place more suitable for the participant (in-person); or online via Microsoft team (if convenient)

7.0 Plans to ensure optimal recruitment and minimise attrition.

Conservative assumptions regarding recruitment have been made with a target recruitment of 3-4 participants per month (out of a possible 8-10 patients per month). This should be achievable based upon the perspective of HCPs within the lung MDT, and on the 44% recruitment rate of the only pre-radiotherapy exercise study for people receiving chemo-radiotherapy for advanced lung cancer (Egegaard *et al.,* 2019).

According to the MRC Framework for Complex Interventions (Skivington *et al.,* 2021), it is necessary to prioritise meaningful engagement with key stakeholders throughout all stages of research to ensure the most optimal intervention is developed, and to overcome any potential barriers or obstacles. Potential stakeholders range those who may be personally or professionally interested, or affected by the research (Skivington *et al.*, 2021). Therefore, in accordance with this core principle, the PhD candidate has hosted two, iterative co-design workshops under PPI, and hosted multiple meetings (minimum of 3 each) with multiple healthcare professionals as part of the lung MDT at the NICC. These included:

PPI

- Four family members of someone who has received a lung cancer diagnosis.
- Two people who are currently receiving lung cancer treatment.
- One person who has completed lung cancer treatment.

Lung MDT:

- Two lung cancer oncologists (Dr Crockett and Dr McAleese)
- Two lung cancer specialist nurses (Chloe Givin and Stephanie Todd)
- One lung cancer specialist radiologist (Linda Young)
- Two research and development radiographers

Additional, unofficial meetings:

- Radiotherapy Department manager (Joanne McCarthy)
- Lead Physiotherapist (Sarah Taggart)

Through running the co-design PPI workshops and regularly meeting the members of the lung MDT in the planning process, the design of this research and its recruitment has been designed to minimise attrition. To elaborate, using PPI involvement allowed the PhD candidate to discuss issues such as barriers to physical activity; how and when to best approach potential participants; optimal screening methods; potential barriers to recruitment etc. Furthermore, early involvement from the lung MDT not only confirms willingness and capacity to support the study, but provides key information that ensures the intervention can be incorporated as part of the standard care pathway, minimising any additional burdens on participants as possible, such as additional hospital visits.

Additionally, to minimise attrition and assure safety, all exercise sessions will be supervised by the PhD candidate. Furthermore, the research team will work with the lead research and development radiologist to align exercise sessions with their scheduled radiotherapy plan. Finally, although the optimal exercise prescription for people with lung cancer is not known, it is important to incorporate successful methods used in other cancer cohorts (Toohey *et al.,* 2024). These include the prescription of a personalised exercise intervention which incorporates participant-led goals and designed in consideration of the individual needs and characteristics (Kilari *et al.,* 2016; Sasso *et al.,* 2015).

Finally, a trials management group (TMG) (Appendix 49) will be established who will meet on a monthly basis throughout the study period to discuss any arising issues, such as low recruitment. All TMG meetings will be recorded on a TMG Report form (Appendix 57).

8.0 Adverse Events

8.1 Definition

An adverse event can be defined as*:* any unfavourable or unintended medical occurrence in participants in the use or receival of a drug, medical product, or intervention which may or may not be caused by the intervention itself.

Within the context of this study, adverse events will only be collected in relation to the pre-radiotherapy exercise. To measure this, baseline health status will be measured before the pre-radiotherapy exercise programme begins. This will allow the research team to document the participant's pre-existing health status to help identify the cause of any new presenting adverse events which may be related to the intervention. For example, is the adverse event related to a pre-existing condition; to radiotherapy treatment; or related to exercise. This process is necessary as adverse events will only be collected if they are in relation to either of the pre-radiotherapy exercise programmes, or fitness testing.

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE) (Appendix 1). All Adverse events will be monitored on an Adverse event monitoring form (Appendix 2).

.

8.1.1 Potential Expected Adverse Event

Intervention related adverse events that would be expected from the pre-radiotherapy exercise programme and fitness testing include:

- Myalgia
- Fatigue
- Muscle or joint injury
- Muscle cramping or strain
- Arrhythmia
- Myocardial infarction
- Blood pressure abnormalities
- Syncope
- Dizziness

- Nausea
- Other cardiovascular events

8.1.2 Unexpected Adverse Event

Intervention-related adverse events not included in the above list will be considered unexpected adverse events.

8.1.3 Serious Adverse Event

A serious adverse event (SAE) is an adverse event that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation (excluding hospital admissions for transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

8.1.4 Potential Expected Serious Adverse Event

Adverse events that would be expected from the study intervention and fitness testing that may result in a serious adverse event include:

- Arrhythmia
- Myocardial infarction
- Syncope
- Other cardiovascular events

8.1.5 Unexpected Serious Adverse Event

Serious adverse events not included in the above list will be considered unexpected serious adverse events.

8.2 Adverse Event Recording and Reporting

8.2.1 Recording and reporting non-serious adverse events

Participants enrolled in the study will be reviewed as per standard-of-care treatment guidelines and their adverse events and current medical history will be updated in the medical records by the treating clinical team. It is expected the majority of events recorded will relate to their radiotherapy treatment, but the clinical team routinely record unrelated events or symptoms that have occurred at planned clinic visits or at unscheduled attendances. To elaborate, throughout radiotherapy, patients are reviewed by a specialist lung cancer radiologist as part of routine care at weeks 3 and 4. However, study participants will additionally be reviewed by the specialist on weeks 1 and 2, documenting any potentially related, or unrelated AE's within their medical record.

The PhD candidate will review the medical records after each scheduled clinic visit to capture any AEs that could be related to the fitness testing or intervention or to radiotherapy and determine whether these were probably or definitely related.

Adverse events related to the exercise programme or fitness testing will also be monitored by the PhD Candidate. The PhD Candidate will assess, monitor, and document information about adverse events during all contact with participants and modify the intervention or fitness testing appropriately. Potentially related adverse events (that are not classed as serious events) will be recorded on the Case Report Form (CRF) (Appendix 10) and in the patient's medical notes, but do not need to be reported by the PhD candidate to the clinical team as participants will be able to self-report these events at their regularly scheduled follow up visits, or to their treating radiographer as required. Any grade 2 adverse events or greater will be reported to the site's Principal Investigator (PI) to determine relatedness to the intervention. Finally, a trials management group will meet monthly to discuss all adverse events to determine relatedness.

8.2.2 Recording and reporting of Serious Adverse Events

The PhD candidate will be provided with a list of serious events (as defined below). If a participant experiences any of these events during contact, or if the PhD candidate becomes concerned regarding the participant's health, then PhD Candidate will escalate the situation immediately via one of the following pathways:

1. Escalation to the specialist lung cancer radiologist within the radiotherapy department
2. Immediate contact with the on-call doctor/registrar within the radiotherapy department
3. Contact with the acute oncology helpline for ongoing management as per standard-of-care guidelines and practice.

The PhD candidate will also report these events within 24 hours of becoming aware of the event to the patient's treating clinical team if they occur.

The list of reportable serious events is defined as:

- Arrhythmia
- Myocardial infarction
- Syncope
- Other cardiovascular events
- Any other event that results in hospitalisation

The PhD candidate is also expected to report these events within 24 hours of becoming aware of the event to the site principal investigator, record the event in the CRF (Appendix 10) and patient's medical notes, and complete a preliminary SAE report form (Appendix 50). The PI will urgently review the SAE for expectedness, relatedness and severity within 24 hours of becoming aware of the event.

All serious adverse events which are unexpected and related (probably or definitely) to the protocol interventions (fitness testing and/or pre-radiotherapy exercise programme) must be reported in an expedited manner. Medical judgement should be exercised in deciding whether expedited reporting is appropriate in other situations (such as important medical events that may not be immediately life threatening, result in death, or hospitalisation) but may still jeopardise the participant or may require intervention to prevent one of the above events.

The PI will be responsible for expedited reporting of all unexpected and related (probable or definitely) SAEs. The SAE report form (Appendix 50) should be updated as much as possible, signed by the principal investigator or CI, and reported to the Sponsor and the ethics committee within 15 days of the research team becoming aware of the event. The SAE form (Appendix 50) should then be updated upon resolution of the SAE. The CI in conjunction with the Sponsor and ethics committee will be responsible for decisions on study suspension based on reported SAEs.

9.0 Regulations, Ethics, and Governance

9.1 Sponsorship

Queen's University Belfast (QUB) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the study. Furthermore, Dr. Cathryn Crockett has agreed to take responsibility as the Principal Investigator at the study site (BCH City Hospital).

9.2 Regulatory and Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee.

9.3.1 Informed Consent

It will be ensured that all potential participants will have the necessary information for informed consent (Appendix 14-17)) and had the opportunity to ask questions regarding study participation. Written consent will be obtained without coercion. Confidentiality will be assured, and the Caldicott Principles (National Data Guardian, 2020) adhered to. Participants will be made aware that any digital recordings will be deleted following transcription. Furthermore, consent will first be obtained for the use of anonymised quotes from participants. All information pertaining to an individual will be anonymised from study beginning. Participants will be made aware that consent that they have the right to withdraw their consent at any time throughout the study without any negative impact on their healthcare or management.

9.3.2 Consent and Data Withdrawal

All study participants (including main study participants and healthcare professionals for interview) may withdraw from the study at any time on request without prejudice. However, it will be reiterated that their data will be retained in the following circumstances:

- Data analysis has already commenced
- They have completed the baseline assessments tests in Phase 1
- Transcription and data analysis has not yet commenced after phase 2 qualitative interviews. In this instance, it will be reiterated to participants that they will be given 24 hours to consider withdrawing their interview before transcription and analysis begins.

Consent withdrawal must be documented using one of the following methods:

- Signed and dated letter from patient confirming withdrawal of consent.
- Signed and dated clinic note documenting the date of discussion with the patient (in person or by telephone) and the withdrawal of consent.
- Signed and dated letter from the investigator documenting the withdrawal of consent.

All details of the withdrawal of consent will be documented in the patient's medical record. This may include letters from the patient, documentation of verbal discussions, telephone calls etc.

Participants may also be withdrawn from the study in the following circumstances:

- Non-compliance with the study protocol, protocol deviation, lack of cooperation, or complete non-compliance.
- Intercurrent clinical deterioration that would lead to undue risk if the study intervention were to continue as assessed by the investigator.

9.4 Non-Maleficence

All members of the research team involved within this study will adhere to the principle of non-maleficence; '*Above all cause no harm to participants'* (Varkey, 2020)

9.5 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee. Changes to the protocol will require ethics committee and Belfast Health and Social Care Trust approval/favourable opinion before implementation, except when modification is needed to eliminate an immediate hazard(s) to patients. The PI in collaboration with the CI and sponsor will submit all protocol modifications to the research ethics committees for review in accordance with the governing regulations.

9.6 Good Clinical Practice

The trial will be completed in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will be required to have GCP training.

9.7 Protocol Compliance

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process.

A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

i) the safety or physical or mental integrity of the subjects of the trial; or

ii) the scientific value of the trial.

The CI is responsible for ensuring that serious breaches are reported directly to the Sponsor within one working day of becoming aware of the breach.

9.8 Patient Confidentiality

In order to maintain confidentiality, all CRF's, questionnaires, study reports and communication regarding the study will identify the patients by the assigned unique trial identifier only.

Any electronic data will be stored on encrypted files on password protected with limited access by only authorised members of the research team (PhD Candidate, Chief Investigator). Physical copies of information will be stored within a locked compartment, within a locked room, within a pass protected department.

Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.9 End of Study

In the instance where a participant provides consent to participate in a post-study qualitative interview, the end of the study will be defined as 24 hours after the qualitative interview has been completed. In the instances where a participant declines the invitation to participate in a qualitative interview, the end of study will upon completion of the end-of-study assessments.

9.10 Post-study Care

Once the study is complete, patients requiring ongoing follow-up or treatment for lung cancer will be treated according to the local NHS standard care. There are no specific post-study provisions for participants.

9.11 Indemnity

Queen's University Belfast will provide indemnity for the management and design of the UK cohort of the study. The NHS indemnity scheme will apply with respect to clinical conduct and clinical negligence.

Queen's University Belfast will provide indemnity for research management and design. In addition, the NHS will indemnify investigators/collaborators for any harm that arises in the conduct of the research'.

There will be no instance of user involvement outside of the UK.

9.12 Data management

Data will be protected under the provisions of the Data Protection Act (2018) and the UK General Data Protection Regulation (UK GDPR). The data will only be used for the purpose of the study; no participant will be identifiable in any way.

During the study, participant site files will be securely stored under lock and key, in a locked office (with restricted access to members of the BHSCT clinical research team), on level one in the Northern Ireland Cancer Centre at the study site. Site files will be under the responsibility of the site PA.

All master copies will be stored under lock and key in a locked office on a floor requiring keypad access in the Medical Biology Centre (MBC). These will be managed under the responsibility of the Chief Investigator, Gillian Prue and PhD Candidate, Matthew Beggs.

Information stored electronically will be stored on a password-protected QUB computer, on Microsoft OneDrive. OneDrive is included in QUB's Office 365 suite and therefore ensures that it will be protected under QUB purchased Microsoft security licenses, and cyber-protection police. Should electronic information need to be transferred, password-protected encrypted pen-drives will be used.

Regarding qualitative interviews, in-person or telephone interviews will be recorded on a portable, audio recording device with no internet connection. A backup-device

may be used to record the interview; however, this file will be securely and permanently deleted as soon the original interview file has been secured.

The PhD candidate has completed a Data Protection Impact Assessment (DPIA), submitted to and approved by Queens University Belfast Research and Governance.

Finaly, at the end of the study period, all site files will be transferred to the MBC for secure storage in compliance with QUB Research Data Management policy, where data will be securely stored at QUB for 5 years from the end of the study. Following this period, all electronic and physical data will be destroyed.

9.13 Competing Interests

The research costs including the cost of the intervention in are funded by the Department of Economy. The CI and research team members have no financial or non-financial competing interests. In the event that a member reports a conflict of interest, advice will be sought from the Sponsor.

9.14 Handling Complaints

In the event of a complaint arising from clinical care, then the NHS/HSC complaints process should be followed.

In the event of a complaint arising from participation within the research study, then Queens University Standard Operating Procedure (SOP) for complaints from research participants will be followed (Appendix 51)

In the instance of a complaint, a member of the research team will provide and assist with the completion of a ‘Raising a concern or complaint’ form which will then be escalated to the study’s Chief Investigator (CI). At this stage, it will be determined whether it is related to:

- A serious event in relation to the study procedure (Serious Adverse Event (SAE)); or
- How the participant has been treated whilst taking part in the study.

**In the event of an adverse event or an SAE, a separate SOP (Appendix 3 and Appendix 52) will be followed accordingly.*

The chief investigator will invite the participants to discuss the issue further and begin an investigation. Once resolution have been satisfied, corrective actions will be implemented. In the event where legal action is raised, the complaint will be investigated by Queens University Legal Services team. The CI will inform QUB Research Governance in the instance of any complaint.

If participants are not satisfied and wish to make a formal complaint, they can do so via contacting the Belfast Heath and Social Care Trust’s Complaints Department via:

Complaints Department,

Musgrave Park Hospital,

McKinney House,

6th Floor,

Stockman's Lane,

Belfast BT9 7JB.

Telephone: (028) 9504 8000

Email: complaints@belfasttrust.hscni.net

10.0 Stakeholder Involvement

This study is supported by an expert advisory group that includes the representation of the chairperson of the Irish Lung Cancer Community, a person who has previously received treatment for lung cancer, bringing their expertise to all aspects of the research. Additional group members include expert academic and healthcare professionals leading within the field of exercise oncology and lung cancer care. The steering group will continue to advise on study design, conduct, and participant documentation.

Furthermore, a series of two co-designed workshops and individual meetings were undertaken as patient and public involvement (PPI) to co-design the pre-radiotherapy exercise programme, and to discuss the study design to increase recruitment, adherence and retention. Taking this approach ensures that the exercise programme would be acceptable to patients and their friends/family members within NI.

Taking this approach aligns the core elements of the MRC complex intervention framework; Engage stakeholders, identify key uncertainties, and refine intervention (Skivington et al., 2021). Incorporating co-design with stakeholders ensure the research programme has been designed to meet the end user's needs, and produce the best conduct, and results. The steering group, and PPI attendees who have indicated interest in further input into this study, will be contacted throughout the study as support to the PhD candidate, advising on study conduct/unforeseen obstacles/barriers, plans for dissemination etc.

11.0 Dissemination and Publication

The findings will be published in national and international peer review journals. In addition, study findings may be presented at both national and international meetings and also to appropriate patient groups.

Due to limited resources, it will not be possible to provide each patient with a personal copy of the results of the trial. However, upon request, patients involved in the trial will be provided with a lay summary of the principal study findings. The most meaningful results will be communicated to the public through a press release by contacting Queens University Belfast's media and communications team.

Reference List

1. Aaronson, N.K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N.J., Filiberti, A., Flechtner, H., Fleishman, S.B., de Haes, J.C.J.M., Kaasa, S., Klee, M.C., Osoba, D., Razavi, D., Rofe, P.B., Schraub, S., Sneeuw, K.C.A., Sullivan, M. and Takeda, F. (1993) 'The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology', Journal of the National Cancer Institute, 85(5), pp.365-376. Doi: https://doi.org/10.1093/jnci/85.5.365 (Accessed: 28th January 2025).
2. Association of Chartered Physiotherapists in Cardiovascular Rehabilitation (2023) Standards for Physical Activity and Exercise in the Cardiovascular Population: 4th Edition. Available at: https://www.acpicr.com/data/Page_Downloads/ACPICR2023StandardsReaderlayout.pdf (Accessed: 5th February 2025)
3. Atun, R., Jaffray, D.A., Bartone, M.B., Bray, F., Baumann, M., Vikram, B., Hanna, T.P., Knaul, F.M., Lievens, Y., Lui, T.Y.M., Milosevic, M., O'Sullivan, B., Rodin, D.L., Rosenblatt, E., Dyk, J.V., Yap, M.L., Zubizarreta, E. & Gospodarowicz, M. (2015)

'Expanding global access to radiotherapy', The Lancet Oncology, 16(10), pp. 1153-1186. Doi: 10.1016/S1470-2045(15)00222-3.

4. Avancini, A., Sartori, G., Gkountakos, A., Casali, M., Trestini, I., Tregnago, D., Bria, E., Jones, L.W., Milella, M., Lanza, M. & Pilotto, S. (2020) 'Physical Activity and Exercise in Lung Cancer Care: Will Promises Be Fulfilled?', Oncologist, 25 (3), pp. e555-e569
5. Balachandran, A. T., Vigotsky, A. D., Quiles, N., Mokkink, L. B., Belio, M. A., & Glenn, J. M. (2021) 'Validity, reliability, and measurement error of a sit-to-stand power test in older adults: A pre-registered study', Experimental gerontology, 145 (111202). DOI: https://doi.org/10.1016/j.exger.2020.111202 (Accessed: 15th December 2024)
6. Barker, H.E., Paget, J.T.E., Khan, A.A. & Harrington, K.J. (2015) 'The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence', Nature Reviews Cancer, 15 (7), pp. 409-25. Doi: 10.1038/nrc3958
7. Beale, L., Carter, H., Doust, J., Brickley, G., Silberbauer, J. & Llyod, G. (2010) 'Exercise heart rate guidelines overestimate recommended intensity for chronic heart failure patients', British Journal of Cardiology, 17, pp.133-137. Available at: https://bjcardio.co.uk/2010/05/exercise-heart-rate-guidelines-overestimate-recommended-intensity-for-chronic-heart-failure-patients/#:~:text=The%20only%20target%20HR%20range,exercise%20intensity%20prescription%20in%20CHF (Accessed: 5th February 2025)
8. Bergman, B., Aaronson, N.K., Ahmedzai, S., Kaasa, S. and Sullivan, M., (1994) 'The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials'. European Journal of Cancer, 30A (5), pp.635-64. Doi: https://doi.org/10.1016/0959-8049(94)90535-5 (Accessed: 28th January 2025)
9. Bradley, P., Merchant, Z., Rowlinson-Groves, K., Grundy, S., Al-Najjar, H., Brown, L., Dand, A., Farran, C., Bayman, N., Banfill, K., Wray, D., Moore, J. & Evison, M. (2021) 'P212 Prehab4Cancer: an innovative regional lung cancer prehabilitation service', Thorax, 76 (1), pp. A204-A205. Doi: https://doi.org/10.1136/thorax-2020-BTSabstracts.357
10. Braun, V. & Clarke, V. (2019) 'To saturate or not to saturate? Questioning data saturation as a useful concept for thematic analysis and sample-size rationales', Qualitative Research in Sport, Exercise and Health, 13(2), pp. 201–216. Doi: 10.1080/2159676X.2019.1704846 (Accessed: 5th January 2025)
11. Braun, V. and Clarke, V. (2020) 'One size fit all? What counts as quality practice in (reflexive) thematic analysis?', Qualitative Research in Psychology, 18(3), pp. 328–352. Doi: 10.1080/14780887.2020.1769238.
12. Brown, M., Rebillard, A., Hart, N.H., O'Connor, D., Prue, G., O'Sullivan, J.M. & Jain, S. (2022) 'Modulating Tumour Hypoxia in Prostate Cancer Through Exercise: The Impact of Redox Signalling on Radiosensitivity', Sports Medicine Open, 8 (48), pp. 1-7. Doi: 10.1186/s40798-022-00436-9
13. Bruce, P.C., Gedeck, P. & Dobbins, J. (2024) 'Surveys and Sampling', in Bruce, P.C., Gedeck, P. & Dobbins, J. (ed.) Statistics for Data Scienve and Analytics. New Jersey: John Wiley & Sons, Inc, p. 190.
14. Byrne, D. (2022) 'A worked example of Braun and Clarke's approach to reflexive thematic analysis'. Quality Quantity, 56, pp.1391–1412. Doi: https://doi.org/10.1007/s11135-021-01182-y
15. Campbell, K.L., Winters-Stone, K.M., Wiskermann, J., May, A.M., Schwartz, A.L., Courneya, K.S., Zucker, D.S., Matthews, C.E., Ligibel, J.A., Gerber, L.H., Morris, S., Patel, A.V., Hue, T.F., Perna, F.M. & Schmitz, K.H. (2019) 'Exercise Guidelines for

Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable', Medicine in Science and Sports Exercise, 51 (11), pp. 2375 – 2390. Doi: 10.1249/MSS.0000000000002116

16. Cella, D. F., Bonomi, A. E., Lloyd, S. R., Tulsky, D. S., Kaplan, E., & Bonomi, P. (1995) 'Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument', Lung cancer (Amsterdam, Netherlands), 12(3), pp.199–220. Doi: https://doi.org/10.1016/0169-5002(95)00450-f (Accessed: 5th January 2025)
17. Church, S., Rogers, E., Rockwood, K., & Theou, O. (2020) 'A scoping review of the Clinical Frailty Scale', BMC geriatrics, 20(1), p. 393. Doi: https://doi.org/10.1186/s12877-020-01801-7 (Accessed: 20th December 2024).
18. Cleland, B. T., Ingraham, B. A., Pitluck, M. C., Woo, D., & Ng, A. V. (2016) 'Reliability and Validity of Ratings of Perceived Exertion in Persons With Multiple Sclerosis', Archives of physical medicine and rehabilitation, 97(6), pp. 974–982. DOI: https://doi.org/10.1016/j.apmr.2016.01.013
19. Colleta, A.M., Basen-Engguist, K.M. & Schmitz, K.H. (2022) 'Exercise Across the Cancer Care Continuum: Why It Matters, How to Implement It, and Motivating Patients to Move', American Society of Clinical Oncology Educational Book, 42. Doi: https://doi.org/10.1200/EDBK_3496
20. Cormie, P., Zopf, E.M., Zhang, X. & Schmitz, K. (2017) 'The Impact of Exercise on Cancer Mortality, Recurrence, and Treatment-Related Adverse Effects', Epidemiologic reviews, 39(1), pp.71–92. Doi: https://doi.org/10.1093/epirev/mxx007
21. Craig, C. L., Marshall, A. L., Sjöström, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J. F., & Oja, P. (2003) 'International physical activity questionnaire: 12-country reliability and validity', Medicine and science in sports and exercise, 35(8), pp.1381–1395. Doi: https://doi.org/10.1249/01.MSS.0000078924.61453.FB (Accessed: 20th December 2024)
22. Delaney, G.P. & Barton, M.B. (2015) 'Evidence-based estimates of the demand for radiotherapy', Clinical Oncology (Royal College of Radiologists (Great Britain)), 27 (2). Doi: 10.1016/j.clon.2014.10.005
23. Department of Health (2012) DH Winterbourne View Review: Concordat: Programme of Action. Available at: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/213217/Concordat.pdf (Accessed: 20th December 2024)
24. Department of Health (2012) Let's Get Moving: Commissioning Guide. Available at: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://assets.publishing.service.gov.uk/media/5a7ba2a440f0b62826a04d73/dh_133101.pdf (Accessed 15th December 2024)
25. Dufresne, S., Gueritat, J., Chiavassa, S., Noblet, C., Assi, M., Rioux-Leclercq, N., Rannou-Bekono, F., Lefeuvre-Orfila, L., Paris, F. & Rebillard, A. (2020) 'Exercise training improves radiotherapy efficiency in a murine model of prostate cancer', FASEB J, 34 (4), pp. 4984-4996. Doi: 10.1096/fj.201901728R
26. Egegaard, T., Rohold, J., Lillelund, C., Persson, G. & Quist, M. (2019) 'Pre-radiotherapy daily exercise training in non-small cell lung cancer: A feasibility study', Reports of practical oncology and radiotherapy : journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology, 24(4), pp. 375–382. Doi: https://doi.org/10.1016/j.rpor.2019.06.003

27. Esteves, M., Monteiro, M.P., Duarte, J.A. (2021) 'The Effects of Physical Exercise on Tumor Vasculature: Systematic Review and Meta-analysis', International Journal of Sports Medicine, 42 (14), pp. 1237-1249. Doi: 10.1055/a-1533-1876
28. Graham-Wisener, L., Dempster, M., Sadler, A., McCann, L., & McCorry, N. K. (2021) 'Validation of the Distress Thermometer in patients with advanced cancer receiving specialist palliative care in a hospice setting', Palliative medicine, 35(1), 120–129. Doi: https://doi.org/10.1177/0269216320954339 (Accessed: 5th January 2025)
29. Harlod, A., Casano, M. & Anjum, F. (2023) 'Six-Minute Walk Test', StatPearls [Internet]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK576420/ (Accessed: 15th December 2024)
30. Hircock, C., Wang, A. J., Goonaratne, E., Sferrazza, D., Bottomley, A., Cella, D., Lee, S. F., Chan, A. W., Chow, E., & Wong, H. C. Y. (2024) 'Comparing the EORTC QLQ-LC13, EORTC QLQ-LC29, and the FACT-L for assessment of quality of life in patients with lung cancer - an updated systematic review', Current opinion in supportive and palliative care, 18(4), pp.260–268. Doi: https://doi.org/10.1097/SPC.0000000000000725 (Accessed: 28th January 2025).
31. Huffman, M. K., Christ, S. L., Ferraro, K. F., Klenosky, D. B., Marceau, K., & Amireault, S. (2021) ' Questions to Measure Enjoyment of and Satisfaction With Physical Activity: Are They Appropriate for Use in an Older Population?', Innovation in aging, 5(4), igab041. Doi: https://doi.org/10.1093/geroni/igab041 (Accessed: 20th December 2024)
32. Kallio, H., Pietila, A., Johnson, M. & Kangasniemi, M.D. (2016) 'SYSTEMATIC METHODOLOGICAL REVIEW: DEVELOPING A FRAMEWORK FOR A QUALITATIVE SEMI-STRUCTURED INTERVIEW GUIDE', Journal of Advanced Nursing, 72 (12), pp. 2954 – 2965. Doi: 10.1111/jan.13031.
33. Karvonen, M.J., Kentala, E. and Mustala, O. (1957) 'The effects of training on heart rate: a longitudinal study', Annales Medicinae Experimentalis et Biologiae Fenniae, 35(3), pp. 307-315
34. Kilari, D., Soto-Perez-de-Celis, E., Mohile, S. G., Alibhai, S. M., Presley, C. J., Wildes, T. M., Klepin, H. D., Demark-Wahnefried, W., Jatoi, A., Harrison, R., Won, E., & Mustian, K. M. (2016) 'Designing exercise clinical trials for older adults with cancer: Recommendations from 2015 Cancer and Aging Research Group NCI U13 Meeting', Journal of geriatric oncology, 7(4), pp.293–304. Doi: https://doi.org/10.1016/j.jgo.2016.04.007
35. Kirkham, A. A., Campbell, K. L., & McKenzie, D. C. (2013) 'Comparison of aerobic exercise intensity prescription methods in breast cancer', Medicine and science in sports and exercise, 45(8), pp.1443–1450. Doi: https://doi.org/10.1249/MSS.0b013e3182895195
36. Koller, M., Musoro, J.Z., Tomaszewski, K., Coens, C., King, M.T., Sprangers, M.A.G., Groenvold, M., Cocks, K., Velikova, G., Flechtner, H.H. & Bottomley, A. (2022) 'Minimally important differences of EORTC QLQ-C30 scales in patients with lung cancer or malignant pleural mesothelioma – Interpretation guidance derived from two randomized EORTC trials', Lung Cancer, 167, pp.65-72. Doi: https://doi.org/10.1016/j.lungcan.2022.03.018 (Accessed: 28th January 2025).
37. Lee, P. H., Macfarlane, D. J., Lam, T. H., & Stewart, S. M. (2011) 'Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review', The international journal of behavioral nutrition and physical activity, 8, p.115. Doi: https://doi.org/10.1186/1479-5868-8-115 (Accessed: 20th December 2024)
38. Liu, Y., Wu, W., Cai, C., Zhang, H., Shen, H. & Han, Y. (2023) 'Patient-derived xenograft models in cancer therapy: technologies and applications', Signals

Transduction and Targeted Therapy, 8, p. 160. Doi: https://doi.org/10.1038/s41392-023-01419-2

39. Ligibel, J.A., Bohlke, K., May, A.M., Clinton, S.K., Demark-Wahnefried, W., Gilchrist, S.C., Irwin, M.L., Late, M., Mansfield, S., Marshall, T.F., Meyerfardt, J.A., Thomson, C.A., Wood, W.A., Alfano, C.M. (2022) 'Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline', Journal of Clinical Oncology, 40 (22), pp. 2491 – 2507. Doi: 10.1200/JCO.22.00687
40. Lumivero (2017) NVivo (Version 12) [Computer software]. Available at: www.lumivero.com (Accessed: 10th January 2025)
41. Macmillan (2023) Physical Activity and Cancer. Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatment/preparing-for-treatment/physical-activity-and-cancer (Accessed: 20th December 2024)
42. McCullough, D.J., Stabley, J.N., Siemann, D.W. & Behnke, B.J. (2014) 'Modulation of blood flow, hypoxia, and vascular function in orthotopic prostate tumors during exercise', Journal of the National Cancer Institute, 106 (4), dju036. Doi: 10.1093/jnci/dju036.
43. Michie, S. Stralen, M.M. & West, R. (2011) 'The behaviour change wheel: A new method for characterising and designing behaviour change interventions', Implementation Science, 6 (42). Doi: https://doi.org/10.1186/1748-5908-6-42.
44. Moreno-Ariño, M., Torrente Jiménez, I., Cartanyà Gutiérrez, A., Oliva Morera, J. C., & Comet, R. (2020) 'Assessing the strengths and weaknesses of the Clinical Frailty Scale through correlation with a frailty index', Aging clinical and experimental research, 32(11), pp. 2225–2232. Doi: https://doi.org/10.1007/s40520-019-01450-w (Accessed: 24th December 2024).
45. Moreton, R., Stutz, A., Robinson, S., Mulla, I., Winter, M., Roberts, J. & Hillsdon, M. (2018) Evaluation of the Macmillan Physical Activity Behaviour Change Care Pathway. Available at: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.macmillan.org.uk/assets/evaluation-of-macmillan-physical-activity-behaviour-change-care-pathway-2018.pdf (Accessed: 20th December 2024)
46. Morgan, B., Hejdenberg, J., Kuleszwicz, K., Armstrong, D. & Ziebland, S. (2021) 'Are some feasibility studies more feasible than others? A review of the outcomes of feasibility studies on the ISRCTN registry', Pilot and Feasibility studies, 7, p. 195. Doi: https://doi.org/10.1186/s40814-021-00931-ya
47. Muz, B., Puente, P., Azab, F. & Azab, A.K. (2015) 'The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy', Hypoxia (Auckl), 3, pp. 83-92. Doi: https://doi.org/10.2147/HP.S93413
48. National Data Guardian (2020) The Eight Caldicott Principles. Available at: https://www.gov.uk/government/publications/the-caldicott-principles (Accessed: 21st January 2025)
49. National Institute for Health and Care Excellence (2014) Behaviour Change: Individual Approaches. Available at: https://www.nice.org.uk/guidance/ph49 (Accessed 15th December 2024)
50. National Institute of Health, (2021). Common Terminology Criteria for Adverse Events (CTCAE). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50 (Accessed: 21st January 2025).
51. National Lung Cancer Audit (2023) Healthcare Improvement Plan. Available at: https://www.lungcanceraudit.org.uk/quality-improvement/ (Accessed: 20th December 2024)

52. Nikitara, K., Odani, S., Demenagas, N., Rachiotis, G., Symvoulakis, E. & Vardavas, C. (2021) ‘Prevalence and correlates of physical inactivity in adults across 28 European countries’, The European Journal of Public Health, 31 (4), pp. 840-845. Doi: 10.1093/eurpub/ckab067
53. Nisar, H., Gonzalez, P.M.S., Brauny, M., Labonte, F.M., Schmitz, C., Roggan, M.D., Konda, B. & Hellweg, C.E. (2023) ‘Hypoxia Changes Energy Metabolism and Growth Rate in Non-Small Cell Lung Cancer Cells’, Cancers (Basel), 15 (9), p. 2472. Doi: https://doi.org/10.3390/cancers15092472
54. Northern Ireland Cancer Registry (2023) Lung Cancer. Available at: https://www.qub.ac.uk/research-centres/nicr/CancerInformation/official-statistics/BySite/Lungcancer/ (Accessed: 20th November 2024)
55. Northern Ireland Cancer Registry (2024) All Cancers: 1993 – 2021. Available at: https://www.qub.ac.uk/research-centres/nicr/CancerInformation/official-statistics/ (Accessed: 20th December 2024)
56. Norton, K.., Norton, L., Sadgrove, D. (2010) ‘Position statement on physical activity and exercise intensity terminology’, Journal of science and medicine in sport, 13(5), pp. 496–502. Doi: https://doi.org/10.1016/j.jsams.2009.09.008
57. Ortmann, B.M. (2024) ‘Hypoxia-inducible factor in cancer: from pathway regulation to therapeutic opportunity’, BMJ Oncology¸3 (1), pp. 1-17. Doi: https://doi.org/10.1136/bmjonc-2023-000154
58. Pearson, N., Naylor, P., Ashe, M.C., Fernandez, M., Yoong, S.L. & Wolfenden, L. (2020) ‘Guidance for conducting feasibility and pilot studies for implementation trials’, Pilot and Feasibility Studies, 6, p.167. Doi: https://doi.org/10.1186/s40814-020-00634-w
59. Peddle-Mclntyre, C.J., Thomas, F.S.R., Newton, R.U., Galvao, D.A. & Cavalheri, V. (2019) ‘Exercise training for advanced lung cancer’, The Cochrane Database of Systematic Reviews, 2 (2), CD012685. Doi: 10.1002/14651858.CD012685.pub2.
60. Penko, A. L., Barkley, J. E., Koop, M. M., & Alberts, J. L. (2017). ‘Borg scale is valid for ratings of perceived exertion for individuals with Parkinson's disease’, International journal of exercise science, 10(1), pp. 76–86. DOI: https://doi.org/10.70252/RVAQ3828
61. Pinto, B.M. & Ciccolo, J.T. (2011) ‘Physical activity motivation and cancer survivorship’ Recent Results Cancer Res, 186, pp. 367-387. Doi:10.1007/978-3-642-04231-7_16
62. Piraux, E., Caty, G., Nana, F.A. & Reychler, G. (2020) ‘Effects of exercise therapy in cancer patients undergoing radiotherapy treatment: a narrative review’, Sage Open Medicine, 17 (8). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7301662/ (DOI: 10.1177/2050312120922657).
63. Reynolds, S.A., O’Connor, L, McGee, A., Kilcoyne, A.Q., Connolly, A., Mockler, D., Guinan, E. O’Neill, L. (2024) ‘Correction: Recruitment rates and strategies in exercise trials in cancer survivorship: a systematic review’, Journal of cancer survivorship: research and practice, 18 (1), pp. 1233-1242. Doi: https://doi.org/10.1007/s11764-024-01716-x
64. Riba, M.B., Donovan, K.A., Ahmed, K., Andersen, B., Braun, II., Breitbart, W.S., Brewer, B.W., Corbett, C., Fann, J., Fleishman, S., Garcia, S., Greenberg, D.B., Handzo, G.F., Hoofring, L.H., Huang, C.H., Hutchinson, S., Johns, S., Keller, J., Kumar, P., Lahijani, S., Martin, S., Niazi, S.K., Pailler, M., Parnes, F., Rao, V., Salman, J., Scher, E., Schuster, J., Teply, M., Usher, A., Valentine, A.D., Vanderlan, J., Lyons, M.S., McMillian, N.R. & Darlow, S.D. (2023) 'NCCN GUIDELINES®

INSIGHTS Distress Management, Version 2.2023', JNCCN Journal of the National Comprehensive Cancer Network, 21 (5), pp. 450-457. Doi: https://doi.org/10.6004/jnccn.2023.0026 (Accessed: 28th January 2025).

65. Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D.B., McDowell, I. & Mitnitski, A. (2005) 'A global clinical measure of fitness and frailty in elderly people', Canadian Medical Association Journal, 173 (5), pp.489-495. Doi: 10.1503/cmaj.050051 (Accessed: 20th December 2024).
66. Sasso, J. P., Eves, N. D., Christensen, J. F., Koelwyn, G. J., Scott, J., & Jones, L. W. (2015) 'A framework for prescription in exercise-oncology research'. Journal of cachexia, sarcopenia and muscle, 6(2), pp. 115–124. Doi: https://doi.org/10.1002/jcsm.12042
67. Seet-Lee, C., Yee, J., Morahan, H., Ross, L.S. & Edwards, K.M. (2022a) 'The effect of aerobic exercise on tumour blood delivery: a systematic review and meta-analysis', Supportive Care in Cancer, 30 (1), pp. 8637 – 8653. Doi: https://doi.org/10.1007/s00520-022-07132-0
68. Sia, J., Szmyd, R., Hau, E., & Gee, H.G. (2020) 'Molecular Mechanisms of Radiation-Induced Cancer Cell Death: A Primer', Frontiers in Cell and Developmental Biology, 8 (41), pp. 1-8. Doi: https://doi.org/10.3389/fcell.2020.00041
69. Skivington, K., Matthews, L., Simpson, S.A., Craig, P., Baird, J., Blazeby, J.M., Boyd, K.A., Craig, N., French, D.P., McIntosh, E., Petticrew, M., Rycroft-Malone, J., White, M. & Moore, L. (2021) 'A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance', British Medical Journal, 374. Doi: https://doi.org/10.1136/bmj.n2061
70. Suveg, K., Plasswilm, L., Iseli, T, Leskow, P., Fischer, G.F. & Putora, P.M. (2022) 'Role of Adjuvant Radiotherapy in Non-Small Cell Lung Cancer—A Review', Cancers (Basel), 14 (7), p.1617. Doi: 10.3390/cancers14071617
71. Tivey, A., Ullah, M., Beech, A., Ng, C., & Cove-Smith, L. (2020) 'Can frailty screening tools predict completion of chemotherapy and chemotherapy toxicity in patients with thoracic malignancy', Journal of geriatric oncology, 11(7), pp.1154–1156. Doi: https://doi.org/10.1016/j.jgo.2020.03.002 (Accessed: 20th December 2024).
72. Toohey, K., Mizrahi, D., Hart, N. H., Singh, B., Lopez, P., Hunter, M., Newton, R. U., Schmitz, K. H., Adams, D., Edbrooke, L., & Hayes, S. (2025) 'Exercise in cancer care for people with lung cancer: A narrative synthesis', Journal of science and medicine in sport, 28(1), pp.16–25. Doi: https://doi.org/10.1016/j.jsams.2024.08.002
73. Totton, N., Lin, J., Julious, S., Chowdhury, M. & Brand, A., (2023) 'A review of sample sizes for UK pilot and feasibility studies on the ISRCTN registry from 2013 to 2020', Pilot and Feasibility Studies, 9, p.188. Doi: https://doi.org/10.1186/s40814-023-01416-w
74. Tran, D. L., Kamaladasa, Y., Munoz, P. A., Kotchetkova, I., D'Souza, M., Celermajer, D. S., Maiorana, A., & Cordina, R. (2022) 'Estimating exercise intensity using heart rate in adolescents and adults with congenital heart disease: Are established methods valid?', International journal of cardiology. Congenital heart disease, 8 (100362). Doi: https://doi.org/10.1016/j.ijcchd.2022.100362
75. United Kingdom Lung Cancer Coalition (2024) Driving Quality Improvements in UK Lung Cancer: Utilising good practice and innovation to deliver optimal care and outcomes. Available at: https://www.uklcc.org.uk/index.php/our-reports/february-2024/driving-improvements-uk-lung-cancer (Accessed: 20th December 2024)
76. Varkey, B. (2021) 'Principles of Clinical Ethics and Their Application to Practice. Medical principles and practice: international journal of the Kuwait University', Health Science Centre, 30(1), pp. 17–28. Doi: https://doi.org/10.1159/000509119

77. Viamonte, S. G., Joaquim, A. V., Alves, A. J., Vilela, E., Capela, A., Ferreira, C., Duarte, B. F., Rato, N. D., Teixeira, M. P., Tavares, A., Santos, M., & Ribeiro, F. (2023) 'Cardio-Oncology Rehabilitation for Cancer Survivors With High Cardiovascular Risk: A Randomized Clinical Trial', JAMA cardiology, 8(12), pp.1119–1128. Doi: https://doi.org/10.1001/jamacardio.2023.3558
78. Vinod, S.K. & Hau, E. (2020) 'Radiotherapy treatment for lung cancer: Current status and future directions', Respirology, 25 (S2), pp. 61-71. Doi: https://doi.org/10.1111/resp.13870
79. Williams, N. (2017) 'The Borg Rating of Perceived Exertion (RPE) scale ', Occupational Medicine, 67 (5), pp. 404-405. Doi: https://doi.org/10.1093/occmed/kqx063
80. World Health Organization (2018) More active people for a healthier world. Available at: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://iris.who.int/bitstream/handle/10665/272722/9789241514187-eng.pdf (Accessed: 20th December 2024)
81. World Health Organization (2023) Lung Cancer. Available at: https://www.who.int/news-room/fact-sheets/detail/lung-cancer (Accessed: 20th June 2024)
82. Ziolkowska-Suchanek, I. (2021) 'Mimicking Tumor Hypoxia in Non-Small Cell Lung Cancer Employing Three-Dimensional In Vitro Models', Cells, 10 (1), p.141. Doi: 10.3390/cells10010141

Appendices: