EXTRA-Meso Feasibility Study

EXercise TheRApy in Mesothelioma – A Feasibility Study

Protocol Version 1.1

Version Date 13/09/2023

IRAS Project ID: 315059

R&I Reference: GN22ON168

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1 STUDY SYNOPSIS

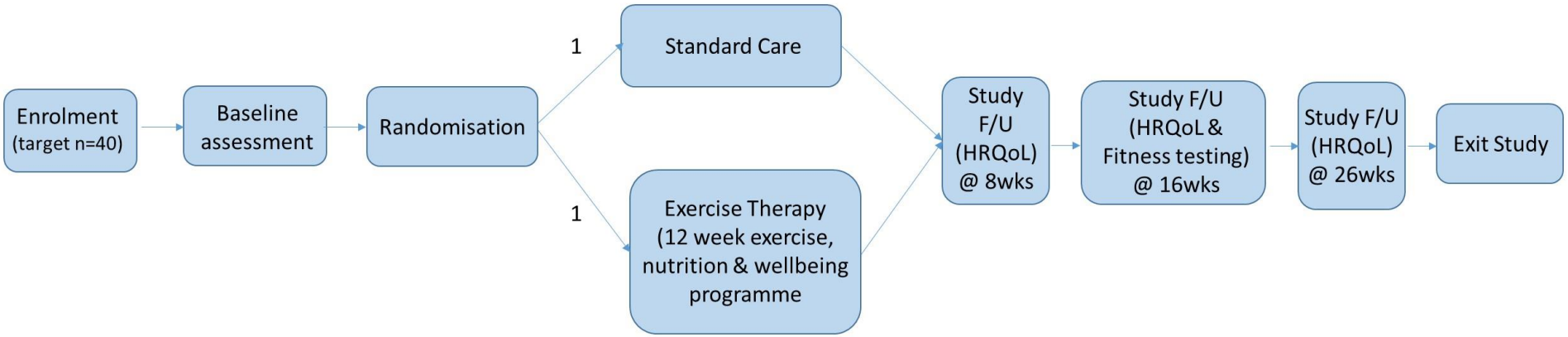
Study Title	EXercise TheRApy in Mesothelioma – A feasibility study (EXTRA-Meso feasibility study)
Study Sponsor	NHS Greater Glasgow and Clyde
Study Design	Randomised feasibility trial
Number of Patients	40
Patient Population	Patients with a diagnosis of mesothelioma
Primary Objective	To determine the feasibility of recruiting patients with mesothelioma to a randomised trial of exercise therapy, in order to inform design of a future phase 3 trial
Secondary Objectives	1. To determine barriers to study recruitment 2. To determine barriers to study retention 3. To determine safety and tolerability of the exercise programme intervention and study assessments
Primary Outcome Measure	Number of patients recruited
Secondary Outcome Measures	1. Proportion of screened patients who are ineligible 2. Reasons for study ineligibility 3. Study drop-out rate 4. Reasons for study drop-out 5. Intervention adherence rate 6. Adverse events 7. Health-related Quality of Life (HRQoL) questionnaire completion rate 8. Framework analysis from qualitative interviews
Eligibility Criteria	Inclusion Criteria: 1. Diagnosis of mesothelioma, ratified by a mesothelioma MDT 2. Performance status 0 -2 3. Clinical frailty score ≤5 4. Informed written consent Exclusion Criteria: 1. Performance status ≥3 2. Clinical frailty score ≥6

	3. Unlikely to be able to participate in an exercise programme (clinician/physiotherapist judgement)
Screening and Consent	Patients with mesothelioma will be identified at mesothelioma MDTs, routine respiratory/oncology outpatient appointments, and during inpatient reviews. Those meeting all eligibility criteria will be provided with a Patient Information Sheet (PIS) and given sufficient time to consider participation.
Randomisation and Allocation	Following consent and baseline assessments, patients will be randomised using an online system (sealedenvelope.com) and allocated 1:1 using random permuted blocks to one of two groups: A. Exercise Therapy B. Standard Care
End of Study	Trial participation will end when the last patient has completed their 26 week visit
Study duration	18 months

2 ABBREVIATIONS

MPM	Malignant Pleural Mesothelioma
WoS	West of Scotland
HRQoL	Health-related Quality of Life
SD	Standard deviation
PS	Performance Status
CFS	Clinical Frailty Score
PIS	Patient Information Sheet
MDT	Multi-disciplinary team
FBC	Full blood count
CRP	C-reactive protein
6MWD	6 minute walk distance
STS	Sit to stand
BMI	Body mass index
MUST	Malnutrition universal screening tool
(S)WEMWBS	Short Warwick Edinburgh Mental Wellbeing Scale
HADS	Hospital anxiety and depression scale
SF-36	36-item short form survey
EQ-5D-5L	EuroQol group 5 item survey
EORTC-QLQ-C30	European organisation for research and treatment of cancer survey
SACT	Systemic anti-cancer therapy
CNS	Clinical Nurse Specialist
PROMs	Patient related outcome measures

3 STUDY FLOWCHART



4 SUMMARY OF STUDY

4.1 Plain English Summary

Malignant pleural mesothelioma (MPM) is an aggressive, strongly associated with asbestos exposure. It most frequently affects the lining of the lung (pleura), but can also affect the other parts of the body, including the lining of the heart and abdomen. The incidence of MPM has been increasing over the last decade, despite legislative control of industrial asbestos use, due to a long latency period between initial exposure and development of the disease, and is predicted to continue to increase over the next 5 – 10 years.

Patients with MPM often experience troublesome symptoms including breathlessness, pain and fatigue. They can also experience anxiety and depression and feel like their quality of life is worse than before they were diagnosed. Sarcopaenia is a complex condition, where there is an interplay between inflammation and cancer, which ultimately results in low skeletal muscle mass. Malnutrition and sarcopaenia is common in individuals with MPM, and is associated with worse outcomes, including in those who get chemotherapy.

Unfortunately, the average life expectancy following a diagnosis of mesothelioma is approximately 12 months. Currently, treatment in patients who are fit enough is aimed at prolonging this life expectancy, and involves drug treatment in the form of either chemotherapy or more recently immunotherapy. Whether a person with mesothelioma receive this treatment can depend on their physical fitness.

Exercise Therapy

Improving health-related quality of life (HRQoL) and physical fitness is a key goal for all patients with MPM, and maximising treatment opportunity has never been more important, following the recent approval of immunotherapy for the treatment of MPM across the UK. Exercise therapy is a rational approach to improving HRQoL and could also improve and/or maintain physical fitness to allow more patients to ultimately receive treatment. There is a growing body of evidence that exercise therapy in other cancers, such as lung cancer, can improve cardio-respiratory fitness, muscle mass, muscle strength, anxiety levels and HRQoL. Exercise may also have a role in breaking the vicious cycle of cancer, inflammation and sarcopaenia. The Prehab4Cancer programme is a successful initiative launched in Greater Manchester for patients with lung cancer. Patients who take part in the programme have reported improvement in their functional fitness and quality of life. We also know that home-based rehabilitation programmes are safe in patients with MPM. However, there is no evidence on the potential benefits of a tailored exercise and nutritional support intervention in mesothelioma. This is the focus of the current study and a planned future phase 3 trial.

EXTRA-Meso Feasibility Study

An exercise intervention study such as this one has never been done in mesothelioma. Before planning a larger phase 3 randomised controlled trial, we are conducting a smaller study to ensure that running an exercise trial in patients with mesothelioma is feasible. This study will determine this feasibility, the number of centres that will likely be needed to recruit to a larger study and define the optimum duration and format of the exercise intervention itself.

4.2 Scientific Summary

High symptom burden, anxiety and depression are common in Malignant Pleural Mesothelioma (MPM), even in those with good performance status (PS). (1,2) Patients with MPM often report poor health-related quality of life (HRQOL), which is itself, associated with poorer survival. (3,4) The treatment of MPM typically involves systemic anti-cancer therapy (SACT), receipt of which may be associated with better maintenance of HRQoL compared with those who decline, as previously reported in the SWAMP trial. (5) However, chemotherapy uptake in MPM is low, often due to reduced physical fitness in patients who are frequently in their 7th or 8th decade of life.

Maximising HRQoL is a key goal for all MPM patients and maximising treatment opportunity has never been more important, following the recent approval of combination immunotherapy, regardless of histology, across the UK. Combination nivolumab and ipilimumab significantly improves overall survival in unresectable MPM compared to standard chemotherapy in the first-line setting. (6) This survival benefit appears amplified in patients with non-epithelioid histology, with maintenance or improvement in HRQOL in responding patients. (7) This is particularly important in this sub-group, in whom standard chemotherapy is rarely effective and symptom burden is frequently high with poor HRQOL. (5)

Exercise therapy is a rational approach to improving HRQOL and could also maximise treatment opportunities in MPM. This reflects a growing body of evidence for exercise interventions in other cancers and particular features of deconditioning associated with MPM recently identified by our group. In non-small cell lung cancer (NSCLC), pre-operative exercise therapy in patients undergoing resection is associated with improved cardio-respiratory fitness, reduced post-operative complications and improved HRQOL. (8) Olivier et al also reported that a home pulmonary rehabilitation programme was safe and feasible in patients with lung cancer and a small number of patients with MPM (n=17). (9) Our group has recently reported that low skeletal muscle mass (sarcopaenia), a feature of the cancer cachexia syndrome is independently associated with adverse survival. This effect was more marked on in thoracic musculature ipsilateral to the tumour (10) and was observed if sarcopaenia was present prior to starting chemotherapy and if patients lost skeletal muscle mass during treatment. (11) These features suggesting a dynamic deconditioning effect, driven directly by MPM, which could be predicted and modified to improve outcomes. In these studies, the presence of sarcopaenia was also notably associated with systemic inflammation. (11)

A recent systematic review and meta-analysis has confirmed poorer progression-free survival and overall survival in patients with sarcopaenia pre-immunotherapy in solid tumours including lung cancer and melanoma. (12) In MPM, malnutrition and ‘pre-sarcopaenia’ has previously been reported in 38% and 54% respectively, with lower activity levels in pre-sarcopenic patients. (13) Exercise intervention in patients with sarcopaenia may improve muscle mass, muscle strength and physical performance. (14) There is also evidence that exercise may have a role in breaking the vicious cycle of cancer, inflammation and cachexia (15). Furthermore, there is evidence that exercise improves quality of life and reduces anxiety in patients with other cancers. (16,17) The ‘Prehab 4 Cancer’ programme, which this study will be utilising, reported improvements in functional fitness and quality of life in patients with NSCLC. (18) However, there is no evidence regarding the potential

benefits of a tailored exercise and nutritional support intervention in mesothelioma. This is the focus of the current study and the planned future phase 3 trial.

5 STUDY OBJECTIVES

5.1 Primary Objective

- To determine the feasibility of recruiting patients with mesothelioma to an exercise therapy study

5.2 Secondary Objectives

- To determine barriers to study recruitment
- To determine barriers to study retention
- To determine safety and tolerability of the exercise intervention and study assessments

6 STUDY DESIGN

This study is a prospective randomised feasibility study, randomising patients 1:1 to exercise therapy intervention versus standard care.

6.1 Study Setting

Patients will be recruited from two mesothelioma centres, the NHS Greater Glasgow and Clyde Glasgow Pleural Disease Unit and Wythenshawe Hospital, Manchester NHS Foundation Trust. These two centres have high rates of mesothelioma. The West of Scotland (WoS) has had between 65 – 75 new diagnoses of mesothelioma per year over the last 3 years (data from the Scottish National Mesothelioma MDT). Similarly, Greater Manchester have seen approximately 50 cases of mesothelioma per year between 2016 – 2018 (data from the National Mesothelioma Audit). The Glasgow Pleural Disease Unit hosts the Scottish National Mesothelioma MDT, where cases across Scotland are discussed. Wythenshawe Hospital hosts the Greater Manchester regional mesothelioma MDT. This set up at both recruiting centres ensures that all patients diagnosed within the West of Scotland or Greater Manchester can be considered for this trial. Both centres have successfully collaborated on numerous research studies, have a proven track record in recruiting patients to mesothelioma trials and have appropriate research infrastructure in place to deliver this study.

6.2 Study Population

6.2.1 Inclusion Criteria

1. Diagnosis of mesothelioma ratified by Mesothelioma MDT
2. ECOG performance status (PS) 0 – 2
3. Clinical Frailty Score (CFS) ≤5
4. Informed consent

6.2.2 Exclusion Criteria

1. ECOG Performance Status >2

2. Clinical Frailty Score ≥6
3. Unlikely to be able to participate in an exercise programme (clinician/physiotherapist judgement)

6.2.3 Identification of participants and consent

Patients will be screened at the respective mesothelioma MDTs and/or identified at respiratory and/or oncology outpatient clinics and/or at inpatient review. Potential participants who meet the eligibility criteria will be approached by a member of the study team. If interested, the patient will be provided with the study Patient Information Sheet (PIS) and given sufficient time to read it, discuss with their family, if they wish, and ask questions before being invited to provide informed written consent to enrol in the study. If a patient has a virtual (telephone or video) appointment, remote "witnessed verbal consent" can be taken. For witnessed verbal consent to be valid, the participant must be witnessed by two members of the research team to agree to each point of the consent form. Both research team members must then sign the consent form and indicate on the form that the consent was taken remotely. All consent documentation will be scanned into the patient's clinical notes. Detailed screening logs will be kept to record reasons for non-enrolment. Should the patient read the patient information sheet but decline to take part, they may be asked to consent to a semi-structured interview with a member of the study team, to explore their reasons for declining to participate, in order to inform future study design. Potential participants who decline to participate will be signposted to locally available community activities and services that are available to promote long-term health improvement if they wish. There is no time limit on time of diagnosis to study enrolment.

6.3 Sample size calculation

The current feasibility study will aim to recruit 40 patients. No formal sample size is feasible or appropriate, but this number is sufficient to allow identification of barriers to recruitment and retention (the latter informing the likely drop-out rate for the future phase 3 trial) and the duration and design of the exercise therapy intervention.

The primary objective of the future phase 3 trial will be to determine whether exercise therapy results in a clinically meaningful improvement in HRQOL at 16 weeks post-randomisation. Assuming a mean population score of 60 (SD 20) based on QoL scores previously reported in other mesothelioma studies, we currently estimate that a sample size of 84 patients in each arm is required to detect a 10-point improvement in EORTC QLQ C30 quality of life scores, with 90% power at 5% two-sided significance level. With a currently assumed 25% drop-out rate, based on the 'Prehab4Cancer' dropout rate in patients with NSCLC, we estimate that we would require a total sample size of 224 patients. Data from the current feasibility study will (a) provide a more robust estimate of baseline mean HRQOL score (based on the population score recorded from all patients at baseline assessment), (b) allow a more precise estimate of drop-out rate based on an optimised exercise intervention and (c) allow us to calculate the number of centres needed based on the recruitment rate achieved.

6.4 Co-enrolment guidelines

Patients may not be entered into any other clinical trial that aims to deploy an exercise programme for the duration of their participation within the study. Access to trials of systemic anti-cancer therapies, radiotherapy or surgery is permitted.

6.5 Withdrawal of patients from the study

Patients will be withdrawn from the study if any of the following occur:

- Patient withdrawal of consent
- Clinical opinion of the doctor that the patient should withdraw

If a patient moves to another area during the trial follow-up period, efforts will be made to complete follow-up in conjunction with the new primary physician / team or general practitioner.

7 BASELINE ASSESSMENT

Having provided written or witnessed verbal informed consent to participate in the study, participants will all undergo the same baseline assessment. This will include recording of:

- Patient demographics, disease characteristics, including subtype and stage, co-morbidities and medication history (including current or prior systemic anti-cancer therapy).
- Routine blood results, including full blood count (FBC), C-reactive protein (CRP) and albumin
- Body Mass Index (BMI) and malnutrition universal screening tool (MUST) score
- Functional fitness measurements in the form of:
    - Hand grip strength
    - 6 minute walk distance (6MWD)
    - 30 second sit-to-stand (STS) test
- Patient related outcome measures (PROMs) via completion of the following questionnaires related to HRQoL, wellbeing and symptoms:
    - Euroquol quality of life survey (EQ-5D-5L)
    - 36-item short form survey (SF-36)
    - European organisation for research and treatment of cancer (EORTC) QLQ-C30
    - Hospital Anxiety and Depression Scale (HADS)
    - Short Warwick Edinburgh Mental Wellbeing Scale ((S)WEMWBS)
- Presence/absence of features of sarcopaenia utilising:
    - Strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) screening questionnaire

- Skeletal muscle area and visceral fat index measurements on routinely-acquired clinical CT scan within the preceding 3 months

8 RANDOMISATION

Randomisation should occur immediately after baseline assessment has been completed. Eligible participants will be randomly allocated using an online system (sealed envelope) to either 'Standard Care' or 'Exercise Therapy' in a 1:1 ratio using random permuted blocks. Randomisation will be performed using an online system (sealedenvelope.com).

9 POST-RANDOMISATION

9.1 Standard Care Arm

Participants randomised to Standard Care will undergo routine clinical follow-up. Refer to schedule of assessments. Relevant clinical updates, including hospital admissions and any treatment updates (e.g. commencement or discontinuation of SACT) will be recorded at 8, 16 and 26 weeks post-randomisation. Participants will complete the questionnaires as per the above PROMs performed at their baseline assessment visit at 8, 16 and 26 weeks post-randomisation. If required, questionnaires can be posted out to patients and returned to the study team using a pre-paid addressed envelope. Study members can assist participants with completion of these questionnaires remotely if required. A study visit will be arranged at week 16 post randomisation to repeat functional fitness measurements as detailed above. Wherever possible, this study visit will be co-ordinated with the patient's routine clinic appointment. If the patient has had any follow-up CT scans performed as part of their routine clinical care during their study follow-up period, this will be reviewed to measure total skeletal muscle area and visceral fat index. If their MUST score indicates malnourishment at baseline assessment, a referral to NHS dietetic services will be made. During the follow-up period, patients will be sign-posted to local community activities and services that are available to promote long-term health improvement. It will be made clear to participants within the standard care arm that they are free to undertake exercise or increased physical activity if they wish. Any increase in exercise activity or participation in local generic community exercise programmes will be recorded at follow-up visits.

9.2 Exercise Therapy (Intervention) Arm

Participants randomised to the Exercise Therapy arm will undergo an individualised assessment by either a physiotherapist or a qualified exercise professional with specialist cancer training, either in hospital or in the community. Refer to schedule of assessments. Following this initial assessment, patients will receive a personalised exercise, wellbeing and nutritional support package. The exercise programme will incorporate 3 sessions per week. One session per week will be supported by the physiotherapist or qualified exercise professional and the other 2 sessions will be independent sessions done in the participant's own home or local health club/gym if available. The total duration of the programme is 12 weeks. The exercise programme will incorporate both cardiovascular and resistance training, and will be progressive throughout the duration of the programme. The exercise programme will be tailored to take into account the participant's current level of fitness and familiarity/confidence with exercise, available equipment and injuries. Participants will be given a diary to record completion of each exercise session. If their MUST score indicates malnourishment at baseline assessment, a referral to NHS dietetic services will be made.

Relevant clinical updates, including hospital admissions and any treatment updates (e.g. commencement or discontinuation of SACT) will be recorded at 8, 16 and 26 weeks post-randomisation. Participants will complete the questionnaires as per the above PROMs performed at their baseline assessment visit at 8, 16 and 26 weeks post-randomisation. If required, questionnaires can be posted out to patients and returned to the study team using a pre-paid addressed envelope. Study members can assist participants with completion of these questionnaires remotely if required. A study visit will be arranged at week 16 post randomisation to repeat functional fitness measurements as detailed above. Wherever possible, this study visit will be co-ordinated with the patient's routine clinic appointment. If the patient has had any follow-up CT scans performed as part of their routine clinical care during their study follow-up period, this will be reviewed to measure total skeletal muscle area and visceral fat index. During the follow-up period, patients will be sign-posted to local community activities and services that are available to promote long-term health improvement.

Any clinical concerns arising during the exercise programme will be highlighted to the patient's clinical team via the mesothelioma CNS.

9.3 Semi-structured Interviews

Up to five patients who were deemed as potentially eligible at screening, read the patient information sheet but decline to participate will be invited to participate in a semi-structured interview to explore their reasons for declining to participate, in order to determine barriers to recruitment.

A further 10 – 20 study participants, including participants who drop-out of the study before completion and those who complete the study, will be invited to a semi-structured interview to examine their views on the randomisation process, the exercise therapy intervention, study outcome measures (including the functional fitness assessments and questionnaires) and follow-up, in order to determine barriers to study retention and inform design of the phase 3 study.

Interviews can be conducted in person, ideally co-ordinated with a routine clinic appointment, or remotely. Audio recordings will be transcribed and anonymised audio transcriptions will be reviewed for qualitative analysis at the University of Surrey.

9.4 Schedule of Assessments

Visit	Pre-screening	Baseline	Week 1 (+/- 7 days)	Week 8 (+/- 2 wks)	Week 16 (+/- 3 wks)	Week 26 (+/- 4 wks)
Routine Clinical Activity						
Mesothelioma MDT review	X					
Outpatient clinic review		X				
Contrast CT thorax	X					X
Routine clinical follow-up				X	X	X
Study Activity						
Review eligibility criteria		X				
If eligible, introduce study and provide PIS		X				
Informed written consent		X				
Study registration		X				
Record baseline data		X				
Complete HRQoL questionnaires[1]		X				
Functional fitness assessment[2]		X				
SARC-F screening questionnaire		X				
Review recent[#] CT for total skeletal muscle area and visceral fat index		X				
Record BMI + MUST score		X				
Randomisation		X				
Remote qualitative Interview (optional)					X	X*
Post-randomisation standard of care arm						
Record relevant clinical and/or physical activity updates				X	X	X
Complete HRQoL/wellbeing questionnaires[1]				X	X	X
Functional fitness assessment[2]					X	
Review follow-up CT for total skeletal muscle area and visceral fat index						X
Post-randomisation intervention arm						
Record relevant clinical updates				X	X	X
Physiotherapist/exercise professional assessment			X			
Commence 12 week exercise programme			X			
Complete HRQoL/wellbeing questionnaires[1]				X	X	X
Review exercise session attendance and exercise compliance				X	X	X
Functional fitness assessment[2]					X	
Review follow-up CT for total skeletal muscle area and visceral fat index						X
Record adverse events				X	X	

[1]EQ-5D, SF-36, HADS, (S)WEBWMS and EORTC QLQ-C30 questionnaires, can be returned by post if no F2F routine clinical visit scheduled
[2]30 seconds sit-to-stand test, 6 minute walk test and hand grip strength
[#]Within preceding 3 months
*If not previously done

10 Statistical Analysis Plan

We will use descriptive statistics to describe the demographics and clinical characteristics of the study population. Means (with standard deviations) or medians (with inter-quartile ranges) will be used to summarise continuous variables, depending on their distribution and proportions to summarise categorical variables.

Total recruitment, recruitment rate, study drop-out rate and intervention adherence rate will be reported by simple descriptive statistics, or proportions where appropriate.

Semi-structured interviews will be analysed using Framework Analysis[19], which will involve a five-step process:

1. Familiarisation with the data
2. Identifying a thematic framework
3. Indexing
4. Charting
5. Mapping and interpretation

The analysis will be predominantly deductive, as it will specifically focus on facilitators and barriers to study retention, and to the uptake and experience of the exercise intervention.

11 End of Trial

Trial recruitment will terminate either 12 months after opening or after 40 patients have been recruited, whichever is soonest. Trial participation will cease once the final patient has completed their 26-week follow-up.

12 Safety Reporting

All Adverse Events will be reported directly to the sponsor.

12.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence that the patient experiences whilst participating in the clinical trial. This includes occurrences that are not necessarily caused by or related to the trial intervention.

12.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any of the following, whether or not considered related to the trial intervention.

- Results in Death
- Life-threatening (i.e. at the time of the event)*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity

- Is a congenital anomaly/birth defect
- Is considered medically significant by the Investigator***

*Life threatening means that the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.

**Requires in-patient hospitalisation should be defined as a hospital admission required for treatment of an adverse event.

***Considered medically significant by the Investigator are events that may not result in death, are not life threatening, or do not require hospitalisation, but may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

12.3 SAEs Related to Study Procedures

Related SAEs will be any SAE that is reported as possibly, probably or definitely related to the prescribed exercise programme. See below for all definitions for the relationship to the protocol intervention.

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship
Possible	There is some evidence to suggest a causal relationship (e.g. the event occurs within a reasonable time after administration of the trial intervention) However the influence of other factors may have been contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship and the influence of other factors in unlikely
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out

12.4 Adverse Event Recording and Reporting

All AEs must be recorded on the patient's medical records. AEs must be recorded as they are reported during the visit. Full details of AEs including the nature of the event, start and stop dates, severity, relationship to study intervention and outcome must be recorded. AEs must be followed until resolution, or for at least 30 days after the trial intervention, whichever comes first or until toxicity has resolved to baseline or ≤ Grade 1, or until the toxicity is considered to be irreversible. Perceived

lack of efficacy is not an AE. An exacerbation of a pre-existing condition is an AE.

12.5 Expected Adverse Events

12.5.1 Exercise Therapy

Common (1 in 10 to 1/100)

- Fatigue
- Musculoskeletal injury
- Joint pain
- Muscle soreness

Rare (<1/100,000)

- Cardiac event such as heart attack or heart rhythm disorder

13 FEASIBILITY STUDY METRICS

Feasibility success metrics collected during this study on recruitment and adherence to study intervention, defined as completion of ≥18 exercise sessions across the 12 week programme) will determine if it is feasible to proceed to a phase 3 randomised trial and defined as:

- Green (proceed with no/minor changes to study design)

- Amber (significant changes to study design before proceeding)

- Red (do not proceed)

Status	Total Study Recruitment	Adherence to study intervention
Green	≥ 20 patients	≥ 50% patients
Amber	5 – 19 patients	10 – 49% patients
Red	< 5 patients	< 10% patients

14 COMPLIANCE, AUDIT AND PROTOCOL DEVIATIONS

14.1 Good Clinical Practice

This study will be conducted in accordance with the protocol, the Sponsor's standard operating procedures, national regulatory requirements, provisions of the relevant ethics committees and Good Clinical Practice (GCP) principles.

14.2 Audits

The study may be subject to audit by NHS Greater Glasgow and Clyde under their remit as Sponsor.

14.3 Protocol Deviation Reporting

A protocol deviation is any departure from the approved protocol. All deviations will be recorded and reported to the sponsor. The sponsor will not authorize prospective protocol deviations/waivers, unless the deviation is necessary to eliminate and immediate hazard.

15 PATIENT AND PUBLIC INVOLVEMENT

A group of patients with mesothelioma and relatives of patients who have previously been diagnosed with mesothelioma were consulted for their views on the overall study premise and study design. Patient facing documentation was also reviewed by these two groups.

16 DATA HANDLING

Data generated by the study will be stored in a linked anonymised fashion in a password-protected computer. Subject paper notes will be stored in a locked filing cabinet in a locked office of a secure building.

16.1 Case Report Forms

Entries to the CRFs will be made in black ballpoint pen and must be legible. Any errors must be crossed out with a single stroke, the correction inserted and the change initialled and dated by the Investigator. Correction fluid must not be used. All data submitted on CRFs are verifiable in the source documentation or that any discrepancies are recorded and explained.

Trial sites should keep a copy of all completed CRFs. The original CRFs should be returned to the Pleural Disease Unit, Queen Elizabeth University Hospital for data entry and computation of relevant end-points and ultimately, statistical analysis. CRFs from the trial will be stored in line with current regulatory requirements. Other essential documents, including source data, consent forms, and regulatory documentation, will be archived by the Investigator, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required.16. Study Closure / Definition of End of Trial

The end of the trial should be outlined clearly, below is sample text.

The study will end when the steering committee agrees that one or more of the following situations applies:

- Last patient last study visit;

OR

i. The planned sample size has been achieved;
ii. The Independent Data Monitoring Committee has advised discontinuation, e.g. because of safety concerns about the trial, or a statistically significant difference in clinical outcomes is evident between the two treatment arms;
iii. There is insufficient funding to support further recruitment, and no reasonable prospect of additional support being obtained;

iv. New information makes it inappropriate to continue to randomise patients to one or other arm of the trial;

Recruitment is so poor that completion of the trial cannot reasonably be anticipated

17. Protocol Amendments

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the Sponsor and any required amendment forms will be submitted to the, ethics committee and sponsor. The CI will liaise with study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC and Research and Development (R&D) office(s).

17. Ethical Consideration

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions.

Favourable ethical opinion will be sought from an appropriate REC before patients are entered into this clinical trial. Patients will only be allowed to enter the study once either they have provided written informed consent. The CI will be responsible for updating the Ethics committee of any new information related to the study.

17. Finance and Indemnity

Brief details on how the study is funded should be included here.

NHS employed researchers will be covered for negligent harm through the NHS CNORIS indemnity scheme. If you are a University employee you may need extra cover for non-negligent harm through your University. Please check this with your Research and Enterprise department.

***Example text*:** The XXX study is sponsored by NHS Greater Glasgow & Clyde. The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

17. Publications

Study results whether, negative or positive, should be disseminated. Details of your plan for dissemination should be included here.

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