A Phase III randomized controlled trial of progressive resistance exercise training on shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy in head and neck cancer survivors.

Short Name: **A Phase III randomized trial of progressive resistance exercise training on shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy.**

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Study Type: Interventional

Funding Entity: National Cancer Institute.

Statement of Compliance

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

1 Protocol Summary

1.1 Synopsis

Title: A Phase III randomized controlled trial of progressive resistance exercise training on shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy in head and neck cancer survivors.

Study Description: Progressive Resistance Exercise Training (PRET) has been known as a promising intervention in addressing shoulder dysfunction in head and neck cancer survivors who have experienced spinal accessory neuropraxia or neurectomy. We want to do a phase III randomized controlled trial to investigate how PRET will affect the shoulder dysfunction caused by spinal accessory nerves.

Study Population: 306 Male or female aged from 20 to 80 and have suffered from shoulder dysfunction caused by spinal accessory nerve. Other detailed criteria can be seen in Section 5.

Phase: III

Description of Sites/Facilities Enrolling Participants: The trial will be conducted at the Cross Cancer Institute and University of Alberta in Edmonton, Canada.

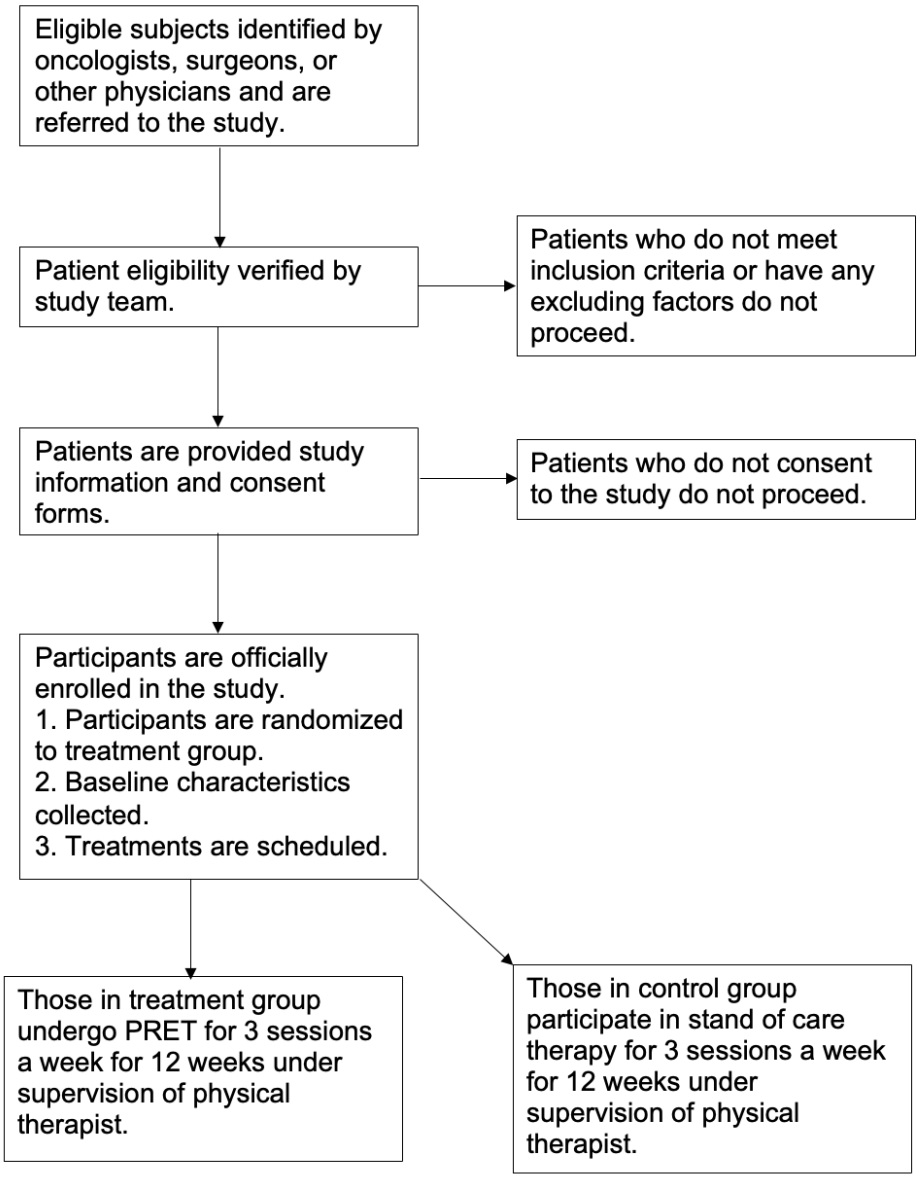
Description of Study Intervention: This is a 12 week intervention study. 306 patients enrolled into either the progressive resistance exercise training (PRET) treatment group or the standard of care (control) group. In each group, patients will be randomly assigned to exercise and standard care intervention by means of computer-generated code. Randomization will be on a 1:1 basis.

Study Duration: 1 year.

Participant Duration: 12 weeks.

1.2 Schema

Below is the study protocol schema flowchart for participants. Participants will be randomized to either PRET or control group evenly. Some patients will be excluded from the eligible subject pool for reasons such as availability.



1.3 Schedule

	Month 1-2	Month 3-4	Month 5-6	Month 7-8	Month 9-10	Month 11-12
Participant recruitment and enrollment	X	X				
Treatment sessions	X	X	X			
Data analysis				X	X	
Drafting manuscript				X	X	X
Finalized manuscript available to funding source						X

2 Introduction

2.1 Study Rationale

Shoulder dysfunction is a significant issue among head and neck cancer survivors coming from damage to the spinal accessory nerve. The spinal accessory nerve, also known as the eleventh cranial nerve, innervates the trapezius and sternocleidomastoid muscles, both of which are critical for normal shoulder function. When this nerve is damaged due to neurapraxia (temporary loss of nerve function) or neurectomy (surgical removal of a portion of the nerve), the result can be debilitating shoulder dysfunction. [Remmler et al. 3]

Shoulder strengthening is a primary component of physical therapy treatment for patients with shoulder dysfunction caused by spinal accessory nerve damage. (Johnson and Aseff 6) However, no guidelines exist for strength training in the head and neck cancer population or specifically for shoulder dysfunction caused by spinal accessory nerve damage. Although anecdotal evidence suggests potential benefit, little effort has been done in establishing the effectiveness of physical therapy interventions. Also, limited randomized controlled trials have been performed in this patient population. [Saunders and Johnson 5, Fialka and Vinzenz 7]

Again, debilitating shoulder dysfunction can be especially stressful and frustrating for head and neck cancer survivors, and a physical exercise regimen may provide, in addition to actual benefits in physical capability, confidence and improved outlooks on health outcomes after surviving head/neck cancer. Therefore, it is of great importance to conduct a study to evaluate the effects of progressive resistance exercise training (PRET) on shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy in head and neck cancer survivors.

2.2 Background

Head and neck cancer is the seventh most common cancer in the world, with 1.1 million new diagnoses reported annually. [Saba et al. 15] There appears to be an increasing incidence of this disease, with potential changes in aetiology proposed given the decline of smoking, particularly in developed countries. [Gormley et al. 17]

Spinal accessory neurapraxia and neurectomy are relatively common complications following head and neck cancer surgeries, particularly those involving lymph node dissection. Damage to the nerve can result in a myriad of issues including shoulder pain, limited range of motion, weakness, and difficulties in performing daily activities. This is primarily due to the altered function of the trapezius muscle, which plays a vital role in the movement and stabilization of the shoulder. [Remmler et al. 3]

The severity of shoulder dysfunction can vary based on the extent of the nerve damage. Neurapraxia, being a temporary and often reversible condition, tends to cause milder symptoms compared to neurectomy. However, even temporary disruption to nerve function can lead to considerable patient discomfort and reduced quality of life. [Köybasioglu et al. 16]

Management and rehabilitation of shoulder dysfunction caused by spinal accessory neurapraxia or neurectomy typically involves physical therapy to strengthen the shoulder muscles and improve range of

motion. Shoulder strengthening is a primary component of physical therapy treatment for patients with shoulder dysfunction caused by spinal accessory nerve damage. [Gordon et al. 10, Chida et al. 11, Salerno et al. 12]

Other than physical therapy, pain management, patient education, and occasionally surgical intervention should also be considered to deal with the cases of nerve damage. Despite these interventions, shoulder dysfunction remains a long-term issue for many head and neck cancer survivors.

2.3 Benefit Assessment

Progressive Resistance Exercise Training (PRET) has been known to be a promising intervention in addressing shoulder dysfunction in head and neck cancer survivors who have experienced spinal accessory neuropraxia or neurectomy. [De Boer et al. 13]

PRET is a specific type of strength training that gradually increases the load or resistance over time as muscles adapt and become stronger. This strategy aims to enhance muscle strength, including the muscles surrounding the shoulder, which are often called to compensate for the weakened or non-functioning trapezius muscle, primarily affected by spinal accessory nerve damage. [Rejeski et al. 18, Taaffe et al. 19]

Implementing PRET for individuals suffering from shoulder dysfunction due to spinal accessory neurapraxia/neurectomy is expected to show promising results. By gradually increasing shoulder strength and range of motion, PRET has the potential to reduce pain and improve function, thus enhancing the quality of life for head and neck cancer survivors.

2.3.1) Known Potential Benefits

Based on the previous pilot and phase II studies there are promising benefits of PRET in both improving shoulder function and quality of life. The standard of care (control) group has been established as a successful treatment plan for oncologists and surgeons.

2.3.2) Known Potential Risks

The previous studies found no serious risks related to the study intervention. Adverse events were determined to be linked to participants' cancer treatment and not due to PRET.

3 Objectives and Endpoints

Objectives	Endpoints	Justification for Endpoints
Primary		
To evaluate if 12 weeks of physical resistance exercise training (PRET) is superior to the standard of care for head and neck cancer survivors who experience shoulder dysfunction caused by spinal accessory neuropraxia/neurectomy from neck dissection with respect to lower shoulder pain and disability index (SPADI).	Shoulder pain and disability index (SPADI)	In a pilot study by McNeely et al., it was shown that there were decreasing trends in shoulder pain and disability index (SPADI). Significant differences were found in the overall difference between groups ($p=0.045$). Because of these positive findings, a larger randomized controlled trial is warranted.
Secondary		
To evaluate if 12 weeks of physical resistance exercise training (PRET) is superior to the standard of care for head and neck cancer survivors who experience shoulder dysfunction caused by spinal accessory neuropraxia/neurectomy from neck dissection with respect to greater quality of life measures via Functional Assessment of Cancer Therapy---Head and Neck (FACT-H&N).	Functional Assessment of Cancer Therapy---Head and Neck (FACT-H&N).	In a pilot study by McNeely et al., it was shown that there were increasing trends in overall quality of life measured via FACT-H&N scores and significant differences were found. Because of these positive findings, a larger randomized controlled trial is warranted.
Safety		
To investigate the safety and tolerability of PRET, effectively adherence and completion of PRET, in head and neck cancer survivors experiencing shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy from neck dissection.	Adherence rates and adverse events	Adherence rates provide an insight into the feasibility for patients. Descriptions of adverse events ensure the safety of patients currently in the study and provide information for future potential patients.
Ancillary/Exploratory		

To examine differences in completion and adherence rates for different sub-groups: age, sex, cancer types, and surgery types.	Completion and adherence rates	Exploratory purposes to determine potential future areas of research.

4 Study Design

4.1 Overall Design

A phase III prospective randomized controlled trial will be conducted to evaluate the effects of progressive resistance exercise training (PRET) on shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy in head and neck cancer survivors. The study will be a year-long study of a 12 week intervention conducted at the Cross Cancer Institute (CCI) and University of Alberta in Edmonton, Canada. Potential subjects will be identified by the oncologist and/or surgeon at a scheduled cancer follow-up appointment and then screened for eligibility. Enrollment will consist of 306 patients total, 153 patients enrolled into either the progressive resistance exercise training (PRET) treatment group or the standard of care (control) group . Patients will be randomly assigned to either the intervention group or standard of care (control) group by means of computer-generated code. Randomization will be on a 1:1 basis. At baseline, demographic and clinical information will be collected on all subjects and medical data obtained from medical records. Past exercise behavior will be assessed with the Leisure Score Index (LSI) of the Godin Leisure Time Exercise Questionnaire. Subjects that are randomly assigned to the exercise arm will immediately begin the 12 week PRET protocol. Participants will exercise three times per week, excluding statutory holidays, for the 12 week intervention period. Therefore, the prescribed number of exercise sessions range from 33 to 35 and any missed exercise sessions will not be rescheduled. The PRET program will be individualized to suit each subject, and a physical therapist and/or physical therapy assistant will supervise all exercise-training sessions. The PRET program, including type, intensity (resistance), duration, and frequency, are based on guidelines for prospective cardiac rehabilitation. Subjects randomly assigned to the control arm made up the standard of care group, which consisted of active and passive ROM and stretching exercises. As per standard of care, at the 6-week follow-up, these subjects will progress to scapular retraction and elevation strengthening exercises with an elastic resistance band, but no progressive resistance exercise training. Subjects in this arm will have the option to participate in the PRET program after the 12 week delay period. Shoulder pain and disability will be measured via the shoulder pain and disability index (SPADI) scores. Quality of life outcomes will be determined via the Functional Assessment of Cancer Therapy–Head & Neck (FACT-H&N) scores.

4.2 Scientific Rationale for Study Design

4.2.1. Selection of Control

This study uses a standard of care control group. The standard of care has been established and utilized by physicians as a promising method to improve shoulder function after surgery. Many patients are recommended to attend some level of physical therapy and so this study aims to compare the established method for recovery to the specific technique of PRET.

4.2.1. Superiority Design

This study aims to show the superiority of PRET over the standard of care. The reason for a superiority design is because PRET can be much more intense for the patient than the standard physical therapy procedures. This study aims to establish that the benefits of PRET outweighs the effort of the participant

and therefore must establish that PRET is superior to the standard of care. This study also aims to provide information to physicians and physical therapists on the best practices for their patients.

4.2.2. Baseline Characteristics:

The Leisure Score Index (LSI) has established reliability and concurrent validity on the basis of various criteria, including objective activity monitors and fitness indices. Participants will be asked to complete the LSI recalling their average exercise over the prior month. Pain medication use will be monitored at baseline, week 6, and week 12.

4.2.3. Physical Measures (ROM):

Active range of motion (ROM) measurements will be taken at baseline, week 6, and week 12. The measurement of shoulder ROM will be performed with a universal goniometer. Goniometric measurements are commonly used in the clinical setting and are highly reliable when repeated by the same investigator. For this study, ROM is used to assess the combined motion of the joints that make up the shoulder complex. Active shoulder movements include flexion, abduction, and external rotation. Passive shoulder movements include flexion, abduction, external rotation, internal rotation, and horizontal abduction. A single investigator that is familiar with and trained in the measurement procedure will be responsible for all ROM measurements for each subject.

4.2.4. Progressive Resistance Exercise Training Program (PRET):

Subjects will be asked to perform a series of six exercises. The specific therapeutic exercises performed will be chosen with the goal of enhancing scapular stability and restoring/maintaining the strength of upper extremity. These exercises consist of rhomboids (scapular retraction); levator scapulae (scapular elevation); biceps (elbow flexion); triceps (elbow extension); infraspinatus, posterior deltoid (external rotation); and middle deltoid and supraspinatus and subscapularis (abduction in the plane of the scapula). The resistance-training program is progressive in terms of number of sets and repetitions performed, as well as the amount of weight lifted, which is dependent on performance status, recovery from surgery, and response to concurrent adjuvant therapy. Early weeks will be characterized by fewer exercises due to limitations of range of motion or pain, fewer sets (one), fewer repetitions (4-6 or to tolerance), and lighter weights (1-2 kg). Subjects progressed to the desired exercise prescription as soon as safely possible based on guidelines for exercise performance: (1) maintenance of proper posture and scapular stability (no winging of scapula); (2) a rate of perceived exertion on the Borg Scale of no greater than 13 of 20 (described as “somewhat hard”). The resistance weight will be increased by one resistance level when all repetitions can be performed, within the set guidelines, in the second set. Subjects will also perform 5-10 minutes of warm up (range of motion [ROM] exercises) and cool-down exercises (stretching) before and after the resistance training component.

4.2.5. Feasibility Measures:

Feasibility is determined by calculating the following rates: (1) recruitment rate (number of participants randomized/number of eligible participants), (2) completion rate (number of participants completing baseline and 12 week intervention assessments/number of participants randomized), and (3) adherence rate (the number of exercise sessions attended/number of exercise sessions scheduled).

Table 1. PRET Summary	
Program Components	**Program Details**
Purpose	Enhancement of muscular strength and endurance of upper extremity and scapular muscles
Warm-up	Range of motion exercises for glenohumeral join in supine
Muscle groups to be strengthened	● Rhomboids ● Levator scapula ● Biceps ● Triceps ● Infraspinatus, posterior deltoid ● Middle deltoid, supraspinatus and subscapularis
Intensity	Start with resistance of 1 to 2 kg weights, progress within guidelines Must be able to maintain posture and scapular stability RPE: no greater than 13 on Borg Scale: “somewhat herd”
Repetitions	15-20 reps: progress to maximum of 25 reps initially when performing only 1 set
Sets	1 set, progress to 2 sets @ 2 sets of 20 increase resistance weight
Rest interval	1-2 min between exercise stations and up to 4 min between sets
Concentric tempo	2-4 sec (exhaling)
Eccentric tempo	4 sec (inhaling)
Total set duration	Approx 20 min/set for 15 reps each. Total for 2 sets of 20 reps each = approx 45 min
Number of exercises	6 exercises
Stretching exercises (cool down)	● Pectoralis major and minor ● Serratus anterior
Reduce workload	● Excessive fatigue after exercise ● Muscle soreness >48 hours ● Increase pain after exercise
Terminate exercise	Pain, dizziness, general malaise

4.2.5. Standard of Care:

The standard of care consists of active and passive ROM exercises and stretching exercises. The goal of standard care is to optimize joint range of motion in glenohumeral joints, strengthen alternative muscles to compensate for loss of trapezius, and prevent or alleviate pain. At the 6 week follow up, subjects of this group progressed to scapular retraction and elevation strengthening exercises with an elastic resistance band, but no progressive training. Subjects of this group have the option to participate in the PRET program after the 12 week delay period.

4.2.6. Shoulder Pain and Disability Index:

The SPADI is a valid and reliable instrument that reflects the pain and disability associated with the clinical syndrome of a painful shoulder. The form is self-administered and requires 5-10 minutes to complete. Scores for the pain and disability subscales range from 0-100, with higher scores indicating greater impairment. The total SPADI score is calculated by averaging the pain and disability subscale scores. The SPADI will be administered at baseline and week 12.

4.2.7. Quality of Life Outcomes:

The Functional Assessment of Cancer Therapy–Head & Neck (FACT-H&N) is a cancer-specific quality of life instrument that consists of a 27-item core to which an 11-item site specific head and neck subscale is added. The measure is completed by the patient and provides a global quality of life score and five subscale scores. The subscale scores cover the following domains: physical (0-28), social (0-28), emotional (0-24), functional (0-28), and head and neck concerns (0-44). The FACT scale has been tested in a large sample of patients with cancer and has been found reliable, valid, responsive, brief, and easy to administer. The FACT-H&N will be administered at baseline and at week 12.

4.3 End of Study Definition

The study is scheduled to end 1 year after the initial start date. All enrolled participants will have the opportunity to complete 12 weeks of treatment regardless of enrollment time. A participant has completed the study when they have either completed all 12 weeks of treatment.

5 Study Population

5.1 Inclusion Criteria

1. Male or female and between ≥ 20 and ≤ 80 years of age on the day of signing informed consent.
2. Subject understands the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agrees to participate by giving written informed consent.
3. Diagnosed with squamous cell carcinoma of the head and neck, histologically confirmed, which had been managed by definitive surgical resection (<1 before enrollment) and has not begun physical therapy as part of their surgical recovery or oncology treatment plan.
4. Subjects with squamous cell carcinoma metastatic to the neck from an unknown primary site are also eligible if, in the opinion of the both the radiation oncologist and the head and neck surgeon/otolaryngologist, the probable occult mucosal origin was in the head and neck.
5. Surgical treatment included radical neck dissection, modified radical neck dissection, and other variants of selective neck dissection.
6. A medical diagnosis of shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy and evidence of trapezius dysfunction (defined as winging of the scapula with shoulder abduction in the coronal plane and limitation of active shoulder abduction range of motion).
7. Ability to participate in mild levels of exercise.
8. Karnofsky performance status of 60% or higher.
9. Ability to understand verbal and/or written instructions from study team and physical therapist.

5.2 Exclusion Criteria

1. Evidence of residual cancer in the neck as and/or any distance metastasis as established by clinical examination, CT, or MRI.
2. History of shoulder surgery including rotator cuff repair, total shoulder arthroplasty, or any bone reconstruction or grafting where motor nerve damage has inflicted the function of the neck and/or shoulder.
3. Musculoskeletal diseases with symptoms that disturb the neck and/or shoulders (e.g., R.A, fibromyalgia, arthritis, neurological disease, industrial injury).
4. Psychiatric or mental illness which would prevent completion of treatment or interfere with follow-up.
5. Patients whose general condition makes it impossible to attend the study sessions.

5.3 Lifestyle Considerations

Participant diet will not be considered as an inclusion or exclusion factor. Exercise level and frequency will be collected at enrollment. We will recommend participants avoid strenuous exercise (e.g., cardio, weightlifting, etc) during the study period. Patients also participating in speech therapy as part of an oncology treatment plan are eligible to join. All written material will be provided in both English and French per Canadian regulation but can be provided in other preferred languages. English language preference is not required and the study team will provide resources (e.g., translators, written instructions,

etc.) for participants who prefer study information and treatment sessions in a language other than English.

5.4 Screen Failures

There will be no screening procedure for enrollment. Diagnoses will be provided by the patient's previous doctors.

5.5 Strategies for Recruitment and Retention

Potential participants identified by oncologists/surgeons/other physicians will be referred to the study team. Potential participants will be provided with study information by the study team before deciding on enrollment. Participants will be made aware of the possibility of receiving either standard of care treatment (standard physical therapy) or the intervention (PRET). Participants will also be made aware they may drop out of the study at any time for any reason. Accommodations will be provided to best of the study team's ability to accommodate participant schedule, availability, and other needs. There will be no financial burden incurred on participants.

6 Study Intervention

6.1.1 Study Intervention Description

The main goal of PRET is to enhance muscular strength and endurance of the upper extremity and scapular muscles. The main purpose of this enhancement is overall compensation for any loss or negative effect of trapezius function as well as development of shoulder alignment and posture.

6.1.2 Intervention Administration

The intervention will be administered by the attending physical therapist and guided by the attending physical therapist with relevant adaptive weight equipment for patients depending on stage in the trial.

6.2.1 Preparation

Preparation will be done in the clinic with appropriate weight lifting equipment such as dumbbells prepared by the physical therapist and clinic. Preparation of equipment includes ensuring that dumbbells from weights 5lbs to 50lbs are available as well as resistance bands. Additionally, special cable machines may be utilized with regards to achieving components of PRET in different muscle groups.

6.2.2 Accountability

Accountability will be verified from both the end of the patient as well as the therapist. The therapist will be required to log patient difficulties or struggles during the exercise therapy. Similarly, the patient will be required to log a small paragraph accounting for their experience at each appointment as well as the exercise that they performed. The therapist will be responsible and held accountable for meeting the program requirements by recording whether certain activities were accomplished at each session for each patient.

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization will be done via simple randomization with a computer generated code. More precisely, for each patient enrolled into the study during the study enrollment period, patients will be randomly assigned with equal likelihood to either the standard of care treatment or PRET intervention. In particular,

With respect to blinding, it will be obvious for patients to tell the difference between the more mild standard of care and the more demanding and rigorous PRET intervention. We avoid any consideration of blinding and rely on the accountability of the attending physical therapist in the clinic to administer either therapy (standard of care, or PRET) reliably and effectively.

In particular, we generate random assignments for each participant by generating a random integer uniformly from 1 through 10. If the participant is given a number less than or equal to 5 and greater than or equal to 1, they will be assigned to the control; if they are given a number greater than 5 and less than or equal to 10, they will be assigned the treatment group. In the sample size section, we compute a required sample size of 306 with at least 153 samples in both the treatment and control arms. The above procedure will necessarily introduce a slight inbalance. For the sake of minimizing sample bias, we place a hard tolerance on the imbalance by accepting at most a 2.5% imbalance between either treatment arms.

For example, a 153-155 is acceptable, whereas 169-153 breaks this imbalance as we have 10% more samples in the control arm compared to the treatment arm. This balance tolerance guarantees a comparable sample in our statistical analysis section keeping the possible spread of imbalances within one standard deviation of possible imbalances.

The Appendix includes an example simple randomization table based off the described procedure for the estimated required sample size of at least 153 in each arm. The table indicates that participants with label "A" are assigned the treatment, and "B" are in the control group.

6.4 Study Intervention Compliance

Study intervention compliance is easily monitored by whether or not the patient adheres to the entirety of their prescribed treatment, be it PRET or standard of care. A big remark to make is that study intervention compliance is not considered to be part of the termination of the exercise of the patient. Termination is determined if the patient experiences considerable pain, dizziness and/or general malaise.
Beyond compliance during the intervention itself, compliance throughout the trial is determined as to whether the patient regularly meets scheduled appointments and meets the frequency of appointments required of therapy in the 12 week period of administration as well as the 1 year monitoring period.

Study intervention will be followed by maintaining records of therapy completion and adherence with the form in Appendix, subsection 12.2.

6.5 Concomitant Therapy

There is no prescribed concomitant therapy to occur during the trial. Patients may be under prescription for relevant pain killers as needed. No other substantial therapies are expected for the patient. Patients may experience nausea during the exercise therapy due to other drug related therapies such as pain killers and other anti-inflammatory relief aids prescribed by the oncologist.

7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention will be defined as a patient missing three consecutive appointments or attending therapy sessions only twice a week for three weeks in a row. The justification for this discontinuation status is that if a patient misses a whole week's worth of training, they fail to put their muscles under necessary stimulation and conditioning that PRET or standard of care aims to achieve. Similarly, for the twice-a-week three-weeks-in-a-row the frequency requirement is motivated by the same justification.

7.2 Participant Discontinuation/Withdrawal from the Study

Participant discontinuation/withdrawal from the study will be noted, but not included in the final data analysis procedure. Such patients will be lost in any final analysis and unaccounted for. This status will be marked by patients leaving a study entirely and having the corresponding clinic aware of their discontinuation as well as noting and recording reasons for discontinuation or withdrawal.

7.3 Lost to Follow-up

Patients lost to follow-up will be treated in the same way as patients discontinuing/withdrawing from the study. They will be excluded entirely from the study and especially from the data analysis process.

8 Study Assessments and Procedures

8.1 Efficacy Assessments

Potential subjects will be assessed based on the eligibility criteria outlined in the study protocol (Section 5). Eligible subjects will be randomized 1:1 to the exercise training arm or standard care arm. In the exercise arm, subjects will immediately begin the 12-week PRET protocol. The PRET program includes a series of six exercises, with intensity, duration, and frequency based on postoperative cardiac rehabilitation guidelines. The exercises are individualized and supervised by a physical therapist or assistant. In the control arm, subjects will follow the standard of care, including active and passive range of motion (ROM) exercises and stretching exercises.

All subjects will be scheduled for follow-up visits at week 12. During this visit, measures of shoulder function, pain, disability, and quality of life will be assessed. Active and passive ROM measurements will be taken using a universal goniometer by a trained assessor. The SPADI score will be used to measure shoulder pain and disability. Quality of life will be assessed using the FACT-H&N. These assessments, taken at baseline and week 12, will form the basis for determining the efficacy of the intervention as per the primary and secondary objectives.

The trial will also explore the adherence and completion rates for the PRET protocol and will assess cross-sectional variations of SPADI and FACT-H&N scores among different ages, neck dissection types, and sex. Adverse events will be diligently recorded and managed as per protocol. The safety and tolerability of PRET will be assessed continuously, with adherence and completion rates serving as indicators of intervention acceptability.

8.2 Safety and Other Assessments

Eligibility criteria have been carefully designed to ensure the suitability of participants for this intervention. Key eligibility criteria include histologically confirmed squamous cell carcinoma of the head and neck, evidence of shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy, a Karnofsky performance status of 60% or higher, and no evidence of residual cancer or distant metastasis. Exclusion criteria are also in place to safeguard the wellbeing of the patients. These include individuals with comorbid shoulder pathology, severe medical illness, or psychiatric illness that may hinder the completion of the intervention or interfere with follow-up. After confirming the eligibility, subjects will be enrolled in the study. This phase will follow the standard ethical procedures, including obtaining informed consent from the participants. This consent form will clearly outline the rights of the participants, maintaining confidentiality, and the potential risks and benefits involved in the study participation.

Following enrollment, participants will be randomized to either the exercise training arm or the standard care arm. For those randomized to the exercise arm, they will start with the Progressive Resistance Exercise Training (PRET) protocol immediately. Participants randomized to the control arm will follow the standard care for shoulder dysfunction post neck dissection. This protocol ensures safety by providing a standard of care to all participants and by closely monitoring those in the exercise group.

Adherence to the protocol and completion rates will be tracked as indicators of intervention acceptability and tolerability. Any adverse events or issues with adherence will be immediately addressed and managed as per the protocol. Unscheduled visits will be arranged if necessary, particularly if there are any adverse effects related to the intervention. Throughout the trial, the safety and tolerability of the intervention will be continuously monitored.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

For this study focusing on PRET, the only anticipated AE based on previous studies is nausea, which could occur as a result of the exercise intervention, especially among patients near the completion of radiation therapy or those with minimal nutritional intake before the exercise session.

8.3.2 Definition of Serious Adverse Events (SAE)

Given the nature of PRET and the overall health profile of the anticipated participants in this trial - head and neck cancer survivors, we do not anticipate any Serious Adverse Events (SAEs) in this study.

8.3.3 Classification of an Adverse Event

For this study, any instance of nausea will be considered an adverse event. The severity of this AE will be assessed using a grading system developed in consultation with our study Medical Monitor. Its relationship to the study intervention will be evaluated, considering factors such as the natural history of the underlying disease, concurrent illnesses, concomitant therapies, study-related procedures, and external factors. While it is not anticipated, the study intervention is always a suspect if an AE occurs. It is noteworthy that no serious adverse events are expected in this study; however, any unexpected occurrences will be reported and managed as per established guidelines.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

During the entire duration of the study, adverse events, such as nausea, will be closely monitored. Participants will be assessed at each section, and are encouraged to report any changes in their health status or unexpected symptoms, such as nausea, in between these scheduled visits. Specific inquiries, including "Have you noticed any nausea since you started the exercise program?", will be used to solicit potential adverse effects. All reported AEs will be followed until resolved or stabilized, with additional unscheduled visits for those experiencing AEs. The data collection will be carefully managed to ensure accuracy and avoid duplication. Any serious adverse events, although not anticipated in this study, will be immediately reported and will prompt a reassessment of the participant's continuation in the trial.

8.3.5 Adverse Event Reporting

In our study, investigators will uphold their responsibility to report all AEs. Non Serious AEs, such as nausea, will be recorded and reported to the sponsor as soon as possible, but no later than within 24 hours

of learning of the event. Details of the AE including severity, onset and end dates, actions taken, and outcomes will be documented in a standardized AE report. The entire study team will be alerted of these events to ensure the participant's well-being is prioritized and any necessary changes to the study procedures can be promptly made.

8.3.6 Serious Adverse Event Reporting

While we do not anticipate any serious adverse events in this study, we remain prepared to handle any such occurrences responsibly. Investigators will immediately report any SAE, regardless of presumed relation to the PRET, to the sponsor. This report will include an assessment of the likelihood that the intervention caused the event.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

Given the nature of our study, we do not anticipate significant unanticipated problems.

8.4.2 Unanticipated Problem Reporting

While we do not anticipate any significant unanticipated problems in our study, if any occur, an unanticipated problem report will be sent to the IRB, institutional officials, and any supporting department or agency.

9 Statistical Considerations

9.1 Statistical Hypotheses

For the primary endpoint (SPADI scores), the formal and testable null and alternative hypotheses will be as follows:

Primary Objective Null Hypothesis: At 12 weeks follow-up, the effect of progressive resistance exercise training (PRET) is not superior to the effect of standard care among head and neck cancer survivors experiencing shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy from neck dissection, as measured by the change in SPADI scores from baseline.

Primary Objective Alternative Hypothesis: At 12 weeks follow-up, PRET is superior to standard care in reducing SPADI scores among head and neck cancer survivors experiencing shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy from neck dissection, as measured by the change in SPADI scores from baseline.

Given that a decrease in SPADI score is considered an improvement, the trial objective is to find a negative value after the comparison between SPADI score at baseline and follow-up. the superiority trial hypothesis is:

$$H_0: Mean_{treatment} - Mean_{control} \geq -MS \ vs \ H_1: Mean_{treatment} - Mean_{control} < -MS$$

Where “Mean” the average of the differences in SPADI scores and MS is the margin of superiority, which is a 5% difference.

For the key secondary endpoint (FACT-H&N scores), the formal and testable null and alternative hypotheses will be:

Secondary Objective Null Hypothesis: At 12 weeks follow-up, the effect of PRET is not superior to the effect of standard care among head and neck cancer survivors experiencing shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy from neck dissection, as measured by the change in FACT-H&N scores from baseline.

Secondary Objective Alternative Hypothesis: At 12 weeks follow-up, PRET is superior to standard care in improving FACT-H&N scores among head and neck cancer survivors experiencing shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy from neck dissection, as measured by the change in FACT-H&N scores from baseline.

Given that an increase in FACT H&N score is considered an improvement, the trial objective is to find a negative value after the comparison between FACT H&N score at baseline and follow-up. the superiority trial hypothesis is:

$$H_0: Mean_{treatment} - Mean_{control} \leq MS \ vs \ H_1: Mean_{treatment} - Mean_{control} > MS$$

Where “Mean” the average of the differences in FACT H&N scores and MS is the margin of superiority, which is a 5% difference.

Both the primary and key secondary endpoints will be analyzed by comparing the change in scores from baseline to the 12-week follow-up. The comparison will assess the superiority of PRET over standard care in terms of the change in SPADI and FACT-H&N scores.

9.2 Sample Size Determination

The sample size was determined based on the paired mean difference between baseline and 12 weeks follow-up for the treatment and control groups considering the three SPADI scores: pain, disability, and total score. The chosen statistical analysis will involve comparing the mean difference distributions using a two-sample independent t-test. The sample size calculation aimed to achieve a statistical power of 90% with a significance level alpha of 0.025, while considering a superiority margin of 5% (Figure 1). Additionally, a completion rate of 85% was taken into account to account for potential attrition with the intervention.

The sample size analysis was performed using the described parameters and considering enough size to guarantee power for all three SPADI scores (pain, disability, and total score). Based on the sample size calculation it was determined that a total sample size of 306 patients (153 patients per group) would be needed to detect a statistically significant difference (e.g., the average of differences in the treatment group is more than 5% lower than the average differences in the control group) in the improvement of the SPADI scores between the treatment and control groups at the 12-week follow-up compared to baseline, considering the 5% superiority margin and an anticipated completion rate of 85%.

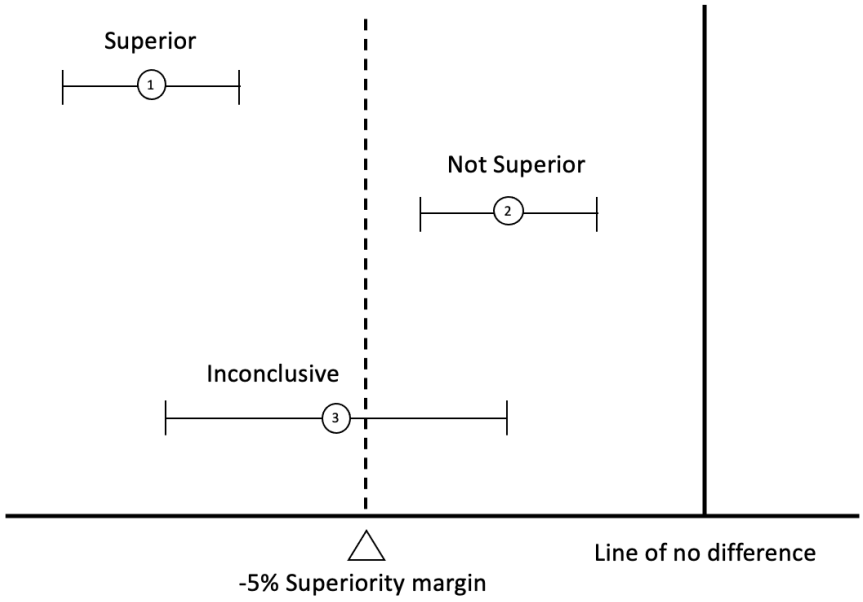


Figure 1. Proposed margin for the Superior trial.

9.3 Populations for Analyses

The analysis datasets for this study will be defined as: Intention-to-Treat (ITT), Safety, and Per-Protocol. The ITT analysis dataset will include all randomized head and neck cancer survivors who received either the PRET or standard care. This dataset will be used to assess the primary and secondary outcomes,

including the changes in SPADI and FACT-H&N scores, regardless of adherence or completion of the intervention.
The safety analysis dataset will consist of all participants who received at least one section of the assigned treatment (PRET or standard care). It will be used to evaluate the occurrence of adverse effects, adherence to the intervention, and overall tolerability of the progressive resistance exercise training. The per-protocol analysis dataset will be a subset of participants from the ITT dataset who complied with the study protocol sufficiently based on the requirements described in section 6.4 (Study Intervention Compliance, e.g., not missing more than 3 treatment sessions in a row or 3 treatment sessions over the course of 3 weeks). This dataset will ensure that the analysis represents the effects of the progressive resistance exercise training according to the scientific model.

9.4 Statistical Analyses

9.4.1 General Approach

For the descriptive analysis, categorical data will be presented as frequencies and percentages. Continuous data will be described using means with standard deviations for normally distributed variables or medians with interquartile ranges for skewed data. The range of values may also be reported to provide additional context.
For the inferential tests, baseline characteristics will be compared between groups using independent samples t-tests for continuous data and Pearson's chi-square test for categorical data. For outcome data analysis, independent samples t-tests will be conducted to compare changes between groups in outcomes from baseline to post-intervention (12-week follow-up). Probability levels of less than 0.025 will be accepted as statistically significant.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

For the primary endpoint, the SPADI scores divided into pain, disability and total score, the measurements represent the level of shoulder pain and disability experienced by head and neck cancer survivors. SPADI scores will be calculated by summing the responses to individual items in the SPADI questionnaire. The scale of SPADI scores is continuous and it is measured as a single endpoint at both baseline and the 12-week follow-up.
The statistical procedure used to analyze the primary endpoint will be a two-sample independent t-test. The change in SPADI scores from baseline to the 12-week follow-up will be compared between the treatment and control groups. The covariate of interest will be the treatment group assignment (PRET vs. standard care). Other potential covariates, such as age, sex, and type of neck dissection, may be included in the analysis using a linear regression model to control for potential confounders if necessary
The results of the statistical procedure will be presented as means with standard errors, indicating the mean change in SPADI scores for each group along with the corresponding standard errors. Additionally, confidence intervals for the mean differences between groups will be provided to assess the statistical significance of the findings.
Assumptions required for the t-test, such as normality of the data and homogeneity of variances, will be checked using appropriate diagnostic methods. If necessary, data transformations or nonparametric tests will be applied to meet these assumptions.

The analysis will be conducted in the ITT analysis dataset (section 9.3), including all randomized participants. Outliers will be identified and evaluated for their impact on the analysis. Nonadherence (section 6.4) and lost to follow-up will be considered as potential sources of bias if the proportion is different between the treatment and control group based on a Pearson's chi-square test or Fisher's exact test. If the test results are significant (p-value < 0.025), further investigation will be performed to understand the underlying reasons for the observed difference in nonadherence and lost to follow up between treatment and control group and the results will be reported in the trial results.

9.4.3 Analysis of the Secondary Endpoint(s)

For the secondary endpoint, FACT-H&N scores, the measurement represents the quality of life among head and neck cancer survivors experiencing shoulder dysfunction. FACT-H&N scores will be calculated by summing the responses to individual items in the FACT-H&N questionnaire. The scale of FACT-H&N scores is continuous and it is measured as a single endpoint at both baseline and the 12-week follow-up. The statistical procedure used to analyze the secondary endpoint will be a two-sample independent t-test. The change in FACT-H&N scores from baseline to the 12-week follow-up will be compared between the treatment and control groups. Similar to the primary endpoint analysis, the covariate of interest will be the treatment group assignment (PRET vs. standard care), and other potential covariates, such as age, sex, and type of neck dissection, may be included in the analysis using a linear regression model to control for confounding if necessary.

The results of the statistical procedure will be presented as means with standard errors, indicating the mean change in FACT-H&N scores for each group along with the corresponding standard errors. Confidence intervals for the mean differences between groups will be provided to assess the statistical significance of the findings and display superiority. Superiority is established if confidence intervals indicated are entirely above the 5% margin of superiority (e.g., both upper and lower bounds have to show >5% lower scores in treatment group)

Assumptions required for the t-test, such as normality of the data and homogeneity of variances, will be checked using appropriate diagnostic methods. If necessary, data transformations or nonparametric tests will be applied to meet these assumptions.

The analysis will be conducted in the ITT analysis dataset (section 9.3), including all randomized participants. Outliers will be identified and evaluated for their impact on the analysis

9.4.4 Safety Analyses

Safety analyses will be conducted to assess the occurrence of adverse effects, adherence, and overall tolerability of the PRET treatment among head and neck cancer survivors experiencing shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy from neck dissection. The safety analysis dataset (section 9.3) ßwill include all participants who received at least one dose of the assigned treatment (PRET or standard care). Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be calculated as the number of AEs experienced by each participant, counted once only.

The safety endpoints will be analyzed using descriptive statistics, presenting the severity, frequency, and relationship of AEs to the study intervention. Information reported for each AE will include the start date, stop date, severity, relationship to the intervention, expectedness, outcome, and duration. Adverse events

leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented either in a table or a listing.
Additionally, the safety analysis will investigate the adherence and completion rates for PRET. Adherence will be defined as the proportion of scheduled PRET sessions completed by each participant, while completion will be determined by the proportion of participants who completed the full course of the intervention. These rates will provide insights into the feasibility and acceptability of maintaining progressive resistance exercise training for longer periods of time.

9.4.5 Baseline Descriptive Statistics

Baseline descriptive statistics will be conducted to compare the intervention groups on various baseline characteristics, including demographics and medical measurements. This analysis aims to provide an overview of the initial characteristics of the participants and assess any potential differences between the groups at baseline.
Categorical data, such as sex and neck dissection type, will be presented as frequencies and percentages to describe the distribution of participants across different categories. Continuous data, such as age and baseline SPADI and FACT-H&N scores, will be summarized using means and standard deviations for variables that follow a normal distribution. Median and interquartile range will be used for skewed data.
To compare baseline characteristics between the intervention groups, independent samples t-tests will be used for continuous variables, such as age. Pearson's chi-square test or Fisher's exact test will be utilized for categorical variables, including sex and neck dissection type. This will allow for the identification of any statistically significant differences in baseline characteristics between the groups.

9.4.6 Planned Interim Analyses

Given the context of this study, it has been determined that no interim analysis will be performed. This decision is based on several factors. Firstly, the intervention period of 12 weeks is relatively short and does not warrant an interim evaluation of the data. Secondly, as the primary and secondary endpoints are measured at the end of the 12-week intervention period, any interim analysis would not provide a full or accurate understanding of the treatment effects. Lastly, while safety is a crucial aspect of any intervention, the PRET is not expected to result in severe adverse effects that would necessitate immediate cessation of the study. Therefore, it is deemed appropriate and more efficient to analyze the data upon completion of the study to assess the full effects of the intervention.

9.4.7 Subgroup Analyses

Subgroup analyses for the primary and secondary endpoints, involving SPADI and FACT-H&N scores respectively, will be conducted based on age (continuous), sex, and type of neck dissection. However, these analyses are for exploratory purposes and are not directly linked to the primary and secondary questions of the intervention. The goal is to uncover potential variations in the effects of PRET across different demographic and clinical groups. Although these analyses might provide additional insights into the applicability of PRET among varied groups, they are not powered to detect differences and their results will be interpreted with caution, not leading to definitive conclusions about the intervention's efficacy. Such analyses include descriptive statistics of baseline characteristics, end-of-study characteristics, and adherence rates. Analysis may include t-tests and linear regression as described for the primary and secondary outcomes.

9.4.8 Tabulation of Individual participant Data

Individual participant data will be arranged and tabulated according to different analysis datasets, namely: Intention-to-Treat (ITT), Safety, and Per-Protocol. For the ITT dataset, all randomized participants' SPADI and FACT-H&N scores at baseline and the 12-week follow-up will be listed, irrespective of intervention adherence or completion. The Safety dataset will contain participant-level data for those who received at least one session of the assigned treatment, including details on adverse events and adherence to the intervention (based on section 6.4). For the Per-Protocol dataset, a listing of participants who adhered (based on section 6.4) to the study protocol will be maintained, detailing their response to the intervention and outcome measures. Across all datasets, demographic and clinical characteristics such as age, sex, and type of neck dissection will be listed, fostering transparency and facilitating detailed exploratory analyses.

9.4.9 Exploratory Analyses

The study incorporates ancillary questions to investigate variations in adherence, completion rates, and the effects of age, sex, and neck dissection type on SPADI and FACT-H&N scores. Cross-sectional analyses will be carried out for these comparisons. Linear regression analyses may be utilized to model the relationship between these factors and outcomes, while controlling for potential confounding variables (e.g., age, sex, cancer type, surgery type). Interactions between factors (e.g., previously listed confounders) will also be examined if necessary. The results of these analyses will be used to identify possible patterns or associations that could inform future research and clinical practice.

10 Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

All participants will be provided a verbal and written explanation of study protocols in their preferred language. Participants will be informed they have equal opportunity to be randomized into the treatment or control group. Participants will provide signed consent and consent will be kept in study team records. Only participants who are able to understand written and/or verbal study instructions will be allowed to participate. Individuals who are unable to provide consent themselves will not be permitted to join the study.

10.1.2 Study Discontinuation and Closure

This study team does not anticipate any SAEs due to the nature of the study. We will allow all participants the opportunity to complete 12 weeks of treatment and will not terminate treatment early for compliant participants.

10.1.3 Confidentiality and Privacy

All participant records will be kept in secure files on encrypted computers and physical records will be kept in a secure office location only accessible to the study team. All team members will be required to participate in confidentiality and ethics training. Team members must keep their training credentials up to date and repeat the training every other year. Data will be de-identified for statistical analysis. Only the study team will be able to link participant ID to participant personal information.

10.1.4 Future Use of Stored Specimens and Data

De-identified data can be made available at the discretion of the funding source. All personal information will remain confidential indefinitely. The study team may use the data in the future for exploratory analysis purposes.

10.1.5 Key Roles and Study Governance

Name	Role
Richard Yim UC Davis rpyim@ucdavis.edu	Principal Investigator
Brittany Lemmon UC Davis blemmon@ucdavis.edu	Medical Monitor, Co-Investigator
Paulo Henrique De Alcantara Rocha UC Davis phrocha@ucdavis.edu	Statistician, Co-Investigator
Xi Chen UC Davis acxchen@ucdavis.edu	Co-Investigator
Julianna Mendez UC Davis jlmendez@ucdavis.edu	Co-Investigator

10.1.6 Safety Oversight

Safety Monitoring Committee (SMC), Data Safety Monitoring Board (DSMB, Safety Assessment Committee, and an Independent Safety Monitor (ISM) will be provided from the University of Alberta.

10.1.7 Clinical Monitoring

Treatment sessions will be monitored by a physical therapist. Any AEs and SAEs will be reported to the study team. AEs and SAEs will be reviewed by the medical monitor in conjunction with the participant's personal physicians to determine if the participant can continue in the study.

10.1.8 Quality Assurance and Quality Control

The statistician will do regular spot checks of data to ensure data quality. All participants, physicians, and physical therapists will be provided the same forms to ensure data collection is consistent across all parties. Several copies of the data will be available electronically to ensure any accidental deletions or changes to the data can be restored.

10.1.9 Data Handling and Record Keeping

The physical therapy clinic will be responsible for keeping records of treatment progress for each patient. The records will be regularly reported to the study team. Only the study team and physical therapy clinic

will have access to patient records. The statistician will have access to all datasets and perform regular data quality checks.

10.1.10 Protocol Deviations

A protocol deviation refers to any failure to comply with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, or Manual of Procedures (MOP) requirements. Such noncompliance can occur among the participant, investigators, or the staff at the study site. When deviations occur, the study team is responsible for promptly developing and implementing corrective actions.

10.1.11 Publication and Data Sharing Policy

All data will remain confidential and private during the course of the study. De-identified data may be made available for research purposes at the discretion of the funding source and monitoring committees. The results of the study will be written both for the funding source but also to produce a manuscript which will be submitted for publication in a peer-reviewed journal. This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical for a successful study. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the monitoring committees has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 Additional Considerations

Transportation to physical therapy treatment may be provided on an individual basis to ensure all participants have equal opportunity to attend treatment sessions.

10.3 Abbreviation

PRET: Progressive Resistance Exercise Training

CCI: Cross Cancer Institute

CT: Computed Tomography Scan

MRI: Magnetic Resonance Imaging

ROM: Range of Motion

SPADI: Shoulder Pain and Disability Index

FACT-H&N: The Functional Assessment of Cancer Therapy-Head and Neck

LSI: Leisure Score Index

QOL: Quality of Life

HNQOL: Head and Neck Quality of Life

IMRT: Intensity Modulated Radiation Therapy

RND: Radical Neck Dissection

MND: Modified Neck Dissection

SND: Selective Neck Dissection

10.4 Protocol Amendment History

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale

11 References

1. McNeely, M. L., Parliament, M., Courneya, K. S., Seikaly, H., Jha, N., Scrimger, R., & Hanson, J. (2004). A pilot study of a randomized controlled trial to evaluate the effects of progressive resistance exercise training on shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy in head and neck cancer survivors. *Head & Neck: Journal for the Sciences and Specialties of the Head and Neck*, *26*(6), 518-530.
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12 Appendix

12.1 Example Randomization Table

ID	Enrollment Order	Random Integer (1-10)	Random Assignment
1	1	10	B
2	2	1	A
3	3	7	B
4	4	4	A
5	5	6	B
6	6	3	A
7	7	7	B
8	8	1	A
9	9	1	A
10	10	3	A
11	11	7	B
12	12	9	B
13	13	9	B
14	14	1	A
15	15	3	A
16	16	1	A
17	17	10	B
18	18	6	B
19	19	9	B
20	20	4	A
21	21	6	B
22	22	1	A
23	23	7	B
24	24	6	B
25	25	7	B
26	26	7	B
27	27	7	B
28	28	5	A
29	29	2	A
30	30	4	A
31	31	2	A
32	32	1	A
33	33	7	B
34	34	5	A
35	35	2	A
36	36	5	A
37	37	3	A
38	38	10	B
39	39	6	B
40	40	9	B
41	41	4	A
42	42	9	B
43	43	4	A
44	44	7	B
45	45	2	A
46	46	2	A
47	47	9	B
48	48	7	B
49	49	3	A
50	50	8	B

ID	Enrollment Order	Random Integer (1-10)	Random Assignment
51	51	5	A
52	52	6	B
53	53	3	A
54	54	3	A
55	55	6	B
56	56	8	B
57	57	1	A
58	58	6	B
59	59	6	B
60	60	10	B
61	61	5	A
62	62	5	A
63	63	2	A
64	64	1	A
65	65	5	A
66	66	6	B
67	67	6	B
68	68	3	A
69	69	3	A
70	70	2	A
71	71	4	A
72	72	10	B
73	73	7	B
74	74	9	B
75	75	1	A
76	76	3	A
77	77	7	B
78	78	7	B
79	79	7	B
80	80	8	B
81	81	3	A
82	82	8	B
83	83	3	A
84	84	10	B
85	85	5	A
86	86	7	B
87	87	6	B
88	88	5	A
89	89	3	A
90	90	4	A
91	91	2	A
92	92	1	A
93	93	1	A
94	94	9	B
95	95	7	B
96	96	9	B
97	97	5	A
98	98	6	B
99	99	9	B
100	100	10	B

ID	Enrollment Order	Random Integer (1-10)	Random Assignment
101	101	6	B
102	102	10	B
103	103	8	B
104	104	9	B
105	105	6	B
106	106	2	A
107	107	9	B
108	108	8	B
109	109	2	A
110	110	6	B
111	111	10	B
112	112	9	B
113	113	5	A
114	114	7	B
115	115	9	B
116	116	9	B
117	117	6	B
118	118	7	B
119	119	2	A
120	120	4	A
121	121	8	B
122	122	6	B
123	123	8	B
124	124	1	A
125	125	3	A
126	126	6	B
127	127	4	A
128	128	9	B
129	129	8	B
130	130	9	B
131	131	1	A
132	132	10	B
133	133	9	B
134	134	2	A
135	135	1	A
136	136	1	A
137	137	6	B
138	138	3	A
139	139	8	B
140	140	8	B
141	141	3	A
142	142	3	A
143	143	3	A
144	144	9	B
145	145	4	A
146	146	5	A
147	147	7	B
148	148	4	A
149	149	10	B
150	150	5	A

ID	Enrollment Order	Random Integer (1-10)	Random Assignment
151	151	8	B
152	152	5	A
153	153	6	B
154	154	9	B
155	155	1	A
156	156	5	A
157	157	4	A
158	158	1	A
159	159	10	B
160	160	3	A
161	161	4	A
162	162	3	A
163	163	7	B
164	164	3	A
165	165	7	B
166	166	1	A
167	167	4	A
168	168	7	B
169	169	4	A
170	170	10	B
171	171	10	B
172	172	6	B
173	173	7	B
174	174	3	A
175	175	4	A
176	176	2	A
177	177	7	B
178	178	10	B
179	179	3	A
180	180	10	B
181	181	5	A
182	182	3	A
183	183	9	B
184	184	5	A
185	185	6	B
186	186	8	B
187	187	4	A
188	188	9	B
189	189	7	B
190	190	2	A
191	191	6	B
192	192	3	A
193	193	7	B
194	194	7	B
195	195	1	A
196	196	2	A
197	197	9	B
198	198	4	A
199	199	1	A
200	200	3	A

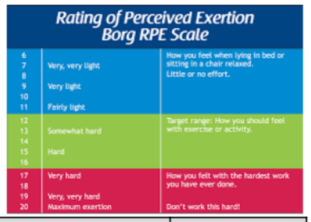
ID	Enrollment Order	Random Integer (1-10)	Random Assignment
201	201	4	A
202	202	8	B
203	203	2	A
204	204	3	A
205	205	10	B
206	206	1	A
207	207	8	B
208	208	7	B
209	209	10	B
210	210	3	A
211	211	1	A
212	212	6	B
213	213	1	A
214	214	8	B
215	215	4	A
216	216	1	A
217	217	4	A
218	218	8	B
219	219	4	A
220	220	8	B
221	221	9	B
222	222	3	A
223	223	10	B
224	224	2	A
225	225	5	A
226	226	3	A
227	227	5	A
228	228	2	A
229	229	5	A
230	230	10	B
231	231	3	A
232	232	1	A
233	233	7	B
234	234	1	A
235	235	4	A
236	236	1	A
237	237	2	A
238	238	6	B
239	239	4	A
240	240	4	A
241	241	5	A
242	242	4	A
243	243	3	A
244	244	10	B
245	245	8	B
246	246	5	A
247	247	4	A
248	248	10	B
249	249	4	A
250	250	9	B

ID	Enrollment Order	Random Integer (1-10)	Random Assignment
251	251	3	A
252	252	2	A
253	253	10	B
254	254	6	B
255	255	5	A
256	256	6	B
257	257	8	B
258	258	1	A
259	259	1	A
260	260	1	A
261	261	8	B
262	262	9	B
263	263	9	B
264	264	6	B
265	265	2	A
266	266	3	A
267	267	9	B
268	268	5	A
269	269	8	B
270	270	3	A
271	271	8	B
272	272	5	A
273	273	7	B
274	274	2	A
275	275	8	B
276	276	9	B
277	277	6	B
278	278	8	B
279	279	8	B
280	280	6	B
281	281	10	B
282	282	3	A
283	283	7	B
284	284	3	A
285	285	5	A
286	286	6	B
287	287	7	B
288	288	10	B
289	289	7	B
290	290	8	B
291	291	3	A
292	292	9	B
293	293	3	A
294	294	1	A
295	295	2	A
296	296	10	B
297	297	3	A
298	298	9	B
299	299	10	B
300	300	8	B

ID	Enrollment Order	Random Integer (1-10)	Random Assignment
300	300	8	B
301	301	8	B
302	302	4	A
303	303	9	B
304	304	2	A
305	305	4	A
306	306	7	B
307	307	6	B
308	308	2	A

12.2 PRET Compliance Form

PRET Completion Form	
Participant ID:	
Date:	
Hour:	
Visit:	
Tester Initials:	



Exercise (15-20 reps)	Completion of 1 set	Completion of 2 sets	Total Time Elapsed	Reason for Not Completing	Comments/Observations	Borg RPE Score (6-20)
Range of Motion Warm Up (1 set 5-10 min)	☐	☐				
Rhomboids: Scapular retraction	☐	☐				
Levator scapula: Scapular elevation	☐	☐				
Biceps: Elbow flexion	☐	☐				
Triceps: Elbow extension	☐	☐				
Infraspinatus, posterior deltoid: external rotation	☐	☐				
Middle deltoid, suprasinatus and subscapularis: Abduction in the plane of the scapula	☐	☐				
Cool Down Stretching (1 set 5-10 min)	☐	☐				