PROTOCOL

Getting Recovery Right After Neck Dissection for Head and Neck Cancer (GRRAND)

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TABLE OF CONTENTS **PAGE**

This study is funded by the NIHR [Health Technology Assessment (HTA) Programme (HTA Project: NIHR158902). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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LIST OF TABLES PAGE

LIST OF FIGURES PAGE

This study is funded by the NIHR [Health Technology Assessment (HTA) Programme (HTA Project: NIHR158902). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

TRIAL SUMMARY

Trial Title	Getting Recovery Right After Neck Dissection for Head and Neck Cancer (GRRAND)	
Internal ref. number	GRRAND	
Clinical Phase	Phase III	
Trial Duration	1st February 2025 to 28th February 2028	
Trial Design	Two-arm, multi-centre, pragmatic RCT with internal pilot, integrated health economic evaluation and process evaluation	
Trial Participants	Adults with Head and Neck Cancer requiring primary neck dissection as part of their treatment with curative intent	
Planned sample size	390 participants (195 in each arm) from at least 12 UK sites	
Intervention	Six (1-hour) sessions of a personalised physiotherapy-led rehabilitation programme (GRRAND programme) delivered over six months	
Comparison	Best usual practice, NHS, post-discharge care	
Treatment Duration	From first postoperative week up to six months	
Follow-up	Postal or electronic at six weeks, three, six and 12 months	
Pilot study	Open four sites and recruit 40 participants within six months	
	Objectives	**Outcome Measures**
Primary	*Clinical Effectiveness:* *Cost-Effectiveness:*	Shoulder pain and function at 12-months using the participant-reported Shoulder Pain and Disability Index (SPADI) questionnaire (total score) Base-case within trial analysis of cost per quality-adjusted life-year (cost/QALY)
Secondary	To quantify and draw inferences on pain, function, quality of life, mental wellbeing, health utility, resource use and adverse events at six weeks, three, six and 12-months after randomisation	All assessed at six weeks, three, six and 12-months unless specified otherwise • SPADI total score (secondary outcomes at six weeks and 6-months only) • Individual SPADI domains (pain and disability) • Health-related quality of life (EQ-5D-5L*; EORTC cancer-specific questionnaires

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		(C30(core); H&N35(head and neck specific)) • Mental wellbeing using the Short Warwick-Edinburgh Mental Wellbeing Scale • Exercise adherence using the Exercise Adherence Rating Scale (EARS) at six-weeks only • Adverse events including surgical complications* • Health resource use questionnaire* (*three-month assessment for adverse events, EQ-5D-5L and health utilisation questionnaire only)
Sub-studies	**Objectives**	**Outcome Measures**
Process Evaluation	To evaluate trial processes, intervention mechanisms, fidelity and context with a multi-methods process evaluation to inform, if appropriate, further implementation	Observation, intervention and trial CRFs, exercise adherence using the Exercise Adherence Rating Scale; individual interviews

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LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
ASA	American Society of Anesthesiologists
CACE	Complier Average Causal Effect
CI	Chief Investigator
CERT	Consensus on Exercise Reporting Template
CIn	Confidence Interval
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DMP	Data Management Plan
EARS	Exercise Adherence Rating Scale
EDI	Equality, Diversity, Inclusion
EORTC	European Organisation for Research & Treatment of Cancer
GCP	Good Clinical Practice
GP	General Practitioner
GRRAND	Getting Recovery Right After Neck Dissection
HEAP	Health Economics Analysis Plan
HNC	Head and Neck Cancer
HPV	Human Papillomavirus
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICEs	Intercurrent events
ICF	Informed Consent Form
ID	Identification
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention To Treat
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council

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NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NRS	Numerical Rating Scale
PEAP	Process Evaluation Analysis Plan
PI	Principal Investigator
PIS	Participant Information Sheet
PPIE	Patient & Public Involvement and Engagement
PROMs	Patient Reported Outcome Measures
QALYs	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SPADI	Shoulder Pain and Disability Index
SWEMWBS	Short Warwick Edinburgh Wellbeing Scale
TiDieR	Template for Intervention Description and Replication
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TMP	Trial Monitoring Plan
TSC	Trial Steering Committee
UHCW	University Hospitals Coventry and Warwickshire
UK	United Kingdom
UKCRC	UK Clinical Research Collaboration
UK GDPR	UK General Data Protection Regulation
VAS	Visual Analogue Scale
WCTU	Warwick Clinical Trials Unit

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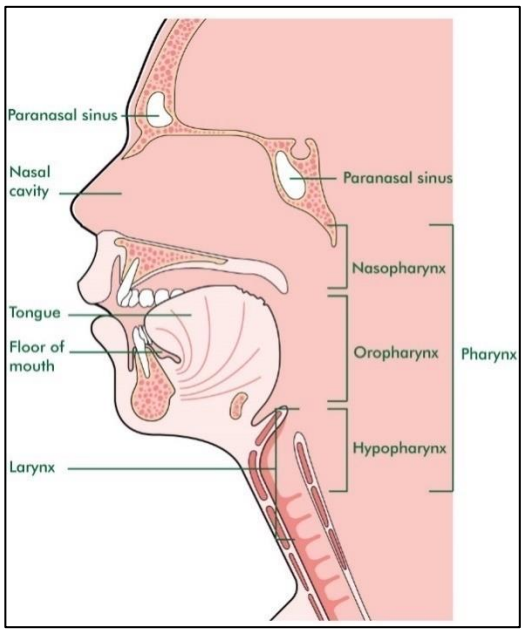
1. BACKGROUND

1.1 Epidemiology and burden of the condition

There is a global increase in head and neck cancer (HNC) incidence, attributed in-part to the impact of the human papillomavirus (HPV) [1-3]. Annually, HNCs are diagnosed in 700,000 people worldwide, with over 12,000 new cases in the UK [2]. These cancers affect the mouth, throat, salivary glands, larynx, nose or sinuses. The incidence of HNC has increased rapidly in the last 20 years, in particular in the oropharynx where the role of HPV has led to a doubling in disease incidence. It is expected to increase until, at least, 2045 when impacts of changes in the HPV vaccination should reduce incidence [4,5]. People affected by HNC are now younger and more active [6,7].

The treatment pathway for HNC is complex due to the varied anatomical sites of disease and patient needs (**Figure 1**). While treatment may involve a single modality of surgery, radiotherapy, chemotherapy or chemo-radiotherapy, many require multimodality approaches. Neck dissection is the most common component of surgical treatment both as primary treatment and following any disease relapse. It involves surgical removal of at-risk lymph nodes in the neck [8]. Although neck dissection surgery has developed over the years, the procedure is still extensive, with incisions ranging from the clavicle to jawbone, and sometimes on both sides of the neck. The aim of surgery is to visualise and extract lymph nodes harbouring, or at risk of harbouring, tumour.

Figure 1: Locations for HNC



Whilst treatment at the primary presentation has improved, treatment-associated morbidity remains a long-term problem, impacting on people's health-related quality of life (HRQoL) and with economic societal/health service consequences. Side-effects from a neck dissection can be debilitating and disabling. They include neck and shoulder problems, difficulties sleeping, fatigue and generalised anxiety [9,10]. Post-operatively, neck dissection surgery is associated with both early and late complications. Shoulder dysfunction is by far the most common and occurs in at least half and sometimes in all patients reported in different surgical series in the literature [11-14]. Over 30% of people still experience shoulder pain and reduced function 12 months post-operatively [15]. Where shoulder and musculoskeletal pain and dysfunction appear as late complications, these can persist for five years and beyond [16]. The sequelae of shoulder dysfunction and psychosocial complications

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are strongly associated with reduced return to work. Up to half of people report an inability to work after treatment due to shoulder disability alone [17,18]. Psychosocial complications are also highly prevalent post-operatively, predominantly anxiety and depression, but people also experience fatigue, social isolation and body image [19].

Currently there are no national guidelines for post-operative rehabilitation after neck dissection for HNC. Physiotherapy and rehabilitation provision in the UK is minimal [20]. Where service provision exists, practice is varied and includes acute respiratory care, range of motion exercises for the neck and shoulder, and advice on positioning the upper limb and shoulder girdle. A booklet or leaflet may be provided to supplement this treatment [20]. Outpatient treatment is minimal, and often reactive, with patients being referred by their GP only if a problem has been identified [21].

For these reasons, the clinical and patient community require an effective, evidence-based rehabilitation programme for people following neck dissection for HNC.

1.2 Existing knowledge

There is clinical uncertainty regarding the most effective form of rehabilitation following neck dissection for HNC.

Our published systematic review of rehabilitation following neck dissection for HNC [22] has been updated for this protocol. The literature search was developed in collaboration with our Clinical Advisory Group using the published literature databases EMBASE, MEDLINE, CINAHL and PubMed. We accessed clinical trial registries for unpublished or ongoing clinical trials including the WHO International Clinical Trial Registry and ClinicalTrials.gov. The search was conducted from database inception to 01 April 2024. No restrictions were placed on the search with respect to date of publication, risk of bias or language of publication.

Six systematic reviews have been conducted on rehabilitation after HNC surgery; one Cochrane review [15] and three non-Cochrane reviews [23-25] investigating physiotherapy for shoulder dysfunction following HNC, a systematic literature review performed as part of the 2016 NICE guidelines [21] and our team's systematic review of hospital and out-patient rehabilitation following neck dissection for HNC [22].

Whilst these highlight 'promise' that rehabilitation may be beneficial for this population, they also emphasise that the current evidence is largely underpowered (sample sizes ranging n=20 to 52 [23,24]), no data on cost-effectiveness, and are of low methodological quality, with an urgent need for high-quality intervention trials to guide treatment [21]. Of six small-scale RCTs investigating rehabilitation after neck dissection for HNC, only one trial (n=32) followed people for up to 12 months after treatment [25].

Six, small-scale, RCTs of low-quality have assessed rehabilitation interventions for people following neck dissection for HNC [23-28]. Trials have been conducted in Canada, India, Taiwan and Scotland. McNeely et al [23,24](N=20; N=52) investigated out-patient exercise-based physiotherapy versus no out-patient physiotherapy. They reported improvements in muscle range of motion and strength at 12-weeks post-treatment, but no statistically significant differences in quality of life, fatigue or neck dissection impairment between the groups at 12 weeks. Lauchlan et al [25] (N=32) investigated the effectiveness of post-operative out-patient physiotherapy for three-months post-neck dissection compared to no out-patient physiotherapy. They reported no between-group differences at 12-months post-operatively although suggested a 'signal' in the effect of the physiotherapy programme on physical well-being. Thomas et al [26] (N=48) compared a post-operative active range of motion

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exercise programme to a muscle energy technique physiotherapy intervention. Outcomes to 10 days indicated limited between-group differences. Finally, Chen et al's [30](N=38)/[28](N=24) trials compared motor-control exercises versus regular exercise for people following neck dissection for HNC. They reported beneficial outcomes on range for some shoulder movements after one month [27] and three months [28] following motor-control exercise. They did not assess wider outcomes such as quality of life, pain or disability [27,28].

We conducted a national survey of rehabilitation following HNC in 2018 [20]. This survey gained data from nine UK high-volume HNC centres. Respondents represented eight geographically and socioeconomically diverse regions of the UK, including the North East, North West, West Midlands, London, South East, South West, Yorkshire and the Humber. The estimated number of neck dissections performed annually in each region ranged from 70-400 (mean: 152). There was national variability in rehabilitation provision post-operatively. No centre routinely offered post-discharge (out-patient) physiotherapy for these patients. Physiotherapy was mostly provided as 'reactive' thus offered when specific complications developed (78% hospitals). The team's UK network and Clinical Advisory Group indicate that this has not substantially changed since 2018. The only established adaptation has been the provision of a hybrid approach to rehabilitation for some patients following the COVID-19 pandemic.

FEASIBILITY STUDY:(conducted 2020 to 2022)[29-31]
In response to a lack of evidence, we developed and tested a newly designed, structured rehabilitation programme. We randomised 36 participants undergoing a neck dissection for HNC from two NHS hospitals (Oxford and Norwich), to receive usual NHS care versus usual NHS care *PLUS* a structured, personalised, physiotherapy-led programme (the GRRAND programme). The study achieved five of six feasibility targets (progression criteria presented in full in [31]). Our recruitment target was lower than planned, 36 of 60 participants over 18 months, due to the COVID-19 pandemic.

We captured patient-reported and clinical outcomes over six months to assess a potential signal of effect. The Shoulder Pain and Disability Index (SPADI) score [32] indicated lower shoulder and arm disability for those who received the GRRAND programme compared to usual care (SPADI disability: mean: -13.6 (95% confidence intervals (CI):-25.5 to -1.6). Higher HRQoL was found at six and 12 months after the GRRAND programme compared to usual care (EQ-5D-5L utility mean: 0.8 (standard deviation (SD):0.1) versus 0.5 (SD:0.5) and EQ-5D visual analogue scale (VAS) scores (mean: 78.4 (SD:18.8) versus 71.5 (SD:14.9)). We found lower pain scores after the GRRAND programme compared to usual care at six months (mean numerical rating score (NRS): 1.7 (SD:1.3) versus 2.8 (SD:2.4)) and 12 months (mean NRS: 4.3 (SD:4.2) versus 2.4 (SD:2.5)).

We interviewed eight participants and five physiotherapists to explore the acceptability of the GRRAND programme [30]. Patients and health professionals felt that current NHS usual care was insufficient and failed to meet patients' rehabilitation needs. They considered GRRAND acceptable, providing much needed, biopsychosocial support. Participants who received the programme reported feeling more confident in performing rehabilitation exercises and more motivated to engage in long-term adaptive behaviour change.

Our feasibility study demonstrated: (1) the GRRAND programme was feasible to deliver and was acceptable to patients and NHS staff; (2) a signal with respect to improved post-neck dissection shoulder/arm function, pain and HRQoL; and (3) found the supportive rehabilitation booklet was acceptable. These provide assurance that this trial can be delivered robustly and per protocol.

1.3 Hypothesis

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Aims: To determine whether a personalised physiotherapy-led rehabilitation programme (the GRRAND programme) or best usual practice, NHS, post-discharge care is the most clinically effective and cost-effective approach for improving health-related outcomes in adults after neck dissection for HNC.

Research Question: For adults undergoing neck dissection for HNC, which recovery strategy is most effective at improving participant-reported shoulder function and most cost-effective; a personalised physiotherapy-led rehabilitation intervention (the GRRAND programme) or usual NHS practice post-discharge care?

1.4 Need for a trial

Shoulder dysfunction is the most reported physical complication following a neck dissection for HNC. The incidence of HNC has increased rapidly in the last 20 years and is expected to increase until, at least, 2045 [4,5]. It presents with impaired joint mobility, reduced strength and chronic pain [9,11]. Additional complications such as adhesive capsulitis are reported in approximately 40% of patients [11]. Associated psychosocial complications are common, with a prevalence of anxiety or depression of up to 35% [13]. These factors impact at an individual and societal level, with reduced work-place productivity and greater reliance on income support. This is particularly important given people affected by HNC are now younger, with higher social expectations post-treatment [6,7]. Rehabilitation has the potential to increase people's functional independence to improve HRQoL, facilitate return to family, work and societal roles, and reducing economic burden.

In the UK, the increasing incidence of HNC in an active, working age population [14] and improved survival, highlights the importance of post-surgical rehabilitation. With this increase in HNC, and change in demographic profile of these patients, identifying a rehabilitation intervention which will effectively serve the needs of this population, is important both for individual outcomes but also health and social costs in NHS utilisation and societal impacts. There is currently no robust evidence-based rehabilitation programme for this population. Accordingly, this trial will test a personalised, structured physiotherapy-led rehabilitation intervention, aimed at improving both physical and psychosocial health following neck dissection for HNC.

1.5 CONSORT

The trial will be reported in-line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement [33].

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

This is a multi-centre, pragmatic RCT with 1:1 allocation, integrated health economic evaluation and process evaluation. The trial will include a six-month internal pilot to test detailed trial procedures, data collection and confirm the feasibility of recruitment and conduct. Participants will be followed over 12-months post-randomisation to assess shoulder function, HRQoL, adverse events and to collect cost data for economic evaluation.

The trial design follows a pragmatic approach and purposefully reflects the realities of treatment delivery in the NHS. The design is sufficiently powered (90% power with 5% significance) to enable us

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to assess the effects of the intervention. We have considered an early stopping rule but have rejected this as the treatment period is quite extended and there is no empirical evidence or intuitive link, between early response and later outcomes.

2.2 Aims and objectives

The overarching aim is to determine whether a personalised physiotherapy-led rehabilitation programme (the GRRAND programme) or best usual practice, NHS, post-discharge care is the most clinically effective and cost-effective approach for improving health-related outcomes in adults after neck dissection for HNC.

2.2.1 Primary objective

1. To compare the clinical effectiveness of the GRRAND programme versus best usual practice, NHS, post-discharge care, on participant-reported shoulder pain and function 12 months after randomisation using the SPADI.

2. To compare the cost-effectiveness of the GRRAND programme against best usual practice, NHS, post-discharge care from an NHS and personal social services perspective.

2.2.2 Secondary objective

Secondary objectives of the trial are to quantify and draw inferences on:

1. Post-operative pain, function, HRQoL, mental wellbeing, resource use, adverse events at six weeks, six months and 12 months after randomisation based on:
    - SPADI Total score and Painand Disability domains at six weeks and six months post-randomisation.
    - EORTC cancer-specific questionnaires (C30(core)[34] and H&N35(head and neck specific)[35] at six weeks, six and 12-months post-randomisation.
    - EQ-5D-5L [36] at six weeks, three, six and 12-months post-randomisation.
    - Exercise Adherence Rating Scale (EARS) [37] at six weeks post-randomisation only.
    - Short Warwick-Edinburgh Mental Wellbeing Scale (SWEMWBS) [38] at six weeks, six and 12-months post-randomisation.
    - Health resource use questionnaire at six weeks, three, six and 12-months post-randomisation.
    - Adverse events and post-operative complications at six weeks, three, six and 12-months post-randomisation.

2. Process evaluation of trial processes, intervention mechanisms including exercise adherence measured with the Exercise Adherence Rating Scale[37] for the GRRAND group at physiotherapy discharge, fidelity and context with a multi-methods process evaluation to inform, if appropriate, further implementation.

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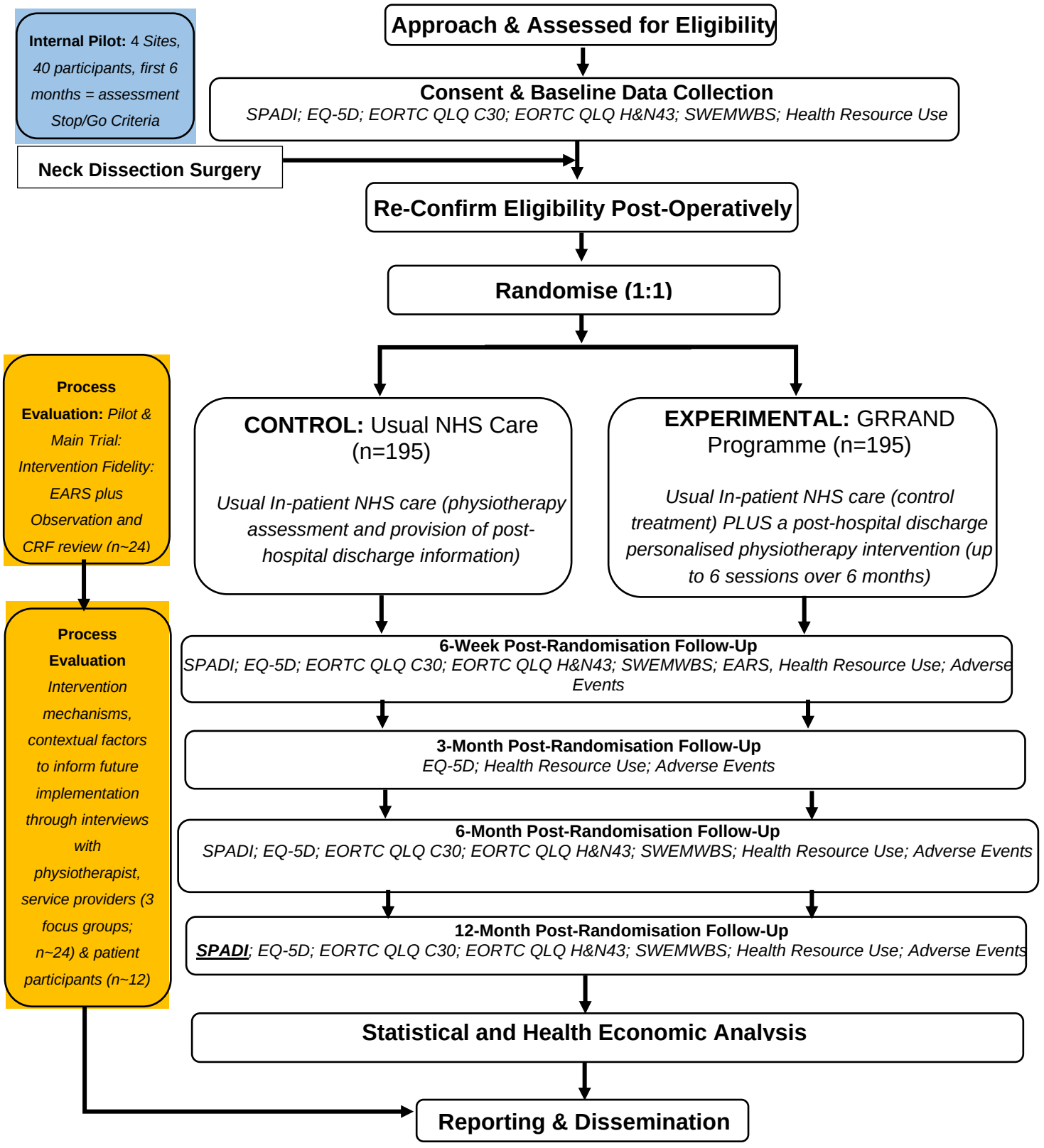
Figure 2: Trial Flow Diagram



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2.3 Outcome measures

2.3.1 Efficacy

The primary outcome is the SPADI (Total score) 12-months post-randomisation. This is a 13-item participant-reported shoulder-specific instrument (0-100, 100 best score). The sum of two domains (pain and disability) determines the full SPADI total score [32,39]. It has been widely used in previous shoulder, neck and upper limb trials [40,41], placing this trial in the context of the wider rehabilitation literature. It has been shown to be responsive to change in both surgical and non-surgical intervention trials [42]. The GRRAND programme is designed to prevent the onset of problems, and to restore function. This is for neck, shoulder and wider upper limb disability. Given the short and longer-term complications which this population report frequently relate to shoulder dysfunction [12], the SPADI is considered an appropriate outcome measure to assess the health technology under investigation.

The selection of the SPADI was confirmed by our PPIE and Clinical Advisory Groups and the qualitative interview data from our feasibility study [30]. Participants found it a short and understandable/acceptable questionnaire. From these sources, shoulder dysfunction was considered the principal challenge faced in the recovery following neck dissection for HNC. A 12-month follow-up has been chosen to allow sufficient time to return to normal levels of daily activity [43] and was considered the meaningful time to 'understand how I have recovered' from our PPIE Advisory Group. There was a signal of effect from our feasibility study that the GRRAND programme may offer superiority to best practice usual NHS care at six-month assessment (SPADI disability: between-group mean difference: -13.56 (95% (CIn):-25.52,-1.60))[31]. Whilst this is not the primary endpoint, it is plausible that this difference could be maintained at 12 months.

Secondary outcome measures collected at baseline, six weeks, six- and 12-months post-randomisation: SPADI score (Total)[32]; SPADI Pain and Disability domains[32], HRQoL using the EORTC cancer-specific questionnaires (C30(core)[34] and H&N35(head and neck specific)[35]; exercise adherence EARS [37] (only at six-weeks), EQ-5D-5L [36] (with additional three month assessment); mental wellbeing using the Short Warwick-Edinburgh Mental Wellbeing Scale (SWEMWBS) [38]; and health resource use questionnaire (with additional three month assessment); adverse events and post-operative complications (with additional three month assessment).

Separate process evaluation measures including the number of staff trained; schedule and location of session delivery (in-patient, out-patient, virtual); hospital and rehabilitation CRFs and site visit observational checklists (for fidelity to protocols) will be measured. Exercise adherence questionnaires (EARS[37]) will be completed for all participants at the six-weeks post-randomisation data collection timepoint. For those randomised to the GRRAND programme, this will also be collected on physiotherapy discharge. . Potential issues for future implementation will be assessed qualitatively using site focus groups (staff) and interviews (participants). Given 0% contamination in the feasibility study [31], contamination will be monitored through review of treatment CRFs, cross-referenced with site delegation logs and site observations.

2.3.2 Safety

Adverse events (AEs) and serious adverse events (SAEs) related to the trial post-consent will be recorded on the appropriate CRF for return to the WCTU Trial Team and reported to the relevant oversight committees. Surgery apart from the index intervention will be considered an outcome. Treatment AE or SAE related to concomitant care such as chemo- or radiotherapy will not be considered recorded adverse events. Persistent pain without new pathology or another event will not be considered an AE as it will be recorded in outcome scores. SAEs will be followed-up until the end of the 12-month follow-up period. All AEs and SAEs will be managed in accordance with WCTU's SOPs.

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2.4 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.4.1 Inclusion criteria

1. People aged 18 years or over
2. Diagnosis of HNC with requirement for a neck dissection as part of their treatment with curative intent. Including those undergoing completion neck dissection following positive sentinel node biopsy or open neck node biopsy.
3. Able to attend out-patient physiotherapy appointments.
4. Provide informed consent.

2.4.2 Exclusion criteria

1. People for whom intensive post-discharge physiotherapy is expected (e.g., scapula/scapula tip and/or latissimus dorsi free flaps or components thereof). This constitutes 3-5% of the neck dissection population and clinical equipoise regarding the role of physiotherapy is less evident [20].
2. People with a pre-existing, long-term disease affecting the shoulder, e.g., hemiplegia.
3. People who had prior neck dissection surgery on the affected side.
4. People undergoing only Lymph Node Biopsy or Sentinel Lymph Node Biopsy.
5. Previous entry in the present trial.
6. Unable to adhere to trial processes.

N.B Patients who have been excluded from the trial due to meeting Exclusion Criteria 4 may subsequently become eligible for inclusion IF they require complete neck dissection.

2.5 Participant identification/screening

After the treatment plan has been discussed as part of a potential participant's multi-disciplinary care and they have been identified as needing a neck dissection, they will be approached, and if willing, screened for eligibility. Information will be given as early after presentation as possible, based on learning from our feasibility study and guided by our PPIE Advisory Group. This will ensure all those eligible are given the opportunity to participate. It is anticipated that this will largely be at surgical out-patient clinics, but the protocol will provide flexibility to ensure potential participants can be identified from other departments including pre-assessment clinics and wider oncology services prior to surgery.

Screening and eligibility will be assessed and confirmed by a clinician who is capable of doing so based on their current role, skills and knowledge and is listed on the delegation log. Eligibility can be assessed by routine clinical evaluation, with no requirement for any specific investigation. Appropriateness for study eligibility will be recorded on a CRF. Screening data will be entered directly on to the trial database (with any identifiers, except trial numbers, redacted for relevant database users). This will include details of the number of people presenting to recruiting clinical teams who are considered eligible, and the number who consent to enter the trial. These data will be monitored at monthly Trial Management Group (TMG) meetings and used to populate the CONSORT statement in the trial report.

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Once screened, potential participants will be given verbal and written information about the trial and invited to discuss the trial with a suitably trained member of the research team. Depending on the trial processes at individual sites, participant information sheets (PIS) may be posted or emailed to potential participants. Potential participants will be asked to read the PIS and to discuss their potential participation with anyone who they feel would provide useful advice such as friends, family, carers or a GP. The PIS will detail no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side-effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. Potential participants will also be provided with contact information for a member of the research team who will be able to answer any questions relating to the trial.

Potential participants will be given sufficient time to consider participation. In most units, there is a window of one to three weeks prior to surgery. Through this approach, participants will be allowed the opportunity to consent either in the out-patient clinic setting prior to surgery, or virtually using remote consent approaches. The consent form will also have the option for participants to be approached (if they wish) to take part in follow-up interviews, as part of the process evaluation.

As successfully adopted in our feasibility study [31], informed consent for participation in the trial and baseline assessments will be completed prior to surgery. After surgery, eligibility will be re-confirmed and if still eligible, participants will be randomised. No participant withdrawal occurred between consent to post-operative assessment in the feasibility study [31]. Patients who do not meet the inclusion criteria or who do not wish to participate will receive standard NHS treatment. We will record anonymous information on the age and sex of those who decline to participate so we can assess the generalisability of those recruited. The reasons for declining will also be recorded.

Consent will be sought pre-operatively. However, following surgery, participant's eligibility will then be verified by reviewing the medical/surgical notes and documents using the eligibility assessment form. Participants will be randomised once their eligibility has been checked post-operatively. This will be done prior to hospital discharge.

Eligible participants who do not wish to participate will be anonymously recorded as part of a screening log to provide information on age and gender, and, when provided, the reasons for declining participation.

2.7 Informed consent

The local PI retains overall responsibility for informed consent at their site and must ensure that any person listed on the site delegation log with the delegated responsibility to participate in the informed consent process, is duly authorised, trained and competent.

The Investigator or their suitably trained and delegated nominee will provide potential participants with both written and verbal information about what the trial entails. They will also answer any questions that the person may have concerning trial participation. Options for taking consent are listed below (Section 2.7.1 and Section 2.7.2).

If a person loses capacity to consent, with no expectation that they will regain it, then they will be treated in a consistent way as someone who has withdrawn (that is we will retain data up to the point that they lose capacity). If they regain capacity we will assume, unless they specifically withdraw it, that their previous consent stands, and will resume data collection activities.

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If any new information arises during the course of the trial that may affect participants' willingness to continue in the trial, they will be informed and, if applicable, renewed consent will be obtained using an amended consent form.

Participants' GPs will be informed by letter that they are taking part in this clinical trial.

We will monitor screening logs to assess for potential participants who are not fluent in written or spoken English and will make translations as necessary.

Trial procedures (i.e., those that occur after consent) including baseline assessments and randomisation, will not be undertaken until written/signed informed consent or witnessed remote verbal consent has been given and appropriately recorded in the patient's medical notes.

2.7.1 Consent of participants non-fluent in English

When taking consent for those not fluent in English, an NHS accredited translator or bilingual researcher will be available to help to ensure that participants receive a full explanation of the trial and to confirm their understanding, according to Warwick SOP 7.

For participating sites from Wales, the Participant Information Sheets and Consent Forms will be translated into Welsh or provided bilingually where this is requested by a participant, to comply with the Welsh Language Act 1993.

2.7.2 In-person consent

Written informed consent for those patients who undertake this in-person will be obtained by means of a participant-dated signature and a dated signature of the person who presented and obtained informed consent. Consent will be confirmed before any trial specific procedures are performed. Consent will be obtained at a patient's hospital appointment. A copy of the signed Consent Form will be provided to the participant, a copy will be stored in the participant's medical notes and the original signed form will be retained at the trial site in the ISF.

Participants, on completing the Consent Form, will provide confirmation that they:

- have read the PIS and had opportunity to consider the information, ask questions and have any questions satisfactorily answered
- understand that participation is voluntary and that they can withdraw at any time without providing reason and with withdrawal not affecting their medical care or legal rights
- consent to relevant sections of their medical notes and trial data to be reviewed by individuals from the sponsor (University of Warwick), regulatory authorities and NHS Trusts where relevant to participating in this research
- agree that their GP will be informed of their participation in the trial
- agree to participate in the trial
- agree treatment sessions may be observed for quality assurance purposes
- agree to the central research team holding a copy of the consent form and also contact details for further study contact and for central study team contact for the purposes of follow up.

With optional consent for:

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- the GRRAND study participant interview as part of the process evaluation

Final verification of eligibility will be ensured after a site research team member has reviewed the post-operative notes. If eligibility is confirmed, participants will be randomised to either the experimental intervention or control intervention prior to discharge.

2.7.3 Witnessed remote verbal consent

Witnessed remote verbal consent is an option and will be obtained via telephone or any NHS Trust approved online video consultation platform e.g., Microsoft Teams. The call/video call must be witnessed by a site staff member who will declare that consent was given appropriately, the trial explained fully, questions answered, and participants were given sufficient time to decide.

Following remote verbal consent, a paper copy of the consent form will be signed by the clinician delegated to take consent and countersigned by the witness. A copy of the signed consent form will be given to the participant (via post, in person or electronically). Participants are not required to sign the paper consent form if they have consented via the witnessed remote verbal consent process. However, the detailed process will be described in the participant's notes and a copy of the countersigned consent filed together. The process for witnessed verbal consent should also adhere to local site policies for this in all cases.

2.7.4 Site Staff Training

The WCTU Trial Team will undertake site initiation visits (SIV) with local Principal Investigators (PI) and clinical and research team members. As well as giving an overview of the trial (key personnel, protocol, management and oversight), the SIV is an opportunity to provide training to those responsible for conducting trial-related procedures including pathways to identify potential participants, confirming eligibility, obtaining consent, collecting baseline data, trial CRF completion, AE and SAE reporting, withdrawals, screening log and data clarifications, as well as performing interventions.

A training log will be used to document who has received training and this log will be held in the Investigator Site File (ISF). Research staff taking part in the trial will sign the site delegation log (along with a confirmatory signature from the PI) and update the trial coordination team when a new member joins or leaves the research team or the local PI changes. Copies of delegation logs will be held securely at WCTU.

2.8 Randomisation

2.8.1 Randomisation

Participants will be randomly allocated to the two treatment groups via a secure, online, central computer-based randomisation system provided by the WCTU's programming team, independent of the trial team. Participants should not be randomised until:

a) Consent has been obtained

b) The baseline questionnaires have been completed

c) Eligibility criteria have been fulfilled and checked post-operatively prior to hospital discharge

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Participants will be individually randomised to: GRRAND rehabilitation programme; or usual care. Best efforts should be made to perform randomisation prior to participant's hospital discharge. The random allocation sequence will be generated, and participants informed of their treatment allocation. Allocation concealment will be maintained by performing randomisation centrally from Warwick CTU.

Participants will be randomised 1:1 using minimisation with a random factor of at least 0.7, stratified by:

- Age
- Hospital site
- Spinal accessory nerve sacrifice

Randomisation will use a variable block size to ensure participants from each trial site have an equal chance of receiving each intervention. Stratifying by hospital site is justified to ensure equivalence between the groups for socioeconomic factors which may influence wider health and economic outcomes. Age and spinal accessory nerve sacrifice were justified as participants of increasing age [44] and those who experience accessory nerve sacrifice [12] may be at risk of poorer outcomes. Accessory nerve sacrifice is rare. In our feasibility study, this was reported in one out of 36 participants (3%)[31].

Randomisation will be performed by any member of the local clinical or research team delegated to do so, using the online system. In the event that the online system is not working, sites should contact the WCTU Trial Team on working days during working hours for guidance. As randomisation is not time critical in the GRRAND trial, waiting until the next working day is not a problem.

Stickers, electronic tags, or equivalent may be used on the participant's clinical notes to flag their eligibility and inclusion in the trial, depending on local site arrangements for flagging inclusion in trials.

A letter will be sent to the participant's GP to notify them of their patient's involvement.

Due to the nature of the intervention, participants and those delivering physiotherapy will be aware of the treatment allocation. By virtue of the design, it is not possible to blind participants, physiotherapists or the site researchers. Accordingly, there is no necessity to provide a code-breaking procedure.

Emergency randomisation will not be required as eligibility assessment and randomisation occur post-operatively and the intervention is aimed to start within approximately 14 days of hospital discharge post-randomisation. Randomisation is therefore not time-critical.

2.8.2 Post-randomisation withdrawals and exclusions

Participants may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial.

Routine NHS data related to their care, for which they have consented (such as medical notes) may be examined for adverse events (such as re-operations) unless they also specifically withdraw from this aspect of the trial on the withdrawal CRF or consent forms. The level of withdrawal i.e. discontinuing from trial treatment or complete withdrawal from the trial will be documented on a trial CRF.

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Should a participant withdraw from the trial at any stage, they will be treated thereafter according to normal clinical practice. A withdrawal CRF should be completed to record their decision. Data collected up to the point of withdrawal will be retained.

Needing to change the intervention for safety reasons after randomisation is not a reason for withdrawal. Participants may be withdrawn from the trial at the discretion of the CI and/or Trial Steering Committee (TSC) or Data Monitoring Committee (DMC) due to safety concerns. Participants would be kept in the trial and their data included in analysis under the intention to treat (ITT) principle.

Some participants may not undergo the allocated intervention either as a personal decision or a clinical decision after randomisation (for example, a change in health status). In such a scenario they will be managed according to the best judgement of the treating clinician but will be kept in the trial for the purposes of data collection on an ITT basis. If an intervention is delayed, the allocated intervention could then be delivered later at an appropriate time, or not at all, based on the decision of the clinical team. Participants will be able to have other treatments including other surgery as determined by their clinical team, although adherence to the allocated intervention will be encouraged where possible. Information about any additional treatment will be collected on follow-up CRFs.

2.9 Trial treatments / intervention

2.9.1 Trial treatment(s) / intervention

EXPERIMENTAL: The GRRAND Programme

Why: The purpose of the intervention is both to prevent the onset of problems, and to restore function and well-being after an invasive surgical treatment. The GRRAND programme was developed in collaboration with the research team, our clinical partners (surgeons and specialist physiotherapists), research literature on rehabilitation pathways for this clinical population, and consultation with PPIE members who have experienced neck dissection for their HNC treatment. Based on these multiple sources of input and advice, we developed a pragmatic intervention that both enhances and builds on current practice within the NHS, whilst also being flexible, sustainable and implementable. It is also based on a solid physiological rationale [40].

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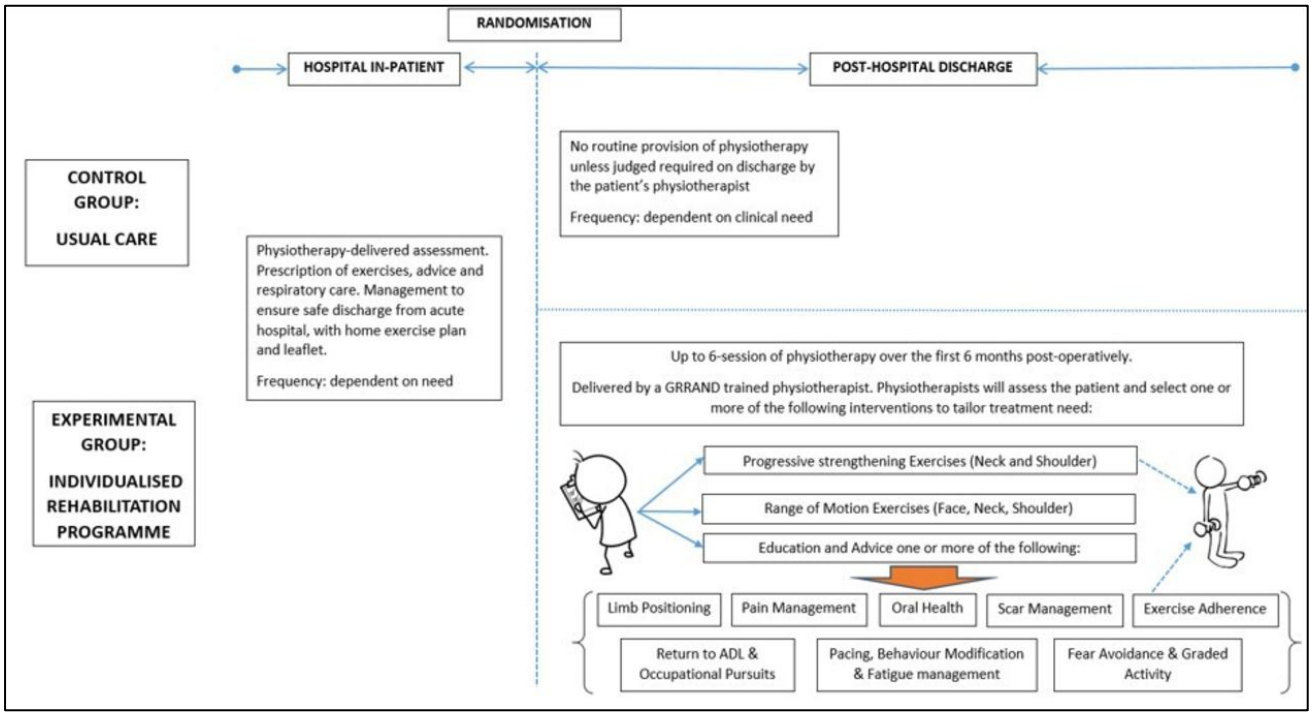
Figure 3: Schema of the GRRAND programme for the experimental intervention group and control group interventions



***What*:** Participants randomised to the experimental group will receive the control group (in-patient) intervention PLUS a personalised physiotherapy-led intervention (the GRRAND programme) comprising of up to six, one-hour out-patient appointments (first session aimed for within 14 days post-hospital discharge) over six-months. From our feasibility study, performed during the COVID-19 pandemic, participants received a mean of 4.1 sessions. In our feasibility study, those randomised to the intervention arm received their first post-discharge physiotherapy session a mean of 9.6 days (SD: 4.9) after in-patient hospital discharge.

Rehabilitation treatment will include the following options:

(1) *Range of motion exercises* targeting muscles and joints of the neck and shoulder impacted by neck dissection. The purpose of these exercises is the prevention of post-surgical contracture and the maintenance of upper body joint mobility. Participants will be taught stretching and joint range of motion exercises for shoulder and neck.

(2) *Progressive resistance exercises* targeting strengthening of the neck and shoulder girdle, and prevention of the onset of adhesive capsulitis. The resistance exercises will target the stabilising functions of the upper quadrant and movements of shoulder internal rotation, external rotation, and abduction. Exercises will be progressed through increasingly elevated shoulder positions and the introduction of weight bearing through the upper limb. Additionally, the exercises will become increasingly 'task specific', targeting the specific functional goals and usual activities of daily living of the participant. Resistance loads (using resistance bands) will initially be set at a moderate level of exertion (determined by a combination of physiotherapist observation and participant-reported exertion based on the modified Borg scale of perceived exertion [45]) to permit progression, enhance motivation and adherence, and reduce the possibility of symptom flare-up. Progression will be achieved by increasing the resistance load, speed and/or the number of repetitions and sets of exercises.

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(3) *Continued education and advice on positioning, oral health and pain management*, based on the GRRAND manual provided to participants at discharge.

(4) *Education and advice on optimising exercise adherence and return to function*. This will be targeted in two ways; firstly, through the introduction of behaviour techniques of goal-setting, pacing, behaviour modification, graded activity and for reducing fear avoidance; and secondly through the discussion of barriers and facilitators to exercise and activity participation [46]. Additionally, pacing and goal-setting have been shown to be effective in improving fatigue, depression and anxiety in people with cancer [47]. Physiotherapists will be trained in Socratic questioning techniques and will use the sessions to counter unhelpful beliefs about pain, tissue damage and exercise after surgery and encourage adherence. They will promote independence and confidence in returning to normal activities of daily living, occupational and social pursuits, and problem-solve the physical neck and shoulder challenges with participants. The programme will use an established, effective approach to introduce these behaviour change techniques [46], developed from our previous clinical trials [48,49], which is within the current scope of practice for physiotherapists to deliver. To assess adherence, the Exercise Adherence Rating Scale [37] questionnaire will be completed by participants at six weeks post-randomisation (sent from the Central Trial Team) and on physiotherapy discharge, provided to the participant by the treating physiotherapist in clinic.

(5) *Education and psychological support to address fatigue, anxiety and sleep hygiene*. Due to the high prevalence of psychological health issues post-operatively, participants will be offered strategies to support self-management of fatigue, anxiety and sleep. These will include written materials in the GRRAND manual and advice on publicly available support services.

***Tailoring*:** At the initial consultation, a physiotherapist will assess the participant to identify modifiable physical and psychosocial factors associated with poor recovery after neck dissection. The participant's personalised GRRAND programme is based on a combination of clinical assessment and participant-identified preferences. Individual programmes may contain *one, several,* or all the treatment options listed in **Figure 3** and above. This will be personalised according to the participant's preferences and clinical presentation over the course of treatment.

***How and When**:* The experimental intervention will be received by participants up to **six times** (one assessment; five follow-up appointments) over a six-month period to facilitate supported recovery. Reflecting the heterogeneity of clinical presentation and need, if clinically indicated, participants will be permitted to receive additional sessions, over a longer duration within the trial. Nonetheless our feasibility study results [31], and Clinical Advisory Group indicate that anticipated treatment should be completed within the six sessions/six-month parameters.

Participants will be prescribed a home exercise programme, supported by the GRRAND manual (paper-based and online) to further facilitate behaviour change and adherence.

Reflecting normal NHS practice, the initial assessment will be 60 minutes as a face-to-face session. Follow-up sessions will be up to 60 minutes in duration either face-to-face or virtual. The timing and mode of delivery are flexible to account for ongoing treatment, physiotherapist judgement and participant preference. The spacing of appointments will allow for maximum progression of the intensity of exercise over sufficient time (anticipated 8-12 weeks) to produce a significant physiological and functional improvement in the neuromuscular system. Importantly, the intervention can be delivered within the current NHS commissioning paradigm [50]. Participants will be asked to perform a home exercise programme at least three times a week for 20 to 30 minutes. The home programme will be supplemented with the GRRAND manual and online materials, demonstrating exercises for participants to follow.

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Who: The GRRAND programme will be delivered by physiotherapists (musculoskeletal or surgical) trained in the intervention. We will use methods of training that we have developed over several trials including our feasibility study [31,49,50,51,52]. These include an online training module. This will: 1) provide information that ensures all intervention physiotherapists have an equivalent level of knowledge about HNC and the aetiology of upper quadrant disability following neck dissection; 2) provide an overview of behaviour change techniques and provide training on Socratic questioning; and 3) introduce the concepts that underpin the prescription and progression of the rehabilitation training programme. Additionally, we will provide training to bring physiotherapists together. This training will focus on ensuring that the principles of the programme are understood, the techniques have been taught, and the need for a standardised, per-protocol, approach re-enforced. Training will be supplemented with the provision of standardised training manuals. The physiotherapists will retain access to the online training resource for the duration of the trial. Before and after the training, physiotherapists will be asked to provide feedback on the training, including rating their confidence in their skills to deliver the intervention. Those indicating they would like more support will be followed-up by the trial team, and support provided as indicated.

Where: The programme will be delivered from out-patient physiotherapy departments, either face-to-face or virtually, tailored to the participant's clinical presentation and preference.

How Well: The content of the GRRAND programme will be recorded in a treatment CRF and monitored by a research physiotherapist. As part of the process evaluation, the research physiotherapist will assess intervention delivery fidelity using observations of practice. This will be performed both in the internal pilot and the main trial, at different stages of intervention delivery i.e., assessment and follow-up appointments (for further details, see Section 3.3). Central monitoring on CRF completion and potential intervention contamination will be monitored through cross-referencing with delegation logs and scrutiny of treatment CRFs by the WCTU team. Actions in re-training of intervention physiotherapists and subsequent monitoring of fidelity will be made if initial fidelity is deemed to be low. This may be detected, for example, as repeated omission of treatment CRF elements or intervention physiotherapist's self-reported lack of confidence or training need.

CONTROL: Best practice, NHS, post-discharge care

Why: There is currently no standard treatment across the UK for rehabilitation following neck dissection for HNC [20,21]. Accordingly, we consulted with the Clinical Advisory Group and the findings from our national survey [20] and feasibility study [30,31] to ensure the content and delivery of a usual practice intervention for this patient group reflects best practice, usual, NHS care.

Where and When: An in-patient physiotherapist will see participants from Day 1 post-operatively as per best practice, usual, NHS care. The frequency and duration of sessions will be determined by clinical need.

What: To standardise the usual physiotherapy care of all participants, each participant, before discharge, will have a visit from a hospital ward physiotherapist who will provide advice to promote recovery. Although not delivered in all sites currently, this is considered a reasonable level for best practice, usual NHS care. This control intervention was delivered successfully in our feasibility study [31].

The 'usual care' is based around the following four areas:

(1) Advice to practice simple range of motion exercises for the face, neck and shoulder impacted by neck dissection, for the purpose of preventing the onset of post-surgical contracture and optimising the functions of swallowing and shoulder girdle movement.

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(2) Respiratory care, targeting the functions of sputum clearance and breathing control.

(3) Mobility assessment to ensure safe hospital discharge.

(4) Education on body positioning to reduce pressure and drag on the shoulder girdle, oral health to reduce food pocketing in the mouth, and pain management to optimise levels of comfort and function.

As part of 'usual care' prior to hospital discharge, the ward physiotherapist will provide participants with a Hospital Discharge Booklet detailing post-operative, self-management strategies in-line with the standards currently used in these settings.

Who: Hospital ward physiotherapists will deliver the control in-patient rehabilitation programme. They will be trained on the expectations of best practice, NHS, usual care and in completing the trial required paperwork but will have no training on the GRRAND programme.

No routine out-patient or follow-up physiotherapy will be provided as per current, best, usual NHS care [20].

How Well: The content of in-patient care will be recorded in a treatment CRF. Actions in re-training of physiotherapists and subsequent monitoring of fidelity will be made if initial fidelity is deemed low, as indicated by repeated omissions on the treatment CRF or self-reported low confidence to trial procedures.

To assess adherence, the Exercise Adherence Rating Scale [37] questionnaire will be completed by participants in the control group at six weeks post-randomisation (sent from the Central Trial Team).

Concomitant Recovery Treatments
In accordance with the pragmatic nature of this trial, participants will not be asked to desist from receiving other forms of treatment during the trial or follow-up periods. These may include contact with their GP, physiotherapist or other health professional, changes in medication, or use of alternative therapies or treatments. Use of these treatments will be recorded through the health utilisation questionnaire at each follow-up period.

2.9.2 Compliance/contamination/adherence

The GRRAND-trained physiotherapists who deliver the experimental intervention sessions will be taught the skills required to deliver the experimental intervention. These physiotherapists, where possible, will not deliver physiotherapy to those in the control group during the study period (and vice versa). This will be highlighted to staff during intervention training and SIV. The details of the physiotherapists delivering sessions will be recorded and reviewed to monitor if this occurs by members of WCTU. This approach will monitor the risk of contamination. Due to the interventions being delivered in an outpatient setting, there is a low risk of participants sharing their knowledge and experience of the interventions between the control and experimental intervention groups, further minimising the risk of between-group contamination.

As part of this trial, participants will only be allocated their randomised intervention. Therefore, those randomised to the control group will not receive the post-discharge GRRAND physiotherapy intervention, and only those randomised to the experimental intervention group will receive the GRRAND post-discharge physiotherapy intervention. During the course of follow-up, participants may require further interventions as part of their recovery, as per routine NHS practice. Further clinical

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interventions will be permitted for trial participants without the participant having to withdraw from the trial.

2.9.2.1 Compliance Thresholds

Attendance to no physiotherapy visits will be considered non-compliance to the GRRAND programme. None, partial and full-compliance will be considered.

Non-Compliance: Attendance to zero, one or two sessions (one assessment and one follow-up appointment) will be considered non-compliance.

Partial Compliance: Attendance to three or four sessions (one assessment and two or three follow-up appointments) will be considered partial compliance for the GRRAND programme.

Full Compliance: Attendance to five or more sessions (one assessment and minimum of four follow-up appointments will be considered full compliance.

However full-compliance will be automatically met if participant-physiotherapy goals are met and agreed, and discharge is made after three appointments (one assessment and two follow-up appointments) onwards irrespective of session number. This detail will be recorded on the GRRAND programme session CRF.

2.10 Blinding

2.10.1 Methods for ensuring blinding

Selection bias: Treatment allocation will be concealed prior to randomisation using a bespoke, independent, randomisation system. To help monitor clinician equipoise, we will assess screening logs and examine reasons why patients are not enrolled.

Performance and detection bias (unblinded study): Treatment allocation will be concealed prior to randomisation. The nature of the trial intervention precludes blinding of participants or care providers following randomisation. It will also not be possible to directly blind *all* WCTU trial team members to treatment allocation, as this information will be collected on the CRFs and will be necessary for monitoring. However, all staff involved in outcome data collection and its subsequent data entry and analyses will be blind to treatment allocation. We will seek to maintain blinding of those who are blinded to group allocation within WCTU to the process evaluation team including the research physiotherapists who will be unable to be blinded to group allocation.

We will seek to ensure that participants do not reveal treatment allocation to any staff making follow-up telephone calls for data collection, where this occurs. Potential participants will be notified about this at contact opportunities and particularly on approach, through the Participant Information Sheet (PIS) and point of randomisation but site research team members.

2.10.2 Methods for unblinding the trial

Due to the nature of the intervention, participants and those delivering physiotherapy will be aware of the treatment allocation. By virtue of the design, it is not possible to blind participants,

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physiotherapists or the site researchers. However, individuals collecting (when via telephone) and inputting data, in addition to the TMG, will be blinded to group allocation until data analysis is complete.

2.11 Concomitant illness and medication

2.11.1 Concomitant illness

Details of any concomitant illness (any illness present at the start of the trial) should be recorded at trial entry. If the change influences the participant's eligibility to continue in the trial, the WCTU Trial Team must be informed.

2.11.2 Concomitant medication

Details of any concomitant medication (any medication that is taken during the trial, including during screening and run-in periods) should be recorded at trial entry. Any changes in concomitant medication should be recorded at each visit. If the change influences the participant's eligibility to continue in the trial, the WCTU Trial Team must be informed.

2.12 Co-enrolment into other trials

Individual requests for co-enrolment onto other trials can be discussed with the TMG to determine if these will affect the delivery or conduct of the GRRAND trial. Co-enrolment will be performed where trial protocols does not preclude the delivery of the trial processes and does not cause unnecessary burden on potential participants.

2.13 End of trial

The trial will end when all participants have completed their 12-month post-randomisation follow-up.

The trial will be stopped prematurely if:

- Mandated by the Research Ethics Committee (REC)
- Following recommendations from the DMC
- Funding for the trial ceases

The REC will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

In the absence of a published core outcome set, outcome measures were selected following our PPIE Advisory Group consultation and interaction with our experienced clinical team to ensure we have chosen appropriate measures and a timeframe that captures the important variables without placing too much burden on participants.

Our PPIE Advisory Group reviewed the planned questionnaire packs which included the proposed primary and secondary outcome measures. They reported taking between 12 to 15 minutes to complete the pack and this was "acceptable".

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3.1.1 Primary Outcome Measure

The primary outcome is the SPADI (total score) 12-months post-randomisation. This is a 13-item shoulder-specific instrument (0-100, 100 greater pain and disability). The sum of two domains (pain and disability) determines the full SPADI total score [32,53]. It has been widely used in previous shoulder, neck and upper limb trials [42,54], placing this trial in the context of the wider rehabilitation literature. It has been shown to be responsive to change in both surgical and non-surgical intervention trials [55]. The GRRAND programme is designed to prevent the onset of problems, and to restore function. This is for neck, shoulder and wider upper limb disability. Given the short and longer-term complications which this population report frequently relate to shoulder dysfunction [12], the SPADI is considered an appropriate outcome measure to assess the health technology under investigation.

The selection of the SPADI was confirmed by our PPIE and Clinical Advisory groups and the qualitative interview data from our feasibility study [30]. Participants found it a short and understandable/acceptable questionnaire. From these sources, shoulder dysfunction was considered the principal challenge faced in the recovery following neck dissection for HNC. A 12-month follow-up has been chosen to allow sufficient time to return to normal levels of daily activity [43] and was considered the meaningful time to 'understand how I have recovered' from our PPIE Advisory Group. There was a signal of effect from our feasibility study that the GRRAND programme may offer superiority to best practice, usual, NHS care at six-month assessment (SPADI disability: between-group mean difference: -13.56 (95% CIn:-25.52,-1.60))[31]. Whilst this is not the primary endpoint, it is plausible that this difference could be maintained at 12 months.

3.1.2 Secondary Outcome Measures

Secondary outcome measures collected at baseline, six weeks, six- and 12-months post-randomisation including: SPADI score (Total)[32]; SPADI Pain and Disability domains[32], HRQoL using the EORTC cancer-specific questionnaires (C30(core)[34] and H&N35(head and neck specific)[35]; exercise adherence EARS [37] (only at six-weeks), EQ-5D-5L [36]; mental wellbeing using the Short Warwick-Edinburgh Mental Wellbeing Scale (SWEMWBS) [38]; and health resource use questionnaire; adverse events and post-operative complications. An additional three-month assessment will be undertaken to collect health resource use, EQ-5D-5L, adverse events and postoperative complications only.

We will minimise missing data utilising experience from the feasibility trial, including paper and online-based solutions, telephone and text reminders, multiple contact details, clinical follow-up. A £15 voucher will be offered to participants with the 12-month follow-up invitation.

3.1.3 Baseline Data Collection

Baseline data will be collected prior to randomisation once consent has been obtained at the pre-assessment clinic appointment or via the telephone/post where face-to-face attendance is not possible. Baseline data will be recollected in the event of the operation being delayed, for any reason, by six months or more, from the date of initial baseline data collection.

Baseline data collected will include: participant demographics and details of treatments received including; site, previous radiotherapy to the head and neck, dominant hand, details regarding operative details such as the levels of the neck dissection performed, unilateral or bilateral neck dissection, preservation or resection of the accessory nerve and treatment to the primary tumour site (including planned receipt of chemo/radiotherapy) along with baseline versions of all outcome measures. Characteristics of age, gender, American Society of Anesthesiologists (ASA) grade, data to assess Equality, Diversity, Inclusion (EDI), body mass index, smoking status and occupational status will also be recorded.

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We will also collect baseline data for all primary and secondary outcome measures: SPADI score (Total)[32]; SPADI Painand Disability domains[32], HRQoL using the EORTC cancer-specific questionnaires (C30(core)[34] and H&N35(head and neck specific)[35]; EQ-5D-5L [36]; mental wellbeing using the SWEMWBS [38]; and health resource use questionnaire; adverse events and post-operative complications recording using the Clavien-Dindo Classification [56] with scores converted to determine the Comprehensive Complication Index [57].

A separate CRF collecting data from the pathology results from the surgery will be completed once pathology results are available at site. This is anticipated to be between four to six weeks in usual NHS practice. This CRF will collect data on type and stage of primary tumour, neck nodal status and the number of nodes reported in the pathology report for a neck dissection (by side).

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Table 1: Trial assessments

Visit/follow-up number	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit/follow-up	**Screening**	**Baseline**	**In-Patient Pre-Discharge**	**Intervention Period**	**6 Weeks Post-Randomisation**	**3 Months Post-Randomisation**	**6 Months Post-Randomisation**	**12* Months Post-Randomisation**
Time after randomisation (±window)	**-**	**0**	**Data to be collected pre-discharge, except for histology data which will be available within 4-6 weeks**	**Data within 4 weeks of completion of allocated treatment**	**(±2wks)**	**(±1m)**	**(±1m)**	**(±2m)**
Check eligibility $	✓							
Invitation to study $	✓							
Informed consent $		✓						
Medical history $		✓						
Inclusion/exclusion criteria $		✓						
Age (years) $		✓						
Gender $		✓						
Weight (kg)/(stone/lbs) $		✓						
Height (cm)/(ft/inches) $		✓						
Ethnicity $		✓						
Drinking status $		✓						
Smoking status $		✓						
Hand dominance $		✓						
List of medical co-morbidities $		✓						
Employment status and current occupation (when appropriate) *		✓			✓	✓	✓	✓

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Shoulder Pain and Disability Index (SPADI)*		✓			✓		✓	✓
EQ-5D-5L*		✓			✓	✓	✓	✓
EORTC QLQ-C30*		✓			✓		✓	✓
EORTC QLQ-H&HN43*		✓			✓		✓	✓
Short Warwick-Edinburgh Mental Wellbeing Scale*		✓			✓		✓	✓
Health resource use questionnaire*		✓			✓	✓	✓	✓
Exercise Adherence Rating Scale*				✓‡	✓			
ASA grade $			✓					
Pre-operative cancer head and neck treatment (chemo or radiotherapy) $			✓					
Complications, AE, SAE details of accident & emergency attendances and hospital admissions (and reasons) $*			✓	✓	✓	✓	✓	✓
Operation date $			✓					
Operative procedure (Level of ND) $			✓					
Early post-operative complications (Clavien-Dindo Classification)			✓					
Location of HNC $			✓					
Preservation or resection of accessory nerve $			✓					
Primary cancer site $			✓					
Stage of tumour$			✓					
Type of tumour $			✓					
Neck nodal status $			✓					
Randomisation $			✓					
Chemotherapy and radiotherapy treatment provision $*			✓		✓	✓	✓	✓
GRRAND intervention CRF (physiotherapist completed) $			✓	✓				

$ site completed; * participant completed; ‡ GRRAND group only

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3.2 Long term follow-up assessments

Data will be collected from participants at six weeks, three, six and 12-months from randomisation. If participants do not return data postally or online, they will be contacted by text-message, email, voice message and/or telephone, and, if appropriate, sent the questionnaires to complete. The WCTU Trial Team will attempt to telephone these participants on up to two occasions to remind them to complete the questionnaires. If these methods fail, we will categorise the participant as a 'non-responder' for that time-point only.

The data collection schedule is presented in **Table 1**.

3.3 Embedded process evaluation

The aim of the process evaluation within this trial is to evaluate trial processes, intervention mechanisms, fidelity and context with a multi-methods process evaluation to inform, if appropriate, further implementation.

The parallel process evaluation objectives are to: 1) inform, design and minor refine session CRFs and patient-facing materials; 2) provide physiotherapists training and evaluate training experiences; 3) monitor fidelity of delivery for intervention and control sessions, providing feedback and additional training if required; 4) further evaluate the GRRAND programme delivery (physiotherapists) and engagement and uptake (participants) to inform what works for whom and in what contexts.

The process evaluation team will be part of the unblinded trial team. They will prepare and deliver the training to site physiotherapists, which will be evaluated using a brief pre- and post-training questionnaire containing questions with Likert scale response options and space for free-text comments. The team will also inform the design of rehabilitation treatment CRFs (administered by WCTU) to enable physiotherapists to report delivery of session elements according to intervention protocols; make refinements to these and patient-facing materials if required, following feedback from the pilot phase; and monitor intervention delivery by observing up to two sessions per site (virtual or in person). Purposive sampling for qualitative enquiry will consider (1) site, number of sessions delivered (physiotherapists) and (2) site, gender and number of sessions attended by intervention participants.

Data will be collected on intervention delivery, to facilitate monitoring and reporting. Within-trial review of CRFs will assist monitoring of intervention fidelity (both groups) and from discussions with site physiotherapists (n~24) we will gain real-time insights into their experiences of the intervention protocols. The responsibility for intervention quality control will be shared with the local site-coordinating physiotherapist. The sites will regularly receive feedback from quality control visits as part of the strategy to maintain or improve fidelity, measured through treatment CRF review and observations by the research physiotherapist. Any issues identified will be addressed by engaging the site staff in additional training and by increasing the intensity of monitoring by the central trial team. If issues persist, they will be escalated to the trial oversight committees.

We will further evaluate experiences of the GRRAND programme after the intervention delivery period through focus groups (n~3) (or interviews if required) with physiotherapists (n~24) and through interviews with participants (n~12) who have received the GRRAND programme, to investigate mechanisms of change and who benefits and in what contexts. Purposive sampling for the qualitative enquiry will consider (1) site, number of sessions delivered (physiotherapists), (2) number of sessions participants attended, their age and EDI characteristics. Patient participants who indicated (at the start of the trial) a willingness to be approached, will be sent a PIS and consent form developed specifically for

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this part of the study. Consent will be obtained following the same protocols as used for the main trial (Section 2.7.1; Section 2.7.2) although anyone opting for a remote interview will not be required to return a signed consent form but instead will have their verbal consent audio-recorded prior to commencing the interview, with the researcher signing and retaining a hard copy. To facilitate participation, data collection will be offered remotely, or in-person and a £15 voucher offered to thank individuals (patient-participants and physiotherapist-participants) for their time. Researchers will follow good practice procedures for any safeguarding alerts, lone working and data protection. Physiotherapist participants will be invited to participant with a specific PIS for these interviews, through the site PI as the gate-keeper. Through this approach and the PIS, physiotherapists will be made aware this interview is entirely voluntary and they are under no obligation to participate. A specific consent form for this part of the study will be completed prior to interviews, using either the hard copy or audio-recorded options as appropriate.

A process evaluation analysis plan (PEAP) will be prepared in conjunction with the Statistical Analysis Plan (SAP). This will identify which quantitative data analysis will be part of the process evaluation work, for example individuals' exercise adherence data will likely be part of the PEAP whereas group differences in exercise adherence will be part of the SAP. Where unique to the process evaluation, quantitative data will be reported using descriptive summaries and statistical tests pre-specified in the PEAP. Missing data will be dealt with in accordance with the SAP. Qualitative data, obtained using semi-structured topic guides during focus groups and interviews will be audio-recorded, transcribed and managed in Nvivo 12 software (QSR International, Melbourne, Australia). Using Interpretative Description [58,59], data will be analysed deductively and inductively to produce emergent themes. Sample topic guides for patient interviews and physiotherapist focus groups (or interviews) are presented as **Table 2** and **Table 3** respectively, these will be iteratively developed if required after initial interviews.

Table 2: Sample topic guide with GRRAND patient-participants

The interview will be structured on the following areas of interest	**Sample questions**
Introduction	Overall, please will you share your experiences of being involved with our research?
Determining participant views of their intervention	First of all, please tell me what physiotherapy treatment you received? (prompt – clarify what was GRRAND programme post-discharge vs. inpatient physiotherapy prior to discharge)
The acceptability of the GRRAND programme	Please tell me more about your treatment…. As a patient after neck dissection, what was your impression of the care? In what way was the GRRAND programme helpful for your recovery? And in what way was it less helpful to your recovery?
What were the strengths of the GRRAND programme	What were the most helpful parts of your GRRAND intervention? What was good about it?

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What were the weaknesses of the GRRAND programme	What were the less helpful parts of the GRRAND intervention? What didn't you like about it?
What modifications they may recommend to the delivery of the interventions	What could we improve in the delivery of the GRRAND programme? (prompt: What do you think is lacking?) How do you think we could better support you with your recovery? (prompt: in organisation of programme, how delivered, where and when) If you met someone who needed to have the same surgery what would you say to them about the GRRAND programme?
Closing remarks	Is there anything else you would like to tell us about? Prompts: to do with your care, your physiotherapy or being in the research. Thank you for taking part in this research / what happens next (explain when results of study may be available / if they would like to receive a summary).

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Table 3: Sample topic guide with Physiotherapist Interviews

The interview will be structured on the following areas of interest	**Sample questions**
Introduction	Overall, could you share your experiences of being involved with our research?
Determining physiotherapists views of the GRRAND programme	First of all, please tell me what you think the GRRAND programme is. What have been your first impressions of the programme?
The acceptability of the GRRAND programme	How did the delivery of the GRRAND programme go? How did you work out what treatments to select? How did you organise spacing of the sessions for each patient? What were the reasons for your decisions (prompt: professional experience, staff / time resource constraints, other factors – please say what they were). What are your views about the content? In what ways were you comfortable with this content? What, if any, parts you did not agree with? Please tell me more about these. Were any modifications made? If so, please tell me what these were……why they were needed……and how well did they work? In your opinion how did the patients get on with GRRAND?
What were the strengths of the GRRAND programme	What were the most helpful parts of the GRRAND intervention? What was good about it?
What were the weaknesses of the GRRAND programme	What were the less helpful parts of the GRRAND intervention? What didn't you like about it?
What modifications they may recommend to the GRRAND programme	What could we improve in the delivery of the GRRAND programme? (prompt: What do you think is lacking?)
Training on GRRAND programme	In what ways did you feel adequately prepared to deliver the GRRAND programme? What, if any, changes would you recommend to the preparation? Prompt: Did you seek out alternative training in preparation for delivering the GRRAND programme? If so, please tell us more about this additional prep. What are your views about needing any additional 'top up' or 'refresher' training sessions? (Prompt – did you receive any,

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	what was it like…. Please tell us your feedback on these sessions). If you met a new physiotherapist joining the surgery rehabilitation team, what would you say to them about the GRRAND programme?
Closing remarks	Is there anything else you would like to tell us about? Prompts: to do with your role, as a physiotherapist delivering this care or being in this research. Thank you for taking part in this research / what happens next (explain when results of study may be available / if they would like to receive a summary).

A convergence matrix [60] will collate findings from all data sources for each PEAP objective. Findings will be discussed in accordance with the underpinning biopsychosocial theory embedded in the intervention design [29,31] and recommendations made for future implementation and sustainability. Part of the process evaluation output will be to determine what the core and adaptable intervention components are to inform future implementation approach. We will also produce implementation recommendations guided by the domains of the recently updated Consolidate Framework for Implementation Research: inner setting (e.g. structural characteristics, communications); outer setting (e.g. local conditions, policies and financing); individuals involved and implementation process domains (e.g. planning, engaging, doing, reflecting and evaluating) in the context of NHS Trust settings, to understand what adaptations were needed for whom, and why [61].

4. ADVERSE EVENT MANAGEMENT

4.1 Assessment and management of risk

The interventions delivered in this trial are standard physiotherapy interventions, predominantly exercise-based. These have a good safety profile, being non-invasive and are used for other shoulder and musculoskeletal conditions routinely in the NHS at present. Risks will be no different from those that occur in normal practice for this population being investigated in the trial.

A risk assessment will be performed according to Warwick SOPs and a monitoring plan developed depending on the risks identified. Risks specific to the trial include risks of data breaches, incorrect allocation, or failure to recognise safety concerns. These risks will all be carefully managed by following Warwick SOPs and careful adherence to the principles of GCP.

4.2 Definitions

Adverse Event (AE)	An AE is defined as any untoward medical occurrence in a participant administered a medicinal product or trial procedure and which does not necessarily have a causal relationship with the administration of the IMP or trial procedure

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Serious Adverse Event (SAE)	A SAE is an AE that fulfils one or more of the following criteria: • Results in death • Is life-threatening • Requires hospitalisation or prolongation of an existing inpatient hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital abnormality or birth defect • Requires medical intervention to prevent one of the above, or is otherwise considered medically significant by the investigator (e.g. participant safety is jeopardised)
Related SAE	An SAE where there is a potential for there to be a causal relationship to the intervention
Related and Unexpected SAE	A related SAE that is also unexpected i.e. the nature, frequency or severity of the event is not consistent with what is expected for the intervention of study

4.3 Recording Adverse Events (AE)

An AE is defined as any untoward medical occurrence which a participant experiences to whom an intervention (control or experimental) has been administered, including occurrences which are not necessarily caused by or related to that intervention. Adverse events related to the intervention will be recorded using the Trial AE form from randomisation to the completion of the allocated intervention, and thereafter using the follow-up questionnaires.

Adverse events will include the following:

- Wound complications (breakdown)
- Medical events that prevent the participant from participating in a session (or more) of the participant's allocated intervention

The following will not be included as AEs:

- Medical or surgical procedures where the condition which leads to the procedure is the AE
- Pre-existing disease or conditions present before treatment that do not worsen
- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic condition

If the AE meets the definition of a SAE and is determined to be related to the intervention, a site SAE form will be completed and proceeded as described in Section 4.3. The following information will be recorded: description, date of onset and end date, and action taken. Follow-up information should be provided as necessary.

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Some events which occur during treatment and recovery will be considered normal aspects of the therapy and post-operative recovery process and will not need reporting as AEs or SAEs unless in the opinion of the clinical team, they are untoward, excessive, or outside of what might normally be expected for the procedure. These are normal events that occur frequently after physiotherapy or surgery and include:

- Nausea and/or vomiting after surgery
- Drowsiness or headache after surgery
- Temporary fluctuating blood pressure after surgery
- Sore throat after surgery
- Itching after surgery
- Post-operative or post-intervention pain in the first six months (note that pain after six months will be collected as an outcome in the study, using the SPADI pain domain)
- Numbness around the surgical wound
- Early wound oozing which spontaneously resolves
- Swelling, within the confines of what is considered normal post-intervention swelling by the treating clinical team
- Restriction of range of motion, within the confines of what is considered normal post-operatively by the treating clinical team
- Bruising, unless this is considered abnormal by the treating clinical team
- Post-intervention pain, muscle soreness or tiredness during or after physiotherapy (in-patient and out-patient) in either group which is above what would be expected as a result of physiotherapy

All reported AEs will be reviewed by the WCTU Trial Team to determine whether they are related to the intervention or not and will be monitored for trends. An outcome of 'not yet resolved' is an acceptable final outcome for non-serious AEs at the end of a patient's participation in a trial. It will be left to the Principal Investigator's (PI) clinical judgment, in liaison with a Chief Investigator (CI) if required, to decide whether or not an AE is of sufficient severity to require the participant's removal from the treatment provided by the trial. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant will be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. Participants who withdraw from treatment will be encouraged to continue with the follow-up where possible.

4.4 Reporting Serious Adverse Events (SAEs) to the coordinating centre

A SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Consists of a congenital anomaly or birth defect

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

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Serious adverse events considered related to the trial intervention as judged by the medically-qualified site PI or medically-qualified nominee, nominated by the site PI. They will be followed up either until resolution, or the event is considered stable, in-line with standard clinical care.

A SAE occurring to a participant will be reported to the REC which approved the study where in the opinion of the medically-qualified CI the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of a CI becoming aware of the event, using the HRA report of SAE form (see HRA website).

4.4.1 Reporting SAEs and Related SAEs

The SAE form should be completed and emailed to the trial resource account grrand@warwick.ac.uk and the wctuqa@warwick.ac.uk resource account in the first instance.

All **SAEs** that meet the reporting criteria for this trial (see Section 4.1.2 and 4.1.3) occurring from the time of randomisation until 12-months post-randomisation, must be detailed on the SAE Form and reported via email to the WCTU Trial Team, grrand@warwick.ac.uk **within 24 hours** of the site research staff becoming aware of the event.

Should the PI be unable to report within 24 hours, or is unavailable, any nominated person on the delegation log may send an unsigned SAE form. Further details should then be sent by site as soon as practically possible.

Events occurring before randomisation will not be recorded.

Any change of condition or other follow-up information should be emailed to the WCTU Trial Team as soon as it is available. Events will be followed-up until the event has resolved or a final outcome has been reached. An outcome of 'unknown' is not considered to be an acceptable final outcome. An outcome of 'not yet resolved' is an acceptable final outcome for SAEs at database lock.

Adverse events or SAEs may be identified by the WCTU Trial Team from the CRFs, either from specific questions or from answers within patient-reported outcome measures (PROMs). If this occurs, the WCTU Trial Team may query the site for details of the event for the purposes of the sites own clinical governance. This will be determined on a case-by-case basis, and the potential to do so will be included in the PIS.

The Trial Manager (TM) will liaise with the investigator to compile all the necessary information. The WCTU Trial Team is responsible for reporting any related and unexpected SAEs to the Sponsor and REC within required timelines. Events which are conclusively assessed by a PI and CI as possibly, probably, or definitely related to the trial intervention and are unexpected, will be reported to the REC within 15 days.

4.4.2 SAEs exempt from reporting

All SAEs that fall between the defined timelines above should be reported. However, for the purposes of this trial, as with AEs, we will only collect SAEs related to the participant's treated head, neck or shoulders, to the treatment they receive in the trial (or any treatment for their HNC) or related to trial processes. Other events that do not meet this definition will not be reported. Normal events defined in Section 4.1.2 will not be reported as AEs or SAEs.

4.5 Assessment of SAEs

For all reportable SAEs an assessment of the relationship between the SAE and the intervention should be done as per Section 4.5.1 Assessment of Causality.

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4.5.1 Assessment of causality

Serious Adverse Events which are thought to have a potential for a causal relationship with the intervention. Causality should be assessed by a medical or clinical delegate of the PI at the investigator site and also by a medical or clinical delegate of the Sponsor. These assessments should be done independently of each other. If either deem an event to have a potential causal relationship, then an expectedness assessment by a delegate of the Sponsor should follow as per Section 4.5.2 below.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by Ihe investigator(s) on the SAE form using the following descriptions:

Relationship to Trial	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out

4.5.2 Assessment of expectedness

All related SAEs should be assessed against the known SAEs related to the intervention.

Expectedness assessment is the responsibility of the Sponsor and will be done by the WCTU Trial Team in response to the causality assessments made by the investigator and Sponsor's delegates.

4.5.3 Expedited report of events to REC

Related and unexpected SAEs are events which are conclusively assessed by the delegated Investigator at a site or the medical or clinical delegate of the Sponsor as possibly, probably, or definitely related to the intervention and are unexpected. Related and unexpected events will be reported to the REC within 15 days.

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The trial coordinating centre is responsible for reporting related and unexpected events to the Sponsor, and REC within required timelines. The WCTU Trial Team must also inform other investigator sites of the event and any implications for the trial.

The following are SAEs that are expected as a result of the intervention and its associated procedures. Those related in general to surgery and anaesthetic include:

- Injury to teeth, mouth, or throat during anaesthetic
- Chest infection
- Nerve or vessel injury due to local anaesthetic (i.e., local blocks or spinal anaesthetic)
- Spinal haematoma
- Stroke or cardiac event
- Death

Those related to the operation itself:

- Exacerbation/persistence of head, neck or shoulder pain beyond what is considered normal by the treating clinical team. As this outcome will be captured in PROMs throughout the trial, only medical or surgical interventions for persistent shoulder or neck pain need to be reported.
- Restriction of range of motion, including need for manipulation under anaesthetic, arthroscopic or open procedures to relieve stiffness
- Surgical site infection
- Wound healing problems
- Fracture, ligament or tendon damage or rupture
- Revision surgery or other corrective surgery
- Thrombosis (deep vein thrombosis, pulmonary embolus, cerebral infarct)
- Damage to nerves or vessels

Those related to physiotherapy (post-surgical rehabilitation or GRRAND programme physiotherapy interventions) which are in excess of what would be expected from routine physiotherapy include:

- Persistent muscle soreness or muscle injury
- Bruising
- Swelling
- Skin damage (for example, from bracing)
- Exercise-related fatigue

Treatments of expected events listed above (such as surgery for infection or wound problems) are also expected events.

If the SAE is not listed above, and is considered to have at least a possible causal relationship to the intervention, the event would therefore be classified as unexpected and will be reported to the REC within 15 days.

4.6 Responsibilities

Principal Investigator (PI):

Checking for AEs when participants attend for treatment/follow-up.

1. Using medical judgement in assigning seriousness and causality
2. Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as

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available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within two working days of initial reporting
3. Ensuring that AEs are recorded and reported to the Sponsor in-line with the requirements of the protocol

A Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit
2. Using medical judgement in assigning causality immediate review of all related and unexpected SAEs
3. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan (TMP)
4. Production and submission of annual reports to the relevant REC

Sponsor or delegate:

1. Central data collection and verification of AEs and SAEs, according to the trial protocol.
2. Expectedness assessment of related SAEs
3. Reporting safety information to a CI, delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit according to the TMP
4. Reporting safety information to the independent oversight committees identified for the trial (DMC and/or TSC) according to the TMP
5. Expedited reporting of related and unexpected SAEs to the REC within required timelines.
6. Notifying Investigators of related and unexpected SAEs that occur within the trial

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

4.7 Notification of deaths

All deaths where there may be a relationship between the trial interventions or the condition being studied (in this case, any head, neck or shoulder condition, or an event related to the anaesthetic, surgery, hospital admission, physiotherapy) will be reported by a PI to the Sponsor via the CI. This report will be as soon as a CI becomes aware of the event. Reporting processes to other organisations (e.g. REC) will be as documented above.

4.8 Reporting urgent safety measures

If any urgent safety measures are taken a CI/the Sponsor shall immediately and in any event no later than three days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

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5. DATA MANAGEMENT

All processes related to data management will be detailed in the Data Management Plan (DMP).

Personal data collected during the trial will be handled and stored in accordance with the UK General Data Protection Regulation (UK GDPR).

Personal identifying information will be held at WCTU for follow-up purposes. We will also request permission from participants to retain contact details to send a summary of the trial at the end of the trial. Handling of personal data will be clearly documented in the PIS and consent obtained.

Disclosure of confidential information will only be considered if there is an issue which may jeopardise the safety of the participant or another person, according to Warwick SOPs (SOP 15 part 1) and the UK or local regulatory framework. There is no reason to expect this situation to occur in this trial more than any other. Data requests from participants would be handled following SOPs (SOP 35).

5.1 Data collection and management

Case Report Forms will be developed to collect all required trial data.

The CRFs will be developed by the TM in consultation with a CI, Trial Statistician, Health Economist, and other relevant members of the trial team. They will be produced in English initially, although translation requirements will be reviewed if screening data reveals that language barriers are affecting participation and a predominant language, or languages, can be identified.

Participants will be given the option to use a website page (developed by WCTU) for follow-up data collection when they consent to join the trial. This should improve the response rate and participant experience in this trial. However, paper forms will still be used for those who prefer them, or for non-responders. These can be returned by post or scanned/returned electronically. We will also give participants the option of telephone follow-up.

All participants will be offered a £15 gift voucher at the 12-month follow-up timepoint, which would remunerate potential inconvenience in completing the data collection questionnaires. This has previously demonstrated to improve response rate in our previous trials [62]. This will be communicated in the PIS and 12-month questionnaire invite.

Reminders will be sent via text messaging, post, telephone or by email to improve response rate. Our PPIE Advisory Group feedback was positive about this as a way of reminding people. As is typical for our unit, we will take multiple contact details, including next of kin, (which will be stored securely in the trial database) to ensure a high response rate. Participants will only provide next of kin details where they have prior permission to do so. Where people do not respond (with prior consent), we will write to their GP or contact the site PI to request information on potential complications or re-operations, to ensure we do not miss critical safety data.

5.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate WCTU Trial Team staff.

5.3 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements, Warwick SOPs and access to stored information will be restricted to authorised

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personnel. All data will be stored in a designated storage facility within hospital sites taking part in the trial, and/or WCTU. Electronic data will be stored on password protected university computers in a restricted access building.

5.4 Data access and quality assurance

All data collected will be de-identified after the collection of the baseline demographic data for each participant, except where this is not possible such as contact details for follow-up, in which case it will be kept separately.

Confidentiality will be strictly maintained, and names or addresses will not be disclosed to anyone other than the staff involved in trial follow-up. Participants will be identified by ID number, initials and age only where necessary. Any identifiable participant data on paper will be held separately in a locked filing cabinet and coded with the trial number to tag identifiable data to the outcome data.

Direct access to source data/documents will be available for trial-related monitoring or audit by WCTU, or REC.

The PI must arrange for retention of trial records on site in accordance with GCP and local Trust's policies.

5.5 Data Shared with Third Parties

De-identified data that underlie the results reported in the trial will be available for non-commercial use, up to one year after publication of the primary outcome trial findings, or from metadata stored in a university repository up to five years without investigator support. A data dictionary will be produced. To access trial data, third parties must complete a data-sharing agreement with the Sponsor, have an ethically approved protocol in place for use of the data, and agree the approved protocol with the GRRAND TMG and WCTU Data Sharing Committee. Data may be used for commercial purposes, according to the conditions above, but will need specific agreements in place prior to access being agreed, this may include a license fee. Analyses may include individual patient data meta-analyses or other purposes as agreed with the GRRAND TMG.

Available data will include (but is not exclusive to) de-identified individual participant data that underlies the results reported in trial publications, the trial protocol, SAP, HEAP, PEAP, master copy of the informed consent sheets and scripts or files used to conduct trial analyses.

After one year following the publication of the final report, the data will be stored in an appropriate repository, it may still be available according to the conditions laid out above but may not receive investigator support.

5.6 Archiving

Trial documentation (including the ISF) and data will be archived for at least five years after completion of the trial.

6. STATISTICAL ANALYSIS

6.1 Power and sample size

Based on the feasibility study's data [31], using our primary outcome of the SPADI at 12-month follow-up, to show a worthwhile difference of eight points with 90% power and 5% level of significance with an SD of 21.1 [53], we need data on 292 participants. Allowing for 25% loss to follow up, a total of 390 participants (195 in each group) will be required with allocation ratio 1:1. We will require a total of 17 physiotherapists

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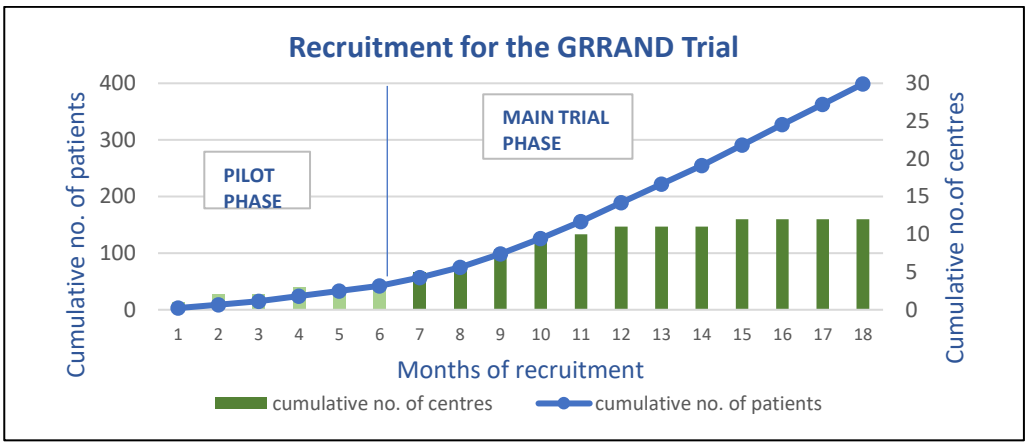
each with an average of 12 patients to deliver the intervention. The loss to follow-up over 12 months has been modelled on 25% based on previous literature[63] and greater proportion of participants in this trial being assessed at 12-month, compared to our feasibility study [31]. We will be striving to achieve a follow-up rate of >75%.

6.2 Statistical analysis of efficacy and harms

6.2.1 Planned recruitment rate

During the 18-month recruitment period, we will randomise a total of 390 participants (**Figure 4** with a target recruitment rate of three participants per site per month across at least 12 sites based on our experiences from the feasibility study and discussion with proposed sites. Recruitment will be monitored closely using established trial recruitment monitoring methods within the WCTU. Retention rates will be monitored in a similar manner.

Figure 4: GRRAND predicted recruitment rate



We have reassurance from our feasibility study that loss of participants to follow-up over time is likely to be minimal. Nonetheless we will monitor this throughout. Potential problems with retention for long-term follow-up will be minimised using participant self-reported PROMs. These will be collected either postal, online or telephone, based on participant preference. We will establish a system of reminders (email, text message and telephone call) and quality assurance checks to ensure the completeness of the information included in the CRFs (e.g., data checking and query on initial receipt of the questionnaire).

6.2.2 Internal Pilot and Stop/Go criteria

The first six months of randomisation will be an internal pilot, with a green target of 40 randomised (approximately 10% of total sample) [64]. The pilot will take place in a minimum of four hospitals, selected to offer diversity across the population whilst also representative of centres/physiotherapists that will take part in the main trial.

The internal pilot will audit: (a) screening logs for information on ineligible and eligible patients according to SEAR framework [65]; (b) recruitment and site set-up rate; (c) randomisation processes; (d) intervention training delivery; (e) receipt of intervention sessions; and (f) data completeness. These factors will inform decisions about progression to the main trial (**Table 4**).

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Table 4: STOP-GO Criteria for Internal Pilot

	RED	AMBER	Green
N participants recruited	≤26 (<66%)	27-39 (66%-99%)	≥40 (100%)
Recruitment rate/site/month	< 1 participant	1-2 participants	3 participants
Number of sites opened	1 site	2-3 sites	4 sites
Intervention Session Attendance*∞	≤27 (<70%)	28-39 (≥70% to <99%)	≥40 (100%)
Loss to Follow-Up ∞	≥10 (>25%)	1-9 (1%-25%)	0 (0%)

**Minimum one assessment and three follow-up appointments (4 sessions in total) or if patient-physiotherapist goals met and agreed discharge made prior to this session number. This was adopted in other cancer surgery rehabilitation trials[51], our feasibility data and recommendations from the PPIE and Clinical Advisory Group.*

∞ Analysed at 12-month follow-up of the cohort randomised in first six months to obtain sufficient data.

If the internal pilot meets amber criteria, we will consult the Funder, inform the TSC, review processes, look to open additional sites or amend trial processes, and review again in six months. If the red criteria are met across all indicators, we will discuss stopping the trial with the TSC and NIHR Health Technology Appraisal (HTA).

6.2.3 Statistical analysis plan

A detailed SAP will be written in-line with the Estimand framework [66] and approved by the DMC prior to the primary analysis taking place. Data will be reported in-line with the CONSORT guidelines [33]. Descriptive statistics will be constructed for baseline and follow-up data. Graphical summaries will also be created to aid interpretation of key results.

Primary outcome analyses will adopt the Estimand framework [66]. The SPADI score will be analysed using the treatment policy strategy (i.e., ITT). Treatment effects (with 95% CIs) will be estimated using mixed-effect linear regression models. Both unadjusted and adjusted (for stratification variables and important patient-level covariates) estimates of the treatment effect will be presented. Secondary outcomes will be analysed using a similar approach to the primary outcome as appropriate to data and its distribution. Secondary outcomes which are categorical will be analysed using mixed-effect logistic regression models. Intercurrent events (ICEs) and strategies for handling ICEs: post-randomisation events that may affect the interpretation of the primary outcome would include non-adherence (including discontinuation of treatment) (ICE1). The ICE1 will be analysed using the complier average causal effect (CACE) analysis

There are no formal interim analyses. Planned subgroup analyses will be conducted. Sensitivity analyses using as-treated and per-protocol analysis populations will also be conducted to aid interpretation. Missing data will be scrutinised and where possible, the reason for missingness recorded. If appropriate, multiple imputation will be used. Any imputation methods used for scores and other derived variables will be carefully considered and justified. In the case of missing outcome data, we will compute sensitivity analyses using imputation techniques to examine the impact of missingness.

6.2.4 Statistical analysis principles

Treatment effects will be presented with appropriate 95% CIs (where relevant), for all analyses. Tests will be two-sided and considered to provide evidence for a statistically significant difference if p-values are

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less than 0.05 (5% significance level). All analyses will be conducted following the ITT principle unless specified otherwise.

6.2.5 Summary of baseline data and flow of patients

Descriptive statistics will be constructed for baseline data to check for any characteristic differences between allocation groups. Graphical summaries will be created to aid interpretation of key results. A CONSORT chart illustrating participant flow throughout the study will also be produced.

6.3 Subgroup analyses

Pre-specified sub-group analyses will be undertaken to explore whether the intervention effect differs between:

- Age group (<60 or ≥60)
- Accessory nerve sacrifice (yes/no)
- Level of GRRAND programme adherence (none, partial, full)

The subgroup analyses will follow the methods described for the primary analysis, with additional interaction terms incorporated into the mixed-effects regression model to assess the level of support for these hypotheses.

The trial is not powered to formally test these hypotheses, so they will be reported as exploratory analyses only, and as subsidiary to the analysis reporting the main effects of the intervention in the full trial population.

6.4 Exploratory analyses

Exploratory models will be investigated to assess the change from pre-intervention scores to the 12-month outcome. This may include the use of latent growth models to assess trajectories of recovery.

6.5 Procedure(s) to account for missing or spurious data

Missing data will be scrutinised and where possible, the reason for missingness recorded. If appropriate, multiple imputation methods in statistical software will be used. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Consistency between cost-effectiveness and clinical effectiveness models will be explored and implemented where appropriate.

The results of the primary outcome model will not include the use of imputed datasets, but a sensitivity analysis using fully imputed datasets would be considered as an appropriate sensitivity analysis in comparison with the primary outcome model.

6.6 Health Economic Evaluation

For the base-case analysis, a parallel, within-trial, economic evaluation from the NHS and personal social services perspective will be conducted, with a broader societal perspective considered in a sensitivity analysis. A health economics analysis plan (HEAP) will be developed prior to data analysis. The methods will adhere to the NICE recommended standards for economic evaluation [67] and the internationally recognised CHEERS guidelines for reporting economic evaluations [68]. Cost of the intervention groups will be estimated to reflect resource inputs associated with rehabilitation and broader health care use. Resource use will be captured using participant questionnaires administered at 6 weeks, 3 months, 6 months and 12 months post-randomisation. Detailed micro-costing exercise for the intervention will be undertaken, including costs of development, training of physiotherapists and delivering the rehabilitation sessions. We also plan to collect information on medication, resource use in primary and community care

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settings (e.g., GP visits, community/district nurse, physiotherapy and other allied health professional visits, home services), out-patient services (e.g., A&E visits, physiotherapy, radiology, diagnostic imaging service, surgical and medicine services), in-patient services (e.g., critical care admission and admission in hospital wards), aids and adaptation used and personal and social services (e.g., meals on wheels, home care worker contacts, social worker contacts), and any broader resource use. Unit costs will be estimated from both local and national sources and reflated to current prices where necessary and presented in £ sterling. HRQoL will be measured at baseline and all follow-up timepoints using the EQ-5D-5L measure. Responses will be used to generate quality-adjusted life years (QALYs) using the appropriate value set recommended by NICE at the time of the analysis [67].

Descriptive statistics will summarise costs and QALYs by the intervention and comparator groups. The pattern of missing data will be examined and accounted for using suitable methods for multiple imputation. Within-trial analysis using bivariate regression of costs and QALYs for the base-case analysis, with imputation of missing data will inform deterministic and probabilistic assessment of incremental cost-effectiveness and results will be expressed as an incremental cost per QALY gained. Sensitivity analyses from a societal perspective will account for productivity losses and personal expenses incurred by participants due to their condition. To measure productivity losses, we will collect information on employment status (i.e., whether retired, student, full or part-time worker) employment details (e.g., employment category, employment details), educational and professional qualifications and number of days off work due to illness. Probabilistic sensitivity analyses will be undertaken to explore parameter uncertainty. Results will be graphically displayed on a cost-effectiveness plane. Cost effectiveness acceptability curves will show the probability of cost-effectiveness at a range of willingness-to-pay thresholds. If costs and outcomes do not converge within the 12 months, economic modelling will be undertaken to explore costs and benefits over an extended time horizon. If an economic model is needed, it will be populated using data from the trial, published literature and expert opinion. A 3.5% discount rate will be applied to both costs and QALYs beyond 12 months.

6.1 Ethical considerations

The trial team has considerable experience in recruiting participants into both physiotherapy and surgical trials of shoulder pain and rehabilitation, and process evaluation methods. Based on the extensive experience of the applicant team in conducting similar trials in this area, we do not anticipate any major ethical concerns.

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and Warwick SOPs. All data will be stored securely and held in accordance with the UK GDPR.

We have considered potential ethical challenges which may arise. These include the possibility of safeguarding alerts occurring during the process evaluation observations, distress arising as participants recall their experiences in the qualitative interviews or participant's disease progressing during the follow-up period. In each instance, duty of care will be adopted to ensure staff and participants are supported by the most appropriate professionals, if each issue were to arise. Our Patient and Public Involvement and Engagement (PPIE) interactions have been very positive when asked about ethical concerns and no such challenges were experienced in our feasibility study [31].

The Chief Investigators (CIs) will ensure that the trial is conducted in full conformity with relevant regulations and with the ICH Guidelines for GCP (CPMP/ICH/135/95) June 2017. Before enrolling patients into the trial, each site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. A site will not be permitted to enrol patients until its R&D department has confirmed Capability and Capacity and a site agreement is in place.

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The trial staff will ensure that participants' anonymity is maintained. Participants will be identified only by a participant identification (ID) number on the case report form (CRF) and ID number and/or code in any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the UK GDPR which requires data to be anonymised as soon as it is practical to do so. Data will be entered into a secure online trial database provided by Warwick Clinical Trials Unit (WCTU). Paper-based CRFs will be stored on site at WCTU under locked conditions for the duration of the trial; these will be considered source documents.

When 12-month follow-up analyses are complete, we will inform participants of the findings of the trial to help their future treatment decisions. Dissemination to trial participants will follow current Health Research Authority (HRA) guidelines (https://www.hra.nhs.uk/planning-and-improvingresearch/best-practice/publication-and-dissemination-research-findings/). They will be informed of the results using lay summaries and infographics on publication of the primary outcome results.

Potential participants will be approached, screened and informed about the nature of the trial verbally by the clinical team and written consent will be taken prior to undergoing neck dissection. Surgery for HNC is a life-changing procedure for many. The options for rehabilitation and recovery are therefore important for patients. Participating in this trial investigating rehabilitation strategies may be a major decision for potential participants. Accordingly, we will provide potential participants with precise, high-quality, information and consent materials, both at the time of consent and throughout the duration of the trial.

We will not restrict participants from further treatment (such as additional surgery or health access outside the trial protocol). This will be at their own discretion and the discretion of a clinician who treats them. This information will be collected on trial CRFs.

Co-enrolment to other trials may be permitted (after discussion between the site PI and TMG), as outlined in Section 2.12.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The University of Warwick will sponsor the trial, although the lead organisation for contracting with NIHR is University Hospital Coventry and Warwickshire (UHCW). The day-to-day running of the trial will be managed according to Warwick SOPs.

7.2 Ethical approval

The trial will be conducted in accordance with all relevant UK regulations and guidelines.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust R&D department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D capacity and capability is received by the WCTU Trial Team.

Substantial protocol amendments (e.g., changes to eligibility criteria, outcomes, analyses) will be communicated by the trial team to relevant parties i.e., investigators, RECs, participants, NHS Trusts, trial registries, as appropriate.

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Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC and Sponsor will be notified of the end of the trial (whether the trial ends at the planned time or prematurely).

The CIs will submit a final report to the required authorities with the results, including any publications within one year of the end of the trial.

7.3 Trial Registration

The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register prior to starting recruitment. A protocol paper will be published prior to completing recruitment.

7.4 Notification of serious breaches to GCP and/or trial protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

In the event of a serious breach:

- the Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
- the Sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of
  (a) the conditions and principles of GCP in connection with that trial; or
  (b) the protocol relating to that trial, as amended from time to time, within seven days of becoming aware of that breach

7.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

7.6 Trial timetable and milestones

Month	By date	Activity	Milestones
Phase 1: Set Up			
-6 to 0	01/09/24	Finalise Protocol HRA/REC submission	Submission to HRA/REC
-2 to 5	01/02/25	Complete HRA approval Prepare trial materials and CRFs Prepare contracts and plan site-initiation Programming/database construction and testing	1st TSC/DMC HRA approval Final versions of all materials approved Completed database

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Phase 2: Internal Pilot			
6 to 12	01/08/25	Start recruitment (staggered start of sites) Recruit 40 participants during internal pilot (allowing 1 month from study opening to first randomisation for consent process)	4 sites open and recruiting to target
	01/09/25	Assess against stop-go criteria (after 6 months randomisation) Decision on trial progression	Report to DMC, TSC and HTA
Phase 3: Main Trial			
6 to 24	01/02/26	Complete trial recruitment	390 participants recruited from a minimum of 12 sites in total
37	01/09/27	Complete 12-month follow-up	All 12-month follow-up closed
Phase 4: Analysis and Dissemination			
37 to 42	01/03/28	Data cleaning Complete Analysis Final data review with DMC/TSC Complete HTA report	Present results to DMC and TSC Final HTA report, and dissemination of results

7.7 Administration

The trial coordination will be based at Warwick Medical School/WCTU, University of Warwick.

7.8 Trial Management Group (TMG)

The TMG, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the TSC or Investigators, as appropriate.

In accordance with the NIHR guidance, a TSC, including an independent chair, at least two other independent members, and two lay members will be established prior to initiation of the trial and meet annually, or at the request of the chair. A separate DMC will also be established, consisting of a minimum of two appropriate clinicians and one statistician. The DMC will meet approximately every 12 months prior to the TSC for the duration of the trial. The TSC will monitor the trial's progress and will provide independent advice. The DMC will monitor data arising from the trial and recommend whether there are any ethical or safety reasons why the trial should not continue.

The trial will be managed by an established team at the UK Clinical Research Collaboration (UKCRC) fully registered WCTU. Warwick CTU will provide further trial expertise of statistical and programming support, the randomisation system and the trial database. The trial will be run in accordance with WCTU's SOPs and operational policies, which all adhere to UK regulatory requirements. The project will be monitored by the Sponsor (University of Warwick) and progress reports will be submitted to the funder.

A TM and Trial Coordinator will oversee all aspects of day-to-day trial management. The TMG will be established, consisting of the core trial team, CIs and co-applicants. The TMG will be responsible for the

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day-to-day running of the trial and will meet monthly to report on progress and ensure milestones are met. Milestones include completion of regulatory requirements such as ethical approval, site set-up, preparation of study materials, completion of the initial internal pilot and recruitment monitoring for the main trial to ensure the strict recruitment targets are met. The PPIE members of the TMG will be invited to attend TMG meetings either in person or by video call, as currently takes place in other trials at WCTU. This means of communication has worked well across the co-applicant team.

7.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent chair-person. Face-to-face meetings will be held as determined by need. Routine business is conducted by email, post or teleconferencing.

The TSC, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

7.10 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC will consist of a minimum of three independent researchers, one who is an appropriate clinician and one who is a statistician. The DMC will meet approximately every six months for the duration of the recruitment and follow-up, although they may choose to meet less frequently at certain stages of the trial, such as when the study is in follow-up. The DMC will meet after the first 10 patients have been recruited and will be held jointly with the TSC (unless quorate numbers for each cannot be achieved, in which case they will be separated). Thereafter, the DMC will meet regularly as a separate committee. Observers will be allowed in open sessions at the discretion of the chair but will not be allowed in closed sessions.

DMC meetings will also be attended by the CIs and Trial Co-ordinator (for non-confidential parts of the meeting) and the trial statistician.

The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC, as detailed in the DMC Charter. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

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7.11 Essential Documentation

A Trial Master File (TMF) will be set up according to Warwick SOP and held securely at the coordinating centre. The coordinating centre will provide an ISF to all recruiting centres involved in the trial.

7.12 Financial Support

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7.13 Safeguarding Researchers and Research Participants

The trial will follow the University of Warwick's safeguarding policy for researchers and research participants. This can be accessed at: https://warwick.ac.uk/services/ris/research_integrity/code_of_practice_and_policies/research_code_of_practice/preventing_harm/

8. MONITORING, AUDIT AND INSPECTION

The trial will be monitored by Quality Assurance (QA) team at WCTU as representatives of the Sponsor, to ensure that the trial is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring will be specified in a Trial Monitoring Plan (TMP) developed and determined by the Risk Assessment undertaken prior to the start of the trial.

The TMP will be agreed by the TMG based on the trial risk assessment. Processes to be considered in the plan will include participant enrolment, consent, eligibility and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy and timeliness of data collection. This plan will be available from the WCTU Trial Team and will also be lodged with the Sponsor. Assessment of fidelity of the interventions will be assessed using the process and fidelity measures documented in Section 3.3.

Sites persistently late in reporting SAEs, receipt of multiple late/poorly completed CRFs, or evidence from CRFs that the trial protocols and procedures are not being adhered to (as assessed by the CIs, or the TMG) may be considered as triggers for on-site monitoring visits. Whilst the monitors who would visit sites work in the same institution as the CIs and trial team (WCTU), they will act independently of the trial team in this role. The sponsors will ensure investigator(s) and/or institutions will permit trial-related monitoring, audits, and REC review, providing direct access to source data/documents as required. Central monitoring will be performed by the WCTU Trial Team exploring the trial dataset or performing site visits, as defined in the TMP and Data Management Plan.

9. PATIENT AND PUBLIC INVOLVEMENT AND ENGAGEMENT (PPIE)

Patients' views have been critical in developing this trial. In the feasibility study, we performed structured interviews with eight participants who had undergone neck dissection for HNC [30]. These have informed the trial design, approach and recruitment strategies, outcome measures, data collection methods and how we monitor and manage the risk of treatment contamination.

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We asked for advice and guidance from a PPIE Advisory Group of an additional four people who had undergone a neck dissection for HNC. All agreed the trial was important. They emphasised their uncertainty on the best recovery strategy after this operation, and reiterated its disabling effects on post-treatment lives. They found both best NHS care and the GRRAND programme acceptable. They also emphasised that shoulder function and quality of life measures were key outcomes to assess at 12 months.

With our PPIE Advisory Group, we explored the trial design in greater depth to ensure we fully captured the patient perspective on our decisions. This was particularly helpful when considering treatment adherence, fidelity and acceptability. The group were very supportive of the trial and reported all would be happy to consent if eligible. They provided detailed advice on how to communicate with potential participants considering the trial, particularly on how best to convey the research question and trial processes.

We specifically asked our PPIE members about whether they would be disappointed if randomised to the usual best practice NHS care group. We acknowledge the potential offer of additional care over usual care may create disappointment in some patient's minds which could influence compliance to trial procedures. The PPIE Advisory Group did not necessarily see this as a negative experience, indicating that as people in the control group would receive what would be offered 'routinely', they did not feel like people in that group would be 'missing out'. For one PPIE member, this emphasised the importance of the trial. In his mind, if the GRRAND programme were superior, he felt this may provide the evidence to ensure future patients could benefit.

The PPIE Advisory Group also reviewed the proposed primary and secondary outcome measures. They felt the length of the questionnaire booklet was 'acceptable', timed at 15 to 20 minutes. They felt that people who had consented to participate probably would not resent this task. They felt the questions and topics being posed were important in their lives and placed favour on the SPADI over a quality-of-life score, as, they felt, overall shoulder function impacts on all aspects of their lives including self-care, work, home life and recreationally. They perceived function as a marker of a successful recovery, representing a clear measure of 'how they were doing' in many areas of their lives. Three of the four preferred an email approach to complete and return of the outcome scores with one PPIE member also liking the option of a paper version, particularly for people who may find completing electronically a "put off". This feedback re-enforced our rationale for planning both online data collection in addition to a paper-based option in this trial.

Two PPIE representatives who both have lived experience of recovering after neck dissection for HNC (Mr Reategui and Mrs Beahan) are co-applicants. They will be integral to the team and have equal voice and representation as all other members of the TMG. We have successfully used this model in multiple previous NIHR trials at WCTU (REPPORT (NIHR134398); iWOTCH (14/224/04), CHESS (RP-PG-1212-20018), ARTISAN (16/167/56)), with patients making substantial contributions to decision-making, design and trial materials at all stages of the trial. This will be important throughout and particularly in ensuring that our planned methods of approach and recruitment materials, especially the PIS, are informative to ensure full and high-quality informed consent across the trial processes. Furthermore, their work in supporting the WCTU Trial Team in developing outcome collection methods and questionnaires (including questionnaire choice, formatting and mode of delivery) has and will be hugely important to promote data completion. Their roles will not be limited to these topics. As fully embedded members of the team, they will be engaged in all aspects of trial design and delivery. Two further patients will be invited to be members of the TSC.

We plan to recruit a wider PPIE Advisory Group to join our current four PPIE members involved with Stage 1 and 2 applications who formed the current PPIE Advisory Group. This will be supported by Smith as trial

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PPI lead. This group will continue to act as a patient reference group. The composition of this group will be monitored to promote EDI in research. They will provide a valuable collaboration to further review the trial, its design and patient-facing materials and gain feedback. As with previous trials, we will pilot questionnaires with particular care and engage in a consultation process to ensure our finalised questionnaire pack has had extensive PPIE review. This will be revisited in the set-up phase of the trial.

All lay representatives will be supported by the trial's PPIE Lead (Smith). Training courses for PPIE members and online modules about PPIE have been delivered by WCTU and will be offered to all PPIE members. All lay representatives will be remunerated according to INVOLVE guidelines. We will record and monitor all PPIE involvements in the trial to ensure accurate reporting to NIHR. This will be in the form of meeting note taking and informal feedback from PPIE members throughout the project to ensure they feel supported and offered appropriate training and development opportunities during the project. This will be led and promoted by Smith in his capacity as trial PPIE lead.

In addition to our PPIE activity, we have formed a Clinical Advisory Group consisting of 11 specialist physiotherapists from the Royal Marsden and Guys and Thomas' in London, Liverpool, Glasgow, Bath, Oxford and Norwich. They have been crucial during the development of this trial. They have agreed to offer ongoing support throughout the project.

10. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the TSC before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of physiotherapists, surgeons, doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the CONSORT guidelines (www.consort-statement.org) [33].

The data generated by NIHR-funded research will remain the responsibility of the organisation that has been contracted to perform research by the Department of Health and Social Care ("the contractor"). The data will be managed as specified in the research contract.

A tailored dissemination and output plan has been proposed to maximise impact to the trial results. This will be developed further by the trial team and PPIE and Clinical Advisory Groups.

Participants and the Public

Participants will be provided with the option of receiving trial results once completion. These will be prepared in conjunction with our PPIE Advisory Group and offered either electronically (as recorded video or summary paper with infographics) or the provision of a lay summary paper postally. We will share the trial results in a hybrid dissemination event which participants (who express an interest to) will be invited to. We will also prepare patient focused materials for charities such as The Swallows and Oracle Cancer Trust to disseminate the findings of the trial across patient groups to support and augment our social media strategy.

We will use press releases to alert the popular press in conjunction with the University of Warwick Communications Team. A trial website will be hosted by WCTU. The website and associated social media channels will be used to promote study progress, increase awareness of this NIHR research, promoting

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social engagement across the UK and promote trial publications. Summary briefing papers, press releases and social media posts will be prepared for the wider community with specific input from our PPIE Advisory Group.

Clinicians and Commissioners
Key findings will be presented at national and international conferences, such as the British Association of Head and Neck Oncologists Scientific meeting. British Academic Otolaryngology Conference. Swallows Head and Neck Cancer Conference and the Chartered Society of Physiotherapy Annual Conference (UK). Our PPIE representatives will be invited to participate in the proposed conferences and, with the support of the team, present findings and experiences from a patient perspective.

The findings from the trial will inform NHS clinical practice for the management of patients undergoing a neck dissection. The trial will be prospectively registered, prior to ethics approval, on the ISRCTN register. The trial protocol will be available via the NIHR HTA website and published in an open-access peer-reviewed journal in accordance with the SPIRIT Statement [69] during the recruitment phase. The trial results will be published as a final report to the NIHR HTA programme. We will simultaneously prepare manuscripts (protocol paper, results paper, health economics analysis and process evaluation papers if better reported separately) for high impact, peer-reviewed journals, in accordance with the NIHR's policy on open-access research. The trial results will be reported following the CONSORT guideline [33], with the TIDieR Statement [70] and CERT checklist [71] used to report the intervention.

We will host an 'Investigator Day' to feed the trial results back to physiotherapists and other members of the site teams. We have also included costs to fund attendance at national conferences over the four-year project timeline to disseminate information about the trial and stimulate interest among the physiotherapy and HNC surgical community.

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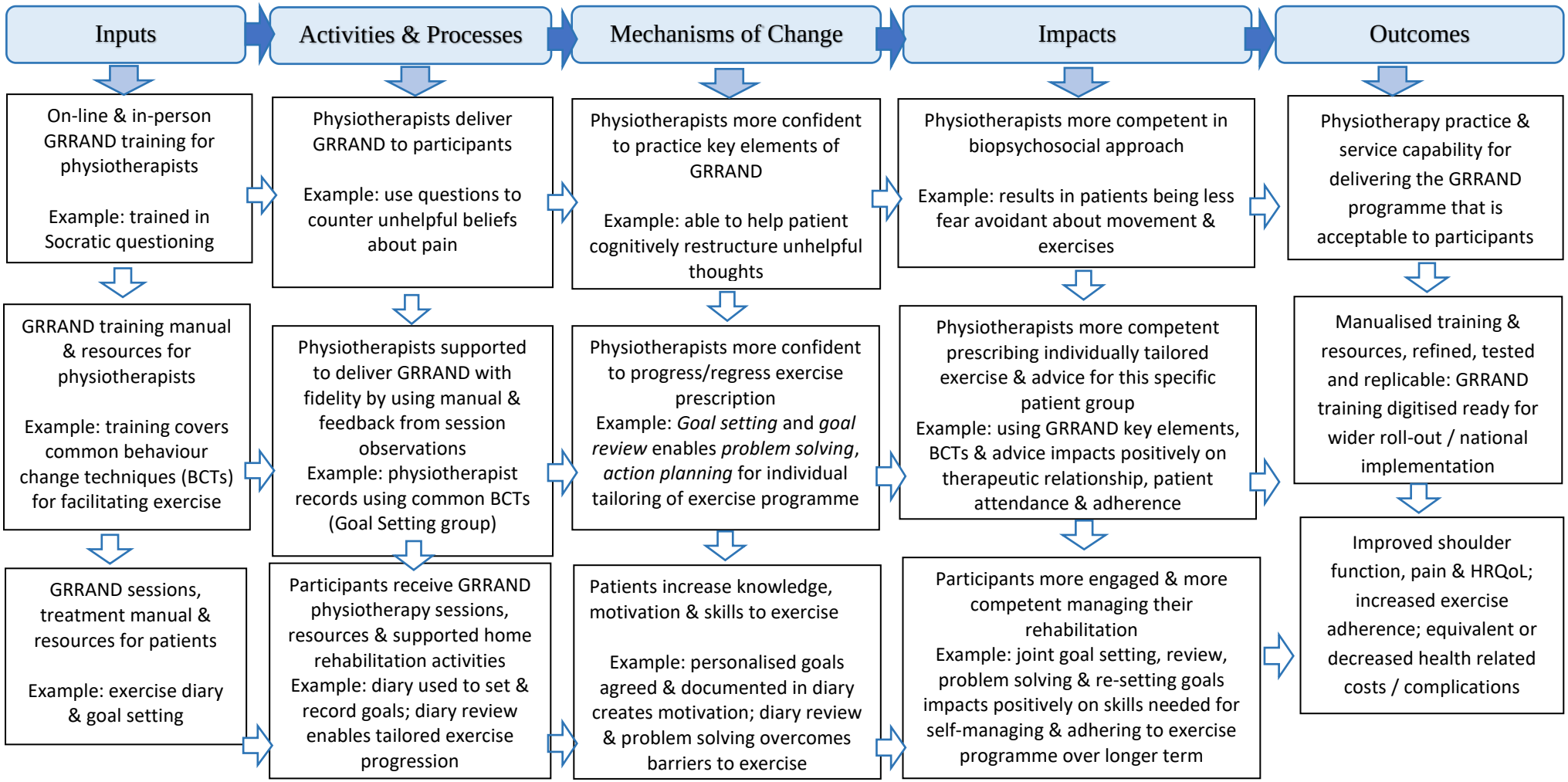
APPENDICES

Logic Model



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