UNIVERSITY OF LIVERPOOL

Short title: Respiratory-**S**wallow **T**raining in **H**ead & **N**eck Cancer **(ReST-HN)**

Full title: Development and feasibility of a respiratory-swallow intervention to improve swallow function for people with head and neck cancer (ReST-HN)

Protocol Version number: 1.7
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Sponsor: University of Liverpool
Sponsor reference number:UofL001843

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:
Signature: Date:
..../...../.....
.....
Name (please print):
Mrs Karen Jennings-Wilding
Position:
Senior Clinical Research Governance Manager

Chief Investigator:
Signature: Date:
..../...../.....
.....

Name: (please print):
.....
.....

Key Study Contacts

Insert full details of the key study contacts including the following;

Chief Investigator/study coordinator **Contact for Clinical Queries**	Dr Michelle Lawton Michelle.lawton@liverpool.ac.uk 0151 795 1359
Sponsor	The University of Liverpool is the research Sponsor for this Study. It is recognised that as an employee of the University the Chief Investigator has been delegated specific duties, as detailed in the Sponsorship Approval letter. For further information regarding the sponsorship conditions, please contact: Mrs Karen Jennings-Wilding Senior Clinical Research Governance Manager Sponsor@liverpool.ac.uk
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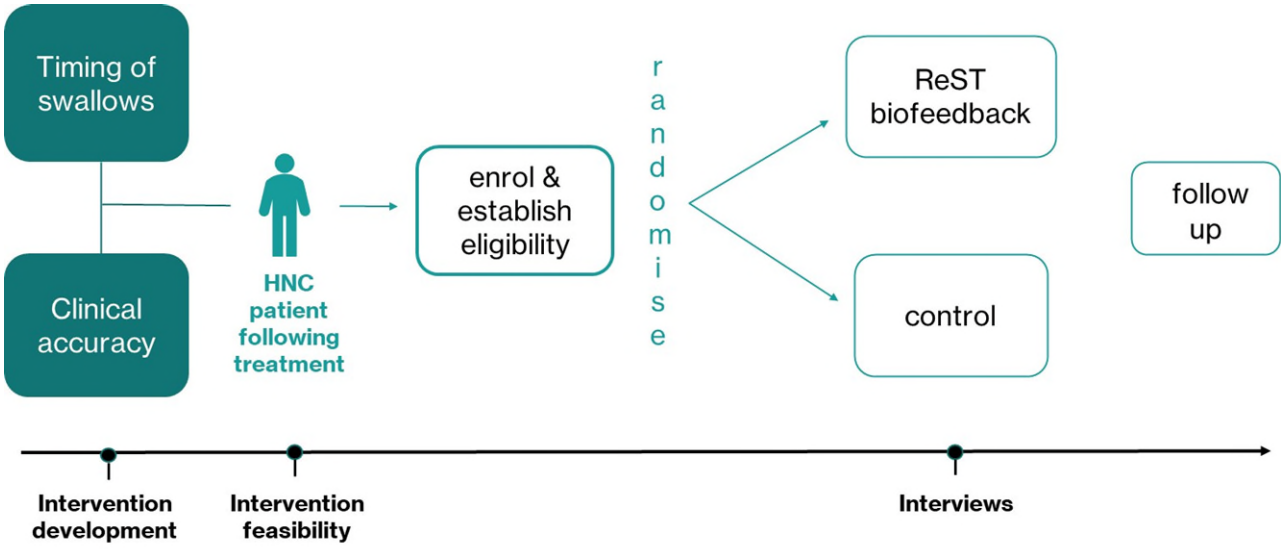
Committees	Working group Steering group (WP3)

Study Summary

Study Design	**WP1: Preliminary development study** A repeated measures study will be undertaken, including 2 conditions: 1) a control condition in which participants swallow without instruction and, 2) a cued swallow condition, in which participants will be given prompts to swallow at multiple time points within the respiratory cycle. **WP2: Preliminary development study** WP2 will determine the accuracy of a minimal instrumentation protocol for respiratory-swallow training **WP3: Feasibility study** A multicentred, two-arm randomised-controlled feasibility trial of RST using biofeedback in patients with dysphagia following HNC will establish parameters for a larger trial.
Study Participants	WP1: n=25 WP2: n=10 WP3: n=40
Follow up duration	WP3: 3-month follow-up
Planned Study Period	WP1: single timepoint WP2: single timepoint WP3: approximately 20 weeks
Research Question/Aim(s)	To develop a respiratory-swallow intervention to improve swallow function for people with head and neck cancer and to evaluate the feasibility of conducting a trial comparing respiratory-swallow training using biofeedback.

Key Words: Dysphagia, Head and neck cancer, Respiratory-swallow training, feasibility, respiratory-swallow co-ordination, rehabilitation.

Figure 1: Schematic representation of the study



Funding and Support in Kind

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Health Education England/ National Institute of Health & Care Research (NIHR) academy-awards@nihr.ac.uk	Advanced Clinical and Practitioner Academic Fellowship (£412,809)

Roles and Responsibilities of Study Management Committees/Groups & Individuals

Project Advisory Group (PAG) member	Role and contribution
Dr Michelle Lawton Michelle.lawton@liverpool.ac.uk 0151 795 1359	Chief investigator Dr Lawton will assume responsibility for overseeing the project.
Professor Joanne Patterson joanne.patterson@liverpool.ac.uk	Co-investigator Prof Patterson (with expertise in dysphagia and respiratory-swallow interventions) will advise on the development, methodology and implementation of the intervention.
Professor Chris Ward	Co-investigator

Chris.ward@newcastle.ac.uk	Prof Ward (with expertise in respiratory physiology) with advise on pulmonary outcomes and respiratory-swallow instrumentation, ensuring the findings are robust.
Professor Mike Drinnan m.drinnan@tees.ac.uk	Co-investigator Prof Drinnan will advise on practical design elements, ensuring sound methods are integrated to promote effective implementation.
Vince Killen vinny.killen@hotmail.co.uk	PPI Mr Killen may be involved in advising on recruitment strategies and troubleshooting, monitoring the process and progress of research and dissemination planning.
Val Bryant val.m.bryant@gmail.com	PPI Mrs Bryant may be involved in advising on recruitment strategies and troubleshooting, monitoring the process and progress of research and dissemination planning.
Sioned Davies sioned.davies@liverpool.ac.uk	Clinical Ms Davies (with expertise in respiratory physiotherapy) will advise on the development of the intervention and training.
Dr Heulwen Sheldrick h.sheldrick1@nhs.net	Clinical Dr Sheldrick (lead head & neck speech therapist) will advise on the research process and progress, providing invaluable clinical insights.
Dr Gemma Cherry gcherry@liverpool.ac.uk	Methodologist Dr Cherry (clinical psychologist) a qualitative methodologist will advise on process evaluation and study conduct.

Glossary of Abbreviations

HRA	Health Research Authority
REC	Research Ethics Committee
HNC	Head and Neck Cancer
RST	Respiratory-Swallow Training
WP	Work package
sEMG	surface electromyograms
RIP	Respiratory Inductance Plethysmography

IDDSI	International Dysphagia Diet Standardisation Initiative
PIS	Participant Information Sheet
CI	Chief investigator
MDT	multi-disciplinary team
PI	Principle Investigator
GCP	Good Clinical Practice
RCSLT	Royal College of Speech and Language Therapists
ADS	Active DataStore
VPN	Virtual Private Network

WP3 (April 2026- June 2028)

12. Feasibility Objectives

Work package 3 will establish key parameters required to inform trial design and aims to:

1. explore the feasibility and acceptability of providing RST in a clinical environment, identifying any barriers to implementation.
2. determine the rate of recruitment, attrition and completion, identifying any associated barriers.
3. determine the acceptability of randomisation
4. test the usefulness and completeness of a range of outcome measures at various timepoints.
5. establish standard deviation of the primary outcome measure to inform sample size
6. establish treatment fidelity
7. determine whether the intended audience gained access to the intervention
8. understand the mechanisms of change and establish sustainability and determinants for implementation

13. Outcomes

13.1. Primary endpoints

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

13.2. Secondary endpoints/outcomes

- Acceptability of intervention at interview
- Acceptability of randomisation at interview
- Completeness of outcome measures (%)
- Standard deviation of primary outcome measure
- Adherence to treatment manual checklist (%)
- Determinants of implementation and mechanisms of change at interview

17.3 Trial outcomes

- Pre and post intervention measures of respiratory-swallow coordination
    - Lung volume
    - Respiratory-swallow pattern
    - Respiratory pause duration
- Pre and post intervention measures of swallow function
    - Penetration-aspiration Scale
    - Modified Barium Swallow Impairment Profile
    - MD Anderson Dysphagia Inventory
    - Performance Status Scale Head & Neck Cancer

14. Study design

This multicentred, two-arm randomised-controlled feasibility trial of ReST using a dual-modality signal biofeedback in patients with dysphagia following HNC, with a nested qualitative study, will establish parameters for a larger trial. The protocol will be guided by the Standard Protocol Items: Recommended for Interventional Trials (SPIRIT) (2013) checklist[29]

A preliminary programme theory represented as a logic model will be developed, with engagement of stakeholders, to explore the potential mechanisms of impact. This will be refined as an ongoing process throughout the study.

15. Study setting

Participant identification will take place in two tertiary cancer treatment centres in England (Liverpool) and one community NHS trust (Mid Cheshire) (to identify potential participants with dysphagia secondary to the late effects of radiation). Patients will be approached about the study via their clinical appointment. The study intervention will take place at either the participant's home (to ensure inclusivity for those who are unable to travel) or at the participating NHS site (clinic), dependent on individual preference and clinical availability (some therapists may only work at NHS sites).

16. Sample and recruitment participant entry

20.1. eligibility criteria

Inclusion
Patients will:

- have a clinical diagnosis of dysphagia on instrumental assessment (VFSS/FEES) as indicated by evidence on outcome measurement (PAS[25]≥3 and Yale Pharyngeal Residue Severity Rating Scale[27] ≥mild in any area or DIGEST[28] ≥1 (efficiency grade))
- have completed chemotherapy, radiotherapy and/or surgical intervention for first-time diagnosis of squamous cell carcinoma for HNC
- be able to give informed consent
- be aged 18 years or above
- have completed HNC treatment with curative intent ≥ 3 months
- be able to tolerate fluids orally (IDDSI 0-3)
- exhibit a suboptimal respiratory-swallow patterns (exhale (EX)- inhale (IN), IN-IN, IN-EX) in ≥20%
- be able to hold the bolus (orally) and resume breathing

Exclusion
Patients with:

- a nasogastric tube, laryngectomy or tracheostomy (tube presence will alter respiratory-swallow coordination)
- a known neurological disease or insult impacting on swallowing
- spinal surgery or insult impacting on swallowing
- chronic COPD (forced expiratory volume<30% on pulmonary function testing)
- recent history (within the last 3 months) of aspiration pneumonia

20.2. Recruitment
Forty patients with HNC will be recruited; 20 in each arm.

20.2.1. Sample identification
Clinicians
Four speech and language therapists (SLTs) will be recruited from the Cheshire and Merseyside region. Clinicians with ≥2 years training will be invited to participate at the identified study sites.

Patients
Participant identification will take place at two tertiary NHS Cancer Centres (Liverpool University Hospitals NHS Foundation Trust, Clatterbridge Cancer Centre) and one NHS community hospital (Mid Cheshire NHS Foundation Trust). The treating NHS clinician (speech and language therapist) or research nurse will screen patients attending outpatient dysphagia clinics (both instrumental and non-instrumental) in line with the eligibility criteria at the participating sites. All patients screened will be recorded on a screening log by the specialist research nurse or PI at the participating sites. Data will be collected including: age, sex, ethnicity and geographical area to determine whether recruitment strategies are reaching all patients. Postcode data will be converted to indices of deprivation at screening (Local Deprivation Explorer 2025), no postcode data will be retained. Patients will be approached about the study when attending standard of care treatment appointments. All eligible patients will be given verbal and written information (participation information sheet: PIS appendix) about the study

Participants meeting the eligibility criteria, who have participated in WP2 and have consented to be contacted, will also be invited to participate in WP3.

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

Full written informed consent will be provided by signing, dating and initialling the consent form (Appendix), which will be witnessed by a person with delegated responsibility to do so. The original signed consent forms will be retained in the Investigator Site File (ISF), with a copy filed in the clinical notes and a copy provided to the patient. The participant's treating GP will be informed of study involvement (appendix).

20.2.3. Screening
The CI will complete additional respiratory-swallow, pulmonary function and swallow screening assessments (if indicated) with the participant in line with the eligibility

criteria. Pulmonary function will be assessed via spirometry. Forced expiratory volume (FEV1) and forced vital capacity (FVC) as a ratio. FEV1 and FVC will be recorded with a digital spirometer (details to follow) for all participants at (T0). Participants will be asked to take a deep breath in, as large as possible, and blow out as hard and fast as possible and keep going until there is no air left. This will be repeated three times. Obstructive lung disease with be calculated as a FEV1/FVC ratio.

Respiratory-swallow movements, using respiratory belts combined with nasal airflow (nasal cannula) and submental sEMGs will be recorded to establish the frequency of respiratory-swallow patterns whilst patients swallow 20 teaspoons of fluids (5ml: IDDSI 0-3).

If an instrumental assessment of swallowing has not been administered as part of usual care, a pre-intervention flexible endoscopic evaluation of swallowing (FEES) will be completed to inform clinical diagnosis of dysphagia and confirm safety of fluids. FEES will be completed by two clinicians (RCSLT level 2 competent) or one expert clinician (RCSLT level 3 competent) trained in using swallow instrumentation at the participating sites. Participants will be seated in an upright position. A flexible endoscope will be passed transnasally, through the most patent nostril, without the use of topical anaesthetic or vasodilators. The tip of the endoscopic will be positioned in the nasopharynx to visualise the pharynx, larynx and sub-glottis prior to and following the swallow (indicated by whiteout). FEES will evaluate swallow function with various bolus volumes and viscosities.

Trials will include teaspoons and sips of fluids (table 1). Further trials will evaluate swallow efficiency with sequentially increasing dietary viscosity (pureed, soft and bite size, regular diet). If a participant reports that they are unable to tolerate a given bolus consistency, no trials will be given of that consistency. The swallow protocol, follows the DIGEST standardised protocol[28] (table 1). In line with the International Dysphagia Diet Standardisation Initiative (IDDSI) recommendations, a flow test will be conducted prior to trial initiation to ensure standardisation of bolus viscosities. Boluses will be coloured using food dyes (blue, green, white) to enable visualisation. Bolus colours will be alternated to allow for discrimination between pre-existing residue and new residue. Participants will be encouraged to self-administer trials unless they are unable to do so. If a participant aspirates and is unable to expectorate the material, no further trials will be given of that volume or greater.

The stopping criterion for safety purposes will be at the discretion of the clinician conducting the FEES, taking into account patients' risk factors. Specific bolus trials may be terminated, or the procedure aborted altogether, if they deem a significant risk to proceeding with the FEES assessment. In the event of significant aspiration, local guidelines for management will be followed. The FEES should be stopped if the patient has more than 50% aspiration on a large bolus (≥10mLs) or at least 3 swallows with silent aspiration, in more than trace amounts.

Table 1: Screening for eligibility swallow trials

Bolus viscosity	**Bolus volume**

	5ml	10ml	Cup sip (self-initiated) 20ml	Bite size
Thin (IDDSI 0)	X2	X2	X2	
Pureed diet (IDDSI 4) Smooth rice pudding	X2	X2	X2	
Regular diet (IDDSI 7) biscuit				X1

20.2.4. Enrolment

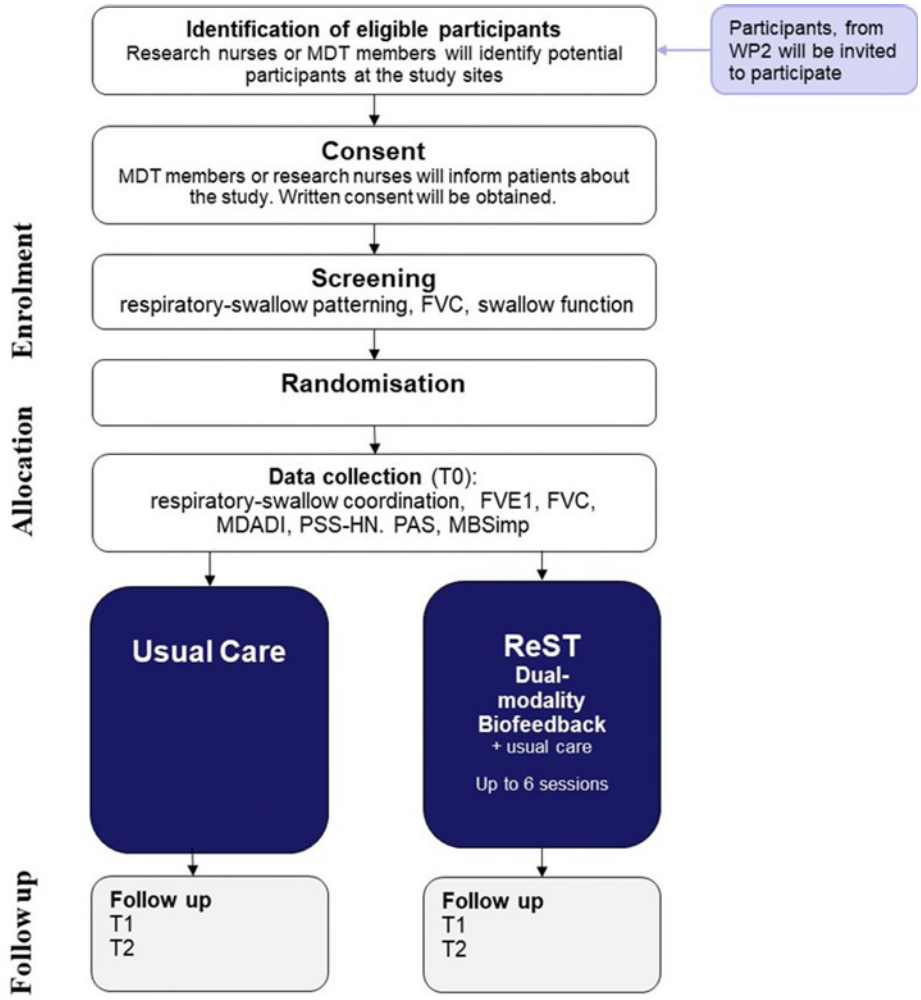
Each participant, meeting the eligibility criteria, will be: allocated a study identification number, entered onto a study enrolment log and randomised to one of two conditions (figure 3):

a) ReST using biofeedback
b) usual care

20.2.5. Randomisation

Participants will be randomised in a 1:1 ratio, stratified by disease stage. The randomisation procedure will be completed by a computer-generated programme and will use a stratified permutated block procedure.

Figure 3: Trial flow chart



21. Intervention

21.1. Development of Respiratory-Swallow Training programme (biofeedback)

A treatment manual will be developed for RST using biofeedback using the TIDieR framework[24] detailing: the equipment set-up, feedback provision, monitoring and measuring of goals for both interventions (to be submitted as a substantial amendment).

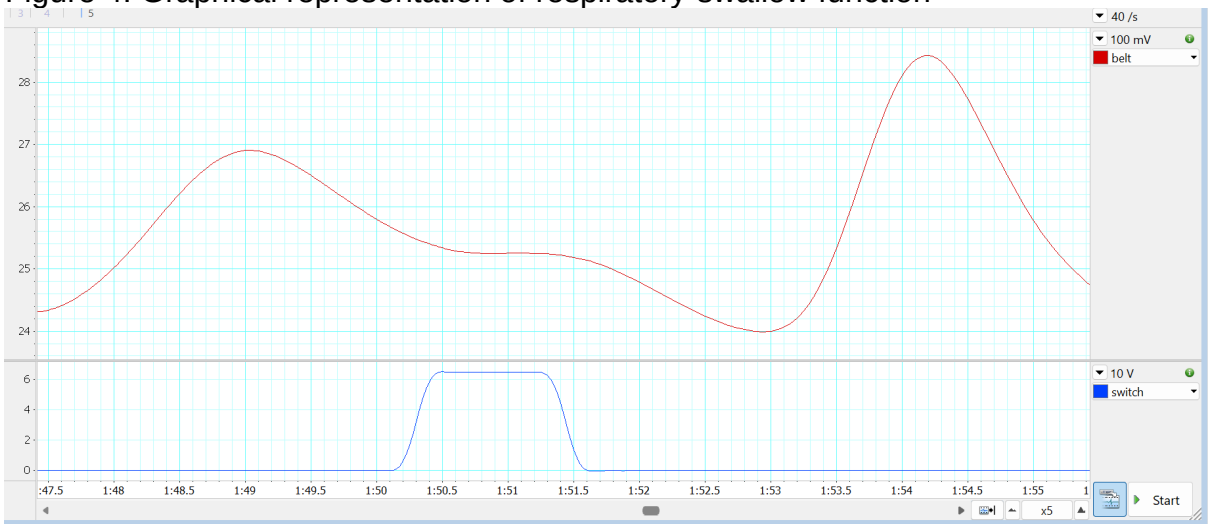
21.2. Respiratory Swallow Training using biofeedback group

Four clinicians (SLTs) will be trained to deliver ReST via biofeedback, as per the treatment protocol. Training will include: theoretical underpinning, treatment procedure, practical application and use of instrumentation. Competency will be determined by successful (100%) identification of optimal respiratory-swallow coordination (exhale-swallow-exhale pattern in mid lung volume range) using visual feedback.

ReST using biofeedback sessions with take place up to 1 hour weekly for up to 6 weeks until mastery is reached. An experienced speech and language therapist, who has received training, will deliver ReST using biofeedback to participants at an NHS clinic or the participant's home, dependent of individual preference or clinical availability. Participants will continue to see their treating therapist as part of usual care (if applicable) whilst receiving ReST. The treatment protocol will follow a tripartite design incorporating principles of motor learning as outlined by Martin-Harris & colleagues [10]. Goals are included which are divided into sub-goals within three learning domains: 1) identification, 2) acquisition, and 3) mastery. Participants will only move onto the next phase when they have demonstrated 80% accuracy (over 10 trials) on any given goal (table 2).

Identification: Participants will be shown a number of static graphical representation of swallowing and respiration, displaying the respiratory cycles and swallow (Figure 4). Participants will be asked to point to targets which demonstrate that they are able to identify: 1) breathing phases, 2) the swallow trigger, indicative of pharyngeal swallow, and, 3) optimal versus suboptimal swallow patterns. Participants will then view similar graphic representations in a dynamic view, on a computer screen. Participants will need to successfully identify 8/10 trials to progress to the next stage. If participants score <8, earlier goals will be revisited. This will be presented as an online module which can be completed at home or with the therapist dependant on patient preference.

Figure 4: Graphical representation of respiratory-swallow function



Acquisition: The aim of the acquisition module is for participants to be able to self-initiate swallows during the expiratory cycle. Participants will view a visual graphical representation of their own swallow on the computer screen, which will be used to provide biofeedback via respiratory Inductance plethysmography and a manual switch, which will be pressed by the therapist to mark the swallow. The clinician will provide verbal feedback to participants in relation to accuracy. Teaspoons of thin fluids will be initially trialled, providing they can be safely swallowed. If participants are unable to swallow thin fluids safely, thicker fluids will be trialled as per the findings on instrumental swallow assessment. Swallow initiation during expiration will

initially be targeted (with and without visually guided feedback). If participants are unable to tolerate dietary consistency safely, these consistencies will be omitted from the intervention. Only dietary consistencies the participant is safely able to tolerate will be used for training (as per the instrumental swallow assessment). Participants will need to successfully complete 8/10 trials at each stage to move on to the mastery phase.

Mastery: The aim of the mastery module is to ensure participants are able to use an optimal respiratory swallow pattern (i.e. exhale-swallow-exhale) with 90% consistency, without visual or verbal feedback. The programme will run for 5-6 weeks.

21.3. Usual care group

Usual care refers to speech and language therapy provided by the treating speech and language therapist as part of routine care. Speech and language therapy (SLT) aims to remediate swallowing, speech and voice difficulties following head and neck cancer. SLT may include assessment (clinician-rated, patient-rated and instrumental), intervention and/or review, which may focus on the use of compensatory strategies, strengthening and range of motion exercises, supporting mood and confidence, working with family/carers and providing information. Therapy is individually tailored and is largely face-to-face, however it may incorporate telehealth or group work. Patients are seen as inpatients, outpatients or in the community. Dysphagia therapy may include but is not limited to: swallow exercises (e.g. effortful swallow, Masako manoeuvre, Mendelsohn manoeuvre, supra-glottic swallow) and non-swallow exercises (e.g. range of movement exercises, shaker head lift, tongue strengthening, expiratory muscle strength training). Therapy may also focus on speech and voice training, directly targeting articulation and vocal quality.

22. Measurement

Swallow and respiratory-swallow evaluations will be conducted by the research associate, an experienced clinician, trained in using swallow and respiratory instrumentation at baseline (T0), post intervention (T1) and at 3-month follow up (T2). Pulmonary function evaluation will be administered by the research associate at baseline. All assessments will be conducted at an NHS clinic on the same day.

22.1. Pulmonary function

Forced expiratory volume (FEV1) and forced vital capacity (FVC) as a ratio, will be measured via spirometry, by the research associate. FEV1 and FVC will be recorded with a digital spirometer (details to follow) for all participants at (T0). Participants will be asked to take a deep breath in, as large as possible, and blow out as hard and fast as possible and keep going until there is no air left. This will be repeated three times. Obstructive lung disease with be calculated as a FEV1/FVC ratio.

22.2. Respiratory-swallow co-ordination

Respiratory movements combined with nasal airflow will be recorded to establish the frequency of respiratory swallow patterns. Chest and abdominal kinematic data will

be recorded by measuring movement of the rib cage (RC) and abdomen (AB) using Respiratory Inductance Plethysmography (RIP). An RC band will be placed around the rib cage at mid sternal level and an AB band will be placed around the abdomen at the level of the lowest rib. Nasal airflow will be recorded using a standard 7 ft nasal cannula connected to a pressure transducer. Surface electromyograms will record swallow onset and offset from the submental muscles. Three 10mm surface electrodes will be placed in a triangular arrangement, 2cm posteriorly to the mental symphysis. Each electrode will be separated by 2mm. All signals will be connected to PowerLab data acquisition system (2/26 PowerLab, AD instruments). Data will then be synchronised and stored on Lab Chart data analysis software (Lab Chart 8, AD instruments).

Participants respiratory-swallow coordination (pattern, lung volume and duration) will be recorded whilst swallowing liquids and solids (table 2). Trials will progress hierarchically from the smallest volume (5ml) to largest (25ml), commencing with thin consistency fluids, moving sequentially to increasing viscosity. If a participant shows signs of aspirating (airway response with/without wet voice)[32] or is unable to expectorate the material, no further trials with be given of that volume or greater.

22.2.1. Respiratory-swallow patterning

Respiratory events occurring before and after swallow apnea (represented by a plateau graphically) will be identified either as expiration (positive polarity) or inspiration (negative polarity). Frequency of respiratory swallow patterns will be recorded as: a) expiration-swallow-expiration, b) expiration-swallow-inspiration, c) inspiration-swallow-expiration or d) inspiration-swallow-inspiration for each participant for each swallow trial. Optimal respiratory swallow pattern will be defined as expiration-swallow-expiration.[17] To test the reliability of the respiratory swallow patterning 30% of the waveforms will be analysed by a second member of the research team, blinded to study allocation. Intra class coefficient coefficients will be calculated to determine inter-rater reliability. If discrepancies are identified between raters, a third analyst will review 100% of the waveforms.

22.3. Swallow function

Assessments of swallow safety and efficiency will be conducted using Videofluoroscopy. Videofluoroscopic examinations will be conducted in a fluoroscopic suite with a radiographer and examining speech and language therapist present. Examinations should be pulsed at a minimum of 15 pulses per second, although the optimal recommendation is 30 pulses per second. Radiation exposure will be limited to <5 minutes. A penny will be taped to the participant's neck just below the earlobe during the swallowing study. (the circular shape of the penny minimizes the impact of head rotation and the known diameter of the coin allows for calibration of pixels per cm and thus calculation of areas and displacement on videofluoroscopy. Videofluoroscopic examination will evaluate swallow function with a range of bolus volumes and viscosities (up to 23 swallows). Barium contrast will be mixed to a viscosity of 40% weight to volume ratio (w/v) and will follow a barium recipe (http://steeleswallowinglab.ca). An IDDSI flow test will be completed prior to testing. Bolus trials will be presented in the precise order listed below:

Lateral / mid-sagittal view

A) 5mL thin fluids (IDSSI L0) (1 trial) with a bolus hold from a teaspoon or cup. Instruction to the patient: *please hold this in your mouth until asked to swallow*. Give the instructions: "swallow when you are ready"
B) 5mL thin fluids (IDSSI L0) (2 trials) from a teaspoon or cup
C) 10mL thin fluids (IDSSI L0) (2 trials) from a cup
D) Self-initiated sip thin fluids (2 trials) from a cup
E) 5mL slightly thick fluids (IDDSI L1) (2 trials) from a teaspoon or cup
F) 10mL slightly thick fluids (IDDSI L1) (2 trials) from a cup
G) Self-initiated sip slightly thick fluids (2 trials) from a cup
H) 5mL mildly thick fluids (IDDSI level 2) (2 trials) from a teaspoon or cup.
I) 10mL mildly thick fluids (IDDSI L1) (2 trials) from a cup
J) Self-initiated sip mildly thick fluids (2 trials) from a cup
K) 5mL moderately thick fluids (IDDSI level 3) (2 trials) from a teaspoon or cup.
L) 5mL pureed diet (custard) (IDDSI level 4) (1 trial teaspoon).
M) 1/4 biscuit (digestive) (IDDSI level 6) - coated with 3 ml (1/2 tsp) of paste contrast (1 trial). Instruction to the patient: *chew this up and swallow when you feel comfortable and ready to swallow.*

Anterior-posterior (coronal) view

Please include an oesophageal sweep at the end of the examination, using a single bolus as described below, for the assessment of oesophageal clearance. No further imaging of the oesophagus is required:

I) 10mL thin (1 trial).

For routine VF, patient radiation dose is estimated to be between 0.2-0.85 mSv, exposure times ranging from 150 sec to 1080 secs. This research protocol is not expected to exceed this dose.

The stopping criterion for safety purposes will be at the discretion of the clinician conducting the VF, taking into account patients' risk factors. Specific bolus trials may be terminated, or the procedure aborted altogether, if they deem a significant risk to proceeding with the VF assessment. In the event of significant aspiration, local guidelines for management will be followed. The VF should be stopped if the patient has more than 50% aspiration on a large bolus (≥10mLs) or at least 3 swallows with silent aspiration, in more than trace amounts.

Swallow safety will assessed using the Penetration Aspiration Scale (PAS)[25]. Swallow efficiency will be evaluated using the standardised Modified Barium Swallow Impairment Profile Protocol[26]. Two clinicians, who have completed MBSImp training (achieving 80% interrater reliability) will provide consensus ratings for MBSImP assessments and scores. Rating clinicians will be blinded to treatment allocation.

Swallow evaluation requires multidimension measurement, incorporating patient-reported and clinician-rated outcomes, in addition to instrumental assessment. Swallow related quality of life will be measured by MDADI[22]. Swallow performance

will be rated via the Performance Status Scale for Head and Neck Cancer (PSS-HN)[21] (table 4).

Table 3: Timeline of baseline and follow up measures

Measures	T0 Baseline	T1 Post intervention (1 week)	T2 Follow up (3 month)
Demographics	✓		
FVC/FEV1	✓		
Respiratory swallow pattern	✓	✓	✓
MDADI[22]	✓	✓	✓
PSS-HN[21]	✓	✓	✓
EORTC QOL-H&N43[33]	✓	✓	✓
MBSimp[26]	✓	✓	✓
PAS[25]	✓	✓	✓

22.4. Economic

Two measures of swallow-related quality of life and the European Organisation of Research and Treatment for Cancer -Head and Neck (EORTC-H&N 43)[33] and MDADI[22] will be collected to determine the most appropriate quality of life measure for use on a larger trial. Cost of delivering the intervention based on relative costs of the clinical service, associated consumables and patient-attributable costs will be collected.

22.5. Feasibility

22.5.1. Quantitative data collection

Treatment fidelity

Treatment sessions will be videoed to analyse dose, treatment fidelity and integrity. To ensure treatment fidelity a random sample of 5% of the video recordings of each therapist will be analysed by another member of the research team. Treatment integrity will be determined by adherence to a checklist, which will measure key parameters identified within the treatment manual. Where treatment fidelity is lower than 80%, training will be reviewed and updated during the feasibility stage.

Recruitment and attrition

Number of eligible patients (comparing screening and enrolment logs), recruitment rate, drop-out and participation rate in both arms will be examined. Recruitment rates will be compared across study sites.

Completion of outcome measures

Completion rates of outcome measures will be used to inform the appropriateness and acceptability of measures, alongside qualitative data collection.

Usual care
Treating clinicians will complete a questionnaire in all arms to identify treatment interventions and frequency of contact and duration as part of usual care at T1.

22.5.2. Qualitative data collection

Initial study discussions (between the referring research clinician and patient) will be audio-recorded and analysed to identify potential barriers (e.g. communication, value systems) to study participation. A sample of patients (*n*=20-25) and staff (*n*=10-15) will be invited to participate in interviews at different timepoints, both during and after the training. Patients will be purposively selected according to their: age, gender, ethnicity, socioeconomic status and treatment allocation. We aim to interview patients that declined the trial as well as those who completed and dropped out, to explore the reasons behind this. A purposive sample of staff (including therapists, commissioners and research nurses) will also be interviewed. A semi-structured open-ended interview frame will explore patient and staff views of trial: implementation, recruitment, attrition, acceptability, mechanisms of impact, context and sustainability (table 4). The interview topic guide will be developed in conjunction with patient and public involvement (PPI) representatives and will be informed by realist methodology[34] and Normalisation Process Theory[35]. Questions will vary depending on treatment allocation and participation status. Interviews will be audio recorded, transcribed verbatim and imported into NVivo v12(QSR) for analysis.

Table 4: Qualitative data collection

Core research domains	**Data source**			
	Patients	Screening clinician/ nurse	Commissioners	Observation
Implementation				
What factors inhibit or facilitate the use of ReST?	✓	✓	✓	
Are ReST sessions delivered with fidelity?	✓	✓		✓
Recruitment				
What are the reasons for declining study participation?	✓			
What are the barriers and facilitators to recruitment?		✓		✓
Attrition				
What are the reasons for withdrawing from the intervention?	✓	✓		
Acceptability				
Are ReST interventions acceptable to stakeholders?	✓	✓	✓	
Is randomisation acceptable?	✓	✓	✓	
Mechanisms of impact				
Are the mechanisms of impact (identified in the logic model) operationalised as hypothesised?	✓	✓		✓
Context				
How are the mechanisms of impact influenced by context?	✓	✓		✓
Sustainability				
Is RST likely to be sustainable and what factors facilitate sustainability?		✓	✓	

23. Data analysis

23.1. Sample size

The selected target was chosen because it likely to be sufficient: 1) to demonstrate feasibility in relation to recruitment, acceptance and attrition, and, 2) to calculate sample size requirements, given that sample sizes of between 36 and >50 have been recommended.[29-30]

23.2. Quantitative data analysis

Analysis will largely be descriptive in nature. Patient demographic data will be summated by trial arm (mean (SD); median (interquartile range)). The number of eligible patients, recruitment rate and loss to follow up in all arms will be examined. All data will be reported with 95% confidence intervals. Participants' socio-economic and ethnicity data will be analysed, during the feasibility stage, to ascertain whether recruitment to ReST interventions is reflective of the intended population (in line with the NIHR INCLUDE ethnicity framework and forthcoming socioeconomic framework). If recruitment is not reflective of the intended population, recruitment strategies will be redesigned, with PPI input, to improve accessibility for under-served populations. Feasibility of data collection methods will be determined by examining missing data, completion rates and emergent patterns. Consistency and frequency of treatment interventions as part of usual care will examined across trial arms.

Standard deviation of the mean change in the primary outcome measure will be used to derive the sample size calculation for a future trial. All quantitative data will be imported into IMB SPSS V26 software for analysis.

23.3. Qualitative data analysis

Qualitative data will be analysed using inductive thematic analysis.[35] The research associate will listen to the audio recording and reread the transcripts on 3 occasions, noting emergent patterns that captured participants' perceptions and understandings. Units of text that convey meaningful information relevant to the research questions will be coded inductively. Themes will be identified at an explicit level, focusing only on the surface meaning of the data. Thematic maps will be created to form a graphical representation of the tentative themes and their relationships, which will be continually refined as part of an iterative process. Tentative themes will then be merged and modified as new data is collected and analysed. Patient and staff data will be analysed separately and triangulated. An iterative approach will be taken regarding qualitative data collection and analysis, allowing for potential changes to the treatment protocol, recruitment strategy and/or training to be implemented during the feasibility stage.[36]

23.4. Triangulation

Quantitative and qualitative data on patients' and healthcare professionals' engagement with the intervention, will be regularly discussed and triangulated at project management groups meetings to identify ways to refine the intervention and study processes while the study is ongoing. The impact of these refinements will then be examined both qualitatively and quantitatively. Procedurally, the "following a thread" framework for triangulation and integrative analysis of qualitative and quantitative data will be adopted. There is no assumption over the primacy of either data type and will look for both convergences and divergences between them and aim to produce categories and themes that accommodate both types of data. Attention to exploring any divergences between the qualitative and quantitative data will be given, as these can often provide important insights. This will generate insights about ways of personalising the intervention to the needs and preferences of patients with head and neck cancer, understanding variation in engagement and outcomes of interventions, and providing insights on the mechanisms by which interventions have an impact.

23.5. Criteria for progression

The feasibility decision to move forward to a full trial will be based on pre-defined criteria prior to study commencement:

1. Recruitment rate reaches an average of 2 participants per month
2. Adherence to treatment protocol ≥80%
3. Acceptance of outcome measures (and instrumentation) as indicated by completion rates of ≥50%
4. Sample size estimate is established
5. Patients experience of ReST interventions are perceived by participants as largely positive at interview
6. Acceptance to randomisation at interview

23.6. Safety considerations

Videofluoroscopy (VF) will be conducted by a speech and language therapist with the required level of competency as set out by the Royal College of Speech and Language Therapists guidelines and/or a Radiographer or Radiologist. The typical effect dose associated with VFSS is 0.2mSv, which is comparatively small in relation to background environmental exposure which ranges from 1.5 to 7.5 mSv per annum depending on where you live.[38] This means that one VF equates to between 2-7 weeks of environmental background radiation. In line with the ALARA (As Low As Reasonably Achievable) principle, examinations will be limited to <5 minutes.

Although no serious adverse effects are expected, it is possible that the use of videofluoroscopy (VF) may expose participants to aspiration of barium. However, incidence of aspiration-related pneumonia in VF are very rare and accounts less than 1% of all cases.[39] The stopping criterion for safety purposes will be at the discretion of the clinician conducting the VF, taking into account patients' risk factors. Specific bolus trials may be terminated, or the procedure aborted altogether, if they deem a significant risk to proceeding with the VF assessment. In the event of significant aspiration, local guidelines for management will be followed. The VF

should be stopped if the patient has more than 50% aspiration on a large bolus (≥10mLs) or at least 3 swallows with silent aspiration, in more than trace amounts.

We do not foresee any serious adverse side effects arising as the result of using Flexible Endoscopic Evaluation of Swallowing, as it is a safe and well-tolerated procedure.[40-41] The procedure will be administered by a clinician trained in using FEES, adhering to safety protocol, in line with the Royal College of Speech and language therapy guideline.[42] There is a chance that participants may experience mild discomfort and develop a nosebleed (epistaxis) following the procedure. The incidence of epistaxis is rare, accounting for 0.07-1.1% of all cases.[40-41] Local procedure for managing epistaxis will be followed.

24. Adverse events

24.1. Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject, including unfavourable and unintended signs, including abnormal laboratory results, symptoms or a disease associated with treatment.
Adverse events may include:

- Aspiration pneumonia
- Breathing difficulties/ shortness of breath
- epistaxis

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject 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
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

No adverse side effects are expected resulting from this study.

24.2. Reporting procedure

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

9.2.1 Non-serious Adverse Events (AEs)
Adverse Events (AEs) are any
All such events, whether expected or not, should be recorded. All AE should be recorded on a Case Report Form (CRF) and in the patient's medical notes.

9.2.2 Serious Adverse Events (SAEs)
Upon identification of an SAE the Principle Investigator should complete a study specific SAE form and send it to the Chief Investigator/Study Team within 24 hours. Relapse and death due to Head and Neck cancer, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

Contact details for reporting SAEs
Please send SAE forms to: michelle.lawton@liverpool.ac.uk
Tel: 0151 795 1359 (Mon to Fri 09.00 – 17.00)

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- **'related'**, i.e. resulted from the administration of any of the research procedures; and
- **'unexpected'**, i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the HRA Non-CTIMP safety report to REC form. The Chief Investigator will also notify the Sponsor of all SAEs.

For NHS REC approved studies please refer to https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/ - (Scroll to Safety reporting for non-CTIMP studies)

24. Data handling

Overall responsibility for data collection lies with the CI. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable data will leave the study site. Written consent forms will be kept securely according to the REC's requirements i.e., filed in the study site file. The study site file will be held in a locked security coded research office. The quality and retention of study data will be the responsibility of the CI. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

Data will be stored at the University of Liverpool Active DataStore (ADS) for the duration of the study. ADS provides a centralised, secure, supported data storage facility for electronic data, with ongoing access for the life span of a project. This space, and its underlying technical infrastructure are fully supported by IT Services who continually review and improve security arrangements. The ADS has many layers of protection, with data replicated between two secure physical locations and backed up regularly. Additionally, a regular tape backup is made to a third physical

location, and segregated from the public network both physically and logically. Data is encrypted in transit using SSL.

25.1. Data collection & handling

Data including the number of patients screened, approached and interested in taking part will be collected via a log completed by staff conducting screening (PI/research nurse).

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

Patients will complete paper and electronic assessment tools as required. The tools will also only be identified using the unique participant identifier number. Paper copies will be scanned onto a University computer at the earliest opportunity and stored on ADS; paper copies will be destroyed.

Fluoroscopic data will be stored at the participating sites on PACS. Data will be anonymised and assigned a participant identifier number by the PI prior to data transfer for analysis. Data will be transferred via NHS SharePoint to the CI's NHS SharePoint account. Therefore, raw data will remain within the NHS IT system. Analysis of raw data (fluoroscopies) will take place at NHS sites. Microsoft 365 employs 256-bit AES encryption to secure data both in transit and at rest which means that whether data is being transmitted over the internet or stored on servers, it is encrypted to prevent unauthorised access. Access can be controlled through permissions, ensuring that only authorised users can view or edit files. Only quantitative data (fully anonymised) following analysis will be transferred via SharePoint/OneDrive and stored securely on the University ADS.

Video recording devices will be kept in a locked cabinet at NHS participating sites. Video data will be transferred to the University ADS via the VPN from individual devices at participating sites. Data will be deleted from individual devices following data transfer. All video files will be edited to remove identifying information to ensure anonymity of respondents. Participants will only be identifiable via participant identifier numbers. Data will be stored on the University ADS.

Audio-recordings of interviews will be transcribed verbatim by a professional transcription agency with a secure up upload facility. Once transcripts have been received these will checked for accuracy and edited to remove identifying information to ensure anonymity of respondent. Each participant will be assigned a code which will give assurance that they cannot be identified. The transcript will be held securely on the password-protected encrypted server at University of Liverpool (ADS). The recording will be deleted once the research team are happy that they will not need to revisit the raw data. Data will be managed using NVivo software.

All data (apart from fluoroscopies) will be transferred directly to the research team via SharePoint/OneDrive. The Research Nurse and delegated staff at the NHS site will transfer; consent forms, CRFs, proformas and interview consent recordings. The CI will store these documents on the University ADS.

Thus, apart from the proforma and consent form no link to patient identifiable data will be present.

25.2. Access to data

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

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

Study data will be stored for 10 years inline the University requirement that research data necessary to support or validate a research project's observations, findings or outputs be retained for this period.

26.Regulatory issues

26.1. Ethics Approval

Before the start of the study, a favourable opinion will be sought from the UK Health Departments Research Ethics Service NHS REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements. Health Research Authority (HRA) approval will be obtained where required.

The study will be submitted to each proposed research site for Confirmation of Capacity and Capability. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

26.2. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and will abide by the Data Protection Act 2018 and the UK GDPR as amended from time to time and any successor legislation in the UK and any other directly applicable regulation relating to data protection and privacy.

26.3. Indemnity

The University of Liverpool holds Indemnity and insurance cover with Newline Insurance Company, which apply to this study.

26.4. Audits

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

27. End of study

The study will be considered as closed at 6 weeks after the last participant contact to allow for all completed assessment tools to be returned and collated, and the completion of the qualitative interviews.

28. Dissemination policy

All research data generated by University of Liverpool academics or research postgraduate students are wholly owned by the University (or NIHR) and remain with the University if the academic leaves the institution.

The findings will be disseminated, in collaboration with patient representatives, to patients and the wider population via patient-supported charities and groups. Factsheets detailing the findings from the research in an accessible format will be distribute to charities and other patient organisations.

Four peer-reviewed articles in high impact journals will be published:

- Preliminary study (WP1)
- Preliminary study (WP2)
- Feasibility protocol (WP3)
- Feasibility study (WP3).

The funding body (NIHR) will be acknowledged within all publications. Participants will given the opportunity to opt in (at consent) to receiving an accessible information summary of the findings, following the completion of each study.

The findings will be presented at specialist conferences to audiences in head and neck oncology, dysphagia and speech and language therapy to increase the visibility of the findings nationally and internationally.

To ensure that the findings are disseminated to health service providers, decision-makers and health care professionals, we will present the findings to members of the Cancer Alliance.

29. Archiving

Data and all appropriate documentation should be stored for a minimum of 10 years at the University of Liverpool repository after the completion of the study.

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