ISRCTN57028065 https://doi.org/10.1186/ISRCTN57028065

Home-based treatment program to improve quality of life and swallowing function in head and neck cancer patients with chronic swallowing disorders after treatment with chemoradiotherapy

Submission date	**Recruitment status**	[X] Prospectively registered
23/06/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
15/07/2021	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
24/10/2022	Signs and Symptoms	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Dysphagia is the medical term for swallowing difficulties. It is one of the most severe functional impairments in head and neck cancer survivors treated with chemoradiotherapy, and results in impaired nutrition, aspiration pneumonia and decreased quality of life. Radiation-associated dysphagia (RAD) may occur temporarily as an acute side effect during or immediately after treatment. However, it may also become chronic (C-RAD) or develop several years after treatment (late RAD). The aim of this study is to investigate the effect of state-of-the-art and innovative rehabilitation methods in patients with C-RAD, comparing the effectiveness and possible detraining effects of mere strengthening exercises (group 1) with a combination of strengthening exercises and functional swallowing therapy (group 2) and non-invasive brain stimulation added to that combination (group 3).

Who can participate?

Adult head and neck cancer survivors with C-RAD who were treated with radiotherapy or chemoradiotherapy

What does the study involve?

Participants will be randomly allocated to one of three groups. The duration, frequency and location of the treatment programs are the same in each group. All participants will practice four times a week for 8 weeks, a total of 32 sessions. The therapy will take place at home under the supervision of a qualified speech-language pathologist. The exercise program differs according to the group.

Participants allocated to the first group receive 8 weeks of exercises aiming to improve the strength of the swallowing muscles. Participants in the second and third group receive a combination of 4 weeks of strength training followed by 4 weeks of functional swallowing therapy. The strengthening exercises in group 2 and 3 are the same as in group 1. In the third

group, non-invasive brain stimulation is added to the strength-functional therapy combination of the second group. The effectiveness of the three treatment programs will be determined based on changes in swallowing function, quality of life and muscle strength. For future clinical implementation, therapy programs must not only be effective but also feasible, tolerable and sufficiently attractive to keep the patient motivated. Therefore confounding factors and adherence-specific measures will be investigated. The ultimate goal is the clinical implementation of effective therapy programs for C-RAD.

What are the possible benefits and risks of participating?
The possible benefit is increased quality of life and swallowing function. There are no known risks with trial participation.

Where is the study run from?
Antwerp University Hospital and University Hospitals of Ghent and Leuven (Belgium)

When is the study starting and how long is it expected to run for?
April 2021 to January 2025

Who is funding the study?
Kom Op Tegen Kanker (Belgium)

Who is the main contact?
Prof. Gwen Van Nuffelen
gwen.vannuffelen@uza.be

Contact information

Type(s)
Scientific

Contact name
Prof Gwen Van Nuffelen

ORCID ID
https://orcid.org/0000-0001-6934-4168

Contact details
Drie Eikenstraat 655
Edegem
Belgium
2650
+32 (0)3 821 34 41
Gwen.VanNuffelen@uza.be

Type(s)
Public

Contact name
Prof Gwen Van Nuffelen

Contact details

Drie Eikenstraat 655
2650
Belgium
2650
+32 (0)3 821 34 41
Gwen.VanNuffelen@uza.be

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Version 3

Study information

Scientific Title
Towards a patient supported, well-tolerated and evidence-based home-based treatment program to improve quality of life and swallowing function in head and neck cancer survivors with chronic radiation-associated dysphagia treated with chemoradiotherapy: a multicentre randomised controlled trial

Acronym
HIT-CRAD

Study objectives
Although the need for evidence-based and patient-supported therapy methods in head and neck cancer survivors is loud and clear and internationally acknowledged, research addressing this issue is very scarce, heterogeneous and levels of evidence are low which retards clinical implementation. This three-arm randomised controlled trial aims to fill in the need for high-level research in this domain.

Previous studies show the efficacy of exercises aiming to improve the strength of the main muscles involved in swallowing. However, transference of changes in muscle strength to changes in swallowing function is often limited. This study design will compare the efficacy and possible detraining effects of mere strengthening exercises (group 1) with a combination of strengthening exercises and functional swallowing therapy (group 2).

In recent years, the role of cortical plasticity in the rehabilitation of the human swallowing motor cortex has become more apparent. It has been demonstrated that pairing transcranial Direct Current Stimulation (tDCS) or High-Definition transcranial Direct Current Stimulation (HD-tDCS) with an active motor task enhances the excitability of the targeted motor network. Hence, pairing HD-tDCS with behavioural swallowing therapy may lead to greater functional gains, in particular in the impaired motor system. Therefore a third group is added to the protocol in

which non-invasive brain stimulation is added to the strength-functional therapy combination of the second group. To evaluate the possible additional effect of HD-tDCS participants in group 2 will receive sham HD-tDCS.

This study aims to investigate the efficacy of these three therapy programs by measuring changes in quality of life, swallowing function and muscle strength. The study hypotheses are therefore as follows:
1. The efficacy of the second and third treatment program will be greater than the first treatment program.
2. The efficacy of the third treatment program will be greater than the second treatment program.
3. A significant increase in muscle strength, swallowing function and swallowing related quality of life is expected in every group.
4. There will be no significant detraining effects in the three groups 4 weeks after the last training session.
5. The degree of adherence depends upon personality, difficulty completing the session, pain and the emotional relationship between client and therapist as well as the degree of agreement on therapy goals and tasks.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/04/2021, Ethics committee of Antwerp University Hospitals (Wilrijkstraat 10, 2650 Edegem, Belgium; +32 (0)3 821 38 97; ethisch.comite@uza.be), ref: B3002021000021

Study design
Interventional multi-centre three-armed randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Home

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Chronic radiation-associated dysphagia in head and neck cancer survivors

Interventions
Participants will be stratified into groups using Qminim. Selected minimization factors are the centre, time between completion of RT or CRT and beginning the swallowing therapy program

and the highest score on the Functional Oral Intake Scale (FOIS). The assignment is done automatically in real-time based on these criteria. Researchers of each centre have access to the program but do not have any precognition of the randomization.

The duration, frequency and location of the treatment programs are the same in each group. All subjects will practice four times a week for 8 weeks. The therapy will take place at home under the supervision of a qualified speech-language pathologist. The exercise program differs according to the group.

Group 1: 8 weeks strength training
Group 2: 4 weeks strength training and 4 weeks functional swallowing therapy combined with Sham HD-tDCS
Group 3: 4 weeks strength training and 4 weeks functional swallowing therapy combined with real HD-tDCS

Patients referred to group 1 will receive evidence-based exercises targeting the main muscle groups involved in swallowing i.e. muscles involved in tongue strength, pharyngeal contraction, laryngeal elevation and upper oesophagal sphincter opening. Tongue strengthening exercises (TSE) will be alternated with chin tucks against resistance (CTAR) and expiratory muscle strength training (EMST). Tongue-strengthening exercises consist of 120 tongue presses and are divided into 12 sets of 10 repetitions with a 30-s rest between sets. Each CTAR session includes 150 repetitions divided into 30 sets of 5 repetitions. Every fifth repetition subjects are asked to push the chin bar towards the chest bar and swallow as hard as they can to practice an effortful swallow. The EMST session involves 25 targeted exhalations, performed in 5 sets of 5 repetitions with a 30-s rest between sets. The program uses existing therapeutic devices offering the possibility to practice with visual feedback and a certain intensity.

Participants in Group 2 and 3 will receive a combination of 4 weeks strength training followed by 4 weeks functional swallowing therapy, where the patient will exercise on vigorously swallowing liquid, semi-solid and solid boluses. The swallowing system will be trained by gradually increasing the volumes within a consistency level and hence increasing the required effort to swallow the food bolus, following the guidelines of the McNeill Dysphagia Therapy Program.

In the third group, HD-tDCS is added to the strength-functional therapy combination to modulate cortical excitability during therapy. The centre electrode will be placed on the swallowing motor cortex (Brodmann area 4 (27)) based on the international 10-20 EEG electrode system (C3 left hemisphere and C4 right hemisphere). A constant direct current of 2 mA is applied for 20 minutes each session with a fade-in/fade-out of 30 seconds. HD-tDCS treatment is provided in a total of 32 sessions and all sessions are completed within 8 weeks (4 sessions per week, 3 days rest). To evaluate the possible additional effects of HD-tDCS on muscle strength and swallowing function, group 2 will receive sham HD-tDCS. Necessary safety measures and internationally recommended exclusion criteria will be taken into account.

Intervention Type
Behavioural

Primary outcome measure
Functional oral intake based on scores from the Functional Oral Intake Scale (FOIS) measured after 8 weeks of training

Secondary outcome measures

All participants will be assessed using the scales described above at baseline, weekly during therapy, after 4 and 8 weeks of therapy and 4 weeks after the last therapy session:
1. Swallowing function measured using:
1.1. Mann Assessment of Swallowing Ability-Cancer score (MASA-C)
1.2. Food Intake Level Scale (FILS)
1.3. Fiberoptic Endoscopic Evaluation of Swallowing (FEES)
1.3.1. Penetration Aspiration Scale (PAS)
1.3.2. Pooling Score (P-score)
1.3.3. Dynamic Imaging Grade of Swallowing Toxicity score (DIGEST-score)
1.3.4. International Dysphagia Diet Functional Diet Scale (IDDSI FDS)
1.4. Eating Assessment Tool (EAT-10)
1.5. Self-perception of swallowing ability, assessed using a visual analogue scale ranging from 'I can't swallow' (0 mm) to 'I don't have any swallowing difficulties' (100 mm)
1.6. Short Nutritional Assessment Questionnaire (SNAQ)
2. Quality of life measured using the Dysphagia Handicap Index (DHI)
3. Muscle strength measured using:
3.1. Maximum isometric tongue pressures (best out of three trials; kPa) measured using the Iowa Oral Performance Instrument (IOPI)
3.2. Maximum muscle strength of the suprahyoid muscles measured using a dynamometer
3.3. Maximal Expiratory Pressure (MEP) measured using a spirometer (best out of three trials)
3.4. Total performed number of exercises per week, based on daily therapist registration
4. Reasons for adherence/non-adherence measured using:
4.1. Recorded after each session through three standardised questions:
4.1.1. How much difficulty patients had completing the session (no difficulties/significant difficulties)
4.1.2. What factors made therapy difficult (e.g. fatigue, feelings of depression/anxiety, pain etc)
4.1.3. Any other important message (free text)
4.2. The work-alliance questionnaire (WAV-12, NL)

Data on the following possible confounders will be collected:
1. Patient and situational characteristics: age, gender, educational level, social status, personality traits using the NEO Five-Factor Inventory (NEO-FFI), frailty using the Clinical Frailty Scale and dental condition with the Oral Health Assessment Tool (OHAT)
2. Disease characteristics: tumour size (TNM classification), tumour site, HPV status (based on p16 immunohistochemistry; cut-off >70% cytoplasmatic and nuclear staining, complaints of xerostomia using the 'Xerostomievragenlijst – NL' and thicky saliva using a visual analogue scale
3. Therapy characteristics: chemotherapy, fractionation, bilateral neck irradiation, duration, time post-treatment

Overall study start date
12/04/2021

Completion date
01/01/2025

Eligibility

Key inclusion criteria
1. Patients with a history of head and neck cancer treated with radiotherapy or chemoradiotherapy
2. Diagnosis of C-RAD, present for at least 3 months, based on the EAT-10 (score ≥3) and/or FOIS

(max level 6 out of 7)
3. Eligible tumour sites: oral cavity, oropharynx, larynx, hypopharynx and nasopharynx
4. At least 6 months post-treatment

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
105, 35 in each group

Key exclusion criteria
1. History of major surgery within the head and neck region
2. Recurrent carcinoma in the head and neck region
3. Neurological history that might adversely affect cognition, muscle strength in the head and neck region or swallowing function
4. Dysphagia prior to CRT
5. Intensive swallowing therapy (> once per week) in the last 6 months
6. Complete dependency on tube feeding during more than 1 year
7. Severe frailty or worse following the Clinical Frailty Scale (CFS) (≥7)
8. Related to HD-tDCS: presence of implanted metal or electronic medical devices in the brain or other sites in the body (e.g. deep brain stimulator, cochlear Implant, pacemaker) except for dental implants, history of migraine, epilepsy, brain damage (stroke) or head trauma followed by impairment or consciousness, skin problems (e.g. dermatitis, psoriasis) and use of medication that interferes with non-invasive brain stimulation

Date of first enrolment
01/09/2021

Date of final enrolment
01/11/2024

Locations

Countries of recruitment
Belgium

Study participating centre
Antwerp University Hospital
Drie Eikenstraat 655
Antwerp
Belgium
2650

Study participating centre
University Hospital Leuven
Herestraat 49
Leuven
Belgium
3000

Study participating centre
University Hospital Ghent
Corneel Heymanslaan 10
Ghent
Belgium
9000

Study participating centre
GZA Sint Augustinus
Oosterveldlaan 24
Antwerp
Belgium
2610

Sponsor information

Organisation
Antwerp University Hospital

Sponsor details
Drie Eikenstraat 655
Edegem
Belgium
2650
+32 3 821 30 00
vragen@uza.be

Sponsor type
Hospital/treatment centre

Website
https://www.grid.ac/institutes/grid.411414.5

ROR
https://ror.org/01hwamj44

Funder(s)

Funder type
Charity

Funder Name
Kom op tegen Kanker

Alternative Name(s)
Fight Cancer

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Belgium

Results and Publications

Publication and dissemination plan
1. Multiple planned publications in high-impact peer-reviewed journals.
2. Dissemination of the project will also be done in collaboration with the Liga voor gelaryngectomeerden and local head and neck cancer organizations.

Intention to publish date
01/03/2025

Individual participant data (IPD) sharing plan
Datasets are entered and stored in a non-publicly available repository. All clinical record forms are managed using Redcap (Research Electronic Data Capture), supported by the ICT-department of the University Hospitals Leuven, which is a secure web application designed to support data capture for research studies. The researchers of each participating institution have access to the data of their patients. The Principle Investigators and the researcher of KU Leuven have access to all collected data. Collected data will not be made publicly available.
All data is pseudonymized, encoded and securely stored for 30 years. Identifying patients information will be safely stored on a secure server of each research centre which can only be accessed by the research team member of that centre.
Eligible participants are informed verbally and in writing by a research member. Prior to participation, written informed consent will be obtained.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		22/10/2022	24/10/2022	Yes	No