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Salivary electro-stimulation for the treatment of dry mouth in patients with Sjogren's syndrome

Submission date 23/07/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 02/08/2018	**Overall study status** Completed	
Last Edited 02/08/2022	**Condition category** Oral Health	

Plain English summary of protocol

Background and study aims

Dry mouth is a common symptom of primary Sjogren's syndrome (pSS) affecting speech, swallowing, oral health and quality of life. It is a distressing and persistent condition which can lead to long-lasting oral discomfort, dental infections, diminished quality of life, social isolation and loneliness. Unfortunately, current treatments for dry mouth are often unsatisfactory, only offering short-term relief, may be expensive and may result in side effects. A new electronic device has recently been developed to treat dry mouth. The device, acting as a "salivary pacemaker", is taken home by the patient and works by being placed in the mouth as and when needed. It harmlessly releases electrical pulses to stimulate the nerves (electrostimulating) associated with saliva production. As the electrical pulse intensity is below the human sensitivity level, it cannot be felt by the patient. The aim of this study is to determine whether the device reduces dry mouth symptoms in patients with pSS.

Who can participate?

Patients aged 18 and over with pSS and dry mouth

What does the study involve?

Participants are randomly allocated to one of two groups. One group receives an active electrostimulating device that provides mechanical/tactile stimulation but also releases electrical pulses. The second group receives a sham device that does not release electricity but provides mechanical/tactile stimulation only. Both groups are asked to use the device for 12 months. Although there are some limitations to the duration and frequency of use (no more than once per hour and for a maximum duration of 10 minutes per hour), participants are largely free to use the device as and when needed. Neither doctors nor participants are aware of which devices are functional or sham to ensure that the study results cannot be influenced. Participants attend 5-6 hospital appointments over 12 months, where they are asked to complete questionnaires regarding their dry mouth symptoms, oral health, quality of life and use of health services. They are also asked to do two simple 5-minute tests which require them to spit their saliva.

What are the possible benefits and risks of participating?
Participants allocated to receive the active device will potentially benefit from a reduction in dry mouth symptoms, improved salivation and an improvement in their quality of life. Participants allocated to receive the sham device are also expected to benefit from some increase in salivation due to the tactile and mechanical stimulation of the sham device although the benefit is believed to be much lower than the benefit due to electrical stimulation. Therefore, although participants will be requested to stop taking pilocarpine (a salivary stimulant used in standard care by about 30% of patients) and will not be able to receive acupuncture for dry mouth (a treatment used by less than 1% of patients in standard care) for the duration of the study, it is anticipated that participants in both groups will benefit from using the device they are allocated to. All participants will also continue to be treated with standard of care treatment for dry mouth with the only exception of pilocarpine or acupuncture. These treatments include salivary substitutes (mouthwash, spray, gel), chewing sugar-free gums or sucking sugar-free pastilles or often simply frequent sips of water. Benefits to the participant include being closely monitored and supported by the research team in addition to the routine care received from the rheumatology or oral medicine teams. Participants will also receive an oral examination at each clinical assessment visit to check the device is not causing any mouth abnormalities, in particular relating to the placement of the electrodes. The results of this study may lead to a more clinically and cost effective way to treat the dry mouth symptoms of pSS in the future. The study team foresee minimal risks as the active device is CE marked with a well known safety profile, available freely to purchase and will be administered by suitably trained and qualified medical professionals. The sham device is a non-electrostimulatory version of the same device, identical in appearance, weight, taste and sensation. The device differs only in respect of the software, meaning the device does not possess any electrostimulation functions and hence raises no further safety concerns.

Where is the study run from?
1. University College London Hospitals NHS Foundation Trust
2. Sheffield Teaching Hospitals NHS Foundation Trust
3. University Hospitals Birmingham Foundation Trust
4. The Newcastle Upon Tyne Hospitals NHS Foundation Trust
5. Great Western Hospital NHS Foundation Trust
6. Royal Liverpool and Broadgreen University Hospitals NHS Trust
7. Leeds Teaching Hospitals NHS Foundation Trust
8. Barts Health NHS Trust

When is the study starting and how long is it expected to run for?
April 2018 to January 2022

Who is funding the study?
Arthritis Research UK

Who is the main contact?
Ms Claire Davies
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
38405

Study information

Scientific Title
SALivary electro-stimulation for the treatment of dry mouth in patients with Sjogren's syndrome: a multicentRe randomISEd sham-controlled double-blind study

Acronym
SALRISE, v1

Study objectives
Dry mouth is a common manifestation of primary Sjogren’s syndrome (pSS) affecting speech, swallowing, oral health and quality of life. It is a distressing and persistent condition which can lead to long-lasting oral discomfort, dental infections, diminished quality of life, social isolation and loneliness.

Unfortunately, current therapies of dry mouth are often unsatisfactory, only offering transient relief, may be expensive and may result in adverse effects.

A novel intraoral electronic device has recently been developed to treat dry mouth. The device, acting as a “salivary pacemaker”, is taken home by the patient and works by being placed in the mouth as and when needed. It harmlessly releases electrical pulses to stimulate the nerves (electrostimulating) associated with salivary gland secretion. However, the electrical pulse intensity is below the human sensitivity level, therefore it cannot be felt by the patient.

The aim of SALRISE is to determine whether the device reduces dry mouth symptoms in patients with pSS.

Ethics approval required
Old ethics approval format

Ethics approval(s)
East of England – Essex Research Ethics Committee, 16/07/2018, ref: 18/EE/0153

Study design
Randomised; Interventional; Design type: Treatment, Device

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Primary Sjogren’s syndrome

Interventions
This is a double--blind randomised study of patients who have primary Sjogren's syndrome. The purpose of the study is specifically to ascertain the role of electro stimulation in the treatment of dry mouth for participants who have primary Sjogren's syndrome. A double-blind trial design has been selected as this minimises the possible introduction of bias.

Patients will be identified for potential recruitment by investigators based in secondary care rheumatology or oral medicine clinics. They will be then approached by one of the clinicians of the study and/or a research nurse and provided with detailed information about the study.

A total of 130 participants will be randomised in a 1:1 allocation to receive i) an active, salivary electrostimulating device that provides mechanical/tactile stimulation but also releases electrical pulses of specific patterns to stimulate the nerves associated with salivary gland secretion or ii) a sham device that does not release electricity but provides mechanical/tactile stimulation only. Both active and sham devices will be indistinguishable in appearance (using identical appearance, packaging, and labelling) and when in use (the electrical pulse intensity is below the human sensitivity level, therefore the electronic stimulus is completely asymptomatic). Neither clinical investigators nor participants will know which devices are active and which are sham. Participants will continue to be treated with standard of care therapy

during the study with the exception of pilocarpine and acupuncture for the dry mouth symptoms of pSS as both these therapies have the potential to interfere with the outcome measures. Whilst the sham device will not release any electrostimulation it is expected that the mechanical /tactile stimulation may have a positive effect upon salivary production.

The aim is to compare the dry mouth symptoms, safety and cost effectiveness of the device in both sets of participants 12 months after initiating use of the device.

Participants will be asked to use the device up to 10 minutes/hour no more than once an hour, for a total of 52 weeks. They will be asked to attend follow-up visits at the secondary care site at weeks 4, 12, 26 and 52.

At each follow-up visit they will be asked to complete questionnaires regarding their dry mouth symptoms, oral health, quality of life and use of health services. They will also be asked to do two simple 5-minute tests (a total of 10 minutes) which require them to spit their saliva into a test tube to measure their salivary production under different conditions i) when resting the mouth (unstimulated) and ii) whilst chewing on a block of paraffin wax (stimulated) and undergo a clinical oro-facial examination by a clinician trained to assess for abnormalities thought to be related to using the device.

In addition, at week 39 they will be sent the same set of questionnaires referred to above to complete at home and return to the Clinical Trials Research Unit in a stamped addressed envelope.

Study participants will also complete a daily diary detailing of the frequency of application of the device per day.

Sample size calculation
This has been calculated with regard to the primary outcome. A total of 130 patients is required to have 90% power for detecting an effect size of 2.5 units for the change in XI score at 52 weeks post-randomisation assuming a between-patient standard deviation of 4 units, 2-sided 5% significance level and 15% loss to follow-up

Timetable for the stages of the research:
-- 24 months for recruitment of participants
- 12 months of clinical trial
-- 7 months for data analysis

Intervention Type
Device

Primary outcome measure
Xerostomia Inventory [XI] score, a validated patient-centred functional outcome measure for xerostomia; Timepoint(s): 52 weeks post randomisation

Secondary outcome measures
1. Longitudinal XI score over 52 weeks
2. Stimulated and unstimulated whole salivary flow to measure salivary gland function over 52 weeks
3. Dry mouth symptoms measured using 0-100 mm VAS over 52 weeks
4. Dry mouth symptoms measured using five-point Likert scale of change in dry mouth severity over 52 weeks (much worse, worse, the same, better and much better)

5. Frequency of device use per day using participant-reported daily diaries over 52 weeks
6. Oral health-related QoL measured using the Oral Health Impact Profile-14 (OHIP-14) over 52 weeks
7. Incremental cost effectiveness of the SaliPen salivary electrostimulating device and sham device over 52 weeks
8. Adverse events and serious adverse events relating to the trial device or oral symptoms of pSS reported over 52 weeks

Overall study start date
01/04/2018

Completion date
31/01/2022

Eligibility

Key inclusion criteria
1. Patients aged ≥18 years at the time of signing the Informed Consent Form
2. Patients with diagnosis of primary Sjögren's syndrome (pSS) according to 2002 EU/US or 2016 ACR/EULAR classification criteria
3. Symptomatic oral dryness (>5/10 on patient-completed Numerical Rating Scale)
4. Evidence of residual salivary gland function, demonstrated by an increase in salivary flow on appropriate stimulation (e.g. chewing paraffin wax) as compared to the unstimulated salivary flow
5. Unstimulated whole salivary flow higher than 0 ml/5min (unstimulated whole salivary flow as measured via sialometry for 5 minutes)
6. Patient has provided written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 130; UK Sample Size: 130

Total final enrolment
136

Key exclusion criteria
1. Patient has a cardiac pacemaker or other implanted electrostimulating device fitted, e.g. deep brain stimulation device, a cardiac defibrillator
2. Patient has epileptic disorder, essential tremor, involuntary muscle movement disorder, e.g.

Parkinson’s disease or trigeminal neuralgia
3. Patient has evidence of chronic erosive/ulcerative disease or chronic keratotic disorders of the oral mucosa (e.g. lichen planus) or jaw osteonecrosis upon oral examination
4. Patient has suspected or confirmed malignant disease or pre-malignancy (dysplasia) of the oral mucosa
5. Patient has active malignancy (any organ other than the oral mucosa)
6. Current pregnancy as confirmed by urine pregnancy test at Eligibility and Baseline Assessment visit
7. Pilocarpine therapy during the 14 days prior to the Eligibility and Baseline Assessment visit
8. Concomitant use of systemic sialogogue therapy (e.g. pilocarpine) throughout the study
9. Unstable dose over the 4 weeks prior to the Eligibility and Baseline Assessment visit of any medication or therapy known to have an effect upon saliva production (or 7 days in the case of antihistamines)
10. Patient has received a rituximab infusion within the 6 months prior to the Eligibility and Baseline Assessment visit
11. Patient has received acupuncture for the dry mouth symptoms of pSS within the 28 days prior to the Eligibility and Baseline Assessment visit
12. Patient previously participated in LEONIDAS-1, already owns a SaliPen device, any of the earlier generations of the device or any other device with a similar electrostimulatory mode of action that acts upon the salivary glands.
13. Expected non-compliance with treatment interventions or is considered unsuitable for trial participation at the discretion of the treating clinician/nurse

Date of first enrolment
13/08/2018

Date of final enrolment
30/04/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Sheffield Teaching Hospitals NHS foundation Trust
Northern General Hospital
Herries Road

Sheffield
United Kingdom
S5 7AU

Study participating centre
University Hospitals Birmingham Foundation Trust
Queen Elizabeth Hospital
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freemans Hospital
High Heaton
Newcastle Upon Tyne and Wear
United Kingdom
NE7 7DN

Study participating centre
Great Western Hospital NHS Foundation Trust
Great Western Hospital
Marlborough Road
Swindon
United Kingdom
SN3 6BB

Study participating centre
Royal Liverpool and Broadgreen University Hospitals NHS Trust
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
Leeds Teaching Hospitals NHS Foundation Trust
Chapel Allerton Hospital

Leeds
United Kingdom
LS9 7TF

Study participating centre
Barts Health NHS Trust (participant identification site only)
Whitechapel Rd
London
United Kingdom
E1 1BB

Sponsor information

Organisation
University College London

Sponsor details
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Sponsor type
University/education

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Arthritis Research UK; Grant Codes: 21233

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
31/01/2023

Individual participant data (IPD) sharing plan
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree suitable requirements for release.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No