

oRLoN: An investigation into whether the methodology used in hypotonic saline cough challenge can be refined

Submission date 21/08/2026	Recruitment status Recruiting	☒ Prospectively registered ☐ Protocol
Registration date 26/08/2026	Overall study status Ongoing	☐ Statistical analysis plan ☐ Results
Last Edited 08/10/2026	Condition category Respiratory	☐ Individual participant data ☒ Record updated in last year

Plain English summary of protocol

Background and study aims

Refractory chronic cough (RCC) is cough that does not respond to treatment. It can have a profound effect on quality of life, with many patients coughing hundreds of times a day without any relief.

Cough challenge tests are used in research to measure how sensitive a person's cough reflex is. These tests allow researchers to compare cough sensitivity between different people and different chest conditions, or before and after medication. This then helps researchers to understand why people develop a chronic cough and how their cough compares with healthy individuals.

The research team are doing this study to try to design a new cough challenge test that they hope could be used in the future to improve the diagnosis of chronic cough. Past studies have shown that cough challenge using hypotonic saline (low chloride, low sodium salty water) is good at distinguishing between people with chronic cough from healthy volunteers. However, the researchers believe this test could be done in a more simplified way. Moreover, the nebuliser and consumables currently used in hypotonic saline cough challenge are being withdrawn from use, so an alternative nebuliser must be found to allow research with this challenge to continue. This study therefore aims to understand whether the current hypotonic saline cough challenge methodology can be refined while retaining its ability to identify patients with RCC versus healthy volunteers.

Phase A of the study will investigate whether we can shorten the hypotonic cough challenge protocol. This will be done by comparing how much people cough when asked to breathe in different amounts of saline solutions, compared to the original challenge.

Phase B will investigate whether an alternative nebuliser device can be used to conduct a hypotonic saline cough challenge. This will be done by comparing the cough response to hypotonic cough challenge using the original device, versus an alternative device.

Who can participate?

1. Patients with refractory chronic cough (RCC) will be recruited from specialised cough clinics at Manchester Foundation Trust (MFT).
2. Healthy volunteers (i.e., those with no clinically relevant medical conditions or history of

respiratory disease) will be recruited from across the University of Manchester and MFT. Participants can be male or female, and must be aged 18 years or over. People on medication that may affect cough (e.g. ACE inhibitors, tricyclic antidepressants or opiate pain killers) cannot participate, as this may affect the results. People with asthma, that are pregnant or breastfeeding, that are currently smoking, vaping or have significant recreational drug use, also cannot take part.

What does the study involve?

This study is split into two phases: Phase A and Phase B.

Phase A:

Phase A involves five visits to the clinical research ward at Wythenshawe Hospital, and a telephone follow up. At visit 1 a researcher will talk through the study and answer any questions. After signing a consent form, the researcher will confirm that the participant is eligible by going through their medical history, medication history and performing a blowing test (spirometry) to make sure the participants lungs work normally.

Participants with chronic cough will be asked to indicate the severity of their cough with a line on a 10 point scale known as a visual analogue scale and complete some cough-related questionnaires.

Cough challenge procedure:

First, the participant will be fitted with a cough monitor to record all sounds (specifically to count coughs) during the cough challenge. This will be removed prior to the end of the visit. The participant will then be asked to wear a nose clip and will inhale the challenge agent (saline) using a nebuliser machine at decreasing osmolarities. This will be randomised to a hypo-osmolar saline solution or a control solution (normal 0.9% saline). The participant will be blinded to the challenge agent used but the researcher will know which agent is being used. The osmolarity of the saline will decrease until the participant wants to stop or the lowest osmolarity is reached. After the challenge the cough monitor will be removed, and the participant will repeat the blowing test. The participant will be asked to give feedback on how they found the challenge test. After this the visit will be over.

Visits 2-5 will follow the same procedures as visit 1, except that no further consent forms need to be completed. Each visit will take place 2-7 days after each other. Each visit will take about 1 hour. The final telephone visit will involve the researcher asking the participant about any changes in their health since the last visit, and should take about 15 minutes. After visit 6, Phase A of this study is over. Participants that take part in Phase A do not have to take part in Phase B, but may express interest in doing so on their consent form.

Phase B:

Phase B involves three visits to the clinical research ward at Wythenshawe Hospital and a telephone follow up.

At visit 1 a researcher will talk through the study and answer any questions. After signing a consent form, the researcher will confirm that the participant is eligible by going through their medical history, medication history and performing a blowing test (spirometry) to make sure the participants lungs work normally.

Participants with chronic cough will be asked to indicate the severity of their cough with a line on a 10 point scale known as a visual analogue scale and complete some cough-related questionnaires.

The participant will be asked to complete three cough challenges over three visits. However, in this phase, the only challenge agent being used will be hypotonic saline: it is the nebuliser device

being used that will differ between the visits. Participants will complete a hypotonic saline cough challenge using the new and old device during the first two visits in a randomized order. In visit three, participants will complete the hypotonic saline cough using the new device again, to assess repeatability over time. Full blinding is not possible due the obvious difference between devices, but participants will not be told which device is the one currently being used, and which is the "new" alternate device. After the cough challenge, the visit will end.

Visit 2 will occur 2-7 days after visit 1. Visit 3 will take place 14-28 days after visit 2 to assess repeatability of the hypotonic saline cough challenge with the new device over time. Each visit is expected to take 1-1.5 hours.

The final telephone visit will involve the researcher asking the participant about any changes in their health since the last visit, and should take approximately 15 minutes. After this telephone call, Phase B is over.

What are the possible benefits and risks of participating?

There will be no direct benefit for participants in this study. However, we hope that the results of this study will help us to understand the mechanisms of coughing and improve treatments in the future.

Cough challenge tests which involve inhaling solutions designed to make participants cough. The solutions have been used in research for many years and have been shown to be safe. Hypotonic saline solutions may cause tightening of the airways in susceptible people (such as those with asthma), although this is rare. Breathing tests are performed before and after the test to monitor any chest tightening, which is easily treated by inhaling salbutamol (a medication to open up the airways). Patients with asthma are therefore excluded from this study and appropriately qualified medical professionals will be present in the department at all times should any participant feel unwell.

Where is the study run from?

The NIHR Clinical Research Facility at Manchester University NHS Foundation Trust (UK), Wythenshawe Hospital (UK)

When is the study starting from and how long is it expecting to run for?

October 2026 to March 2028

Who is funding the study?

1. Manchester Biomedical Research Council (UK)
2. Vitalograph (USA)

Who is the main contact?

Shannon Galgani, cough.research@manchester.ac.uk

Contact information

Type(s)

Public, Scientific, Principal investigator

Contact name

Ms Shannon Galgani

ORCID ID

<https://orcid.org/0000-0002-9100-0326>

Contact details

Cough Research Team, Manchester University NHS Foundation Trust, North West Lung Research Centre, Wythenshawe Hospital, Southmoor Road
Manchester
United Kingdom
M23 9LT
+44 (0)161 291 5031
cough.research@manchester.ac.uk

Additional identifiers

Integrated Research Application System (IRAS)
368306

Central Portfolio Management System (CPMS)
72947

Study information**Scientific Title**

A comparison and validation study of cough challenge responses evoked using different hypotonic saline protocols and nebuliser systems

Acronym

oRLoN

Study objectives**Ethics approval required**

Ethics approval required

Ethics approval(s)

Approved 17/08/2026, London - Camberwell St Giles Research Ethics Committee (2 Redman Place Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8000; camberwellstgiles.rec@hra.nhs.uk), ref: 26/LO/0556

Primary study design

Interventional

Allocation

Randomized controlled trial

Masking

Blinded (masking used)

Control

Placebo

Assignment

Crossover

Purpose

Basic science

Study type(s)

Health condition(s) or problem(s) studied

Chronic cough

Interventions

This study is split into two phases.

Phase A: Assessing changes to the challenge protocol

60 participants with refractory chronic cough and 30 healthy volunteers will be recruited from a single UK centre and undergo inhalational cough challenges at 2-7 day intervals with hypo-osmolar saline and isotonic saline in a randomised order. Each of the hypo-osmolar challenges will have a slightly different methodology.

Participants will be randomised to a sequence group defining the order in which cough challenges are to be performed, according to a computer-generated schedule. Participants will be blinded to the nature of each challenge agent but the investigator performing the challenges will not due to the nature of the challenges.

Phase B: Assessing the challenge using different nebuliser devices

12 participants with refractory chronic cough and 12 healthy volunteers will be recruited from a single UK centre and undergo inhalational cough challenges at 2-14 day intervals with hypo-osmolar saline. Participants will be randomised to a sequence group defining the order in which nebuliser devices are to be used for each challenge, according to a computer-generated schedule. Patients will be blinded to which challenge is using the "original" nebuliser device and which is using the new "alternate" nebuliser device. The investigator performing the challenge will not be blinded due to the nature of the devices.

Intervention Type

Other

Primary outcome(s)

1. Phase A: Agreement between the original challenge and other challenge protocols in classification of disease status measured using by the cough response at to each cough challenge
2. Phase B: Agreement in the classification of disease status using the original nebuliser device and the alternative device measured using by the cough response at to each cough challenge

Key secondary outcome(s)

1. Evidence of any systematic differences in disease classification (RUCC vs HV) between the original challenge protocol and other challenge protocols measured using based on the cough response at to each challenge
2. Cough responses in all subjects measured using Emax and ED50 at each challenge visit

3. Patient reported cough triggers and sensations measured using the TOPIC questionnaire at baseline
4. Patient reported cough quality of life measured using the Leicester Cough Questionnaire (LCQ) at baseline (Phase A and Phase B) and at the last visit (Phase B)
5. Patient-reported sensations measured using visual analogue scale at before and after each inhalational challenge
6. Participant-reported acceptability of the cough challenge measured using set questions at the end of each challenge
7. Repeatability of evoked cough responses to hypotonic saline challenge using an alternative device measured using Emax and ED50 at least 2 weeks apart
8. Evidence of any systematic differences in disease classification (RUCC vs HV) between the challenge using the original device versus the alternative device (Phase B) measured using based on the cough response at to each challenge

Completion date

01/03/2028

Eligibility

Key inclusion criteria

All participants:

1. Males and females aged ≥ 18 years
2. Non-smokers, or ex-smokers with ≤ 20 pack years smoking history and ≥ 6 months abstinence
3. Spirometry within normal limits (defined as forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) predicted values $\geq 70\%$ and FEV1/FVC ratio of $\geq 70\%$)
4. Has capacity to consent
5. Able to attend all the scheduled visits at the clinical research facility (CRF) within the protocol timeline

Healthy volunteers:

1. No clinically relevant medical conditions (self-reported), which, in the opinion of the investigator may affect participation or study results
2. No history of or current respiratory disease

Chronic cough patients:

1. Have a physician diagnosis of refractory and/or unexplained chronic cough as defined by British Thoracic Society (BTS)/European Respiratory Society (ERS) guidelines
2. No evidence of asthma during clinical evaluation of chronic cough e.g. elevated FeNO, bronchodilator reversibility, abnormal methacholine responsiveness

Healthy volunteers allowed

Yes

Age group

Mixed

Lower age limit

18 Years

Upper age limit

100 Years

Sex

All

Total final enrolment

0

Key exclusion criteria

All participants:

1. Pregnancy or breastfeeding
2. Upper or lower respiratory tract infection or significant change in pulmonary status within 4 weeks of enrolment
3. Treatment with ACE inhibitors
4. Treatment with tricyclic antidepressants
5. Any therapy that may modulate cough (e.g. opioids, gabapentin)
6. Patients with asthma
7. Current or regular vaping <6 months
8. Current or previous significant recreational drug use (including inhalation)

Date of first enrolment

05/10/2026

Date of final enrolment

19/01/2028

Locations**Countries of recruitment**

United Kingdom

England

Study participating centre

Manchester University NHS Foundation Trust

Southmoor Road

Wythenshawe Hospital

Manchester

England

M23 9LT

Sponsor information

Organisation

University of Manchester

ROR

<https://ror.org/027m9bs27>

Funder(s)**Funder type****Funder Name**

Manchester Biomedical Research Centre

Alternative Name(s)

NIHR Manchester Biomedical Research Centre, Manchester BRC, NIHR Manchester BRC, NIHR Manchester Biomedical Research Unit, Manchester NIHR BRC, Manchester NIHR Biomedical Research Centre, Biomedical Research Centre, BRC, NIHR BRC

Funding Body Type

Government organisation

Funding Body Subtype

Research institutes and centers

Location

United Kingdom

Funder Name

Vitalograph

Results and Publications**Individual participant data (IPD) sharing plan****IPD sharing plan summary**

Not expected to be made available