ISRCTN96855098 https://doi.org/10.1186/ISRCTN96855098

Comparing different responses of the cough reflex

Submission date	Recruitment status	[_] Prospectively registered
10/09/2021	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
16/09/2021	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
20/06/2025	Respiratory	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Cough challenge testing is widely used to see how sensitive someone's cough reflex is. This can be very useful when studying treatments for cough or how cough affects people with different lung conditions. The challenge involves a person inhaling increasing doses of a substance which usually makes people want to cough by irritating the throat and activating nerves in the airways. There are different pieces of equipment used to deliver these substances. The aim of this study is to compare the performance of two pieces of equipment to see if they give the same cough responses in people.

Who can participate?
Healthy volunteers aged 18 years and over

What does the study involve?
The study involves two visits. The first visit will involve completing a consent form after talking through the study with a researcher. Participants will then be asked about their medical history and any medications they are taking. Their height and weight will be measured and their BMI calculated. They will then be asked to perform a blowing test (spirometry) so that the researcher can check that they meet the eligibility criteria for the study. Participants will then be asked to complete a cough challenge. They will be fitted with a recording device, a cough monitor, throughout the challenge to enable the researcher to listen back and count how many times they cough. Capsaicin or citric acid will be given to them to inhale using one of the pieces of equipment. The dose will increase and they will be asked to take four breaths of each dose. The test will end when either the participant has inhaled all of the doses or when they ask to stop because the feeling from inhaling the capsaicin or citric acid is too unpleasant. They will be asked to fill in a questionnaire about how they found the challenge and then the blowing test will be repeated to ensure that their airways have not tightened. Participants will be asked to return 3-7 days later to repeat the cough challenge with the other piece of equipment.

What are the potential benefits and risks of participating?
No benefits.
Spirometry can cause light-headedness in participants.
Capsaicin (naturally occurring extract of red chilli peppers) and citric acid inhalation can cause

discomfort, including a temporary burning sensation in the throat, eye-watering, runny nose and coughing.
Cough challenge can cause bronchoconstriction, although this is rare in healthy volunteers.

Where is the study run from?
The NIHR Clinical Trials Facility and MFT Wythenshawe Hospital (UK)

When is the study starting and how long is it expected to run for?:
August 2021 to December 2024

Who is funding the study?
Manchester NIHR BRC charitable funds (UK)

Who is the main contact?
Joanne Mitchell
cough.research@manchester.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Jaclyn Smith

ORCID ID
https://orcid.org/0000-0001-8837-4928

Contact details
2nd Floor ERC
Wythenshawe Hospital
Southmoor Road
Manchester
United Kingdom
M23 9LT
+44 (0)161 291 5031
jacky.smith@manchester.ac.uk

Type(s)
Public

Contact name
Mrs Joanne Mitchell

Contact details
North West Lung Research Centre
Wythenshawe Hospital
Southmoor Road
Manhester
United Kingdom
M23 9LT

+44 (0)161 291 5921
joanne.sale@manchester.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
288804

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
20-CAS-001

Study information

Scientific Title
A comparison and validation study of cough challenge responses evoked using two different bronchial provocation systems

Acronym
CasCaDe

Study objectives
Current study hypothesis as of 21/06/2024:
The aim of this study is to compare maximum cough responses to capsaicin and citric acid in healthy volunteers between two bronchial challenge systems: the Koko dosimeter and an alternative bronchial provocation system; ProvoX.

Previous study hypothesis:
The aim of this study is to compare maximum cough responses to capsaicin in healthy volunteers between two bronchial challenge systems: the Koko dosimeter and an alternative bronchial provocation system; ProvoX.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/09/2021, University of Manchester Research Ethics Committee 1 (Research Governance, Ethics and Integrity, 2nd Floor Christie Building, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK; +44 (0)161 306 6000; research.ethics@manchester.ac.uk), ref: 2021-11272

Study design
Single-centre randomized cross over trial

Primary study design

Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Cough challenge responses

Interventions
Current interventions as of 21/06/2024:
Participants will be asked to attend two visits. At the first visit, informed consent will be taken, followed by a screening visit to ensure study eligibility. This will involve the recording of medical history and current medications; measurement of height and weight; and spirometry to measure the participant's FEV1 and FVC. Upon confirmation of eligibility, the participant will be asked to complete either a capsaicin cough challenge or a citric acid cough challenge. This is done by inhaling doubling doses of capsaicin or citric acid using one of the systems. The challenge will be continued until the participant reaches their maximum tolerated dose. The cough challenge will be recorded on a VitaloJAK audio cough monitoring device.

Spirometry will be performed following the completion of the challenge. The participant will be asked to return for a second visit where they will repeat the spirometry and cough challenge using the other piece of equipment. The order of the equipment will be allocated in a randomised order created using Graphpad, a piece of statistical software with randomisation capabilities.

Previous interventions:
Participants will be asked to attend two visits. At the first visit, informed consent will be taken, followed by a screening visit to ensure study eligibility. This will involve the recording of medical history and current medications; measurement of height and weight; and spirometry to measure the participant's FEV1 and FVC. Upon confirmation of eligibility, the participant will be asked to complete a capsaicin cough challenge by inhaling doubling doses of capsaicin using one of the systems. The challenge will be continued until the participant reached their maximum tolerated dose. The cough challenge will be recorded on a VitaloJAK audio cough monitoring device.

Spirometry will be performed following the completion of the challenge. The participant will be asked to return for a second visit where they will repeat the spirometry and cough challenge using the other piece of equipment. The order of the equipment will be allocated in a randomised order created using Graphpad, a piece of statistical software with randomisation capabilities.

Intervention Type
Device

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
-

Primary outcome measure
Maximum cough response (Emax) is measured at visit 1 and visit 2

Secondary outcome measures
Current secondary outcome measures as of 21/06/2024:
1. Capsaicin and citric acid concentrations evoking at least 50% of the Emax cough number (ED50) is measured at visit 1 and visit 2
2. Concentration of capsaicin evoking at least two coughs (C2) is measured at visit 1 and visit 2
3. Capsaicin and citric acid concentrations provoking at least five coughs (C5) is measured at visit 1 and visit 2

Previous secondary outcome measures:
1. Capsaicin concentrations evoking at least 50% of the Emax cough number (ED50) is measured at visit 1 and visit 2
2. Concentration of capsaicin evoking at least two coughs (C2) is measured at visit 1 and visit 2
3. Capsaicin concentrations provoking at least five coughs (C5) is measured at visit 1 and visit 2

Overall study start date
01/08/2021

Completion date
04/12/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 21/06/2024:
1. Aged ≥18 years
2. Normal spirometry (FEV1 and FVC %predicted of ≥80%)
3. No current or past history of chronic cough or any other respiratory disease
4. No current or history of chronic pain, irritable bowel syndrome, psychiatric illness or chronic headaches
5. No previous experience of performing cough challenges (capsaicin study arm only)
6. Must cough at least 2 times on a single inhalation of any dose of capsaicin/citric acid during the visit 1 cough challenge

Previous inclusion criteria:
1. Aged ≥18 years
2. Normal spirometry (FEV1 and FVC %predicted of ≥80%)
3. No current or past history of chronic cough or any other respiratory disease
4. No current or history of chronic pain, irritable bowel syndrome, psychiatric illness or chronic

headaches
5. No previous experience of performing cough challenges
6. Must cough at least 2 times on a single inhalation of any dose of capsaicin during the visit 1 cough challenge

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
24

Total final enrolment
26

Key exclusion criteria
Current exclusion criteria as of 21/06/2024:
1. Current smoker or ex-smoker with >20 pack-year history, and/or <6 months abstinence
2. Upper respiratory tract infection within the last 4 weeks
3. Use of ACE inhibitors
4. Use of anti-depressants
5. Use of centrally acting medications that may alter the cough reflex e.g. opiates
6. History of drug or alcohol abuse
7. Current pregnancy or breastfeeding
8. Concomitant conditions that may alter cough reflex sensitivity e.g. diabetes mellitus, Parkinson’s disease, cerebrovascular disease
9. Previous cough challenge experience (only applicable for capsaicin study arm)

Previous exclusion criteria:
1. Current smoker or ex-smoker with >20 pack-year history, and/or <6 months abstinence
2. Upper respiratory tract infection within the last 4 weeks
3. Use of ACE inhibitors
4. Use of anti-depressants
5. Use of centrally acting medications that may alter the cough reflex e.g. opiates
6. History of drug or alcohol abuse
7. Current pregnancy or breastfeeding
8. Concomitant conditions that may alter cough reflex sensitivity e.g. diabetes mellitus, Parkinson’s disease, cerebrovascular disease
9. Previous cough challenge experience

Date of first enrolment
12/09/2021

Date of final enrolment
27/11/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
NIHR Clinical Research Facility - MFT Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

Sponsor information

Organisation
University of Manchester

Sponsor details
Faculty of Biology, Medicine and Health
5.012 Carys Bannister Building
Manchester
England
United Kingdom
M13 9PL
+44 (0)161 275 5436
FBMHethics@manchester.ac.uk

Sponsor type
University/education

Website
http://www.manchester.ac.uk/

ROR
https://ror.org/027m9bs27

Funder(s)

Funder type
Charity

Funder Name
Manchester NIHR BRC charitable funds

Results and Publications

Publication and dissemination plan
The researchers plan to publish the results of this study in a peer-reviewed journal.

Intention to publish date
31/07/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available as the study is purely a validation study and we are doing this research because the current equipment being used for cough challenge testing is being withdrawn from use and it is important that we find an alternative which produces reliable results comparable with the previous research carried out.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.2	10/09/2021	16/09/2021	No	Yes