Manchester University
NHS Foundation Trust

STaRR

Sensations and Triggers of Coughing pre- and post-treatment in Chronic Cough

STUDY PROTOCOL
Version 4.0 27
September 2023
IRAS No: 288299
Sponsor Number: G73936/ B01379
Registry Number:

Sponsor Name: Manchester University NHS Foundation Trust

This project will be conducted in accordance with the study protocol and the ethical principles outlined by Good Clinical Practice (GCP) and the Declaration of Helsinki in its most current version.

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):

.....
Position:

.....

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

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

.....

CONTACT DETAILS

Chief Investigator: Dr Paul Marsden
Job Title: Consultant Respiratory Physician/Honorary Senior Lecturer
Address Details: North West Lung Centre
Wythenshawe Hospital
Southmoor Road
Manchester
M23 9LT
Tel 0161 291 5031
Email: paul.marsden@mft.nhs.uk

Sponsor: Manchester Foundation Trust NHS Foundation Trust
Contact: Dr Lynne Webster
Job Title: Head of Research Office

Address Details: Manchester Foundation Trust,
Southmoor Rd,
Manchester,
M23 9LT
Email: Research.sponsor@mft.nhs.uk

CONTENTS

1. INTRODUCTION

1.1. Hypothesis

We hypothesize that the sensations associated with chronic cough as captured by the ToPiC questionnaire change following standard treatment for chronic cough. We also hypothesize that these changes correlate with both objective/subjective measures of cough and cough-specific quality of life and that the ToPiC questionnaire will be able to differentiate between those with RCC/UCC and non-RCC/UCC.

2. BACKGROUND

2.1. Prior Literature and Studies

Chronic cough (cough present >8 weeks) is a common problem seen in both primary and secondary care services. It has a significant impact for the individual in terms of quality of life, and for society in terms of healthcare utilisation and loss of productivity.[1] Despite this, few effective therapies for this condition exist and relatively little is known about the impact of these therapies for the individual. Most therapies have been evaluated using subjective cough severity scales (e.g., visual analogue scales [VAS] or numerical Likert scales) or cough related quality of life scores. More recently, with the development of cough monitoring devices (e.g., the VitaloJAK monitor) potential new therapies have been assessed with objective cough rates as an outcome measure.[2,3]

Refractory Chronic cough and Unexplained Chronic cough (RCC/UCC) are increasingly being recognised as due to a hypersensitivity of the cough reflex, with evidence for both peripheral (at the level of pulmonary vagal afferents) and central sensitisation. Currently the diagnosis is one of exclusion following systematic trials of treatment for other potential causes for cough. However, patients referred to our specialist cough clinic give a characteristic history describing similar sensations (e.g., an ‘itch’ in the throat) and triggers (e.g., change in atmosphere or temperature) of cough, which is likely related to cough reflex hypersensitivity, and therefore has the possibility of identifying patients with RCC/UCC at an earlier stage and thus those appropriate for novel anti-tussive therapies such as gefapixant.[4]

Our group is therefore developing a validated questionnaire describing the sensations and triggers provoking cough, the ToPiC questionnaire, (see attached copy). Patient interviews and focus groups have been completed and analysed to generate the questionnaire items and an initial long version of the questionnaire developed. Uniquely, this questionnaire has been applied not only to patients with both RCC/UCC but also cough associated with common respiratory diseases including asthma and idiopathic pulmonary fibrosis. This data is currently being used to reduce the number of items in the long questionnaire to those most able to discriminate between cough associated with an underlying disorder (non-RCC/UCC) and RCC/UCC; data on repeatability of these items has also been collected and is

being analysed. This reduced item version will be the ToPiC questionnaire used for the first time in this study. The ToPiC questionnaire is being developed to help identify patients with RCC/UCC at an earlier stage who would be eligible for specific treatment for this condition.

There are several important differences between the TOPIC questionnaire and the Hull Airway Reflux Questionnaire (HARQ)

1) The HARQ questionnaire was not developed using currently accepted methodology for questionnaire development. It is a modification of a questionnaire developed by an ENT surgeon (the Reflux Symptom Index, RSI) to diagnose patients with laryngo-pharyngeal reflux. The origin of the original 9 items in the RSI is unclear and the additional 5 items in the HARQ were added following a literature review rather than consulting with patients about their symptoms.
2) The HARQ has only be validated to differentiate chronic cough from healthy controls. A questionnaire able to distinguish between RCC/UCC and chronic cough would be much more valuable and relevant to clinical practice. The TOPIC questionnaire has uniquely been developed with this in mind, collecting data from patients with cough associated with asthma, IPF etc. as well as RCC/UCC.
3) The HARQ does not differentiate well between healthy controls and chronic cough patients as there was overlap in the scores between these groups. This suggests either some of the healthy controls were not truly healthy or some of the items have poor specificity for chronic cough. Further optimization of the items has not been performed.
4) The name of the HARQ implies a role for reflux disease in those scoring highly however the HARQ has never been correlated with any measure of reflux disease. This is confusing and misleading for those not familiar with the field of chronic cough.

The next step in the development of our questionnaire is to apply it to a larger group of patients with chronic cough, to evaluate internal reliability, concurrent validity, and responsiveness to change in patients attending a tertiary cough clinic for the first time. This does not represent a validation study, rather further development and refinement of the ToPiC questionnaire to optimize performance. As approximately

70% of clinic attendees have RCC/UCC we will also start to explore the ability of the questionnaire to discriminate these subjects compared with the 30% with non-RCC/UCC. [5,6,7.] This larger dataset will also allow us to explore the possibility of developing a short form of the ToPiC questionnaire e.g. 3-4 items that may be valuable to those working in primary care to allow early identification of possible RCC/UCC patients, facilitating appropriate care such as access to new anti-tussive agents.

3. STUDY OBJECTIVES

3.1. Primary Objective

Whether the triggers and sensations provoking captured by a newly developed questionnaire (ToPiC) change following standard treatment for cough.

3.2. Secondary Objectives

Whether these changes correlate with changes in cough related quality of life and subjective/objective measures of cough in patients referred to a specialist cough clinic

Whether ToPiC questionnaire responses differ between those with refractory (RCC)/unexplained (UCC) chronic cough and those with another cause for cough e.g. asthma (non-RCC/UCC)

3.3. Outcome measures

Primary outcome
Change in ToPiC questionnaire score before and after treatment

Secondary outcome
Correlation between change in ToPiC questionnaire score before and after treatment and changes in (LCQ), cough VAS, verbal cough score and objective cough counts (24hr and mean cough frequency / hour) .

4. STUDY DESIGN

4.1. Overview/Design Summary

This study is an observational study involving 100 subjects who are referred as new patients to the specialist cough clinics.

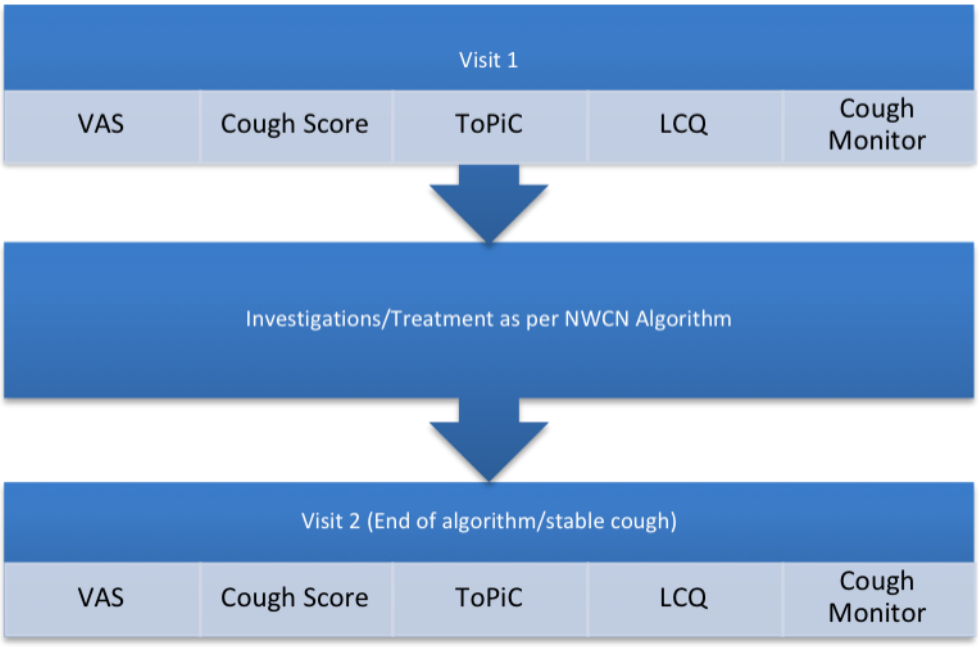
Subjects will be recruited from the specialist Cough Clinics and undergo the following procedures:

Visit 1/Baseline:

- Cough visual analogue scale (VAS) and Verbal (0-10) cough score
- Cough related quality of life questionnaire (Leicester Cough Questionnaire[LCQ])
- ToPiC questionnaire
- 24 hour cough monitoring (VitaloJAK)

Subjects will then undergo investigation and treatment according to the North West Cough Network guidelines which have been developed locally and based upon published guidelines and evidence.

Once the end of the algorithm has been reached and/or cough has reached stability, patients will undergo identical procedures as at baseline.



4.2. Inclusion Criteria

- Anyone over the age of 18
- Referred to our tertiary chronic cough clinic.
- Non smokers or ex smokers <20 pack years and greater than 6 months abstinence
- Persistent cough of at least 8 weeks duration

4.3. Exclusion Criteria

- Currently taking angiotensin converting enzyme (ACE) inhibitors
- Recent history of upper or lower respiratory tract infection within 4 weeks of enrolment.
- Current smoker or smoking history >20 pack years

All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation except where the study inclusion and exclusion criteria EXPLICITLY state otherwise.

4.4. Ethical Considerations

We do not believe this study poses any significant ethical issues

4.5. Recruitment and Consent Process

Potential participants will be identified from respiratory clinics by the direct clinical care team members. Prior to the appointment a PIS will be sent to the patient explaining the study. Participants will be able to ask further questions about the study at the time of their appointment from the research staff if they consent to

being approached by them. Written consent will be obtained from patients prior to the completion of questionnaires.

4.6. Associated Risks and Benefits

There are no direct benefits or significant risks to patients taking part in this study. All participants will receive up to £55 per study visit, to compensate them for their time and travel expenses.

4.7. Early Withdrawal of Subjects

As part of the consent process, all participants are informed that taking part is entirely voluntary and that they may withdraw at any time if they wish to do so, without giving any reason. Any data that has already been collected will be retained, but no further trial procedures will be carried out or data obtained.

5. STUDY PROCEDURES

5.1. Screening for Eligibility and first visit

Data Collection: A demographic sheet will be completed by the researcher to collect clinical information about recruited patients (e.g. gender, age, diagnosis, latest clinical spirometry and smoking history).

ToPiC Questionnaire: Participants will be asked to complete the TOPIC Questionnaire. This is a 15 item questionnaire where participants will grade on a likert scale specific sensations and triggers in relation to their cough. This questionnaire was developed as a tool to aid the discrimination of cough in refractory or unexplained chronic cough (RUCC) compared to cough in other respiratory conditions. 100 participants will be requested to complete the questionnaire at visit 1 and visit 2.

Leicester Cough Questionnaire: Participants will be asked to complete the Leicester Cough Questionnaire (cough patients only). This 19 item questionnaire asks subject to grade the impact of their cough on different aspects of their daily life on a scale of 1 to 7. The questionnaire gives a total score and three domain scores: physical, psychological and social effects.

Visual analogue score (VAS) and Verbal Cough Score: The participant will be provided with a visual analogue score (VAS). This is a 100mm line on which they can rate the severity of their cough during the day and night (two separate lines) while wearing the monitor by placing a vertical mark on the line, where 0mm is no cough and 100mm is the most severe cough ever experienced. Separately the patient will also be asked to give a verbal cough score (0-10, with 10 being most severe).

Cough Monitoring: Participants will be fitted with a VitaloJAK ambulatory cough monitor. This will be done at the clinic, the Clinical Research Facility or in certain circumstances, remotely, within 7 days of consent and prior to starting antitussive treatments. If done

remotely, instructions will be provided on how to fit the cough monitor. The patient will also be offered a telephone or video call with a researcher, to guide them through the fitting.

The device will be worn for 24 hours, recording all sound via 2 microphones, one attached to the subject's chest wall and one attached to the subject's clothing. The device will automatically stop recording when the 24 hours has passed. Participants will be made aware that all sound, including speech will be recorded. They will also be informed that the device cannot get wet and therefore they will be unable to shower while wearing it. We will ask participants whether they would be happy to consent to have their recording added to our database of anonymized cough monitor recordings, RaDAR. This is described in more detail in the section data handling and storage of cough recordings. Participation in RaDAR is completely voluntary and will not affect study participation. Participants will be asked to either return the cough monitor to the clinic, or in certain circumstances collection will be arranged. Cough monitors are provided by VitaloJak – with provision for maintenance and replacement if needed.

5.2. Follow-up/ Visit 2 (After cough treatment algorithm completed)

The follow up visit will occur at the end of the study. This will be defined as completion of cough algorithm, which will be defined by completion of investigation and treatment or stability of symptoms (not set time for this but estimated to be 6-12 months after visit 1).

All assessments outlined in Section 5.1 will be repeated at this visit. Additionally, medical history in relation to the clinical care of cough will be collected and will include; final diagnosis, treatments tried and any clinical investigations undertaken.

6. SAFETY AND ADVERSE EVENTS

6.1. SAE / AE COLLECTION IN STUDY

We will collect all AEs and SAEs during the study period from consent to the end of the second visit, however this would be unexpected given the nature of the study.

- **Safety Reporting**

The Manchester University NHS Hospital Foundation Trust R&D will be informed of any incident which may have caused serious injury or death or a serious deterioration in an individual's state of health, by emailing adverse.events@mft.nhs.uk within 24 hours of becoming aware of the event.

The CI will be responsible for the reporting of related and unexpected Serious Adverse Events (SAEs) to be submitted to the REC. These will be sent within 15 days of the chief investigator becoming aware of the event. All parties will comply with the agreed MFT SOPs for AE and SAE reporting.

7. STATISTICAL PLAN

7.1. Sample Size and Power Calculation

The investigator and team will be responsible for analyzing the study data.

Variables/Time Points of Interest

The outcomes detailed above will be analyzed at the end of the study following completion of the last study visit.

Statistical Methods

For the primary and secondary endpoints, comparing baseline with post-study measurements, a paired t-test will be used. Should the data be non-parametric, it will be log transformed prior to analysis

For correlations, Pearson (for parametric) and Spearman's (for non-parametric) correlation coefficients will be calculated.

To compare baseline ToPiC scores between RCC/UCC and non-RCC/UCC, an independent-samples t-test will be used. Data will be log-transformed prior to analysis if it is non-parametric.

In order to assess the internal reliability of the ToPiC questionnaire, we will use Cronbach's Alpha test.

Multiplicity
Due to the number of outcomes, a statistical correction should not be required.

Power/Sample Size:
As this is an exploratory study, a sample size of 100 subjects with a complete data set has been selected.

8. DATA HANDLING

8.1. Confidentiality and Security

Data collected during the study will be stored on a secure database with limited access and password entry. A unique identifier made up of numbers and letters will be allocated and used on all study documentation and in patient case notes. All personal data collected during the study will be handled in accordance with the NHS code of practice for confidential patient information. All data collected will be treated with the usual standards of confidentiality as outlined in the GMC booklet titled "Confidentiality".

Electronic data, such as cough recordings from the VitaloJAK™ ambulatory cough monitor will be stored on the secure University of Manchester server and backed up

on secure servers to which only members of the research team will have access. The data will be analysed on the UoM server within the CRF.
Additionally, we will complete a Data Protection Impact Assessment (DPIA) for the study. This is designed to help ensure 'privacy by design', to identify the most effective way to comply with data protection law, and to protect the rights and freedoms of individuals, be they study participants, staff or members of the public. This should assist in identifying the risks of processing and sharing personal data, and in creating solutions to reduce them.

8.2. Training

It will be ensured that all members of the research team who handle the data are familiar with the policies governing the confidentiality and security of the data collected during the study and SOPs specific to the study, where applicable, will be adhered to. Good Clinical Practice (GCP) training will be maintained and certificates retained during the course of the study.

8.3. Case Report Forms and Source Documents

Lead and participating sites will be required to complete a Source Data Location Log, which will detail source data types and locations.

All data from participating sites will be entered into a validated database 'REDcap' by sites, managed by Manchester University NHS Foundation Trust. Additional data management plan has been completed and approved by Sponsor.

REDCap is a secure web application for building and managing online surveys and databases. In this study, it is being used to host online CRF/questionnaires, and transcribe paper CRFs/questionnaires. The system is specifically designed for research and data is stored on an MFT server (not shared with any third party). MFT servers are backed up at the end of each day and are maintained by MFT Informatics Team. If data is lost, it can be recovered via the Trust IT back up service for the REDCap server.

The lead site, Manchester University NHS Foundation Trust uses an electronic patient system, HIVE. All patient medical information is stored within the electronic system, and any research data collected will also be entered into HIVE.

Printouts from equipment, such as spirometers, questionnaires and reports of cough counts will be considered to be the study source data. All of these documents will be stored in a locked and secured office locations.

8.4. Records Retention

All research related documentation including the site file, case report forms etc. will be archived by individual sites and stored with their preferred archiving facility. The name and location of archiving facilities are to be shared with the Sponsor upon receiving authorisation to archive the study from the Sponsor. All archived records

are to be kept for 5 years following the end of the study, providing that the data has been published within this time frame. It will then be destroyed in keeping with local SOPs. Prior to destruction a log will be made of all the documents that are being destroyed

8.5. RaDAR

All subjects will be asked to allow their 24-hour cough recording to be entered into the RaDAR (REC reference: 18-NW-0254) database. RaDAR is a database of pseuononymized cough recordings, used to test and improve cough detection algorithms by ourselves and collaborating research teams. If a subject agrees, the full 24-hour recording will be listened to by a trained member of staff. Any identifiable information will be muted, and all coughs will be electronically tagged. The recording will be entered into the database under a RaDAR identification number, along with basic demographic data, such as age, gender and diagnosis.

All recordings, whether included in RaDAR or not, will be stored on a secure University of Manchester server, located at Wythenshawe Hospital, to which only members of the research team will have access. All information heard on the recordings will be kept confidential, unless the research team member analysing the recording hears something which endangers the participant or someone else, in which case the information will be passed to the relevant authorities, following local SOPs.

The participant will have the choice to consent to recordings may be made available to internal and external researchers for further research. Any recordings released for further research will be subject to an application process and approved by the RaDAR Management Team. If they wish to opt out of RaDAR and consent to the secure storage of their cough recordings under the terms of this study only, these recordings will be kept for a maximum of 20 years after the study has closed and will not be used for further research.

9. STUDY ADMINISTRATION

9.1. Organization and Participating Centres

This is a multi site study, with leading hospital being:

Wythenshawe Hospital,
Manchester University NHS Foundation Trust,
Southmoor Road,
Wythenshawe, M23 9LT.

9.2. Funding Source

Merck Sharpe and Dohme UK limited
120 Moorgate, London, EC2Y9AL

9.3. Subject Payments

Participants will be paid for each completed visit.
Visit 1: £20 (plus up to £35 for travel expenses)
Visit 2: £20 (plus up to £35 for travel expenses)

9.4. Study Monitoring

The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust in line with applicable MFT SOPs and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the research team.

9.5. Study Management

Before the start of the study, a favourable opinion will be sought from an NHS Research Ethics Committee (REC) for the study and all the supporting documents including the protocol, information sheets, informed consent forms and other relevant documents. The lead study team will be responsible for the maintenance of a Trial Master File at lead site (Wythenshawe Hospital) , in which all current and superseded study documents will be retained. Also contained in the Trial Master file will be the approval documentation including correspondence with relevant authorities such as the HRA and REC. Each study site will be provided with a Investigator Site File Index Template and all relevant documents to be printed and stored within their Investigator Site File. The file must be made available to the Sponsor upon request.

The study team at Wythenshawe Hospital are responsible for producing progress reports throughout the study, including annual reporting (APR) to REC as required. The Chief Investigator will notify the REC of the end of the study, and will submit a final report with the results, including any publications/abstracts, to the REC within 12 months of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. No participants will be enrolled into this research study prior to the study being reviewed by the relevant regulatory authorities and receiving HRA and REC approvals, as well as approval from the R&D office at Manchester University NHS Foundation Trust.

9.6. Amendments to the Protocol

Any amendments to the study shall be reviewed by the sponsorship team prior to submission. Any non-substantial amendments shall be notified to the HRA and any substantial amendments, along with amended documentation, shall be approved by the REC, and HRA, prior to implementation as per nationally agreed guidelines. The Chief Investigator or designee will work with the R&D department to put the necessary arrangements in place to implement the amendment and to confirm their support for the study as amended.

9.7. Indemnity

The NHS indemnity scheme will apply to this study to ensure it meets the potential legal liability of the sponsor, equipment, employer and investigators/collaborators for harm to participants arising from the management, design and conduct of the research. No arrangements will be made for the payment of compensation in the unlikely event of harm

10. PUBLICATION POLICY

We will aim to publish this study in leading academic journals. We will inform our participants through a newsletter. This will be sent to participants via emails and/or post and we will request the consent to send this and best method of contact on the consent form.

11. REFERENCES

[1] Morice AH, McGarvey L, Pavord I. Recommendations for the Management of Cough in Adults. *Thorax* 2006; 61(Suppl I):i1-i24
[2] Abdulqawi R, Dockry R, Holt K, Layton G, McCarthy BG, Ford AP, Smith JA. P2X3 receptor antagonist (AF219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet* 2015; 385(9974):1198-205
[3] Khalid S, Murdoch R, Newlands A, Smart K, Kelsall A, Holt K, Dockry R, Woodcock A, Smith JA. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. *J Allergy Clin Immunol* 2014; 134(1):56-62
[4] Hilton E, Marsden P, Thurston A, Kennedy S, Decalmer S, Smith JA. Clinical Features of the Urge-to-Cough in patients with Chronic Cough *Respir Med* 2015; 109(6):701-7
[5] F Solari, K Sunger, J Yorke, A Caress, J A Smith. The sensations provoking cough: a qualitative investigation. *Thorax* December 2011 Vol 66 Supp 4 S143
[6] SV Oliver, D Yuill, J Yorke, AL Caress, JA Smith. The language of cough: a focus group study in respiratory diseases. *Thorax* 2012;67(Suppl 2):A130
[7] YK Huong, D Yuille, A Caress, J Smith, J Yorke. P102 The sensations provoking cough: quantitative study. *Thorax* Dec 2017, 72 (Suppl 3) A138-A139

12. Appendix

	Visit 1	Visit 2
STUDY PROCEDURES	**Demographics** **Diagnosis** **VAS** **LCQ** **Verbal Cough Score** **24hr Cough Recording** **Topic Questionnaire**	**Medical history in relation to received clinical care for cough** **VAS** **LCQ** **Verbal Cough Score** **24hr Cough Recording** **Topic Questionnaire**