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Early View

Study Protocol

The NEUROCOUGH Chronic Cough Registry: A protocol for a pan-European observational study

Peter S. P. Cho, Surinder S. Birring, ClÍona McDowell, Tony Brown, James H. Hull, Jaclyn A. Smith, Laurent Guilleminault, Peter Kardos, Jan W. van den Berg, Christian Domingo, Paul Marsden, Marco Idzko, Federico Lavorini, Matthew J. Martin, Claire Slinger, Silvia Demoulin-Alexikova, Daiana Stolz, Arent Jan Michels, Madara Tirzite, Brigita Gradauskiene, Joao Carlos Winck, Ossur Ingi Emilsson, Georgios Kaltsakas, Charlotte Hyldgaard, Kian Fan Chung, Eva Millqvist, Ajit Narayanan, Lisa Gossage, Khan Buchwald-Mackintosh, Richard J. Siegert, Marianne Schulte, Abitha Nair, Jemma Nelson, Sean M. Parker, Marta Dąbrowska, Alyn Morice, Lieven J. A. Dupont, Lorcan McGarvey

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The NEUROCOUGH Chronic Cough Registry: A protocol for a pan-European observational study

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ABSTRACT

Chronic cough is a common clinical problem which is burdensome for patients and can be difficult to treat. Individual centres of cough expertise have been set up in countries across Europe but to date there has been no means to collate and analyse clinical data from such sites to gain a more comprehensive understanding of cough phenotypes, disease burden and the natural history of this condition.

The NEw Understanding in the tReatment Of COUGH (NEuroCOUGH) registry is the first pan European prospective observational study of adult patients referred for evaluation of chronic cough. Patients (≥18 years old) with a cough lasting more than 8 weeks with no chest radiology findings to explain the cough will be recruited. Key exclusion criteria include current or recent (<12 months) smoking, significant smoking history (≥20 pack years) and obstructive spirometry (FEV_1/FVC ratio <0.6). The study aims to recruit 2500 patients across 13 European sites by 2026, and participants will be followed up at 12-monthly intervals for 36 months. The Registry comprises comprehensive clinical, physiological and biological data on chronic cough, along with data on the impact and longitudinal outcome of chronic cough.

The NEuroCOUGH Registry has been established at a time of considerable advance in the field of cough. It will serve as a valuable clinical and research resource which will extend our current understanding of this difficult to treat condition. The initiative is also intended to encourage the establishment of new specialist cough clinics, thus creating much needed clinical trial infrastructure throughout Europe to ultimately improve patient care.

INTRODUCTION

Chronic cough is a common clinical problem which can be difficult to treat especially when therapy directed at common pulmonary and extrapulmonary causes is ineffective. Patients with chronic cough typically report the problem as one persisting for many years requiring repeated healthcare visits and numerous negative investigations, often with little or no response to medication leaving them frustrated and generally dissatisfied with their treatment journey [1, 2]. The recognition that clinical management of chronic cough needed to improve prompted the development of international consensus on its evaluation and treatment [3, 4]. A welcome consequence of this initiative was the establishment of specialist cough clinics in a number of countries around the world [5]. The clinical experience from these centres suggests that distinct demographic and clinical patterns or phenotypes commonly exist [6]. To date, no cross-sectional or longitudinal studies of multinational chronic cough patient cohorts have been undertaken, undoubtedly due to the high level of multidisciplinary cooperation needed to undertake such studies. To that end, in 2018, the NEw Understanding in the tReatment Of COUGH (NEuroCOUGH) Clinical Research Collaboration (CRC) was established as part of the European Respiratory Society (ERS) initiative to support the coordination of activities in respiratory medicine between multiple stakeholders and centres across Europe (https://www.ersnet.org/science-and-research/clinical-research-collaboration-application-programme/) [7].

A primary objective of the ERS NEuroCOUGH CRC was to establish a network of clinics across Europe and beyond to encourage the evaluation and management of chronic cough patients in an agreed and standardised manner internationally [4, 7]. A further priority was the creation of a Europe-wide registry of well-characterised patients with chronic cough for recruitment to multicentre clinical studies of novel antitussive therapies. Here, we describe the protocol of the NEuroCOUGH Chronic Cough Registry which had the following objectives: to establish the first pan-Europe multicentre

chronic cough registry with clinical, physiological and biological data collected at baseline and annual follow up for 36 months; to describe demographics, cough characteristics, co-morbidities, aetiologies, management and impact of chronic cough, and its various phenotypes and endotypes across Europe; to encourage and facilitate the establishment of clinical trial infrastructure for cough in European countries where such has not yet been established; to foster and maintain strong multicentre clinical and research collaboration in the field of chronic cough.

METHODS

Study design

The NEuroCOUGH CRC Registry is a multicentre, prospective, observational cohort study designed to enrol adult patients with chronic cough referred to secondary and tertiary centres with a specialist interest in chronic cough across Europe. Comprehensive data across domains of demographics, anthropometrics, co-morbidities, cough characteristics, aetiologies, investigations, treatment trials and impact of chronic cough will be collected at baseline (recruitment) with a more focused data set at yearly follow up.

The study is sponsored by Queen's University Belfast, Belfast, Northern Ireland and received ethics approval from the Multi-centre Research Ethics Committee in the UK on 26 July 2021 (20/EE/0213) with local ethics approval for each European site obtained by the relevant principal investigator. The study uniform resource locator (URL) is https://europeanlung.org/neurocough/.

Participants

Patients should have a primary problem of chronic cough and meet the following inclusion and exclusion criteria. The inclusion criteria are:

- Adult (≥18 years of age);
- Chronic cough of >8 weeks in duration;
- No chest radiology findings suggestive of pathology causing chronic cough.

The exclusion criteria are:

- Current smoker or smoking within last 12 months;
- Cumulative smoking history of ≥20 pack-years;
- Forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio <0.60;
- Acute respiratory tract infection within 4 weeks of baseline;
- Patients who are unable or unwilling to provide informed consent.

Recruitment and follow up

Patients with chronic cough will be identified from those referred to clinics in secondary or tertiary care settings with an interest in chronic cough. Patients will be managed by the responsible clinical teams according to the local procedures and policies. Following completion of baseline data collection, all participants will be invited to enter annual (±3 months) follow up over the following 36 months (Figure 1 and Table E1). Longitudinal data on cough characteristics, investigations, treatment trials, aetiology, severity, complications and impact of cough, and mortality will be collected (Table E2).

Data collection and entry

Data will be collected at distinct time points: baseline (data obtained at study enrolment) and annual review at 12, 24 and 36 month follow up where data is obtained at scheduled 'in person' clinic visit or alternatively a phone call/virtual clinic follow up can be undertaken. Data will be entered through a collection platform supported by University of Dundee Health Informatics Centre (HIC) https://hicsesrvices.staging.dundee.ac.uk/neurocough.

The data fields were agreed following consultation with cough specialists across Europe with input from the NEuroCOUGH and European Lung Foundation (ELF) Patient Advisory Group (PAG) and are summarised in Tables E1 and E2. The intent is for an extensive dataset, which will enable additional ancillary studies to be proposed by investigators. All data will be entered on an electronic case report form (eCRF) (Figure 2). In addition, participants are invited to provide consent for future contact regarding participation in clinical trials and studies.

Cough characteristics, triggers and complications

Participants self-report duration of cough, cough frequency and sputum production, including volume and appearance. In addition, participants self-report any triggers of cough, relieving factors for cough, and respiratory symptoms and complications associated with cough.

Severity and impact

Cough severity and urge to cough are self-reported on visual analogue scales (VAS; range: 0-100 mm) and modified Borg scales (mBorg; range: 0-10) (both VAS and mBorg: higher scores indicating more severe cough or worse urge, respectively) [8–10]. Cough-specific health status is assessed with the self-administered 19-item Leicester Cough Questionnaire (LCQ), which is validated in chronic cough and widely translated (range: 3-21; higher scores indicate better health status) [11, 12]. Generic health status is assessed with the EuroQol EQ-5D-5L, and responses will be converted to a numeric score (range: 0-1; one indicates full health, zero indicates death and below zero indicates a health status considered worse than death) [13].

Aetiology

The aetiology of chronic cough is determined by the clinician responsible for the patient based on their interpretation of investigational data and outcome of treatment trials in line with consensus statements [3, 14]. The following categories are included with the option to include multiple aetiologies and provision for free text should additional aetiological descriptors be required: Refractory Chronic Cough; Unexplained Chronic Cough; Post-Infective; Classic Asthma; Cough Variant Asthma; Eosinophilic Bronchitis; Gastroesophageal reflux disease; Upper Airway Cough Syndrome; Aspiration; Not yet determined (under further investigation).

Lung function

Raw values for FEV_1, FVC, anthropometrics and ethnicity are collected to enable the appropriate calculations for predicted values [15]. Bronchodilator response, bronchial challenge testing, fractional

exhaled nitric oxide (FeNO) and cough provocation testing are recorded where available. Raw values for body plethysmography and transfer coefficient for carbon monoxide are also collected where available. Spirometry, body plethysmography and transfer coefficient are all performed as per the recommendations of the American Thoracic Society/ERS guidelines [16].

Radiology

The results of the most recent chest radiology (chest radiograph and/or CT chest), preferably within 2 years, will be recorded. Although study inclusion criteria require the absence of any chest radiology findings that could potentially explain chronic cough, provision is made for free text to record co-existent radiological features considered unrelated to chronic cough.

Blood investigations

The serum eosinophil value at baseline and the peak serum eosinophil value within the preceding 24 months are collected, whilst RAST for common allergens are collected where available.

Treatment trials

All pharmacotherapy and non-pharmacotherapy received to date along with therapeutic response to said treatments are recorded.

Genetic and transcriptomics

Participants provide blood samples (10 mL PAXgene DNA and 10 mL PAXgene RNA) for genetic testing and transcriptomics at baseline on an optional basis. All samples are stored locally (-80 freezer) prior to transfer to central laboratories (Queen University Belfast, Belfast, Northern Ireland). Transfer and storage of material will be tracked using a sample tracking database. All samples are stored in accordance with the Human Tissue Act (2004) for at least 15 years. Samples shall not be redistributed or released to any individuals other than for the purpose of the protocol or ancillary studies approved by an appropriate ethics committee and in accordance with the participants' consent.

Quality control

The database comprises an automated logic check to alert users of any out-of-range values, and such values are prevented from being entered. Each case is manually verified by a member of the study team and data queries are resolved with the study site. Cases with missing core cough or demographic data that remain unresolved despite efforts of quality control team will be excluded from analysis. Each study site may be subjected to random inspection and audit for data verification and to ensure adherence to the protocol.

Sample size and statistical analysis

The sample size is empirically determined at 2500 patients across Europe, and the registry has no maximum number of patients. A short-term target of 1000 patients in the first 3 years of the project was reached at the end of 2024, with patients recruited from 12 sites across 7 European countries. A further 10 sites from 8 additional countries will be activated in 2025 (Figure 3). Taken together, we

believe the registry data will be broadly representative of the characteristics and management of chronic cough patients across Europe.

Descriptive analyses of the baseline data will be carried out with baseline demographic, clinical and cough data summarised as mean, standard deviation (SD), median, inter-quartile range (IQR), or numbers and frequencies (%) as appropriate. This will depend on the scale of measurement and distribution broken down by refractory and unexplained chronic cough, and by gender. There will be no significance testing performed initially.

When 12 month data collection is complete, we will use paired t-tests on these questionnaires to test for changes against the baseline data. Alternatively, Wilcoxon signed-rank tests will be used depending on whether assumptions are violated in the paired t-test. When 24 month and 36 month data are complete, we will use the repeated measures ANOVA or the Friedman test based whether assumptions are violated, to compare across multiple groups.

Exploratory analysis to identify new phenotypes of chronic cough that may lie hidden in patterns of responses within and across subpopulations (e.g. within aetiology, between locations) will be undertaken through the application of advanced statistical and machine learning techniques, such as clustering and network analysis. Results from such techniques will be scrutinised for clinical relevance and understanding so that future observational studies can develop specific hypotheses for clinical application and possible new targets for treatments.

Governance and data sharing

The registry is held securely in the University of Dundee HIC and anonymised data are accessible to approved investigators through the Safe Haven framework. The HIC "Safe Haven" platform is a virtual desktop (Trusted Research Environment; TRE) which allows secure data access and data analysis but prevents copying or alteration of data, thereby ensuring complete data security. The HIC Services Security Policy is available at https://hicservices.atlassian.net/wiki/spaces/HICSOP/pages/460128257/Information+Security+Policy. Investigators and other stakeholders will have unrestricted access to their own data. Requests to analyse the database as a whole will be managed by submission of a study protocol to the NEuroCOUGH scientific committee. Requests for data access from external agencies or investigators will be discussed on a case-by-case basis by the NEuroCOUGH Scientific Committee. The HIC database and governance processes surrounding data management and access are fully compliant with the Data Protection Act 2018 and the Data Protection Directive 95/46/EC of the European Parliament and of the Council (1995). A full list of HIC Standard Operating Procedures are listed here: https://hicservices.atlassian.net/wiki/spaces/HICSOP/overview.

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP). A favourable ethical opinion will be obtained by each partner Site from the appropriate research ethics committee. Additionally, any other necessary approvals required by partner sites will be obtained prior to commencement of the study at site. All patients must provide written informed consent to participate. It is the responsibility of the investigators at individual sites to obtain the appropriate approvals and to ensure that informed consent is in place. The online supplement summarises registry governance, data access and publication policy (Appendix 1).

Study results will be disseminated in the format of official newsletters or reports, conference abstracts and peer-reviewed publications (https://europeanlung.org/neurocough/).

Patient participation and involvement

An overarching principle of NEuroCOUGH CRC has been the inclusion of people with chronic cough and with support from the European Lung Foundation (ELF), a cough patient advisory group (PAG) was established (https://europeanlung.org/en/news-and-blog/meet-the-elf-cough-pag/). The PAG comprises 12 patients with chronic cough from 6 different European countries currently. The PAG provides input to the study design and implementation of the registry and NEuroCOUGH activities, thus ensuring NEuroCOUGH activities are patient focused. In addition, the PAG will support the dissemination of NEuroCOUGH outputs by providing patient resources on diagnosis and management, and through public awareness activities.

DISCUSSION

Chronic cough is an extremely common respiratory problem, and yet our understanding of the clinical features and characteristics of this condition is drawn mainly from the experience of single-centres or a few relatively small national patient registries [17–19]. The ERS NEuroCOUGH Registry represents the first multi-national dataset comprising clinical, physiological and biological data from patients referred for management of chronic cough. It has been developed by incorporating a number of the features employed by the successful European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) registry [20]. This includes a minimum required dataset that would be

captured ordinarily during the clinical evaluation and management of patients with chronic cough. This pragmatic approach the lessens burden on patients and participating sites. Coupled with a shared data entry platform coupled with regular quality assurance checks, it will provide a valuable resource for advancing current understanding of chronic cough including its natural history, the range and prevalence of clinical phenotypes, and the severity and burden reported by people with chronic cough over an extended period of time. A recent preliminary descriptive analysis of almost 1000 chronic cough patients from the NEuroCOUGH Registry confirmed clinical characteristics, patient demographics, comorbidities and cough burden consistent with that reported in smaller studies and comparable to the patients typically recruited to clinical trials of novel anti-tussives [21].

Recent clinical and mechanistic understanding of cough, including a recognition of the concept of cough hypersensitivity syndrome, has accelerated drug discovery in this field with the need of largescale multicentre clinical trials of novel cough therapies. The NEuroCOUGH Registry will be well placed to provide a suitable platform to facilitate such endeavours. Indeed, to date, NEuroCOUGH sites have participated as recruiting centres for a number of phase II and III clinical trials of new cough therapies [22–26]. It is anticipated that with the recent approval by the European Medicines Agency for gefapixant for the treatment of refractory and unexplained chronic cough, and the longitudinal design of the NEuroCOUGH Registry, determining the clinical and biological characteristics of responder and non-responders to this therapy in a real-world setting will be possible [27].

The NEuroCOUGH CRC initiative also encourages investigator-initiated ancillary studies which are assessed by the Scientific Committee. To date, successful proposals include a network analysis to provide novel insight into the dependencies between phenotypes of chronic cough, studies to determine the predictive value of blood eosinophil count and the utility of chest CT scanning in the

management of chronic cough, the utility and feasibility of ambulatory cough recording beyond 24 hours and an international comparison of clinical characteristics between the NEuroCOUGH Registry and the Korean Chronic Cough Registry [17].

While the NEuroCOUGH Registry aims to recruit patients across 20 European countries, there is an intention to establish similar registries in North America, Latin America and Asia and so provide a greater real-world perspective on this common and difficult to treat condition.

In conclusion, the NEuroCOUGH pan-European cough registry represents a significant advancement in the field of chronic cough by providing comprehensive insights to its prevalence, diagnostic patterns, associated conditions, and long-term progression. This multinational initiative will not only enhance our understanding of cough phenotypes but also serve as a robust platform for clinical and translational research, ultimately guiding the development of more effective diagnostic and therapeutic strategies.

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Additional information

Further information on study protocol, and copies of the participant information sheet, informed consent form and data collection *pro forma* are available on the NEuroCOUGH website (https://europeanlung.org/neurocough/)

REFERENCES

1 Kum E, Guyatt GH, Munoz C, *et al.* Assessing cough symptom severity in refractory or unexplained chronic cough: findings from patient focus groups and an international expert panel. *ERJ Open Res* 2022; 8(1): 00667-2021.

2 Brindle K, Morice A, Carter N, *et al.* The "vicious circle" of chronic cough: The patient experience – qualitative synthesis. ERJ Open Res 2023; 9(3): 0094-2023

3 Morice AH, Millqvist E, Bieksiene K, *et al.* ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *European Respiratory Journal* 2019; 55: 1901136.

4 Song WJ, Dupont L, Birring SS, *et al.* Consensus goals and standards for specialist cough clinics: the NEUROCOUGH international Delphi study. *ERJ Open Res* 2023; 9(6): 00618-2023.

5 Dicpinigaitis P V., Birring SS, Blaiss M, *et al.* Demographic, clinical, and patient-reported outcome data from 2 global, phase 3 trials of chronic cough. *Annals of Allergy, Asthma and Immunology* 2023; 130: 60–66.

6 Mazzone SB, Chung KF, McGarvey L. The heterogeneity of chronic cough: a case for endotypes of cough hypersensitivity. *Lancet Respir Med* 2018; 6: 636–646.

7 McGarvey L, Dupont L, Birring SS, *et al.* New understanding in the treatment of cough (NEUROCOUGH) ERS Clinical Research Collaboration: Improving care and treatment for patients with cough. European Respiratory Journal 2019; 53(5): 1900787.

8 Morice AH, Fontana GA, Belvisi MG, *et al.* ERS guidelines on the assessment of cough. *European Respiratory Journal* 2007; 29: 1256–1276.

9 Wilson RC, Jones PW. A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. *Clin Sci* 1989; 76: 277–282.

10 Martin Nguyen A, Bacci ED, Vernon M, *et al.* Validation of a visual analog scale for assessing cough severity in patients with chronic cough. *Ther Adv Respir Dis* 2021; 15: 1-13.

11 Birring SS, Prudon B, Carr AJ, *et al.* Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003; 58: 339–343.

12 Cho PSP, Birring SS, Fletcher H V, *et al.* Methods of Cough Assessment. *Journal of Allergy and Clinical Immunology: In Practice* 2019; 7: 1715–1723.

13 Herdman M, Gudex C, Lloyd A, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research* 2011; 20: 1727–1736.

14 Parker SM, Smith JA, Birring SS, *et al.* British Thoracic Society Clinical Statement on chronic cough in adults. *Thorax* 2023; 78: S3–S19.

15 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *European Respiratory Journal* 2012; 40: 1324–1343.

16 Graham BL, Steenbruggen I, Barjaktarevic IZ, *et al.* Standardization of spirometry 2019 update an official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 2019. p. E70–E88.

17 Jo EJ, Lee JH, Won HK, *et al.* Baseline Cohort Profile of the Korean Chronic Cough Registry: A Multicenter, Prospective, Observational Study. *Lung* 2023; 201: 477–488.

18 van den Berg JWK, Baxter CA, Edens MA, *et al.* The demographics, clinical characteristics and quality of life of patients with chronic cough from the Isala Cough Clinic in the Netherlands. *ERJ Open Res* 2022; 8(4): 00232-2022.

19 Kukiełka P, Moliszewska K, Białek-Gosk K, *et al.* Prevalence of refractory and unexplained chronic cough in adults treated in cough centre. *ERJ Open Res* 2024; 10(5): 00254–02024.

20 Chalmers JD, Aliberti S, Polverino E, *et al.* The EMBARC European Bronchiectasis Registry: protocol for an international observational study. *ERJ Open Res* 2016; 2: 00081–02015.

21 Cho PSP, Birring SS, Narayanan A, *et al.* Characteristics of chronic cough patients across Europe: A descriptive analysis from the ERS NEuroCOUGH CRC Registry [Abstract]. *European Respiratory Journal* 2024; 64: PA2130.

22 McGarvey L, Smith J, Birring SS, *et al.* Response in Patient-reported Cough Severity in Soothe, a Phase 2b Trial of Camlipixant in Refractory Chronic Cough. *Am J Respir Crit Care Med* 2023; A2533.

23 Smith JA, Mcgarvey L, Morice AH, *et al.* Improvements in Awake Cough Frequency in SOOTHE, A Phase 2b Trial of BLU-5937 in Refractory Chronic Cough (abstract). *European Respiratory Journal* 2002; 60: 810.

24 Morice A, Smith JA, McGarvey L, *et al.* Eliapixant (BAY 1817080), a P2X3 receptor antagonist, in refractory chronic cough: A randomised, placebo-controlled, crossover phase 2a study. *European Respiratory Journal* 2021; 58(5): 2004240.

25 McGarvey LP, Birring SS, Morice AH, *et al.* Efficacy and safety of gefapixant, a P2X3 receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-

2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet* 2022; 399: 909–923.

26 McGarvey L, Smith JA, Morice A, *et al.* A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 2b Trial of P2X3 Receptor Antagonist Sivopixant for Refractory or Unexplained Chronic Cough. *Lung* 2023; 201: 25–35.

27 Papapetropoulos A, Topouzis S, Alexander SPH, *et al.* Novel drugs approved by the EMA, the FDA, and the MHRA in 2023: A year in review. Br J Pharmacol 2024. p. 1553–1575.

Legends of figures

Figure 1. Study flowchart

Figure 2. NEw Understanding in the tReatment Of COUGH (NEuroCOUGH) cough registry data collection platform (https://neurocough.hicservices.dundee.ac.uk/).

Figure 3. NEw Understanding in the tReatment Of COUGH (NEuroCOUGH) countries across Europe

Online supplement

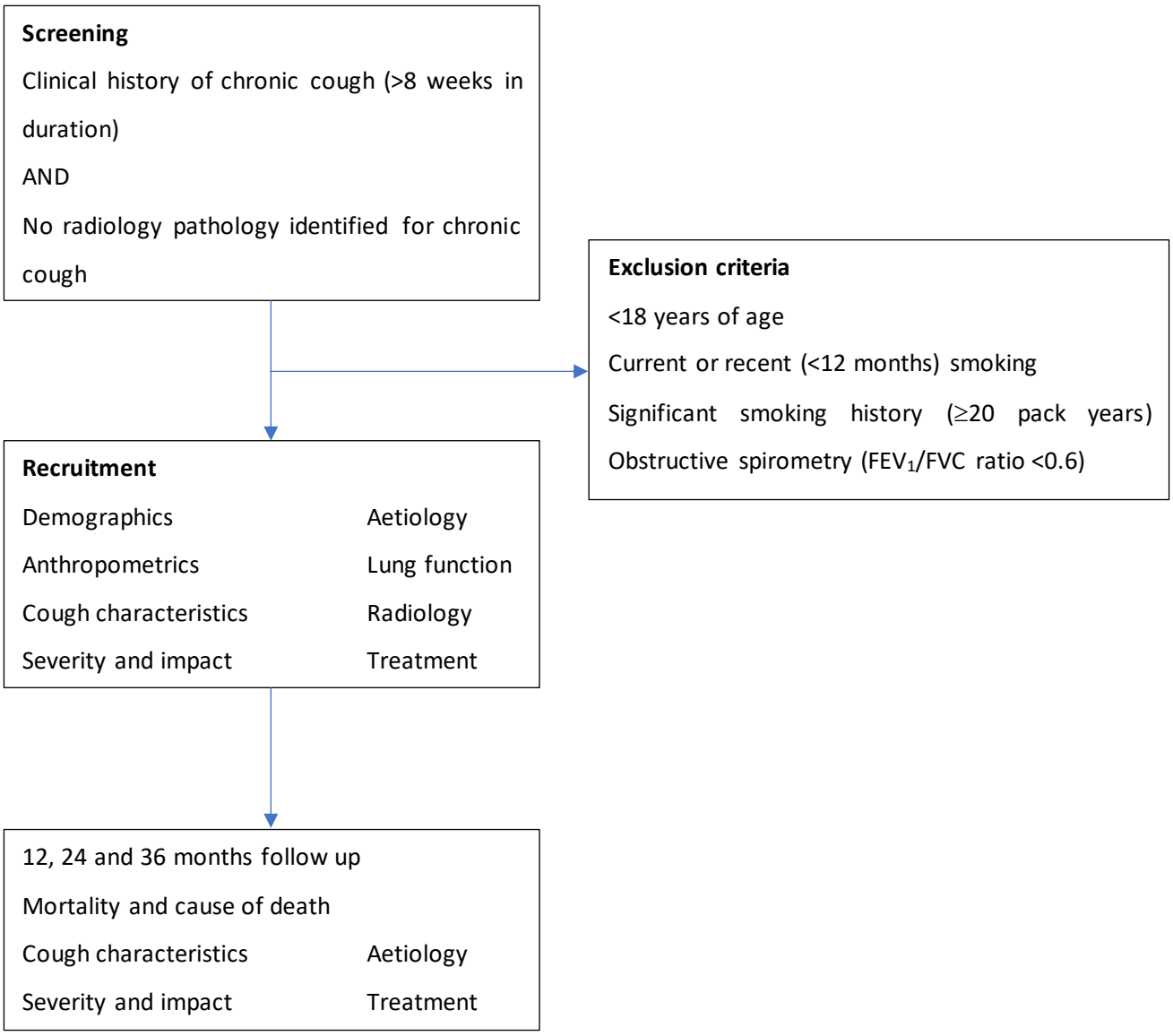
Legends of tables

Table E1. Summary of data fields of the NEw Understanding in the tReatment Of COUGH (NEuroCOUGH) cough registry at baseline

Table E2. Data fields of the NEw Understanding in the tReatment Of COUGH (NEuroCOUGH) cough registry at annual follow up

Appendix 1. Registry governance, data access and publication policy

Figure 1. Study flowchart



FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity

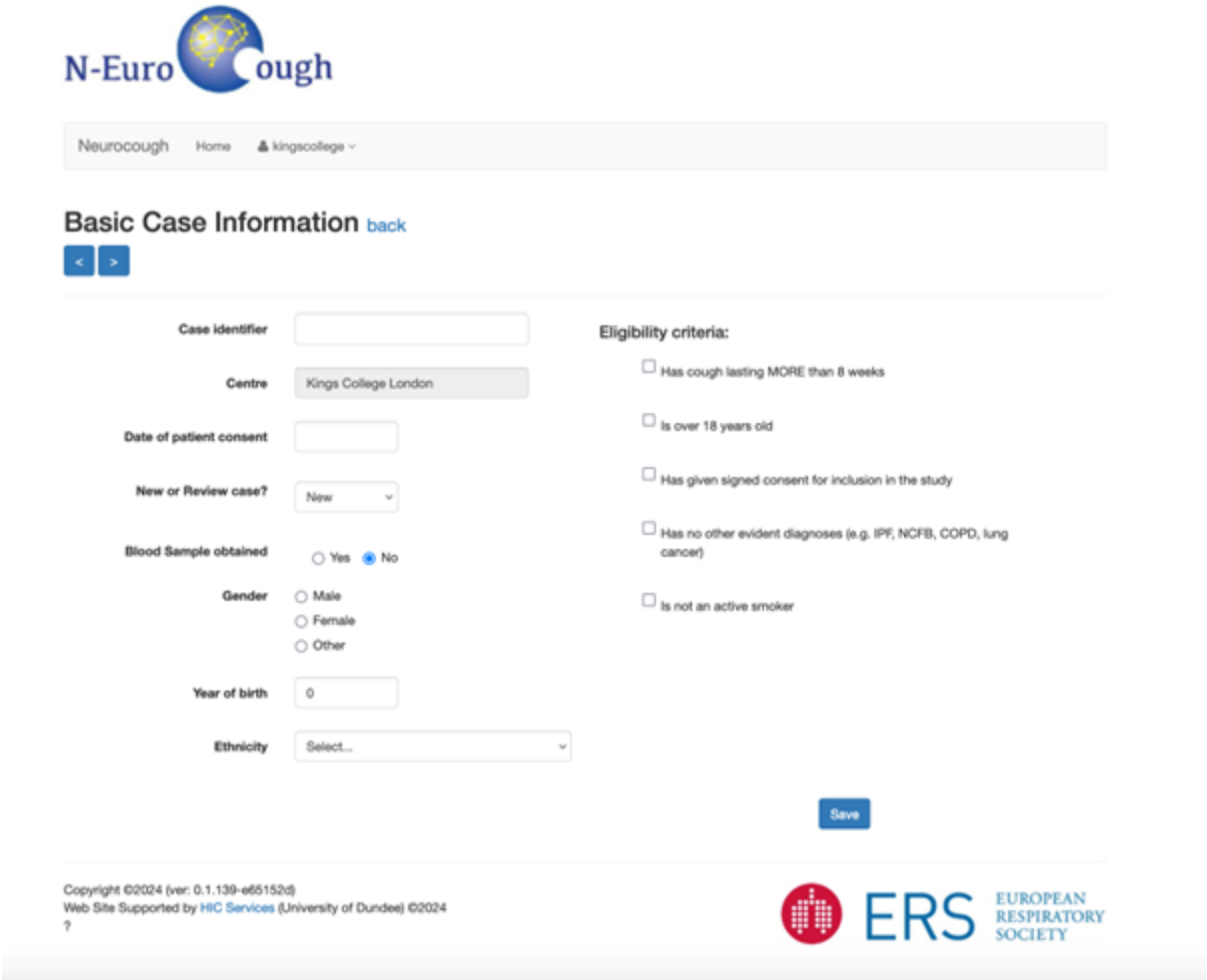


Figure 2

Figure 3

Table E1. Data collected by the NEw Understanding in the tReatment Of COUGH (NEuroCOUGH) cough registry at baseline

Categories	Variables
Demographics and anthropometrics	Age Sex BMI
Smoking history	Smoking status Pack year history
Cough characteristics	Duration Frequency Sputum production and volume
Cough triggers[a]	Temperature change Fragrance Talking Exercise
Co-morbidities[a]	Rhinosinusitis Gastro-oesophageal disease Neuralgia Anxiety Depression
Medications[a]	ACEi Anti-histamine Neuromodulator Opioid
Lung function	FEV1 FVC Bronchoprovocation[b] FeNO[b]
Serum	Eosinophil

	RAST
Radiology	Chest radiograph Chest computed tomography[b]
Severity and impact	VAS LCQ EQ-5D-5L
Aetiology[a]	Asthma Chronic rhino-sinusitis Gastro-oesophageal diseases Refractory chronic cough Other
Treatment[a]	Inhaler therapy PPI Nasal steroid Neuromodulator Opioid
Complications[a]	Syncope Urinary incontinence Sick leave

BMI = body mass index, EQ-5D-5L = 5-level EuroQoL, FeNO = fractional exhaled nitric oxide, LCQ = Leicester Cough Questionnaire, PPI = proton pump inhibitor, VAS = visual analogue scale

[a]Examples provided and non-exhaustive

[b]Not included in minimum required data set

Table E2. Data fields of the NEw Understanding in the tReatment Of COUGH (NEuroCOUGH) cough registry at annual follow up

Categories	Variables
Mortality	Date of death Cause of death
Cough characteristics	Frequency Sputum production and volume
Severity and impact	VAS LCQ EQ-5D-5L
Aetiology[a]	Asthma Chronic rhino-sinusitis Gastro-oesophageal diseases Refractory chronic cough Other
Treatment[a]	Inhaler therapy PPI Nasal steroid Neuromodulator Opioid
Complications[a]	Syncope Urinary incontinence Sick leave

EQ-5D-5L = 5-level EuroQoL, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, LCQ = Leicester Cough Questionnaire, PPI = proton pump inhibitor, VAS = visual analogue scale

[a]Examples provided and non-exhaustive

Appendix 1. Registry governance, data access and publication policy

REGISTRY GOVERNANCE ARRANGEMENTS

NEuroCOUGH is composed of a Steering Committee comprising the Co-chairs, 3 members of the Committee of National Leads (rotating on an annual basis), a member of the Patient Advisory Group (PAG) and the Early Career Member responsible for the oversight of the CRC as well as for the reporting to ERS. A NEuroCOUGH Registry Scientific Committee responsible for the running of the registry will be developed. The Registry Scientific Committee will have direct responsibility for the conduct of the registry including ensuring compliance with the protocol. The Registry Scientific Committee will work with the Steering Committee to provide direction on the strategic development of the Registry. The Registry Scientific Committee will have the primary role for screening applications for access to registry data and the monitoring of progress with projects.

MEMBERSHIP AND ROLES

The membership of the Registry Scientific Committee comprises a maximum of 7 members elected from the Steering Committee and Committee of National Leads and must include a member of the PAG. The Chair of the Registry Scientific Committee will be determined by a vote of members of the Registry Scientific Committee. Appointments to the Registry Scientific Committee are for a period of 2 years, renewable once.

There must be >50% of the Registry Scientific Committee members present at a meeting in order for decisions to be taken. A majority decision is taken in all cases. In the event of a tied vote the agenda item will be deferred to the next meeting and re-presented. Two episodes of tied votes indicates there is not a majority and the proposal will be declined.

Agenda Items and Papers

The Registry Scientific Committee agenda, with attached meeting papers will be distributed at least 30 days prior to the next scheduled meeting.

The Chair has the right to decline to list an item on the formal agenda, but members may raise an item under "Other Business" if necessary and as time permits.

Full copies of the Minutes, including attachments, shall be provided to all Steering Committee members no later than 30 working days following each meeting.

By agreement of the Committee, out-of-session decisions will be deemed acceptable. Where agreed, all out-of-session decisions shall be recorded in the minutes of the next scheduled Steering Committee meeting.

Frequency of Meetings

The Chair shall convene Registry Scientific Committee meetings at a minimum frequency of twice yearly with teleconferences as required throughout the year. If more than 4 proposals are expected at a steering committee meeting the Chair will call an additional meeting. The meetings should be aligned where possible with the NEuroCOUGH general meetings or the ERS annual congress. Additional unscheduled meetings will be called as needed with no less than 60 days notice.

DATA ACCESS

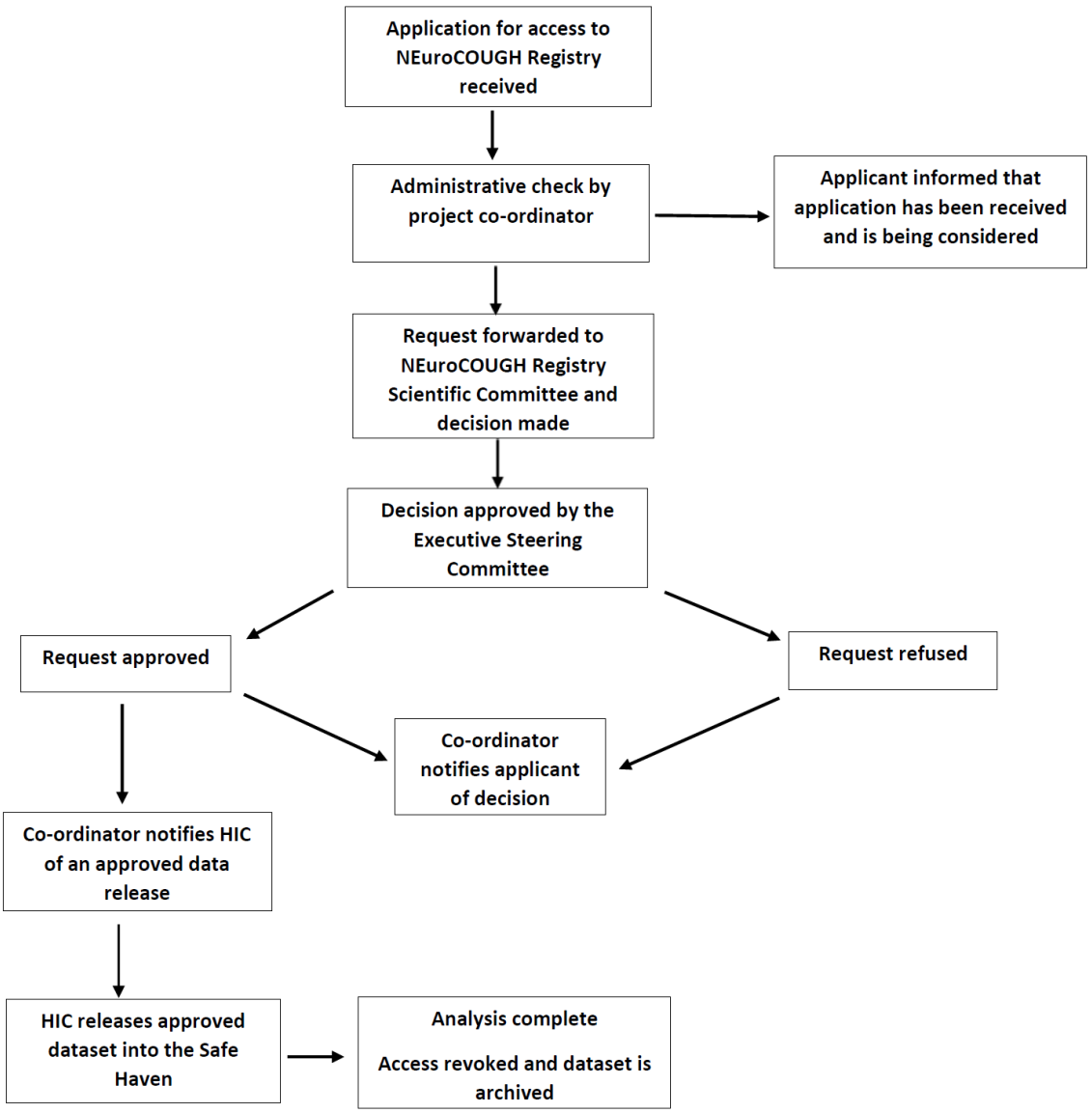
The guiding principle is that access to data generated by NEuroCOUGH CRC will be granted to all partners, including all the contributing funding partners. This access will allow partners to use the data for internal questions or evaluations. For new project proposals (see below) for which additional funding is provided by some of the funders only, access to these data will be initially limited to these funders, ultimately becoming available to all upon publication. Access to data for publication purposes

is set out in line with a specific Data Access and Publication process to ensure maximum benefit and to avoid overlap (see flow diagram below).

The NEuroCOUGH Registry Scientific Committee will have the primary role for screening applications for access to registry data and monitoring of progress with projects. They will be expected to act in accordance with the principles of the NEuroCOUGH registry protocol and to comply with agreements between contributing centres. In particular, the following principles should apply to decisions regarding data access

- Access to anonymised data through the "Safe Haven" platform will be possible for all Investigators and partner stakeholders throughout the study
- Active Investigators and other stakeholders will have unrestricted access to their own data.
- Request for data from industry or external agencies will be considered by the NEuroCOUGH Registry Scientific Committee but will incur a fee for service unless the parties have a prior agreement that supersedes this.
- Requests for data from individuals who do not contribute to the registry will be considered but may incur a fee for service at the discretion of the Registry Scientific Committee
- Identifiable patient data will never be released

Workflow for analysis of NEuroCOUGH Registry data



AUTHORSHIP AND PUBLICATIONS

It is anticipated that all clinical study reports arising from work undertaken by NEuroCOUGH investigators and partners will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of their study. However, the final decision to publish any aspect of the NEuroCOUGH study data rests with the Registry Scientific Committee. Investigators wishing to publish aspects of the study must submit a proposal for discussion and approval by the Registry Scientific Committee. NEuroCOUGH partners may ask to see publications

prior to submission and may request a reasonable delay in publication in order to protect intellectual property and/or to request removal of any confidential information belonging to the Sponsor, funder or collaborators.

The NEuroCOUGH CRC will follow the International Committee of Medical Journal Editors (ICMJE) recommendations regarding authorship. These are shown below for reference;

An author must take responsibility for at least one component of the work, should be able to identify who is responsible for each other component, and should ideally be confident in their co-authors' ability and integrity. Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship/contributorship defined above, and editors will ask these individuals to complete journal-specific author and conflict-of-interest disclosure forms. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments. The NLM indexes the group name and the names of individuals the group has identified as being directly responsible for the manuscript; it also lists the names of collaborators if they are listed in Acknowledgments.

It should be noted that;

- Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All questions regarding publication or authorship will be addressed by the Registry Scientific Committee, who will have the final authority over these decisions.