New understanding in the treatment of cough (NEUROCOUGH) ERS Clinical Research Collaboration: improving care and treatment for patients with cough

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The NEw Understanding in the tReatment Of COUGH (NEUROCOUGH) ERS Clinical Research Collaboration: improving care and treatment for patients with cough.

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Complete List of Authors:	McGarvey, Lorcan; Queen's University of Belfast, Centre for Infection & Immunity Dupont, Lieven; KU Leuven, Clinical and Experimental Medicine, Laboratory of Pneumology Birring, Surinder; King's, Asthma, Allergy and Lung Biology; Boyd, Jeanette; European Lung Foundation, Chung, Kian Fan; Imperial College, National Heart & Lung Institute Dabrowska, Marta; Warsaw Medical University, Pneumonology DOMINGO, CHRISTIAN; HOSPITAL DE SABADELL, PULMONARY MEDICINE; Universitat Autonoma de Barcelona Facultat de Medicina, Medicine Fontana, Giovanni; Università di Firenze, Area Critica Medico Chirurgica Guilleminault, Laurent; CHU, Hôpital Larrey, Pulmonology Kardos, Peter; Maingau Hospital, Respiratory; Group Practice, Millqvist, Eva; Asthma and Allergy Research Group, Department of Respiratory Medicine and AllergyAsthma and Allergy Research Group Morice, Alyn; Castle Hill Hospital, Medicine Smith, Jaclyn van den Berg, Jan Willem; Isala klinieken, Pulmonology Van de Kerkhove, Charlotte; Universitaire Ziekenhuizen Leuven, respiratory diseases
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Abstract:	

The NEw Understanding in the tReatment Of COUGH (NEUROCOUGH) ERS Clinical Research Collaboration: improving care and treatment for patients with cough.

Lorcan McGarvey[1], Lieven Dupont[2]; Surinder S Birring[3], Jeanette Boyd[4], Kian Fan Chung[5], Marta Dabrowska[6], Christian Domingo[7], Giovanni Fontana[8], Laurent Guilleminault[9], Peter Kardos[10], Eva Millqvist[11], Alyn H Morice[12], Jaclyn A Smith[13], Jan Willem van den Berg[14], Charlotte Van de Kerkhove[15] on behalf of the NEUROCOUGH Clinical Research Collaboration[16]

Affiliations: [1]Centre for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland. [2]Department of Respiratory Diseases, University Hospital Leuven, Katholieke Universiteit Leuven, Belgium. [3] Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, King's College London, London. [4]European Lung Foundation, Sheffield, United Kingdom. [5]National Heart and Lung Institute, Imperial College London, United Kingdom. [6]Medical University of Warsaw, Poland. [7]Servicio de Neumología, Hospital Parc Taulí, Sabadell, Autonomous University of Barcelona (UAB) Barcelona, Spain. [8]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy. [9]Service de pneumologie-allergologie, pôle des voies respiratoires, hôpital Larrey, Toulouse, France and Center for Pathophysiology Toulouse Purpan, INSERM U1043, CNRS UMR 5282, Toulouse III University, Toulouse, France. [10]Centre for Allergy, Respiratory and Sleep Medicine at Red Cross Maingau Hospital, Frankfurt , Germany. [11]Department of Allergology, Institution of Internal Medicine, The Sahlgrenska Academy at University of Gothenburg, Sweden. [12]Hull York Medical School, Castle Hill Hospital, Hull, United Kingdom. [13]Division of Infection, Immunity and Respiratory Medicine, University of Manchester, United Kingdom.

[14]Department of Pulmonology, Isala Hospital, Zwolle, Netherlands. [15]Universitair Ziekenhuis Leuven, Leuven, Belgium. 16 A full list of members of the NEUROCOUGH Clinical Research Collaboration can be found at the end of this article.

Corresponding Author: Lorcan McGarvey[1]Centre for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland. Email: l.mcgarvey@qub.ac.uk

Introduction

Chronic cough is a common and troublesome clinical problem and currently there are no effective treatments (1). While individual specialist cough clinics have been set up in some European countries there is no formal mechanism to develop common management approaches. Furthermore, the vast majority of clinical trials of novel anti-tussive treatment have been conducted in a limited number of sites in the United Kingdom and United States with little in the way of cough clinical trial infrastructure across Europe (2-7). The NEw Understanding in the tReatment Of COUGH (NEUROCOUGH) Clinical Research Collaboration seeks to address this through creating a platform allowing clinicians together with researchers in academia and industrial partners across Europe and beyond to exchange ideas and facilitate collaborations geared towards improved care and treatment for patients with cough. The core aims of NEUROCOUGH are to;

i) Create a Registry of Europe-wide Specialist Cough Clinics operating according to agreed and standardised protocols.

ii) Establish a Europe-wide registry of 'clinical trial ready' chronic cough patients suitable for multi-centre experimental medicine studies and later phase precision medicine clinical trials.

iii) Seek public engagement to provide input into NEUROCOUGH based on the priorities and unmet needs of patients

iv) Encourage early career researchers and clinicians into the field of cough

In time, we envisage NEUROCOUGH will bring clinicians, scientists, patients and industry together for larger scale cough projects in a way that to date has not been possible. NEUROCOUGH will place Europe at the forefront of clinical improvements in chronic cough and provide a strong platform for attracting major clinical trials of anti-tussives, thus speeding up drug discovery with the ultimate aim of providing better treatments for patients with chronic cough.

What is the clinical rationale for NEUROCOUGH?

Chronic cough, defined as one persisting for more than 8 weeks, is among the commonest clinical problems encountered by doctors both in general and hospital practice (1). Chronic cough is recognised globally as an important clinical problem and to address the extent of this, a number of the NEUROCOUGH researchers undertook a review of over 10,000 patients to determine the demographic profile attending specialist cough clinics worldwide (8). Particularly evident from this study were the characteristics of patients seeking specialist help for cough. In many cases the cough had persisted for years and with no effective treatments available, many such patients are left frustrated with their clinicians unsure how best to manage this condition. To understand the scope of the problem more completely, the NEUROCOUGH researchers also undertook a survey in collaboration with the European Lung Foundation (ELF) involving almost 2,000 people throughout Europe living with chronic cough. Key findings were that the cough impacted considerably on patients' daily-life activities with many reporting deterioration in health-related quality of life and feeling

fed-up and depressed (9). Many of those surveyed reported a complete lack of awareness among their primary care physicians of cough as a distinct clinical problem and reported seeing numerous clinicians and undergoing many failed trials of therapy. While there is some consensus on the use of systematic protocols for the diagnosis and treatment of chronic cough, standardisation across centres is variable (10). Furthermore, chronic cough can exist as a distinct clinical entity termed 'refractory', 'unexplained' or 'idiopathic' chronic cough, when no associated cause is apparent, or treatment of any associated causes is ineffective.

Cough can also be a prominent and troublesome symptom for patients with common lung conditions including asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and bronchiectasis. Cough is also considered as one of the potential treatable traits of airway disease and acknowledging this more widely may help clinicians adopt a more individualised approach to treating their patients (11). For example in asthma, patients with cough are often given oral corticosteroids, yet this may not deliver adequate control while exposing patients to the unacceptable side-effects of high dose steroids. In COPD, cough is reported in 70% of patients (12), and many consider it to be extremely severe (13) contributing to impaired quality of life (14). Cough is also a central clinical feature of bronchiectasis and during an exacerbation the cough can become much worse and contributes to impaired health status (15). In Sarcoidosis, chronic cough is a common symptom and is associated with a heightened cough reflex (16). In idiopathic pulmonary fibrosis (IPF), a chronic dry cough is as troublesome as breathlessness and remains difficult-to-treat (17). Chronic cough remains difficult to manage and many patients self-medicate with 'over the counter' (OTC) cough therapies despite a lack of evidence supporting their efficacy (18, 19). Current estimates suggest that almost 3 billion Euros are spent annually throughout Europe on OTC therapies that have little antitussive effects (20).

How NEUROCOUGH can improve mechanistic understanding of cough?

There is a growing recognition that chronic cough is a heterogeneous condition in terms of its presentation and causes and the underlying mechanisms are poorly understood representing a significant knowledge gap (21). A number of the NEUROCOUGH researchers have been instrumental in developing the concept that the common pathophysiological mechanism of cough, regardless of the aetiology, is an inflammation-induced injurious effect of the nervous system (neuro-inflammation). This leads to a cough hypersensitivity syndrome whereby neural pathways (in the airway and the brain) become damaged by factors including viral infection, and physical and chemical irritants (22, 23). This neural damage (neuropathy), analogous to that driving some forms of chronic pain, is central to the clinical problem of cough. The challenge is in defining the complex and heterogeneous neuronal mechanisms responsible to help identify targets for suppressing problematic cough whilst maintaining the protective cough that is essential for normal lung health. Recent work has led to greater understanding of the fundamental mechanisms of cough pathophysiology (24-28) and recent international collaboration through a European Respiratory Society (ERS) initiative has led to the innovative concept of Cough Hypersensitivity Syndrome (CHS) (23). While evidence for this concept needs to be strengthened, the emerging potential in this field is underpinned by recent and remarkable progress in novel target discovery in neurobiology (2) highlighting the timely nature of the NEUROCOUGH initiative.

How can NEUROCOUGH help to deliver better treatments for cough?

A key unmet need is the lack of effective antitussives and to date assessment of novel targets in early 'proof of concept' clinical studies has come with mixed success. Although efficacy has been observed with gabapentin (29) and the blocker of the ATP receptor, P2X3 (2, 7) in subsets of cough patients, compounds directed at a range of potentially promising targets including TRPV1(3), TRPA1(4) and voltage-gated sodium channels (6) have failed. This has raised two important issues; firstly can we improve the predictive value of existing pre-clinical cough model systems. In this regard it is our ambition that partnership activities initiated through NEUROCOUGH, will pave a way forward to enhance translation of basic discoveries into clinical success. Secondly, how can we identify the genetic and biological characteristics that define the subgroups of 'responsive' cough patients to novel anti-tussive therapies. Establishing a pan-European registry of well-phenotyped patients as detailed in our second core objective below will provide future capacity for multicentre studies to determine pathophysiological mechanisms and enable translation into later phase precision medicine clinical trials.

Why do we need NEUROCOUGH now?

Europe's cough researchers and clinicians have no formal mechanism to develop common investigative and management approaches or to facilitate collaboration either with each other or with partners from industry. Individual centres of cough expertise have been set up in many countries across Europe but to date there has been no means to standardise and harmonise the activity in these specialist clinics. In simple terms we have no idea currently how patients with chronic cough are evaluated and managed between countries within Europe. In addition, while there have been efforts to provide consensus on the optimal management strategies this has been largely at an individual national level e.g. Germany,

Spain, Britain, France (30-33). Recently an ERS Taskforce on Cough has been established with the first meeting of members held at the 2017 ERS Scientific Assembly in Milan and the resulting publication soon to be published. A number of Taskforce members are National Leads for NEUROCOUGH and will champion the Taskforce recommendations within their respective countries. Finally, and perhaps most importantly, the vast majority of single and multi-centre clinical trials of novel anti-tussives have to date, been conducted in the United Kingdom and United States (2-7). As the number of potential novel compounds for cough is growing and the need to conduct large Phase III studies of the most promising compounds is pressing there is an opportunity for Europe to play a leading role as the ideal environment for such studies by creating a unified approach to patient management and phenotyping. To deliver on this objective NEUROCOUGH CRC will support the establishment of new specialist cough clinics so creating much needed clinical trial infrastructure throughout Europe.

In summary, recent advances in mechanistic understanding of cough coupled with interest in its neurobiology and the development of novel therapeutic options has provided the perfect environment in which to establish a CRC for cough. We strongly believe the NEUROCOUGH network will advance cough research and clinical management throughout Europe and generate a framework for future clinical trials.

NEUROCOUGH objectives

NEUROCOUGH seeks to achieve the following core objectives:

i) Quality Improvement in Clinical Care: To address the under provision of clinical expertise in cough so evident in our patient survey we will undertake a real world questionnaire based survey to accurately record how clinicians across the 1st wave of NEUROCOUGH partner

sites manage patients with chronic cough. The nature and extent of discordance between sites will be reviewed and consensus on core assessment protocols will be reported and serve as a template for those seeking to set up new specialist clinics in the future.

Anticipated output: The creation of a Registry of Europe-wide Specialist Cough Clinics operating according to agreed and standardised protocols, which will be incorporated into future guidelines.

ii) Establish a Chronic Cough Patient Registry: We aim to establish the first Europe-wide chronic cough patient registry comprising pre-specified clinical, physiological and biological data. An electronic data collection form for all these variables is being developed in conjunction with the Health Informatics Centre (HIC) based at the University of Dundee. NEUROCOUGH will generate a registry of carefully characterised chronic cough patients (including those with refractory and unexplained cough) at existing 1st wave sites (Figure 1) and then through an 'open-door' policy encourage 2nd wave cough centres across Europe to join NEUROCOUGH and enter data.

Anticipated output*:* This resource will provide for the first time a Europe-wide registry of 'clinical trial ready' chronic cough patients suitable for multi-centre experimental medicine studies and later phase precision medicine clinical trials.

iii) Public Engagement: With support from the European Lung Foundation, a Cough Patient Advisory Group (PAG) is currently being established to provide input into NEUROCOUGH's design and implementation based on the priorities and unmet needs of patients. The PAG will support the dissemination of the NEUROCOUGH outputs by providing resources for patients about diagnosis and treatment options, and through public awareness activities. Specific attention will be given to improving awareness of cough amongst primary care clinicians through links with ERS Assembly 1. The PAG will provide

perspective on study design, recruitment plans and assist with developing patient information sheets and consent forms and improve ways to recruit participants to clinical trials.

Anticipated output: Disseminate and communicate the importance of diagnosing and treating chronic cough.

iv) Enhance training and research capacity: NEUROCOUGH will provide the ideal platform in collaboration with the ERS Research Agency and Assembly 5 to run themed Postgraduate workshops led by expert clinical and scientific partners to encourage clinicians and researchers in the early part of their career to form a specialist interest in cough. We anticipate that in time, NEUROCOUGH would seek support for Research and Training Fellowships to undertake innovative projects based on access to the NEUROCOUGH clinical registry and any future associated biobanks. The output from the planned activities will be available to all through a comprehensive communication strategy.

Anticipated output: Encourage early career researchers and clinicians into the field of cough

How will NEUROCOUGH achieve its objectives?

NEUROCOUGH has assembled a multidisciplinary team of leading cough specialist clinicians together with clinical and basic science researchers from both academia and industry to work with patients and the public in an integrated fashion.

NEUROCOUGH CRC 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. The Steering Committee will work closely with the appointed representatives from each of Industry Partners. 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 and the monitoring core activities (Figure 2).

A look forward with NEUROCOUGH

It is anticipated that NEUROCOUGH, in collaboration with the ERS Research Agency, will seek external funding support to develop a programme of work designed to address the research priorities in cough and the unmet needs in the development of novel anti-tussives. A number of these are listed in Table 1. Furthermore, there is a need to raise awareness of cough as important and difficult to manage clinical problem in lung diseases including COPD, asthma, IPF and bronchiectasis. NEUROCOUGH CRC envisages fruitful collaborations with others within the ERS CRC family including but not limited to EMBARC (34), SHARP (35) and CADSET (36).

Conclusion

NEUROCOUGH CRC brings together for the first time clinicians, scientists, patients and industry to work in partnership with a vision to advance clinical management of chronic cough throughout Europe, enhance research capability and generate a framework for clinical trials. The purpose of this editorial is to inform and invite all who are interested in the field of cough to join us in achieving these goals.

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Members of the NEUROCOUGH CRC are:

Lorcan McGarvey (chair), Lieven Dupont (co-chair);

National Leads: Surinder S Birring (UK); Kian Fan Chung (UK); Maria Dabrowska (Poland); Christian Domingo (Spain); Giovanni Fontana (Italy); Laurent Guilleminault (France); Peter Kardos (Germany); Eva Millqvist (Sweden); Alyn H Morice (UK); Jacky Smith (UK); Jan William Van den Berg (Netherlands)

Early Career Member: Charlotte Van de Kerkhove (Belgium)

European Lung Foundation: Courtney Coleman, Jeanette Boyd

International Advisory Board: Ian Adcock (UK); Peter Dicpinigaitis (US); Piero Geppetti (Italy); Peter Gibson (Australia); Kefang Lai (China); Stuart Mazzone (Australia); Clive Page (UK); Ian Pavord (UK); Woo-Jung Song (S Korea)

References

1. Chung, KF & Pavord, ID. Prevalence, pathogenesis and causes of chronic cough. Lancet 2008;371,1364-137420.

2. Abdulqawi R, Dockry R, Holt K, Layton G, McCarthy BG, Ford AP, Smith JA. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. Lancet. 2015 Mar 28;385(9974):1198-205

3. Belvisi MG, Birrell MA, Wortley MA, Maher SA, Satia I, Badri H, Holt K, Round P, McGarvey L, Ford J, Smith JA. XEN-D0501, a Novel TRPV1 Antagonist, Does Not Reduce Cough in Refractory Cough Patients. Am J Respir Crit Care Med. 2017 [Epub ahead of print]

4. Morice AH. TRPA1 receptors in chronic cough. Pulm Pharmacol Ther. 2017 May 12

5. Morice AH, McGarvey L, Pavord ID, Higgins B, Chung KF, Birring SS.Theobromine for the treatment of persistent cough: a randomised, multicentre, double-blind, placebo-controlled clinical trial. J Thorac Dis. 2017;9(7):1864-1872

6. Smith JA, McGarvey LPA, Badri H, Satia I, Warren F, Siederer S, Liefaard L, Murdoch RD, Povey K, Marks-Konczalik J. Effects of a novel sodium channel blocker, GSK2339345, in patients with refractory chronic cough. Int J Clin Pharmacol Ther. 2017;55(9):712-719

7. Smith JA , Kitt MM, Morice AH , Birring SS , McGarvey LP , Sher MR , Ford AP. MK-7264, a P2X3 Receptor Antagonist, Reduces Cough Frequency in Patients with Refractory Chronic Cough: Results from a Randomized, Controlled, Phase 2b Clinical Trial. Am J Respir Crit Care Medicine 2017;195:A7608

8. Morice AH, Jakes AD, Faruqi S, Birring SS, McGarvey L, Canning B, Smith JA, et al; Chronic Cough Registry. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. Eur Respir J. 2014;44(5):1149-55

9. Chamberlain SA, Garrod R, Douiri A, Masefield S, Powell P, Bücher C, Pandyan A, Morice AH, Birring SS. The impact of chronic cough: a cross-sectional European survey. Lung. 2015;193(3):401-8

10. French CT, Diekemper RL, Irwin RS, et al; CHEST Expert Cough Panel. Assessment of Intervention Fidelity and Recommendations for Researchers Conducting Studies on the Diagnosis and Treatment of Chronic Cough in the Adult: CHEST Guideline and Expert Panel Report. Chest 2015;148(1):32-54

11. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J. 2016;47(2):410-9

12. Rennard, S. Decramer M, Calverley PM.et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. Eur Respir J 20, 799-805 (2002);

13. Kessler, R, Partridge MR, Miravitlles M et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J 2011; 37, 264-272

14. Smith, J, Woodcock, A. Cough and its importance in COPD. Int J of COPD 2006;1, 305-314

15. Polley, L, Yaman N, Heaney L et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. Chest 2008;134: 295-302.

16. Predictors of objective cough frequency in pulmonary sarcoidosis. Sinha A, Lee KK, Rafferty GF, Yousaf N, Pavord ID, Galloway J, Birring SS. Eur Respir J. 2016 May;47(5):1461-71)

17. Ryerson CJ, Abbritti M, Ley B et al. Cough predicts prognosis in idiopathic pulmonary fibrosis. Respirology. 2011;16(6):969-

18. Smith, S. M, Schroeder K, Fahey T.et al. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. Cochrane Database Syst Rev 11, (2014);

19. Chang CC, Cheng AC, Chang AB Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. Cochrane Database Syst Rev 3 (2014);

20. Dicpinigaitis PV. Cough: An unmet clinical need. Br J Pharmacol 2011;163:116-124.

21. Mazzone SB, Chung KF, McGarvey L. The heterogeneity of chronic cough: a case for endotypes of cough hypersensitivity. Lancet Respir Med. 2018;6(8):636-646.

22. Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. Lancet Respir Med. 2013 Jul;1(5):414-22

23. Morice AH, Millqvist E, Belvisi MG, Bieksiene K, Birring SS, Chung KF, Dal Negro RW, Dicpinigaitis P, Kantar A, McGarvey LP, Pacheco A, Sakalauskas R, Smith JA. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. Eur Respir J. 2014;44(5):1132-48

24. Undem BJ, Zaccone E, McGarvey L, Mazzone SB. Neural dysfunction following respiratory viral infection as a cause of chronic cough hypersensitivity. Pulm Pharmacol Ther. 2015 33: 52–56.

25. Ando A, Farrell MJ, Mazzone SB. Cough-related neural processing in the brain: a roadmap for cough dysfunction? Neurosci Biobehav Rev (2014) 47: 457–468.

26. Bonvini SJ, Birrell MA, Smith JA, Belvisi MG. Targeting TRP channels for chronic cough: from bench to bedside. Naunyn Schmiedebergs Arch Pharmacol. 2015 Apr;388(4):401-20

27. Chung, KF. NMDA and GABA receptors as potential targets in cough hypersensitivity syndrome. Curr Opin Pharmacol 22, 29-36, (2015);

28. Pacheco A, Domingo Ch. Airway reflux: an emerging topic in respiratory medicine. Lancet Respir Med 2018 Nov;6(11):810-812

29. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet. 2012;380(9853):1583-9

30. Kardos P, Dinh QT, Fuchs KH, Gillissen A, Klimek L, Koehler M, Sitter H, Worth H. Guidelines of the German Respiratory Society for Diagnosis and Treatment of Adults Suffering from Acute, Subacute and Chronic Cough. Pneumologie 2019; 73: 143-180.

31. Pacheco A, de Diego A, Domingo C, Lamas A, Gutierrez R, Naberan K, Garrigues V, López Vime R. Chronic Cough. Arch Bronconeumol 2015;51:579-89

32. Morice AH, McGarvey L, Pavord I; British Thoracic Society Cough Guideline Group. Recommendations for the management of cough in adults.Thorax. 2006;61 Suppl 1:i1-24

33. Recommendations for clinical practice: chronic cough in the adult]. Société Française d'ORL et de Chirurgie de la face et du cou. Rev Pneumol Clin. 2006;62(5):271-81.

34. Aliberti S, Polverino E, Chalmers JD, Altenburg J, Shteinberg M, Goeminne PC, Welte T, Shoemark A, Almagro M, Blasi F; EMBARC Clinical Research Collaboration. The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) ERS Clinical Research Collaboration. Eur Respir J. 2018 Nov 29;52(5). pii: 1802074. doi: 10.1183/13993003.02074-2018

35. Djukanovic R, Adcock IM, Anderson G, Bel EH, Canonica GW, Cao H, Chung KF, Davies DE, Genton C, Gibson-Latimer T, Hamerlijnck D, Heuvelin E, Louis R, Korn S, Kots M, Kwon N, Naddaf R, Wagers SS; SHARP Clinical Research Collaboration; Members of the CRC-SHARP. The Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) ERS Clinical Research Collaboration: a new dawn in asthma research. Eur Respir J. 2018 Nov 29;52(5). pii: 1801671. doi: 10.1183/13993003.01671-2018

36. Agusti A, Faner R, Donaldson G, Heuvelin E, Breyer-Kohansal R, Melén E, Maitland-van der Zee AH, Vestbo J, Allinson JP, Vanfleteren LEGW, van den Berge M, Adcock IM, Lahousse L, Brusselle G, Wedzicha JA; on behalf of the CADSET Clinical Research Collaboration; Current members of the CADSET Clinical Research Collaboration. Chronic Airway Diseases Early Stratification (CADSET): a new ERS Clinical Research Collaboration. Eur Respir J. 2019 Mar 18;53(3). pii: 1900217. doi: 10.1183/13993003.00217-2019

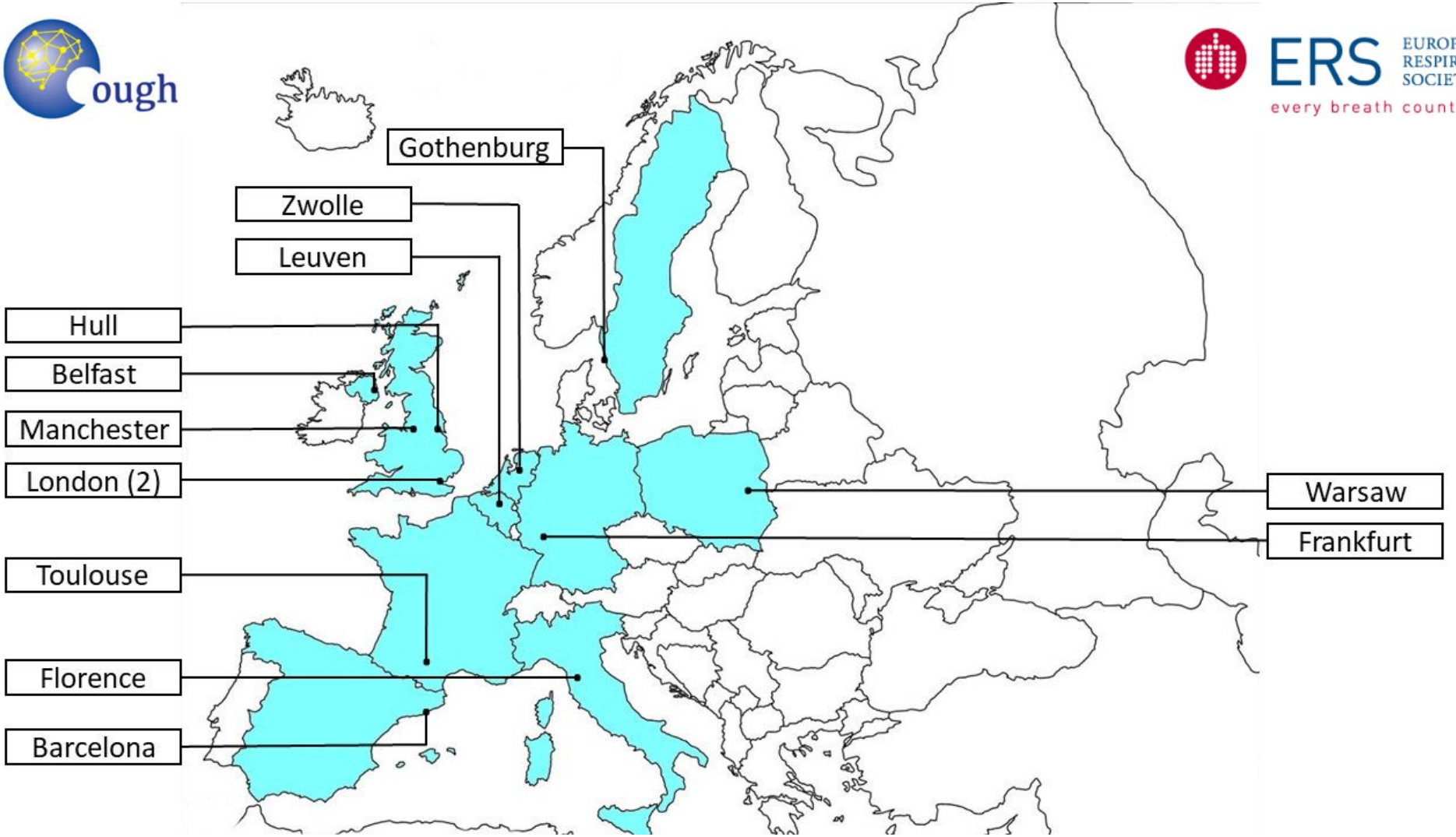

Figure 1: The NEw Understanding in the tReatment Of COUGH (NEUROCOUGH) CRC 1st wave Specialist Cough Centres participating in Europe-wide Registry of Chronic Cough patients

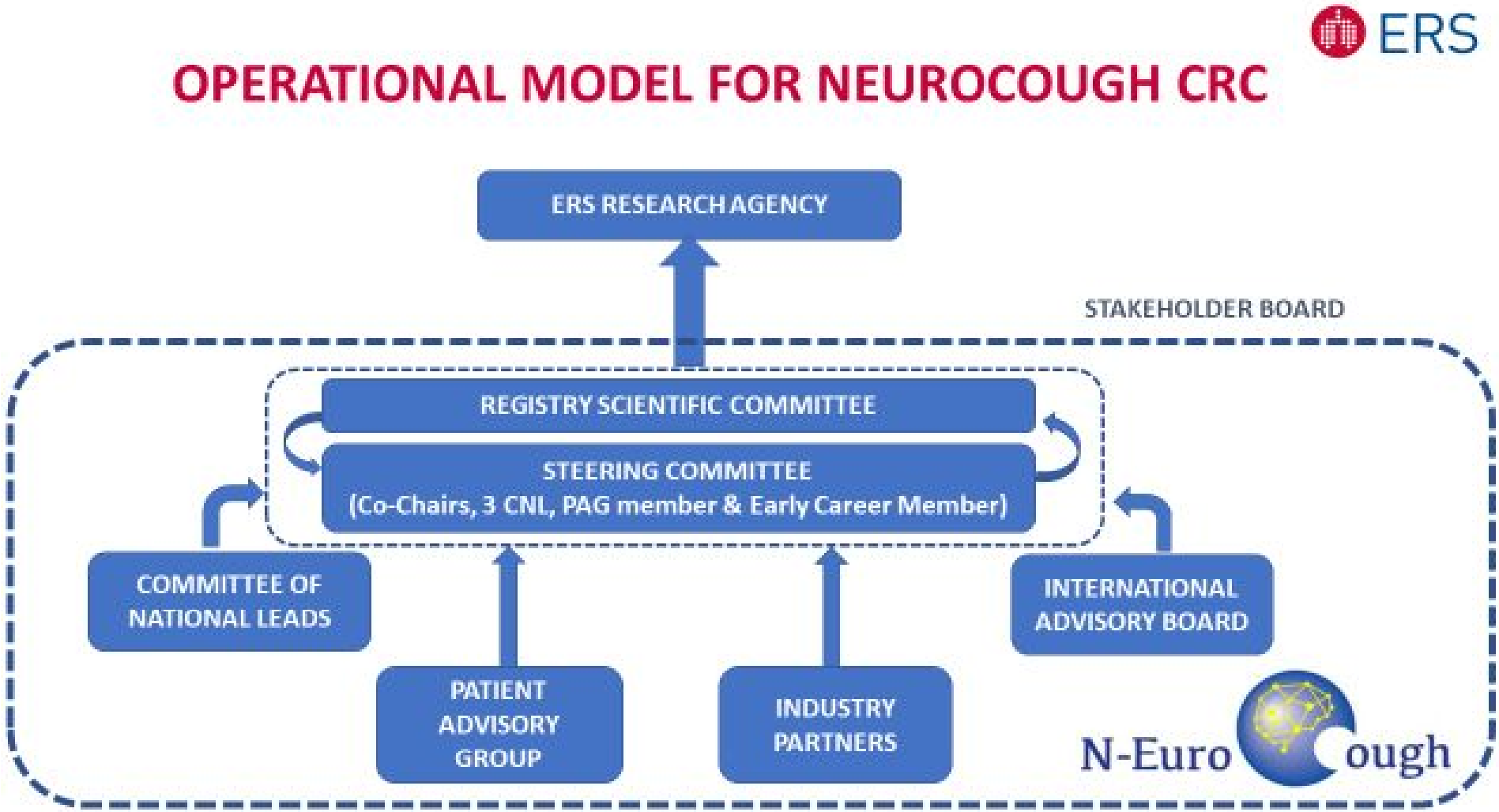

Figure 2. Structure of NEUROCOUGH Clinical Research Collaboration