PROTOCOL CHECKLIST

Required area	Included in protocol? Yes	No	If no, reason for omission
Study investigator team	X	☐	
Roles, responsibilities and resources	X	☐	
Funding statement	X	☐	
Objective, specific aims	X	☐	
Background and rationale	X	☐	
Study design	X	☐	
Study population, including estimate of expected or required patient number	X	☐	
Selection of comparison group(s) or controls	☐	X	**Descriptive study, no controls**
Exposures, outcomes and covariates	X	☐	
Data analysis	X	☐	
Approvals and registration	X	☐	
Limitations of the study design, data sources and analytic methods	X	☐	
Plans for disseminating and communicating study results, including proposed authorship	X	☐	

Please note, your protocol will be returned to you for completion if you do not provide a response to every item in this checklist and/or if you answer 'No' to any of the items without a justification for the omission.

REG STUDY PROTOCOL

TITLE (LONG): BURDEN OF COUGH IN UK PRIMARY CARE

TITLE (SHORT): BURDEN OF COUGH

REG Project code: REG-RES1701

Version no. 8.0
Date: 7th January 2018

Research Protocol developed by Lorcan McGarvey in collaboration with The Respiratory Effectiveness Group

CONTENTS PAGE

1. INVESTIGATION TEAM

Principle investigator
Name: Lorcan McGarvey
Affiliation: Queen's University Belfast
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Submitting / corresponding investigator and affiliation, if different from above:

Name:
Affiliation:
Contact email:

REG research lead
Name: Naomi Launders
Contact email: naomi@effectivenessevaluation.org

Steering committee

The steering committee will be responsible for oversight of the study, providing comment on the protocol, final report and dissemination materials. The members of the steering committee are all members of the REG cough working group.

Name	Organisation
Jacky Smith	University of Manchester
Alyn Morice	Hull University
Ian Pavord	University of Oxford
Surinder Birring	King's College London
Fan Chung	Imperial College London
Daryl Freeman	
John Haughney	
David Price	Optimum Patient Care

2. ROLES, RESPONSIBILITIES AND RESOURCES

Study phase	Responsibility	Estimated REG time requirement	Estimated PI time requirement	Indicative time line: Completion date
Initial study idea	PI	NA	NA	Month 0
Protocol development and approval	PI with input from REG lead and with steering committee sign off	12 days	3 days	Month 0
Funding and contracts	PI, REG CEO & OPC	1 day	1 day	Month 1
Data provision/collection	OPC in kind donation	1 day	NA	Month 2
Data analysis	REG lead	19 days	NA	Month 3
Final report	REG lead with input from PI and steering committee sign off	14 days	1 day	Month 5
Manuscript writing and submission	REG lead with input from PI and steering committee sign off	21 days	3 days	Month 7
Conference abstracts and presentations	PI, REG lead then steering committee	5 days	1 day	Dependent on conference schedules

3. FUNDING STATEMENT

It is proposed that this initial characterization study is unfunded, with potential for a funded follow up study.

2. AIM & OBJECTIVE

This study aims to determine the epidemiological pattern and characteristics of cough in UK primary care, and prescribed treatments. Specifically:

1) Prevalence and incidence of cough in UK primary care
2) Demographic and clinical characteristics associated with cough in UK primary care
3) Prescribed treatments for cough in UK primary care

3. BACKGROUND & RATIONALE

Cough was found to be the most common illness symptom for which patients sought medical attention, in the American National Ambulatory Medical Care Survey, 2006[1]. It is estimated that in the UK over £100 million is spent annually on over-the-counter remedies for the self-treatment of cough and cold symptoms (Proprietary Association of Great Britain, 2005)[3]. Cough can be categorised as acute or chronic; acute cough lasts less than three weeks while chronic cough is defined as a cough persisting for more than eight weeks.

Acute cough is a common occurrence usually seen with viral upper respiratory tract infections, where it is usually self-limiting. The seasonality of influenza-like illnesses means occurrences of acute cough in the general population will typical follow a seasonal pattern[2]. Acute cough can also occur due to bacterial infections, inhaled foreign bodies or toxic fumes, and in acute asthma or COPD exacerbations[2]. Cough can also be classed as subacute if it lasts 3-8 weeks, such coughs are typically post-viral or due to *Bordetella pertussis* (whooping cough)[3].

Chronic cough is one of the most common clinical problems encountered by doctors in both general and hospital practice[4] and is arbitrarily define as have a duration of more than 8 weeks. The most common causes of chronic cough in patients presenting to specialist cough clinics are asthma, gastroesophageal reflux disease and upper airway cough syndrome (previously termed postnasal drip syndrome)[5]. Chronic cough can often represent a significant problem for patients with pulmonary conditions, including chronic obstructive pulmonary disease, lung cancer, idiopathic pulmonary fibrosis and bronchiectasis, and in those with other non-pulmonary conditions, such as heart failure[2]. Chronic cough can be due to ACE inhibitor medication or due to occupational/environmental factors, including tobacco smoke[3]. However, in up to 20 % of referrals to cough clinics the cause of chronic cough remains unclear after extensive

investigations and treatment trials; in these patients' cough is considered unexplained or idiopathic[2]. Some causes of chronic cough can be effectively treated, with adequate doses of appropriate medication (e.g. such as a decongestant and an antihistamine to treat upper airway cough syndrome[6]) or discontinuation of ACE inhibitors/smoking[3,6]. However, in many cases, especially where no cause is found, chronic cough is extremely difficult to treat[2]. Chronic cough often persists for many months or years, and is associated with a significant impairment in health status; in a European survey of 1120 people with chronic cough the majority reported considerable impact on their daily-life activities, which often led to feeling fed-up and depressed[7]. There is still a lack of detailed understanding of the basic mechanisms underlying chronic cough and a need for more effective antitussives.

The epidemiology of cough has not been well studied; previous work has highlighted the large heterogeneity in cough, not only in its longevity, but also in the types of cough, e.g. dry, productive, nocturnal which vary geographically and with gender[8], and also demonstrated the need for further work in this area. Despite cough appearing to be prevalent in the community, there is a paucity of information regarding the extent of the problem and the different types of cough, particularly in general practice where most patients are managed. Indeed, little is known about how cough presents to primary care; in particular the patterns of attendance, investigations, treatments and subsequent outcomes have not been described. Understanding the burden of cough and its characteristics is the first step in improving both the understanding of the mechanisms of chronic cough and how its management might be optimised.

NEUROCOUGH (NEw Understanding of the tReatment Of COUGH) is a multi-disciplinary partnership bringing together world-leading researchers comprising of academic clinicians, scientists and pharmaceutical partners to improve the management of chronic cough. A core objective is to provide information on the demographic and epidemiological pattern of cough in a 'real life' patient setting, which to date has been overlooked. To achieve this, we will conduct a retrospective database study using the Optimum Patient Care Research Database (OPCRD) which is a large, longitudinal, primary care database of almost 4 million patients from ~600 UK general practices across England, Scotland, Wales, and Northern Ireland.

4. DATA SOURCE, STUDY DESIGN AND METHODOLOGY

Study design

This study will be a retrospective, observational analysis of electronic medical Records (EMR) from the Optimum Patient Care Research Database (OPCRD). It will provide an assessment of the epidemiological pattern and the burden of cough, in terms of the scale and characteristics of the problem, seen in UK general practice.

Data Source

The OPCRD is a large, longitudinal, primary care database comprising almost 4 million patients from over 600 UK general practices across England, Scotland, Wales, and Northern Ireland. OPCRD offers anonymised research quality data with a focus on respiratory disease, and the electronic medical records are complemented by patient reported data. Over the past 5 years the OPCRD has been used as a data source for over 50 publications.

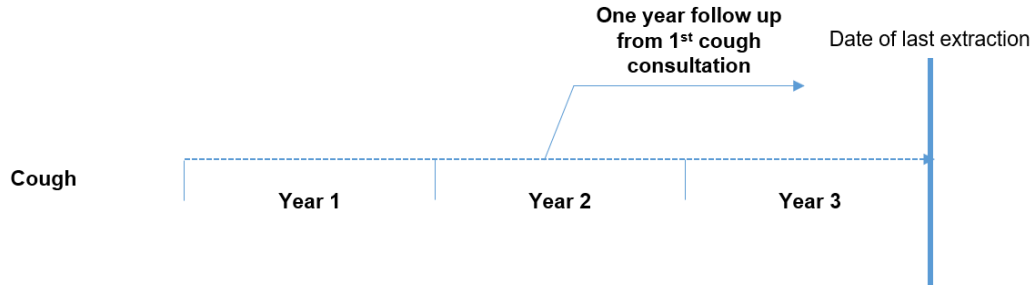
Study Period

The study period will cover index dates in the period from 1 January 2013 and 31 December 2017. Given that cough is frequently recorded in the database, the study period may be reduced to two years (1 January 2016 to 31 December 2017) if the dataset becomes unmanageable.

Evaluation Period

The study will consider the three years prior to last extraction for each patient, consisting of:

- An index date of first consultation of cough during the one year period from two years to one year prior to date of last extraction.
- A baseline characterisation period consisting of at least one year prior to index date.
- A one year follow up period after index date.



5. STUDY POPULATION

The population will be split into those with cough in the baseline period and those without.

Inclusion criteria

For inclusion in the study individuals must meet the follow criteria:

- Have at least one episode of cough in the one year period from two years to one year prior to date of last extraction
- Have three years of continuous EMR prior to the date of last extraction
- Aged 18 years or older at index date

Exclusion criteria

No additional exclusion criteria will be applied to ensure a broadly representative population that reflects the heterogeneous population treated in routine care.

6. MEASURES

Primary outcomes:

1) Burden of cough in the OPCRD, per year and cumulatively stratified by age and gender
   a) Incidence of patients with cough
   b) Number of cough consultations per patient in baseline and outcome period
   c) Time to second consultation for cough
2) Comparison of baseline characteristics in those with one cough episode and those with different patterns of cough consultations in baseline and/or outcome.
3) Categorisation of cough type (dry, productive, nocturnal etc) as determined by Read codes on index date, stratified by number of cough consultations in outcome period
4) Seasonal mapping of cough by type and frequency of consultation
5) Comparison of clinical characteristics and consultation frequency according to cough type

Secondary outcomes:

1) Categorisation of consultations and patients according to primary cause of cough (i.e. acute viral or bacterial infection/ respiratory comorbidity/ non-respiratory comorbidity/ idiopathic cough)
    a) Infective cough will be defined by the presence of fever index date or the presence of a Read code for respiratory tract infection. Those prescribed antibiotics in the week following diagnosis will be defined as bacterial and those without antibiotic prescriptions in the week following diagnosis as viral.
2) Healthcare utilisation and treatment, stratified by cough frequency in outcome
    a) Number of consultations with referrals to secondary care on index date and within seven days, split by referral type (inpatient/outpatient/A&E)
    b) Investigations carried out on index date and within seven days, two months and three months.
        i. X-ray
        ii. CT scans
        iii. GI endoscopies and testing
        iv. Lung function testing
        v. Fractional nitric oxide concentration (FeNO)
        vi. Referral to respiratory specialist
        vii. Referral to GI specialist
        viii. Referral to ENT specialist
    c) Treatment in the 28 days following index date
        i. Respiratory medications (ICS/SABA/SAMA/LABA/LAMA/Theophylline etc)
        ii. Antibiotics, split by class
        iii. Oral steroids
        iv. Allergy medication
        v. GERD medication
        vi. ACE inhibitors (including type)
        vii. Prescribed antitussives
3) Determination of chronic and acute cough
    d) Exploratory sensitivity analysis using a range of time intervals between consultations to better define “chronic” and “acute” cough in the OPCRD database.

Clinical characteristics

- Gender
- Age (5 yr bands)
- Geography, (by regions and by Office of National Statistics urban/rural classifications)
- Month and season of first instance of cough
- Smoking status
- Height
- Weight
- BMI
- Blood eosinophils
- Respiratory comorbidities (including date of diagnosis and split into before, on or after first instance of cough)
    - COPD (first instance)
    - Asthma (first instance)
    - IPF (first instance)
    - Bronchiectasis (first instance)
    - Lung cancer (first instance)
    - Rhinitis (first instance and if active in baseline or index date)
    - Other chronic respiratory conditions (first instance)
    - None
- Non-respiratory comorbidities (including date of diagnosis and split into before, on or after first instance of cough)
    - Ischemic Heart Disease (first instance)
    - Cardiovascular Heart Disease (first instance)
    - Heart failure (first instance)
    - GERD (first instance and if active in baseline or index date)
    - Eczema (first instance and if active in baseline or index date)
    - Depression & Anxiety (first instance and if active in baseline or index date)
    - Hypertension (first instance)
    - Diabetes (first instance)
    - Osteoporosis (first instance)
    - Chronic Kidney Disease (first instance)
    - Myocardial Infarction (first instance)
    - Cerebrovascular Disease (first instance)
    - Thyroid disorders (first instance and if active in baseline or index date)
    - Incontinence (first instance)
    - Menopause – as defined as Read code, presence of HRT and/or age (first instance)
    - None
- Charlson Comorbidity Index

7. DATA ANALYSIS AND STATISTICS

Descriptive statistics will be used for all outcomes.

The number of patients/observations and percentage per category, mean plus standard deviation and median plus inter-quantile range will be given, as appropriate.

Statistical testing will be used to explore the characteristics of those patients with different categories of cough, focusing on comparing those with idiopathic cough versus those were a cause of cough is determined. Statistical tests (e.g. F-tests, t-tests, chi-squared tests) and models (e.g. linear models) will be used, as appropriate.

Statistically significant results will be defined as $p<0.05$.

The analyses will be carried out using R (www.r-project.org).

Population size / power calculation:

Being descriptive, there is no formal sample size calculation in this study. The OPCRD database to be used for this study includes around 5.2 million patients. An initial search for cough suggest around 2 million patients with a Read code for cough.

8. APPROVALS & REGISTRATION

The OPCRD has been approved by Trent Multi Centre Research Ethics Committee for clinical research use, and this study protocol will be submitted to OPCRD's Anonymised Data Ethics Protocols and Transparency (ADEPT) Committee for approval to sanction the use of the OPCRD for the purposes of the proposed study. The study will be registered with European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), and we will apply for an ENCePP study seal.

9. LIMITATIONS OF STUDY DESIGN / ANALYSIS

A limitation of the study is that it will be conducted in a dataset comprising UK practice data only, which may limit its generalisability to non-UK cough patient populations treated in different healthcare settings. Moreover, although the OPCRD comprises records of patients drawn from a wide and heterogeneous range of UK practices (~600), the practices have not been specifically selected to be representative of the UK as a whole. As such, the findings of this study should be considered in conjunction with those of other study designs to ensure consideration of the full evidence base.

This study will also be limited by health-seeking behaviours. Not everyone with cough will seek medical treatment; certain groups will be more likely than others to access healthcare, for example women are more likely to access healthcare, so may be over represented in our data compared to men. Many patients may self-treat with over-the-counter treatments and so will not be included in the analysis.

10. DATA DISSEMINATION PLANS

Results of this study will be presented initially as a conference abstract, followed by a manuscript submitted to an appropriate peer-reviewed scientific journal within 12 months of completion of the study. The primary investigator an REG lead researcher will be lead authors on the resultant manuscript. The steering committee will be co-authors.

It is envisaged that the results of this project will feed into a second phase. The proposed phase II study is a cohort study comparing the clinical characteristics, healthcare utilisation and treatment of those with chronic cough, acute cough, and those not experiencing cough. A subgroup analysis of the chronic cough cohort will also be performed, comparing idiopathic cough with cough of a known cause.

12. REFERENCES

1) Cherry, DK et al. Natl Health Stat Report 3: 1–39. (2008)
2) Morice, AH et al. Thorax 61:1-24 (2006)
3) Dicpinigaitis, PV et al. Br. J. Pharmacol 163:116-124. (2011)
4) Chung, KF & Pavord, ID. Lancet 371, 1364-1374 (2008)
5) Morice, AH et al. Eur Respir J 24: 481-492 (2004)
6) Benich, JJ & Carek, PJ. American Family Physician 84:887-892 (2011)
7) Chamberlain, SA et al. Lung 193, 401-408 (2015)
8) Kauffmann, F & Varraso, R. Pul. Pharmacol. Ther. 24:289-294 (2011)

13. APPENDIX 1

Dummy tables

Primary outcome 1a: Incidence of at least one consultation for cough

	Crude		Age-standardised	
	Incidence	95% CI	Incidence	95% CI
Annual incidence				
2011				
2012				
2013				
2014				
2015				
2016				
Gender				
Females				
Males				
Age*				
18-29				
30-59				
60+				
Total				

*Exact grouping dependent on analysis

Primary outcome 1b: Number of cough consultations per patient

	Total		In baseline		In outcome	
	Median*	Interquartile range	Median*	Interquartile range	Median*	Interquartile range
Gender						
Females						
Males						
Age*						
18-29						
30-59						
60+						
Total						

*Measure of central tendency dependent on distribution

Primary outcome 1c: Time to second consultation of cough in outcome period

	n (%)
During 1 year follow up*, n(%)	
1 consultation	
2 consultations	
3 consultations	
4 consultations	
>4 consultations	
Time to subsequent consultation*, n(%)	
Under 1 week	
1-4 weeks	
4-10 weeks	
10+ weeks	

*Exact grouping dependent on analysis. Survival analysis will also be performed. Sub-analysis by "type of cough" (**Primary outcome 5d**) will also be investigated.

Displayed as a Kaplan-Meier plot

Primary outcome 2: Comparison of baseline characteristics in those with and without cough

	No cough	Cough	p-value
Gender (n [%] male)			
Age, n (%)			
18-24			
25-29			
30-34			
35-39			
40-44			
45-49			
50-54			
55-59			
60-64			
65-69			
70-74			
75-79			
80+			
Mean age, (SD)			
Region, n (%)			
North East			
North West			
Yorkshire & Humber			
East Midlands			
West Midlands			
East of England			
London			
South East			
South West			
Urban/Rural, n (%)			
Urban			
Major conurbation			
Minor conurbation			
City and town			
City and town (sparse)			
Rural			
Town and fringe			
Town and fringe (sparce)			
Village and dispersed			
Village and dispersed (sparce)			
Hamlets and isolated dwellings			
Hamlets and isolated dwellings (sparce)			
Smoking status, n (%)			
Smoker			
Ex-smoker			
Never smoked			
Missing			
Height (cm)			
Mean (SD)			
Missing, n (%)			
Weight (Kg)			
Mean (SD)			
Missing, n (%)			
Body mass index, n (%)			
Underweight			

Normal	
Overweight	
Obese class I	
Obese class II	
Obese class III	
Mean BMI, (SD)	
Respiratory comorbidities at baseline, n (%)	
COPD	
Asthma	
IPF	
Bronchiectasis	
Lung cancer	
Rhinitis	
Active	
Ever	
Other chronic respiratory conditions	
No respiratory comorbidities	
Non-respiratory comorbidities at baseline, n (%)	
Ischemic heart disease	
Cardiovascular disease	
Heart failure	
GERD	
Active	
Ever	
Eczema	
Active	
Ever	
Depression & Anxiety	
Active	
Ever	
Hypertension	
Diabetes	
Chronic kidney failure	
Myocardial infarction	
Cerebrovascular disease	
Thyroid disorders	
No non-respiratory comorbidities at baseline	
Charlson Comorbidity Index	
Median (IQR)	
Min/Max	
Score > 0, n (%)	

Primary outcome 2: Clinical characteristics before, at time of cough and in one year follow up

	Cough			**No cough**		
Diagnosed at:	Baseline	Index	Outcome	Baseline	Index	Outcome
Respiratory comorbidities, n (%)						
COPD						
Asthma						
IPF						
Bronchiectasis						

Lung cancer
Rhinitis
Active
Ever
Other chronic respiratory conditions
No respiratory comorbidities
Non-respiratory comorbidities, n (%)
Ischemic heart disease
Cardiovascular disease
Heart failure
GERD
Active
Ever
Eczema
Active
Ever
Depression & Anxiety
Active
Ever
Hypertension
Diabetes
Chronic kidney failure
Myocardial infarction
Cerebrovascular disease
Thyroid disorders
No non-respiratory comorbidities at baseline

Primary outcome 3: Comparison of baseline characteristics in those with a single cough consultation with those with cough in baseline or outcome

	Single episode	Cough in baseline	Cough in outcome	p-value
Gender (n [%] male)				
Age, n (%)				
18-24				
25-29				
30-34				
35-39				
40-44				
45-49				
50-54				
55-59				
60-64				
65-69				
70-74				
75-79				
80+				
Mean age, (SD)				
Region, n (%)				
North East				
North West				
Yorkshire & Humber				
East Midlands				
West Midlands				
East of England				
London				
South East				
South West				
Urban/Rural, n (%)				
Urban				
Major conurbation				
Minor conurbation				
City and town				
City and town (sparse)				
Rural				
Town and fringe				
Town and fringe (sparce)				
Village and dispersed				
Village and dispersed (sparce)				
Hamlets and isolated dwellings				
Hamlets and isolated dwellings (sparce)				
Smoking status, n (%)				
Smoker				
Ex-smoker				
Never smoked				
Missing				
Height (cm)				
Mean (SD)				
Missing, n (%)				
Weight (Kg)				
Mean (SD)				
Missing, n (%)				

Body mass index, n (%)
Underweight
Normal
Overweight
Obese class I
Obese class II
Obese class III
Mean BMI, (SD)
Respiratory comorbidities at baseline, n (%)
COPD
Asthma
IPF
Bronchiectasis
Lung cancer
Rhinitis
Active
Ever
Other chronic respiratory conditions
No respiratory comorbidities
Non-respiratory comorbidities at baseline, n (%)
Ischemic heart disease
Cardiovascular disease
Heart failure
GERD
Active
Ever
Eczema
Active
Ever
Depression & Anxiety
Active
Ever
Hypertension
Diabetes
Chronic kidney failure
Myocardial infarction
Cerebrovascular disease
Thyroid disorders
No non-respiratory comorbidities at baseline
Charlson Comorbidity Index
Median (IQR)
Min/Max
Score > 0, n (%)

Primary outcome 3: Clinical characteristics before, at time of cough and in one year follow up in those with a single and multiple cough consultations

	Single cough episode			Multiple cough episodes		
Diagnosed at:	Baseline	Index	Outcome	Baseline	Index	Outcome
Respiratory comorbidities, n (%)						
COPD						
Asthma						
IPF						
Bronchiectasis						
Lung cancer						
Rhinitis						
Active						
Ever						
Other chronic respiratory conditions						
No respiratory comorbidities						
Non-respiratory comorbidities, n (%)						
Ischemic heart disease						
Cardiovascular disease						
Heart failure						
GERD						
Active						
Ever						
Eczema						
Active						
Ever						
Depression & Anxiety						
Active						
Ever						
Hypertension						
Diabetes						
Chronic kidney failure						
Myocardial infarction						
Cerebrovascular disease						
Thyroid disorders						
No non-respiratory comorbidities at baseline						

Primary outcome 4: Type of cough as determined by Read code*

	Single cough episode	Multiple cough episodes
Dry		
Productive		
Chronic		
Reflux		
Croupy/brassy/bovine/barking		
Allergic		
Exercise related		
Nocturnal		
Morning		
Evening		
Spasmodic		
Effective		
Painful		
With fever		
Psychogenic		
Bronchial		
Chesty		
Smokers'		
Whooping cough		
Coughs up sputum		
Coughs up blood		
Unspecified		

*It is likely that many of these will have small numbers and therefore be grouped as "other".

Primary outcome 5: Seasonality of cough*

Month, n(%)	Any cough	Infectious cough	Non-infectious cough
January			
February			
March			
April			
May			
June			
July			
August			
September			
October			
November			
December			
Season, n(%)			
Winter			
Spring			
Summer			
Autumn			
Year, n(%)			
2011			
2012			
2013			
2014			
2015			

2016	

*Other comparisons will be made depending on the results and how cough is grouped.

Primary outcome 6: Clinical characteristics and consultation frequency according to cough type

	Any cough	Infectious cough	Non-infectious cough
During 1 year follow up*, n(%)			
1 consultation			
2 consultations			
3 consultations			
4 consultations			
>4 consultations			
Time to subsequent consultation*, n(%)			
Under 1 week			
1-4 weeks			
4-10 weeks			
10+ weeks			

*Other comparisons will be made depending on the results and how cough is grouped.

Secondary outcome 1: Categorisation according to primary cause

	Single cough episode	Multiple cough episodes
Infectious		
By Read code		
Prescribed antibiotics		
Presence of fever		
Exacerbation of chronic condition		
Asthma		
COPD		
Other		
Comorbidity likely cause		
Asthma		
COPD		
GERD		
Smoking		
Allergy		
Idiopathic		

Secondary outcome 2: Healthcare utilisation

	Single cough episode	Multiple cough episodes
Referral to secondary care, n (%)		
In patient		
Out patient		
Accident and Emergency		
Investigations on first instance of cough		
X-ray		
CT scan		

GI endoscopies and testing	
Lung function testing	
Fractional nitric oxide testing (FeNO)	
Referral to respiratory specialist	
Referral to GI specialist	
Treatment in the 28 days prior to cough	
Respiratory medications	
ICS	
SABA	
SAMA	
LABA	
LAMA	
Theophyline	
Other	
Antibiotics*	
	Penicillins
	Tetracyclines
	Macrolides
	Other
Oral steroids	
Allergy medication	
GERD medication	
Ace inhibitors	
Prescribed antitussives	

*Antibiotics listed will depend on numbers in each group.