CLINICAL STUDY PROTOCOL

A CROSS-SECTIONAL STUDY TO MEASURE COUGH IN SEVERE ASTHMA.

Sponsors: **Queen's University Belfast**

Version of Protocol: 11
Date of Protocol: 12/12/2018

Protocol Approval – Principal/Coordinating Investigator

Study Title A cross-sectional study to measure cough in severe asthma

Protocol Number 11
Protocol Date 12/12/2018

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Abbreviations

Abbreviation	Definition
ACQ	Asthma Control Questionnaire
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
BMI	body mass index
BTS	British Thoracic Society
CCL	chemokine ligand
CQLQ	Cough specific quality of life questionnaire
CT	computed tomography
CRF	case report form
ERS	European Respiratory Society
FAS	Full-analysis set
FeNO	fractional exhaled nitrous oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
ICF	informed consent form
ICS	inhaled corticosteroids
LCM	Leicester Cough Monitor
LCQ	Leicester Cough Questionnaire
MiniAQLQ	Mini asthma quality of life questionnaire
EC	Ethics committee
Ig	immunoglobulin
IL	interleukin
LABAs	long-acting β-2 agonists
OCS	oral corticosteroids
OTC	over the counter
PRO	patient-reported outcome
SABAs	short-acting β-2 agonists
SAP	Statistical analysis plan
T2	Type-2 eosinophilic inflammation
TB	tuberculosis

1.0 Background

1.1 Cough and Asthma

Asthma is a respiratory disease that affects 1-18% of the worldwide population. It is characterised by a collection of symptoms which include shortness of breath, chest tightness, wheeze and cough and by variable expiratory airflow limitation. These usually tend to vary over time and in intensity and can be triggered by a range of stimuli.(1) The condition is typically recognised as one that consists of periodic exacerbations coupled with chronic inflammation of the airways with or without structural airway changes. This may also be associated with persistent symptoms and a reduced lung function.(2)

Asthma has been traditionally 'stratified' on the basis of response to 'step-wise' incremental treatment with inhaled corticosteroid (ICS) therapy forming the cornerstone of this approach (1,3). However, more recently, asthma has been stratified on the basis of inflammatory phenotype to better understand disease heterogeneity with a view to developing biomarkers of therapeutic response and for the better targeting of both new and existing treatments (4,5). Using sputum analysis (5,6), and more recently whole genome expression profiling (4), it is clear that even in mild steroid-naive asthma, approximately 50% of patients do not have a typical Type 2 (T2)-driven eosinophilic inflammation, and are called 'T2-low asthma'. Perhaps more significantly, based on the normal diagnostic criteria for asthma, this T2 low group is indistinguishable from the typical 'T2-high'/eosinophilic group. In the context of therapeutic response, the T2-low patients have a minimal response to ICS therapy (5,6). In severe disease, the T2-low profile is also prevalent (7,8), and in case series of difficult-to-treat patients with asthma, there is evidence that inappropriate escalation of corticosteroid treatment is frequent, with significant morbidity due to systemic corticosteroid exposure (9-11). The RASP-UK programme is exploiting the use of composite biomarkers of T2 biology to define patient sub-groups using easily measurable biomarkers (blood eosinophil count, fractional exhaled nitric oxide (FeNO) and serum periostin) (http://www.rasp.org.uk/)

Despite its troublesome occurrence in disease, cough is important in normal human health in maintenance of the respiratory system. Its role in removal of foreign material and in enhancing mucociliary clearance helps to protect the airways when stimulated by extrinsic factors or in the presence of disease.(12) Cough becomes disordered in asthma and is thought to be due to the associated inflammation in the lungs, which causes sensitisation of cough reflexes and can lead to upsetting attacks of cough due to minimal stimulation or changes in the environment.(13)

Cough is one of the main reported symptoms in asthma. Although symptoms such as wheeze and shortness of breath may be more prevalent in the condition, cough in asthmatic patients is often described as the most problematic.(14) It is therefore surprising that although there are a number of tools available to aid in management of cough (15), there has been little consideration given to the assessment how severe a patient's cough is in asthma.

When a patient's cough is poorly controlled, it tends to drive escalation of corticosteroid therapy. This is not always appropriate and often fails to achieve adequate disease control and often unnecessarily exposes patients to the unacceptable side effects of high dose corticosteroid therapy. A novel approach has been developed to manage patients

and their treatment based on individual inflammatory biomarker profiles. Only half of patients with asthma have typical eosinophilic airway inflammation driven by 'Type 2' cytokines (interleukin IL-4, IL-5 and IL-13). In severe asthma, this proportion drops to between 25-50%. For the remainder of patients there is little evidence that T2 cytokines play a major role in their condition and so respond less well to steroid therapy. These patients have been termed 'T2-Low'.

Therefore, it is important to accurately define how cough is related to the clinical and biological phenotypes in asthma.

1.2 Study Rationale

We hypothesise that cough represents a significant burden in severe asthma which can be defined using subjective and objective cough measures. It is also hypothesised that cough morbidity is over-represented in the T2-low severe asthma population and this may represent mechanistic pathways that are suitable for exploitation for novel anti-tussive drug discovery.

This study will use a combination of subjective and objective cough measures to assess the frequency of cough as well as its related morbidity in severe asthmatics. Comparisons will be made between T2-High, T2-Low and T2-intermediate patients defined using a composite biomarker profile (blood eosinophil count and FeNO) to assess the role of cough in each and these results will be compared to the transcriptomic and proteomic measurements in the RASP-UK where the same biomarker profiling is being used to define clinical sub-groups of severe asthma. This study aims to also improve characterisation of the T2-Low population and identify possible mechanisms for the pathophysiology of this group.

A population of patients will be assessed after screening at a single visit to enable the summary of clinical characteristics and allow these data to be related to the biomarkers measured in serum, plasma and sputum.

Four patient groups will be investigated in the study and will be defined as follows:

Group A
T2-High Severe Asthmatics
- Persistent blood eosinophil count ≥0.3x10^9/mL **and**
- Persistent high FeNO levels ≥30 ppb) **and**
- Adherence to inhaled and oral corticosteroid therapy

Group B
T2-Low Severe Asthmatics
- Persistent blood eosinophil count ≤0.2x10^9/Ml **and**
- Persistent low FeNO levels (<30ppb)

These measurements are undertaken routinely at each clinic visit at the Difficult Asthma Service in Belfast HSC Trust.

Group C
Mild/moderate Asthmatics

- mild/moderate severe asthmatics (defined as step 2/3 using the GINA classification of severity) recruited from general respiratory clinics in the Belfast HSC Trust

Group D
T2 – intermediate
- Persistent blood eosinophil count ≥ $0.3x10^9$/mL OR
- Persistent FeNO levels ≥ 30 ppb

We believe that these patient groups will show differences in their cough frequency and severity and this novel research may provide information that will help to further characterize these phenotypes in the future. We believe that cough as a symptom in asthma is independent of Type-2 inflammation pathways and so further research into this symptom may help to uncover alternative pathways driving the condition. We aim to understand cough in relation to specific biomarkers in this population and how differences in cough frequency and severity relates to them. It is important to understand the nature of cough in these patients and how it changes in response to treatment.

2.0 Objectives

2.1 Primary Objectives

The primary objectives for this study are as follows:

- To objectively measure cough frequency in different phenotypes of severe asthma (T2-high, T2-low and T2-intermediate) and a mild/moderate asthma control group using a validated ambulatory cough monitor (Leicester Cough Monitor)

- To objectively measure cough reflex sensitivity in different phenotypes of severe asthma and a mild/moderate asthma control group using citric acid cough challenge testing

- To subjectively measure cough severity and quality of life in different phenotypes of severe asthma and a mild/moderate asthma control group using the Leicester cough questionnaire (LCQ), Cough Quality of life Questionnaire (CQLQ) and visual analogue scales

2.2 Exploratory Objectives

The exploratory objectives for this study are as follows:

- To determine the relationship between objective and subjective measures of cough and established biomarkers of asthma severity and symptom control including sputum eosinophils (as defined by % eosinophils), blood eosinophil count, FeNO (ppb), lung

function (FEV1), and Asthma Control Questionnaire (ACQ-5).

- Exploratory analysis will be undertaken to determine the relationship between the objective and subjective cough measures, biomarker profile and transcriptomic and proteomic measurements in blood and urine samples from severe asthma patients using learning from the RASP-UK programme in relevant stored samples.
- Reproducibility of objective and subjective measures of cough in a severe asthma population will also be explored.

2.3 Description of Study

This is a cross-sectional study, in patients aged 18 to 75 years (inclusive), with severe asthma, as defined by the GINA step 4/5 classification of asthma severity (1). Prior to screening, patients will have been assessed using a systematic protocol to exclude other causes of apparently uncontrolled asthma (16). It is expected that approximately 60 patients will be enrolled at the study centre. Following review after clinical attendance, patients will be invited to take part in the study and attend for a screening visit. Patients will be provided with an information sheet and have a telephone follow-up after at least 24 hours to ask if they remain interested in participation and if so, they will then be asked back for a baseline visit.

3.0 Patient and Methods

3.1 Patients with severe asthma (Groups A, B and D)

The study will recruit patients aged 18 to 75 years, inclusive, with severe OCS-dependent asthma (GINA step 5 classification of asthma severity).

3.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Ability and willingness to comply with the study procedures
2. Age ≥18 to ≤75 years at the time of informed consent
3. Severe asthma (as defined by GINA step 4/5 classification of asthma severity) after a detailed systematic assessment
4. History of asthma treatment with high doses of ICS (≥1000 µg beclomethasone dipropionate daily, or equivalent) and an additional controller
5. Three patient groups with severe asthma will be investigated in the study and will be defined as follows:

T2-High Severe Asthmatics (Group A)

- Persistent blood eosinophil count ≥0.3x10^9/mL **and**
- Persistent high FeNO levels ≥30 ppb **and**

- Adherence to inhaled and oral corticosteroid therapy

T2-Low Severe Asthmatics (Group B)
- Persistent blood eosinophil count ≤0.2x10^9/Ml **and**
- Persistent low FeNO levels (<30ppb)

T2 – Intermediate Severe Asthmatics (Group D)
- Persistent blood eosinophil count ≥ 0.3x10^9/mL OR
- Persistent FeNO levels ≥ 30 ppb

As stated above, these measurements are made at each clinic visit as part of routine care and will be available on all subjects prior to Inclusion

6. A chest x-ray or CT scan obtained within 12 months before the time of informed consent and showing no new pathology requiring investigation as a potential cause for their cough

3.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Baseline FEV1 ≤50% of predicted or ≤ 1.0L
2. Asthma exacerbation within 28 days before the time of informed consent or during Screening
3. Major episode of infection requiring any of the following:
   - Admission to hospital for ≥24 hours within the 28 days before the time of informed consent
   - Treatment with intravenous antibiotics within the 28 days before the time of informed consent or during Screening
   - Treatment with oral antibiotics within the 14 days before the time of informed consent or during Screening
4. For adults: Active tuberculosis (TB) requiring treatment within the 12 months before the time of informed consent (patients are also required to have no recurrence of symptoms in the 12 months following completion of TB treatment), or
5. Known history of severe clinically significant immunodeficiency, including, but not limited to, human immunodeficiency virus infection and/or currently receiving or have historically received intravenous Ig for treatment for immunodeficiency

   Note: Immunodeficiency encompasses a wide spectrum of human conditions and/or diseases. A relative IgG deficiency that is thought, but not proven, to be a feature of severe asthma would not be exclusionary for the study.
6. Diagnosis or history of malignancy, or current investigation for possible malignancy
7. Other clinically significant medical disease that is uncontrolled despite

treatment or that is likely, in the opinion of the investigator, to require a change in therapy or affect the ability to participate in the study

8. History of alcohol, drug, or chemical abuse that would impair or risk the patient's full participation in the study, in the opinion of the investigator
9. Current smoker or former smoker with a smoking history of >15 pack-years

   A current smoker is defined as someone who has smoked one or more cigarettes per day (or marijuana or pipe or cigar) for ≥30 days within the 24 months before the time of informed consent and for whom cotinine testing is positive.

   A former smoker is defined as someone who has smoked one or more cigarettes per day (or marijuana or pipe or cigar) for ≥30 days in his or her lifetime (as long as the 30-day total did not include the 24 months before the time of informed consent) and for whom cotinine testing is negative.

   A pack-year is defined as the average number of packs per day times the number of years of smoking.
10. Initiation of or change in allergen immunotherapy within three months before the time of informed consent
11. Treatment with an investigational agent within 30 days of informed consent or 5 half-lives of the investigational agent, whichever is longer
12. Female patients who are pregnant or lactating

3.2 Control Population (Group C)

Mild/moderate severe asthmatics (who have received a diagnosis of asthma from a physician and are defined as step 2/3 using the BTS/SIGN classification of severity and ACQ<1.5) aged 18-75 years inclusive will be recruited from general respiratory clinics in the Belfast HSC Trust. Patients must have the ability and willingness to comply with study procedures.

Patients within this population will also be recruited through selected General Practice surgeries. Patients attending general asthma review clinics within their surgery will be approached by practice nurses and informed about the study and given the appropriate study information (patient information sheet, invitation letter from GP surgery etc). Patients may then contact the study coordinator if interested in taking part in the study.

Exclusion criteria for this group is as detailed in section 3.1.2.

3.3 Study Assessments

3.3.1 Baseline study visit

Following written informed consent participants will undergo the following baseline study procedures:

- Demographic details, height, weight, spirometry, FeNO and vital signs

- Patient reported outcomes:
    - Asthma Mini-Asthma Quality of Life Questionnaire (mini-AQLQ) - abbreviated version of Juniper AQLQ
    - Asthma Control Questionnaire (ACQ-5 (5 questions);
    - Leicester Cough Questionnaire, the Cough-specific quality-of-life Questionnaire and Cough Hypersensitivity Questionnaire will be used to assess the impact of cough;
    - Visual analogue scales (VAS) for cough (VASc) and urge to cough (VASu) will be used as a measure of cough severity.

- Blood samples – a sample of blood will be taken for whole blood transcriptomic and serum analyses (see section 4.3.6.1 below)
- Citric acid cough challenge test will be used to measure cough reflex sensitivity in each phenotype.
- Spontaneous sputum sample - if patients produce a sputum sample during spirometry or citric acid challenge, this will be recorded and the sample will be retained for sputum differential cell count and storage of processed soluble components.
- On completing the above procedures, patients will be asked to wear a validated ambulatory cough monitor (Leicester Cough Monitor) for a 24-hour period to assess the frequency of cough and if they agree, will be fully instructed in its use.

All assessments to be performed during the study are summarised in Table 3.1.

3.3.2 Follow-up visit

The follow-up visit will be performed 2 weeks after the baseline visit and is to assess reproducibility of cough measurements (objective and subjective) in this patient group.

The following procedure will be performed:

- FeNO
- Patient reported outcomes:
    - Asthma Mini-Asthma Quality of Life Questionnaire (mini-AQLQ) - abbreviated version of Juniper AQLQ
    - Asthma Control Questionnaire (ACQ-5 (5 questions 1 minute);
    - Leicester Cough Questionnaire, Cough-specific quality-of-life Questionnaire and Cough Hypersensitivity Questionnaire will be used to assess the impact of cough;
    - Visual analogue scales (VAS) for cough (VASc) and urge to cough (VASu) will be used as a measure of cough severity.
- Citric acid cough challenge test will be used to measure cough reflex

sensitivity in each phenotype.

On completing the above procedures, patients will be asked to wear a validated ambulatory cough monitor (Leicester Cough Monitor) for a 24-hour period to assess the frequency of cough and if they agree, will be fully instructed in its use.

All assessments to be performed during the study are summarised in Table 1.

Table 1 Schedule of Assessments

	Visit 1[a] (N=60)	**Visit 2 (N=25)**
	DAY	
	0	15
Informed consent	X	
Patient eligibility (inclusion/exclusion criteria)	X	
Demographic data	X	
General medical history and baseline conditions	X	
Weight	X	
Height	X	
AE assessments	X	X
Pregnancy test [b], where appropriate	X	
Concomitant medications	X	
Patient-reported outcomes		
ACQ-5	X	X
Mini AQLQ	X	X
LCQ	X	X
CQLQ	X	X
VASc and VASu	X	X
Cough Hypersensitivity Questionnaire	X	X
Objective measurements		
FeNO	X	X
Cough Frequency (LCM)	X	X
Citric acid cough challenge	X	X
Physical Examination	X	
Vital sign measurements	X	
Serum for periostin	X	
Serum for biomarker[c]	X	
Plasma for biomarker[d]	X	
Heamatology (blood eosinophil and neutrophil count)	X	
Serum Chemistry	X	
Urine Sample	X	
Plasma and serum sample for storage	X	
Spontaneous sputum sample	X	

[a] Baseline visit should not take place on a Friday

[b] After informed consent

[c] including but not limited to asthma related biomarkers described in the body of the protocol i.e. CCL13, CCL17, CCL18, IgE, IL17A)

[d]Asthma related biomarkers that cannot be measured in serum or are better measured in plasma (eg CXCL13, CXCL1)

3.4 Medical History, Concomitant Medications and Demographic Data

Medical history is defined as clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, and use of alcohol and drugs of abuse within the past year. All medications (e.g. prescription drugs, over-the-counter (OTC) drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 90 days before the screening visit will be recorded as part of the patient's medical history. Medical history will include specific information pertaining to diseases commonly associated with asthma such as but not limited to the following: allergic rhinitis, atopic dermatitis, type 2 diabetes mellitus, arthritis osteoporosis, and heart disease. Demographic data will include age (date of birth), sex, and self-reported race/ethnicity.

3.4.1 Vital Signs

Vital signs will include measurements of oral body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position having rested for approximately 10 minutes before measurements are performed. All measurements completed with standard clinical procedures. Vital signs will be measured at the time points shown in Table 3.1.

3.4.2 Physical Examinations

A complete physical examination at Screening and Visit 1 will include, but is not necessarily limited to, the following: an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified during screening should be recorded on the general medical history and baseline conditions page in a paper CRF which will then be transferred onto a study database.

3.4.3 Height and Weight Measurements

Height and weight measurements will be recorded at the time points shown in Table 4–1. Patients will be asked to remove their shoes and coats before measurements are taken.

3.5 Asthma-Related Assessments

3.5.1 Spirometry

Spirometry, including the procedure for bronchodilator testing, will be conducted as per the BTS registry standards and according to the ATS/European Respiratory Society (ERS) Consensus Statement (Clausen and Wanger 2003). Spirometric measurements to be collected will include FEV_1 and FVC values (volume, L) and peak expiratory flow values (L/min) in addition to the flow-volume and volume-time curves. The percent-predicted FEV_1 and FVC will be derived from these volume measurements using the equations derived from the National Health and Nutrition Examination Survey data set (Hankinson et al 1999).

3.5.2 Fractional Exhaled Nitric Oxide

Measurement of FeNO will be performed with a standard device in accordance with guidelines published by the ATS. Patients will be assessed with the same system at each visit.

3.5.3 Spontaneous Sputum

Sputum induction will be performed according to the individual routine protocol at the study centre. The following is a description of the procedure; the patient will have an FEV_1 measurement as per ATS guidelines (this will be the Baseline measurement). All patients will be asked to blow their noses and rinse their mouths thoroughly prior to being asked to cough into a sputum jar. If spontaneous expectoration results in a good quality sputum sample, the procedure is considered complete. Inability to provide a spontaneous sputum sample is not an exclusion criterion. Sputum will be processed (ideally within 1 hour) according to standard procedures as described in the study manual provided and a differential count will be obtained.

3.5.4 Laboratory Assessments

Laboratory assessments will be completed at the time points shown in Table 4–1.

3.5.4.1 Blood Sample

A blood sample will be taken on study visit 1 for exploration of the biomarkers listed below. A total of 70ml (approximately 4 tablespoons) of blood will be taken at study visit 1 and will not be repeated at any follow up visit. These samples will be stored for a maximum of 10 years after all study data has been collected and may be used in the future for more research related to asthma. The data resulting from the stored samples will be kept confidential.

3.5.4.2 Samples for Biomarkers

The following dynamic biomarker specimens will be collected for exploration of biomarkers. These biomarkers can include, but are not limited to, biomarkers related to asthma, IL13, periostin, eosinophilic airway inflammation, corticosteroid signaling and putative inflammatory pathways in severe steroid dependent asthma and cough hypersensitivity

- Serum (e.g. CCL-13, CCL-17, CCL-18, IgE, IL 17A)
- Plasma (e.g. CXCL1), serum Interleukin (IL)-1beta, IL-6, tumor necrosis factor (TNF)-alpha, IL-8,
- neurotrophins e.g. brain derived neurotrophic factor (BDNF), nerve growth factor (NGF) (e.g. BDGF, NGF)
- sputum Interleukin (IL)-1beta, IL-6, tumor necrosis factor (TNF)-alpha, IL-8, and

Samples will be transferred to Queen's University Belfast under the standard BSHCT MTA. Specimens will be taken and stored in line with the authorised use of specimens as specified in this protocol and in the informed consent form.

Samples will be destroyed no later than 10 years after the date of final closure of the associated clinical database. The storage period will be in accordance with applicable laws (e.g., health authority requirements).

3.5.5 Objective Cough Measurement

Cough frequency will be measured in patients using a validated ambulatory cough frequency monitor. This will allow comparisons of cough frequency to be made between different asthma phenotypes based on objective measurements. The monitor will be distributed to patients following other study assessments and patients will be asked to wear the monitor for a set period of time in order to gather the relevant data.

3.5.5.1 Leicester Cough Monitor (LCM)

The LCM is a validated ambulatory cough frequency monitor that will allow the measurement of cough frequency in distinct asthma phenotypes over a period of 24-hours. Distribution of the LCM will take place as per the schedule of assessments (Table 4–1).

3.5.5.2 Citric Acid Cough Challenge

The Citric Acid Cough Challenge will be used to assess the cough reflex sensitivity in each phenotype and will be performed as per the study centre’s protocol. The cough challenge will take place as per the schedule of assessments (Table 4–1).

3.5.6 Patient-Reported Outcomes

Patient-reported outcome (PRO) data will be requested from the patients to assess the level of asthma control and the impact of cough. The PRO instruments, translated as required in the patient’s primary language, will be distributed by the asthma study staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the study before the completion of other study assessments.

3.5.6.1 Mini Asthma Quality of Life Questionnaire

The mini-AQLQ (Appendix 8.1) will be used to assess the patients’ asthma-specific health-related quality of life (Juniper et al 2005). The

questionnaire contains four domains: activity limitations, symptoms, emotional function, and environmental stimuli. The mini-AQLQ has been validated for use in this study population and has a recall specification of 2 weeks. The mini-AQLQ will be administered to the patient before all other non-PRO assessments and before the patient receives any disease-status information during that assessment. The mini-AQLQ will be completed as per the schedule of assessments (Table 4–1).

3.5.6.2 Asthma Control Questionnaire - 5

Asthma control will be measured by the ACQ-5 (Appendix 8.2) (Juniper et al 1999).This is a fully validated measurement tool that can detect small differences between patients with different levels of asthma control. The ACQ-5 will be completed before the Mini-AQLQ

3.5.6.3 Leicester Cough Questionnaire (LCQ)

The Leicester Cough Questionnaire (Appendix 8.3) is a valid, repeatable 19 item self-completed QOL measure of chronic cough that is responsive to change. This tool assesses cough related QOL in three domains: Physical, Psychological and Social. This will allow for the measurement of QOL in relation to cough and for comparisons to be made between asthma phenotypes. The LCQ will be administered to the patient before all other non-PRO assessments and before the patient receives any disease-status information during that assessment. The LCQ will be completed as per the schedule of assessments (Table 4–1).

3.5.6.4 The Cough Specific Quality of Life Questionnaire

The Cough-Specific Quality of life Questionnaire (Appendix 8.4) is a valid, repeatable 19 item self-completed QOL measure of chronic cough that is responsive to change. This tool assesses cough related QOL in three domains: Physical, Psychological and Social. This will allow for the measurement of QOL in relation to cough and for comparisons to be made between asthma phenotypes. The LCQ will be administered to the patient before all other non-PRO assessments and before the patient receives any disease-status information during that assessment. The LCQ will be completed as per the schedule of assessments (Table 4–1).

3.5.6.5 Visual Analogue Scale for Cough (VASc)

The VASc (Appendix 8.5) is a 100mm scale on which patients indicate the severity of cough. The scale ranges from no cough (0mm) to worst cough ever (100mm) and patients can mark the severity of their cough on the scale as appropriate. The VASc will be administered to the patient before all other non-PRO assessments and before the patient receives any disease-status information during that assessment. The VASc will be completed as per the schedule of assessments (Table 4–1).

3.5.6.6 Visual Analogue Scale for Urge to Cough (VASu)

The VASu (Appendix 8.6) is a 100mm scale on which patients indicate their urge to cough. The scale ranges from no urge (0mm) to severe urge (100mm) and patients can mark the

severity of their urge to cough on the scale as appropriate. The VASu will be administered to the patient before all other non-PRO assessments and before the patient receives any disease-status information during that assessment. The VASu will be completed as per the schedule of assessments (Table 4–1).

3.5.6.7 Cough Hypersensitivity Questionnaire (CHQ)

The Cough Hypersensitivity Questionnaire (Appendix 8.7) is a 23 item questionnaire that evaluates the presence of cough triggers, urge to cough and laryngeal symptoms suggestive of neuropathic paraesthesia. The CHQ will be administered to the patient before all other non-PRO assessments and before the patient receives any disease-status information during that assessment. The CHQ will be completed as per the schedule of assessments (Table 4–1).

4.0 Statistical Considerations and Analysis Plan

4.1 Determination of Sample Size

No formal sample size calculation has been performed as the study is exploratory

4.2 Analysis Sets

The full-analysis set (FAS) will be used in all statistical analyses. The FAS will consist of all patients who meet the criteria for entering the study.

4.3 Statistical Analysis

Demographic, baseline, and outcome data will be listed and summarised using descriptive statistical methods. Baseline weight, height, BMI, bronchodilator reversibility, spontaneous sputum results will be summarised. General medical history and baseline conditions will be listed. Patient disposition will be presented accompanied by the number and percentage of patients entering and completing the study. Reasons for withdrawal will be summarised. Concurrent medications and rescue medications will be listed and summarised.

4.4 Exploratory Analysis

Exploratory outcome measures will be listed and summarised appropriately by patient group and visit. The relationship of cough with each exploratory outcome will be investigated by presenting scatterplot matrices for each patient group and visit, or other appropriate methods with appropriate between group comparison.

5.0 Ethics and Confidentiality

5.1 Patient Information and Consent

It is the responsibility of the investigator, or a person designated by the investigator to obtain signed informed consent from patients prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The Consent Forms must be signed and dated by the patient before his or her participation in the study.

Before recruitment and enrolment, each prospective patient will be given a full explanation of the study and be allowed to read the approved Patient Information Sheet (PIS). Once the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original informed consent(s) and give a copy of the signed original to the patient

5.2 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without written permission from the patient, except as necessary for monitoring and auditing.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose, other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

6.0 Safety Reporting

6.1 Definition of Adverse Events

The definitions of adverse events is given in Table 2.

Table 2. Terms and Definitions for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant resulting from administration of any of the research procedures
Serious Adverse Event (SAE)	Any adverse event that • results in death, • is life-threatening • requires hospitalisation or prolongation of existing hospitalisation*, • results in persistent or significant disability or incapacity or is otherwise considered medically significant by the investigator

6.2 AE Reporting

The Chief Investigator or their delegated investigator is responsible for recording adverse events observed during the study period. Both adverse events and serious adverse events, will be recorded in the CRF.

The investigator should attempt, if possible, to establish a diagnosis based on the subject's signs and symptoms. The investigator must be follow all adverse events observed during the study until they are resolved or stabilized, or the events are otherwise explained. All adverse events must be treated appropriately. The action taken to treat the adverse event will be recorded in the CRF. The CI will report all related and unexpected SAEs to the REC and Sponsor within 15 days.

The investigator must record the adverse events, seriousness as well as duration (start and end dates). All adverse events must be included in the annual progress report submitted to the sponsor and Research Ethics Committee.

7.0 References

(1) Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2016.

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8.0 Appendices

8.1 Appendix: Mini Asthma Quality of Life Questionnaire

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE (MiniAQLQ©)
SELF-ADMINISTERED

PT NAME : _____ PT ID _____ DATE _____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
1. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
2. Feel bothered by or have to avoid DUST in the environment?	1	2	3	4	5	6	7
3. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
4. Feel bothered by COUGHING?	1	2	3	4	5	6	7
5. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
6. Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?	1	2	3	4	5	6	7
7. Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?	1	2	3	4	5	6	7
8. Have DIFFICULTY GETTING A GOOD NIGHT'S SLEEP as a result of your asthma?	1	2	3	4	5	6	7
9. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel bothered by or have to avoid going outside because of WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN DURING **THE LAST 2 WEEKS** DOING THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
12. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
13. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
14. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
15. WORK-RELATED ACTIVITIES (tasks you have to do at work*)	1	2	3	4	5	6	7

** If you are not employed or self-employed, these should be tasks you have to do most days.*

Analysis (Results for overall score and all domains will be between 1 = severe and 7 – no impairment		
DOMAIN		**RESULT**
OVERALL SCORE	Mean of **all 15** responses Add all 15 responses together and divide by 15	
SYMPTOMS	Mean of the responses to **items 1, 4, 6, 8, 10** Add the responses to these 5 items and divide by 5	
ACTIVITIES	Mean of the responses to items **12, 13, 14, 15**	
EMOTIONS	Mean of the reponses to items **3, 5, 9q**	
ENVIRONMENT	Mean of the responses to items **2, 7, 11**	

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8.2 Appendix: Asthma Quality of Life Questionnaire – 5

ASTHMA CONTROL QUESTIONNAIRE

Please answer questions 1 - 5. Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
0 Never
1 Hardly ever
2 A few times
3 Several times
4 Many times
5 A great many times
6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
0 No symptoms
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Quite severe symptoms
5 Severe symptoms
6 Very severe symptoms

3. In general, during the past week, how **limited were you in your "daily" activities** because of your asthma?
0 Not limited at all
1 Very slightly limited
2 Slightly limited
3 Moderately limited
4 Very limited
5 Extremely limited
6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
0 None
1 A very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

5. In general, during the past week, how much of the time did you **wheeze?**
0 Never
1 Hardly any of the time
2 A little of the time
3 A moderate amount of the time
4 A lot of the time
5 Most of the time
6 All the time

8.3 Appendix: Leicester Cough Questionnaire

LEICESTER COUGH QUESTIONNAIRE

This questionnaire is designed to assess the impact of cough on various aspects of your everyday life. Read each question carefully and answer by SELECTING the response that best applies to you. On the next page, there is an example from a completed questionnaire. Please answer ALL questions, as honestly as you can. This questionnaire is confidential.

Name……..

Date of Birth…./…/……

Date..……

Developed 2001

EXAMPLE PAGE

(Not to be completed)

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

2. In the last 2 weeks, my cough has made me feel frustrated.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

3. In the last 2 weeks, my cough has interrupted conversation or telephone calls.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

LEICESTER COUGH QUESTIONNAIRE

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1. Every time
2. Most times
3. Several times
4. Sometimes
5. Occasionally
6. Rarely
7. Never

3. In the last 2 weeks, have you been tired because of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

4. In the last 2 weeks, have you felt in control of your cough?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A good bit of the time
6. Most of the time
7. All of the time

5. **How often during the last 2 weeks have you felt embarrassed by your coughing?**

1. All of the time
2. Most of the time
3. A good bit of the time

4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

6. In the last 2 weeks, my cough has made me feel anxious.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

9. In the last 2 weeks, exposure to paints or fumes has made me cough.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

10. In the last 2 weeks, has your cough disturbed your sleep?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time

5. A little of the time
6. Hardly any of the time
7. None of the time

11. In the last two weeks, how many times a day have you had coughing bouts?

1. All the time (continuously)
2. Most times during the day
3. Several times during the day
4. Sometimes during the day
5. Occasionally through the day
6. Rarely
7. None

12. In the last 2 weeks, my cough has made me feel frustrated.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

13. In the last 2 weeks, my cough has made me feel fed up.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

15. In the last 2 weeks, have you had a lot of energy?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A good bit of the time
6. Most of the time
7. All of the time

16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

18. In the last 2 weeks, my cough has interrupted conversation or telephone calls.

1. Every time
2. Most times
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends.

1. Every time I cough
2. Most times when I cough
3. Several times when I cough
4. Sometimes when I cough
5. Occasionally when I cough

6. Rarely
7. Never

Thank you for completing this questionnaire.

8.4 Appendix: Cough Specific Quality of Life Questionnaire

The Cough-Specific Quality-of-Life Questionnaire (CQLQ)

NAME (OPTIONAL): _____ STUDY RECORD #: _____
DATE: _____

Please indicate below how your cough affects you. Circle the answer that best describes your agreement with each item. Please respond to every item. Thank you for your help.

1.	**Family and or close friends can't tolerate it any more.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
2.	I have experienced prolonged absences from important activities such as work, school, or volunteer services.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
3.	**I have been completely prevented from engaging in important activities such as work, school, or volunteer services.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
4.	I have lost my appetite.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
5.	**I am sick to my stomach and vomit.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
6.	I cough and it makes me retch (dry heaves).	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
7.	**I have a fear that I might have AIDS or tuberculosis.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
8.	I have headaches.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
9.	**I am concerned that I have cancer.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
10.	I am dizzy.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
11.	**I wet my pants.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
12.	I soil my pants.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
13.	**I sweat.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**

14.	I am hoarse.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
15.	**It hurts when I breathe.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**

					STRONGLY AGREE
17.	**I cannot sleep at night.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
18.	I have difficulty speaking on the phone.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
19.	**I can no longer sing, for instance in church.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
20.	I have stopped going to social activities such as movies, plays, town meetings.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
21.	**I have had to change my lifestyle.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
22.	I ache all over.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
23.	**I am exhausted.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
24.	I am embarrassed.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
25.	**I am upset by people thinking that I have something wrong with me.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
26.	I want to be reassured that I do not have anything seriously the matter with me.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
27.	**I am self-conscious.**	**STRONGLY DISAGREE**	**DISAGREE**	**AGREE**	**STRONGLY AGREE**
28.	I am concerned that I have something seriously the matter with me.	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE

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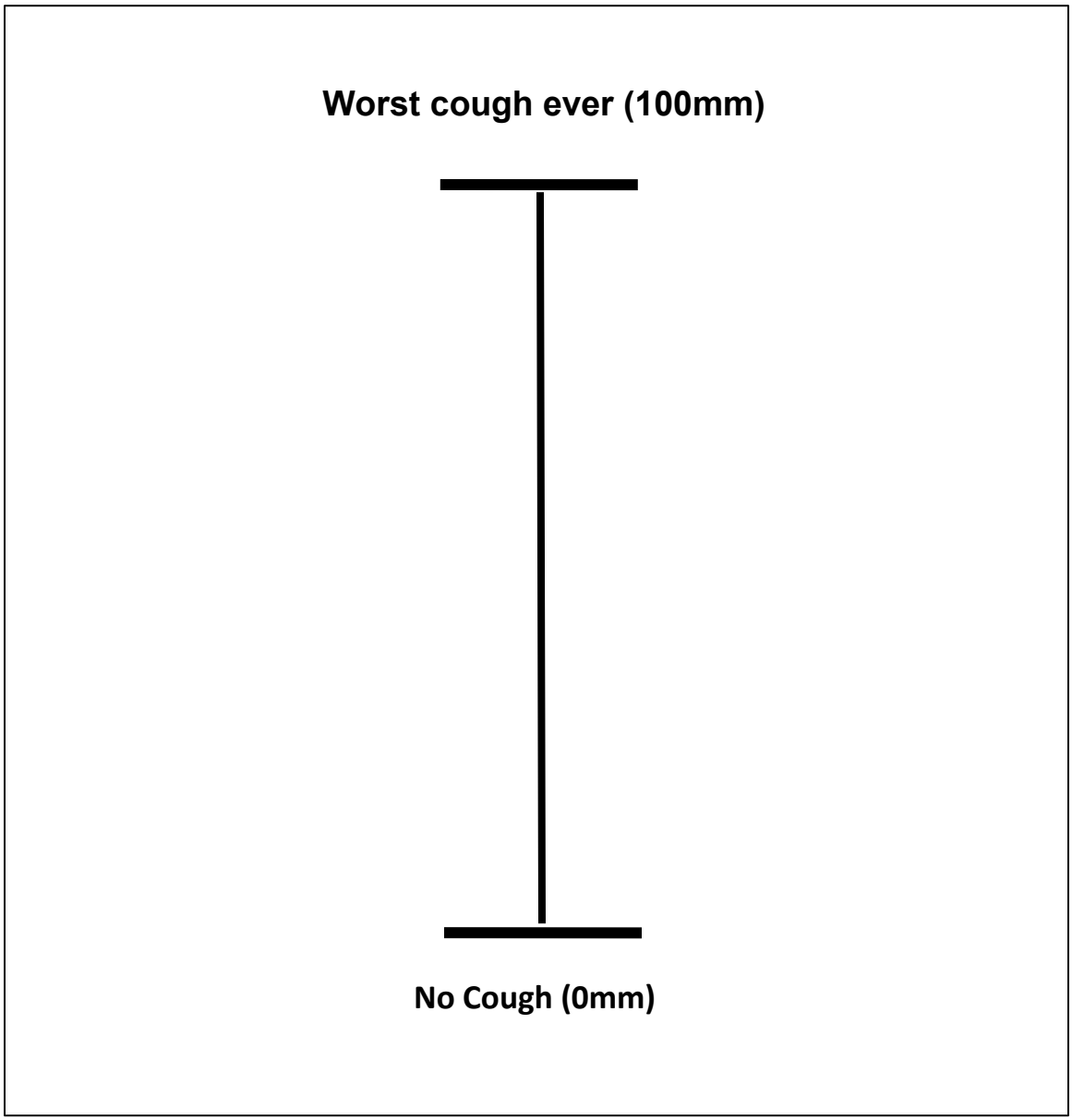
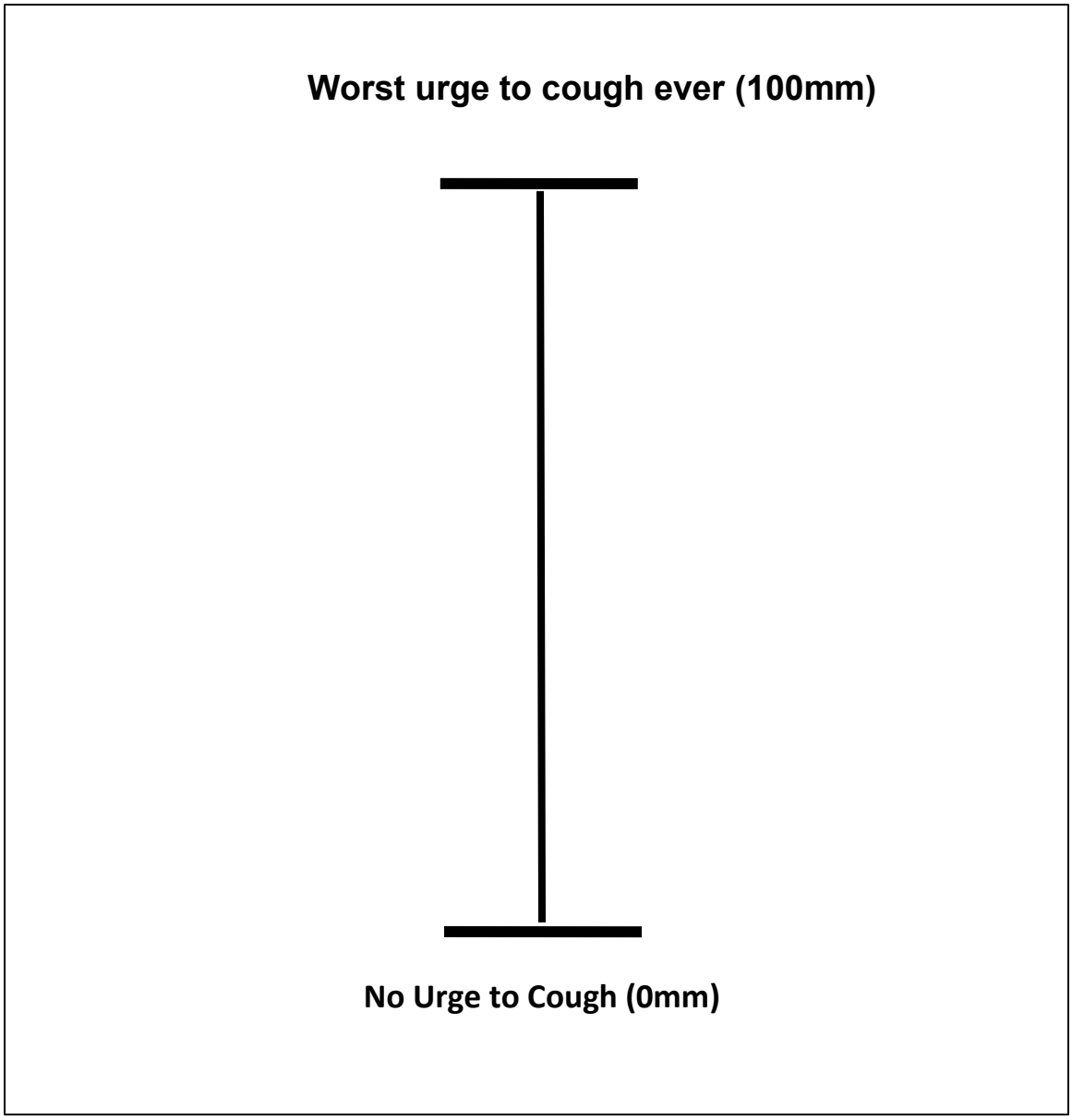
CQLQ - United States/English - Mapi ID050905 / CQLQ_AU2.0_eng-USori.doc

8.5 Appendix: Visual Analogue Scale for Cough



8.6 Appendix: Visual Analogue Scale for Urge to Cough



8.7 Appendix: Cough Hypersensitivity Questionnaire (CHQ)

Cough Hypersensitivity Questionnaire: assessing triggers of cough

This questionnaire assesses the sensations, urges and triggers associated with your cough.

Please answer all questions.

Have you experienced any of the following in relation to your cough within the last 2 weeks?	
Noticeable urge to cough before coughing starts	Y/N
Tickle in throat	Y/N
Itchy throat	Y/N
Dry throat	Y/N
Irritation in throat	Y/N
Throat clearing	Y/N
Sensation in the chest before you cough	Y/N

Do any of the following trigger your cough?	
Cold air	Y/N
Hot air	Y/N
Dry air	Y/N
Damp conditions	Y/N
Perfumes or scents	Y/N
Smoke or smoky atmosphere	Y/N
Talking	Y/N
Laughing	Y/N
Eating	Y/N
Heartburn	Y/N
Indigestion	Y/N
Change in body position (for example lying down)	Y/N
Exercise	Y/N
Brushing teeth	Y/N
Sputum (phlegm)	Y/N
Post-nasal drip (dripping sensation in back of the throat)	Y/N

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