FUTURE ASTHMA RISK: Using real-life patient records to help identify predictors of future exacerbation risk

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A Respiratory Effectiveness Group Protocol

PROTOCOL

BACKGROUND

While some people with asthma have no exacerbations and others may only experience them rarely, others experience more regular exacerbations and may constitute a "frequent exacerbator" subgroup. For example, in a US study of ≥3,000 patients presenting with acute asthma to 83 Emergency Departments, 73% of patients reported at least 1 visit for asthma in the prior year, yet 21% reported 6 or more visits.[1]

Although poor day-to-day symptom control increases the risk of an exacerbation, it is evident from epidemiological studies (e.g. the European Network for Understanding Mechanisms of Severe Asthma[2] [ENFUMOSA] and The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens[3] [TENOR]) that control neither fully defines nor completely predicts risk of asthma exacerbations.

The TENOR study—a 3-year, multi-center, observational study of the natural history, treatment regimens, and outcomes of severe, or difficult-to-treat asthma—concluded that recent severe asthma exacerbations are a strong independent factor predicting future exacerbations. Compared with patients without a recent history of exacerbations, those who had had a severe exacerbation in the prior 3 months were at increased odds of future exacerbations (odds ratio=6.33; 95%CI 4.57, 8.76), even after adjustment for demographics and clinical factors (odds ratio=3.77; 95% CI 2.62, 5.43), asthma severity (physician-assessed: odds ratio=5.62; 95% CI 4.03, 7.83), National Asthma Education and Prevention Program severity classification (odds ratio=5.07; 95% CI 3.62, 7.11), Global Initiative for Asthma severity classification (odds ratio=5.32; 95% CI 3.80, 7.47), and asthma control, assessed by the asthma therapy assessment questionnaire (ATAQ) (odds ratio=3.90; 95% CI 2.77, 5.50).[4] It is also of note that a significant percentage of patients experience multiple exacerbations (requiring ≥3 oral steroid prescriptions over the course of a year) across all levels of severity: mild (5%), moderate (13%), and severe (54%).[5] Thus, it is likely that there is a subgroup of asthmatics whose susceptibility to exacerbations is not fully described by traditional measures of asthma control[6] or severity.[5]

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[1] *Griswold SK, Nordstrom CR, Clark S, Gaeta TJ, Price ML, Camargo CA Jr* Asthma exacerbations in North American adults: who are the "frequent fliers" in the emergency department? *Chest. 2005 May; 127(5):1579-86*

[2] Romagnoli M, Caramori G, Braccioni F, Ravenna F, Barreiro E, Siafakas NM, et al. Near-fatal asthma phenotype in the ENFUMOSA Cohort. Clin Exp Allergy. 2007 Apr;37(4):552-7.

[3] Miller MK, Lee JH, Blanc PD, Pasta DJ, Gujrathi S, Barron H, et al. TENOR risk score predicts healthcare in adults with severe or difficult-to-treat asthma. Eur Respir J. 2006 Dec;28(6):1145-55.

[4] Miller MK, Lee JH, Miller DP, Wenzel SE, TENOR Study Group Recent asthma exacerbations: a key predictor of future exacerbations. Respir Med. 2007;101:481-9.

[5] Koga T, Oshita Y, Kamimura T, Koga H, Aizawa HCharacterisation of patients with frequent exacerbation of asthma. Respir Med. 2006 Feb; 100(2):273-8.

[6] Miller MK, Lee JH, Miller DP, Wenzel SE, TENOR Study Group Recent asthma exacerbations: a key predictor of future exacerbations. Respir Med. 2007;101:481-9.

While previous studies have identified factors associated with an increased risk of asthma exacerbations, such as: previous exacerbations;[7,8,9] extrinsic factors, such as cigarette smoking, medication noncompliance, psychosocial factors; intrinsic factors, such as deficient epithelial cell production of the anti-viral type I interferons (IFN-α and IFN-β)[1,10]persisting airways or systemic inflammation, and co-morbidities, such as gastroesophageal reflux disease, rhinosinusitis, obesity, and salicylate sensitive asthma.[11] Further work is required to better understand how such factors overcome canalization (i.e. whether having one is sufficient and risk is linear, or whether two or three "hits" are required to produce a substantial increase in risk). Further studies are also required to establish whether such factors are also associated with increased risk of *frequent* exacerbations and whether the frequent exacerbator subgroup is a stable group with "inherent characteristics" that persist throughout their disease or whether frequent exacerbations constitute transitory periods of unstable disease following a specific trigger (or number of concomitant triggers).

Increased understanding of exacerbation patterns and the individual and clusters of risk factors associated with them could help to define 'frequent exacerbators' more meaningfully (e.g. as a persistent group of patients at the high end of the control continuum, or a dynamic group population made up of patients experiencing disease phases during which their exacerbation risk is elevated due to specific triggers). Improved understanding of the relationships between patient characteristics and frequent exacerbation risk will help to inform the development of new assessment tools, treatment strategies and interventions aimed at reducing the significant morbidity (and cost) associated with asthma exacerbations.

OBJECTIVE

This study aims to identify patient characteristics recorded within routine primary care datasets that are associated with increased risk of frequent asthma exacerbations, with the ultimate goal of:

1. Characterising the frequent exacerbator subgroup of asthma patients
2. Identifying individual risk factors associated with increased future exacerbation risk
3. Exploring clusters of risk factors associated with increased risk of future exacerbation risk.

[7] O'Connor RD, Bleecker ER, Long A, et al. Subacute lack of asthma control and acute asthma exacerbation history as predictors of subsequent acute asthma exacerbations: evidence from managed care data. J Asthma. 2010;47(4):422-8.
[8] Sims EJ, Price D, Haughney J, et al. Current control and future risk in asthma management. AAIR. 2011;4:217–225.
[9] Haselfom T, Zeiger RS, Chipps BE, et al. Recent asthma exacerbations predict future exacerbations in children with severe or difficult-to-treat asthma. JACI. 2009;124:921–7.
[10] Dougherty RH, Fahy JV. Acute Exacerbations of Asthma: Epidemiology, Biology and the Exacerbation-Prone Phenotype. Clin Exp Allergy. 2009 February; 39(2): 193–202.
[11] Boulet LP. Influence of comorbid conditions on asthma. N Engl J Med. 2009;33(4):897–906.

STUDY DESIGN

Data source

This validation study will use data from the Optimum Patient Care Research Database (OPCRD).

The **OPCRD** comprises data extracted through the Optimum Patient Care clinical service evaluation. The clinical evaluation involves a combined review of (anonymised) electronic medical records (EMRs) and patients' responses to disease-specific questionnaires[12] and characterizes patients in terms of their demography, disease control and exacerbation history and makes guideline-based recommendations for possible management changes that may help to optimise control at the lowest possible therapeutic dose and reduce risk of future exacerbations. A full data dictionary for the OPCRD, which indicates the data fields within the dataset, is detailed in **Appendix 2**.

At the time of writing, OPCRD contains anonymised, research-quality data for approximately 350,000 patients with asthma (and 100,000 patients with chronic obstructive pulmonary disease [COPD]) collected from more than 350 practices across the UK that subscribe to OPC for respiratory review service.

Ethics

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.

Study Period

The study period will run for a continuous 3-year period – the latest such period available for each patient eligible for inclusion in the study.

Study population

Inclusion criteria

To be eligible for inclusion in the study, patients must meet the following inclusion criteria:

- ≥3 years of continuous medical records (the latest such period available for each patient)
- Age 12–80 years[13] ("study age" will be based on age on day one of the 3-year study period)[14]

[12] See **Appendix 1** for a copy of OPC's asthma questionnaire

[13] As asthma diagnosis may be less accurate in older patients due to lack of formally assessment, "exacerbations" in the elderly population may not be driven by morbidities other than asthma (e.g. COPD. post-viral wheeze). Age stratified analyses (12–60 years; >60 years) will be conducted to minimize the possibility of age being inappropriately flagged as a risk factor.

- Have physician diagnosed asthma (Read coded diagnosis)

Exclusion criteria

As this is a real-life study designed to explore (rather than pre-empt) patient characteristics associated with increased frequent exacerbation risk, no exclusion criteria will be applied.

Study Phases & Analysis

The study will consist of three main elements:

(1) A **descriptive analysis of longitudinal patient data**.
(2) A **bivariate analysis** to explore which individual patient characteristics are associated with frequency of asthma exacerbations and also what proportion of the "frequent exacerbation" trait is explained by each factor (e.g. a common/frequently-occurring characteristic that conveys a small increment of increased risk or a little-seen characteristic that conveys a significant increase in risk in those patients in whom it is present).
(3) A **multivariate analysis** to explore composite characteristics most strongly associated with exacerbation frequency to help profile patients in terms of their future exacerbation risk.
(4) Hierarchical **longitudinal analysis** (including practice ID to take into account observations among patients within practices) using 6-month intervals, and alternatively code time flexibly (i.e. consider the exact dates of events) to examine variations in exacerbation occurrence within the 3-year study period, and to predict exacerbations based on the predictors of interest.

1. A descriptive analysis of longitudinal patient data

MAPPING

As asthma is an inherently variable disease and can also be subject to seasonal changes, the pattern of disease will be characterised by mapping (and tabulating) the following across the 3 study years (cumulatively and split by year). Where the raw variable data are continuous, both continuous and categorical data will be plotted to help identify and explore patterns (and their relationship to future exacerbation risk) as fully as possible:

- **Control status** (see **Appendix 3** for definitions):
    - Global Initiative for Asthma (GINA) control category (totally controlled; partially controlled; uncontrolled)

[14]Due to differences in the nature of paediatric and adult asthma, the characteristics associated with exacerbation risk may be affected by patient age. This study will focus on an adolescent and adult patient population, but work is also required in the paediatric population, so the protocol may be (tailored in collaboration with pediatricians and) repeated in a younger population at a later date.

Control status will also be plotted (with seasonal labels) against time to explore seasonal patterns of asthma exacerbations and whether they exist for some, but not all, patients within the study dataset.

- **Exacerbations** (see **Appendix 3** for definitions):
  - Exacerbations (based on American Thoracic Society / European Respiratory Society Joint Taskforce definition)
  - "Real-life Exacerbations" (modification of the ATS/ERS definition including episodes of respiratory ill-health treated with antibiotics coded as being infective, as exacerbations can be mistaken for LRTIs in routine care`

  Time plots will also be produced (and an auto-regression model used) to explore the time period between exacerbations to help understand whether the occurrence of past exacerbations predicts future exacerbations.

- **Exacerbation disaggregated components:**
  - Oral steroid prescriptions
  - Hospitalisations for asthma or lower respiratory conditions
  - A&E attendance for asthma or lower respiratory conditions
  - Antibiotic prescriptions for lower respiratory tract infections (LRTIs)

Patients' 3-year exacerbation frequency will be explored using exacerbation frequency as both a continuous and categorical variable. The following tables reflect the exacerbation categories that will be used in the categorical evaluation.

Table: Risk classification defined by exacerbation frequency (illustration only; to be informed by study population characteristics)

Risk category	Exacerbation Frequency (mean number of annual exacerbations)	Number of exacerbation (total number over 3 years)
None	0	0
Very low	>0 and ≤0.33	1
Low	0.34–1.00	2–3
Moderate	1.01–2.00	4–6
High	2.01–3.99	7–11
Very high	≥4.00	≥12

PATIENT CHARACTERISATION

To inform the analysis of patient features potentially associated with frequent exacerbations, patients will be characterised:

(a) **Annually** for a subset of time-varying characteristics for which stability of the characteristic over the 3-year period may be of clinical relevance
(b) **"Point Characterisation**: Over the first year of their 3-year study period only for time-invariant characteristics.

Covariates for annual evaluation (a):

Characterised annually over the 3-year analysis period:

- **Controller therapy**:
  - Management step: Global Initiative for Asthma (GINA) treatment step (based on first prescription in each one-year period)
  - Prescribed drugs (split by drug class)
  - Number of prescriptions issued.
  - Average ICS daily dose (or LTRA dose where non-ICS therapy is used).
  - Prescribed ICS dose (based on first prescription in each one-year period)
  - Adherence to core maintenance therapy (ICS, ICS/LABA, LTRA): evaluated as medication possession ratio (i.e. number of days' supply of controller therapy divided by 365 days)
  - Change in therapy (from prior year):
    – Switch (drug change)
    – Step-up (add-on or dose increase)
    – Step-down
- **General Practitioner (GP) consultations**:
  - Total GP consultations
  - Asthma-related consultations
  - Consultations resulting in oral steroid prescriptions
  - Consultations resulting in antibiotic prescriptions for lower respiratory tract infections
  - Asthma review conducted outside asthma clinic
- **Reliever therapy**:
  - Number of short-acting beta-agonist (SABA) prescriptions issued.
  - Average daily dose of SABA (calculated based on the total combined dose of refilled SABA prescriptions averaged over 365 days)
- **Smoking status**:
  - Non-smoker
  - Ex-smoker
  - Recent ex-smoker (if quit at some point during the study period)
  - Continuous active smoker

Asthma UK Triple A Test

Features identified as possible predictors within the Asthma UK Triple A Test[15] will also be captured with a view to linking different streams of research in this area. The Triple A test incorporates the following:

- Sex
- Country of residence with in Great Britain (i.e. England, Scotland, Northern Ireland, Wales)
- Age (≤18 years; 19–34 years; 35–54 years; ≥55 years)
- Patient-reported diagnosis of asthma (OPCRD proxy = diagnostic code for asthma)
- Patient perceived risk of asthma attack (at risk / not at risk)[16]
- Use of / prescriptions for ≥3 asthma medications
- Attended A&E for asthma in the prior 6 months

[15] The Asthma UK Triple A Test is a UK-wide initiative pioneered by Asthma UK to reduce hospital admissions: www.asthma.org.uk/advice-the-triple-a-test

[16] Some patients in the OPCRD will have questionnaire answers relating to patient perceived need for therapy, which could be used as a proxy for perceived risk, but numbers are typically low and the connection tenuous so could only be used for the purposes of an exploratory investigation

- SABA use ≥5 puffs daily
- History of anaphylaxsis (or severe food allergy)
- ≥1 courses of oral steroids in the prior 6 months
- Forgets to take maintenance therapy when feeling well
- Comorbid rhinitis
- Depression.[17]

Comorbid conditions and markers

- Blood eosinophil count
- Atopic features:
  - Presence / absence of comorbid rhinitis:
    – Diagnosis ever and/or prescriptions for rhinitis therapy over the 1-year characterisation period.
    – Where rhinitis is present, use of nasal steroids for its treatment.
  - Presence / absence of comorbid eczema (diagnosis ever and/or prescriptions for eczema therapy over the 1-year characterisation period)
- Presence of anxiety and/or depression (diagnosis ever or prescriptions 1-year characterisation period)
- Presence of GERD (diagnosis ever and/or prescriptions for GERD therapy over the 1-year characterisation period)
- Presence of anxiety and/or depression (contemporaneous treatment of antidepressants or anxiolytics during the characterisation period)
- Aspirin or non-steroidal anti-inflammatory drug (NSAID) allergy or intolerance
- Diabetes (diagnosis ever or prescriptions 1-year characterisation period)
- Charlson Comorbidity Index
- Height of patient
- Weight of patient
- Body Mass Index (BMI) (in sub-group where BMI can be evaluated)

Assessment of exacerbations (see Appendix 3)

- Number of prescriptions for any respiratory therapy (split by number of prescriptions for each):
- ICS drug
- Markers of asthma exacerbations:
  - A&E attendance[18] for asthma
  - Oral steroid prescriptions for asthma
  - Courses of antibiotics prescribed for lower respiratory tract infections (LRTIs)[19]
- Seasonal occurrence of asthma exacerbation markers (split by month of event / prescription date)
- Month of respiratory prescriptions (split by maintenance / controller) to enable evaluation of seasonal variance via longitudinal models.
- Disaggregated components of primary care attendance / usage, specifically:
  - Total number of primary care consultations

[17] Read codes for depression and/or anxiety

[18] A&E attendance for asthma in the prior 6 months forms part of the Asthma UK Triple A test. Annualised exacerbation rate can be halved as an indicator of average attendance over 6 months

[19] In routine practice, some asthma exacerbations may be treated with an antibiotic for an LRTI rather than an oral steroid

  - Number (%) of primary care consultations resulting in a respiratory prescription:
    – An oral steroid
    – An antibiotic for an LRTI
  - Number (%) of primary care consultations not resulting in a respiratory prescription
- Disaggregated components of secondary care attendance / admission, specifically:
  - Number of hospital outpatient attendances with asthma specified as the reason for referral
  - Number of hospitalisations for asthma (or "possibly asthma respiratory related", defined as a non-specific hospitalisation code and an asthma / respiratory code within a one week window).
  - Number of hospital outpatient attendances where asthma and/or other respiratory illness was specified as the reason for referral.
  - Number of hospitalisations for asthma and/or respiratory illness (including non-specific hospitalisations with an asthma / respiratory code within a one week window).

Asthma control status (see Appendix 3 for full definitions)

- Control will be assessed in terms of GINA control (totally controlled; partially controlled; uncontrolled) for patients with questionnaire responses that allow GINA classification to be evaluated.

Symptoms

- Objective measure: SABA usage will be used as an objective proxy for presence of symptoms.

For patients with questionnaire responses:

- Symptoms will be assessed Royal College of Physicians (RCP) 3 questions.

Additional covariates for point characterisation in year 1 only (a):

Potential confounders examined at day one (or closest available date) of each patient's 3-year analysis period:

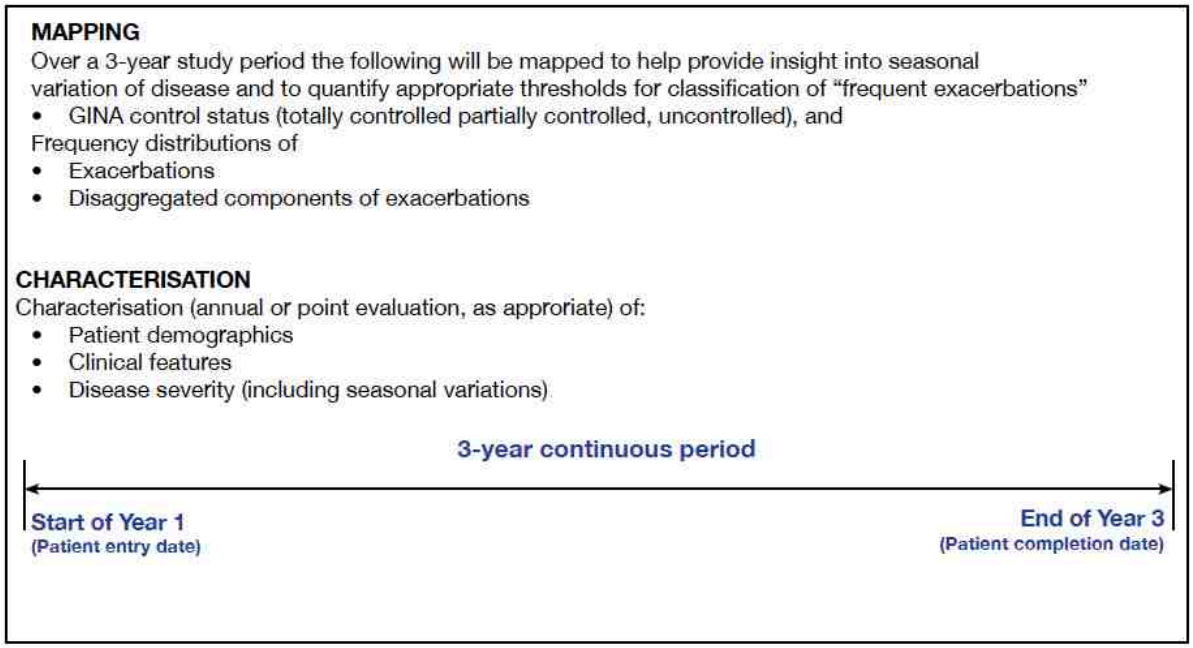
- Age of patient
- A marker of socio-economic status where possible, i.e. post codes
- Gender of patient
- Ethnicity
- Lung function, in terms of percent predicted PEF[20] prior to index date
- Smoking status
- SABA drug device
- ICS device type

Potential confounders examined over year 1 of the 3-year analysis period:

- Date of first asthma diagnosis
- Duration of asthma

[20] Calculated using Roberts' Equations

- Other important unrelated co-morbidities, expressed using the Charlson Comorbidity Index (CCI)
- Multi-morbidity (continuous variable, i.e. 0, 1, 2, 3)
- Presence of cardiac disease (diagnosis ever and/or prescriptions for cardiac drugs
- Other medications that might interfere with asthma control:
  - Number of paracetamol prescriptions.
  - Number of non-steroidal anti-inflammatory drugs (NSAIDs) prescribed
  - Number of beta-blocker prescriptions (including eye drops)
- Device:
  - Controller device
  - Reliever device
  - Use of mixed device types (MDI and DPI) for controller and reliever inhaled therapies.
- Spacer use / prescription.



2. Bivariate analysis: individual characteristics associated with frequency exacerbations

From the first phase of the study population will be well characterised in terms of:

(a) Disease severity: assessed in terms of:
  a. GINA management step (steps 1–3 vs 4)
  b. Mean daily SABA usage (≤200mcg salbutamol vs >200mcg salbutamol)
  c. GINA control category (controlled or partially controlled vs uncontrolled)
(b) Risk (based on the exacerbation frequency)

Of particular interest (in terms of potentially informing clinical practice changes) are common characteristics, or risk predictors, in patient groups where management modifications may be rational and feasible, i.e. patients who are:

- **High or very high risk, but with apparently mild/moderate disease:** these

patients may benefit from closer monitoring

- **No, low or very low risk, but have apparently severe disease:** reduced management may be appropriate in such patients.

Categorisation of characteristics for evaluation

Risk category (annual exacerbation rate / total over 3 years)	**"Disease severity" defined in terms of GINA Management Step**	
	Treated at Steps 1-3 (implying mild/moderate disease)	Treated at Step ≥4 (implying severe disease)
"No risk" (0 / 0)		High drug usage / low exacerbation risk
Very low risk (>0 but ≤0.33 / 1)		
Low (0.34–1.00 / 1–3)		
Moderate (1.01–2.00 / 4–6)		
High risk (2.01–3.99 / 7–11)	Low drug usage / moderate–high exacerbation risk	
Very high risk (≥4.00 / ≥12)		

The interaction between different predictors and GINA Management step in relation to exacerbations will also be tested to:

- Establish whether exacerbation risk needs to be addressed differently for different GINA management steps (i.e. where a significant interaction is observed)
- Help to establish whether impact of exacerbation predictors varies depending on GINA management step and, if so, the threshold at which point one predictor becomes relevant.

Risk category (annual exacerbation rate)	**"Disease severity" defined in terms of mean daily SABA usage**	
	Low SABA usage: ≤200mcg salbutamol / ≤500mcg terbutaline	High SABA usage: >200mcg salbutamol / >500mcg terbutaline
"No risk" (0 / 0)		High SABA usage / low exacerbation risk
Very low risk (>0 but ≤0.33 / 1)		
Low (0.34–1.00 / 1–3)		
Moderate (1.01–2.00 / 4–6)		
High risk (2.01–3.99 / 7–11)	Low SABA usage / moderate–high exacerbation risk	
Very high risk (≥4.00 / ≥12)		

The interaction between different predictors and SABA usage in relation to exacerbations will also be tested to help establish whether the impact of exacerbation predictors varies depending on degree of SABA use and, if so, the threshold at which point one predictor becomes relevant.

Risk category (annual exacerbation rate)	**"Disease severity" defined in terms of GINA Control Status**	
	Controlled or Partially Controlled	Uncontrolled
"No risk" (0 / 0)		Uncontrolled disease but low exacerbation risk
Very low risk (>0 but ≤0.33 / 1)		
Low (0.34–1.00 / 1–3)		
Moderate (1.01–2.00 / 4–6)		
High risk (2.01–3.99 / 7–11)	At least partially controlled disease but moderate–high exacerbation risk	
Very high risk (≥4.00 / ≥12)		

The interaction between different predictors and GINA control category in relation to exacerbations will also be tested to help establish whether the impact of exacerbation predictors varies depending on control category and, if so, the threshold at which point one predictor becomes relevant.

Subgroups

Age: Findings will be stratified by age (12–60; ≥61 years[21]) in recognition that accuracy of asthma diagnosis may be poorer in older patients (in part due to a lack of formal assessment), which may affect the apparent exacerbation risk in elderly patients.

Overall analysis

The predictive quality of independent characteristics will be evaluated by using a longitudinal dataset including:

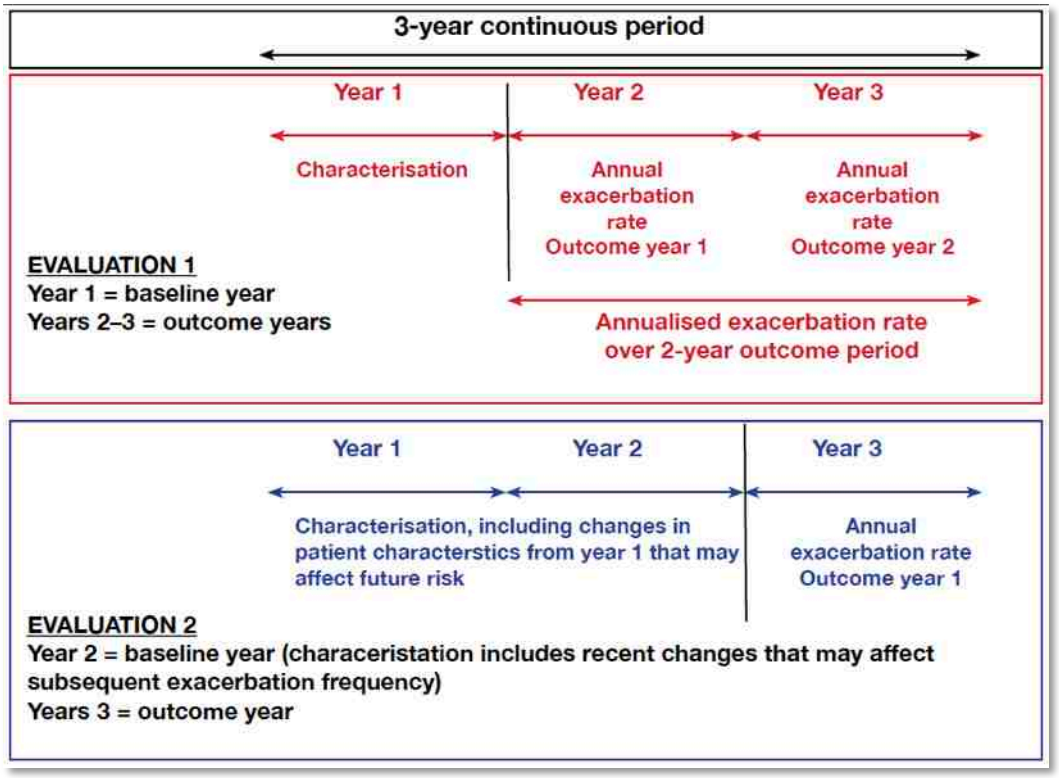
(i) Time-invariant predictors (age, gender, etc)
(ii) Time-varying predictors (treatment, asthma control, etc),
(iii) Number of exacerbations in last year (0, 1, 2…) as outcome.

Association between patient characteristics in:

- Year 1 of the 3-year study period and the exacerbation rate in the following 1 and 2-year periods (separately and cumulatively).
- Years 1–2 (separately and cumulatively) of the 3-year study period and the exacerbation rate in the following 1-year period.

See schematic below.

[21] Exact age categories will be informed by the distribution of age within the study population



3. Multivariate analysis: composite characteristics associated with frequency exacerbations.

Based on the findings of the bivariate analysis combinations of **≤6 characteristics** that combine to provide the greatest predictive power for future exacerbations will be explored. Predictors will be listed as in rank order in terms of (i) **prevalence** and **(ii) predictive power in recognition that** some characteristics will be common to a large proportion of patient but not necessarily substantially predictive of future risk. While others may be rare characteristics that have a sizeable predictive quality and may be of significant importance at an individual patient level, but could be overlooked when identifying population-level risks. Clusters of risk factors will be grouped follows:

(i) **As any group of risk factors most predictive of future exacerbation risk:** Intrinsic risk factors (e.g. gender, age) have utility in providing red flags for patients who may be at elevated risk and may benefit from closer monitoring, these will be reported:

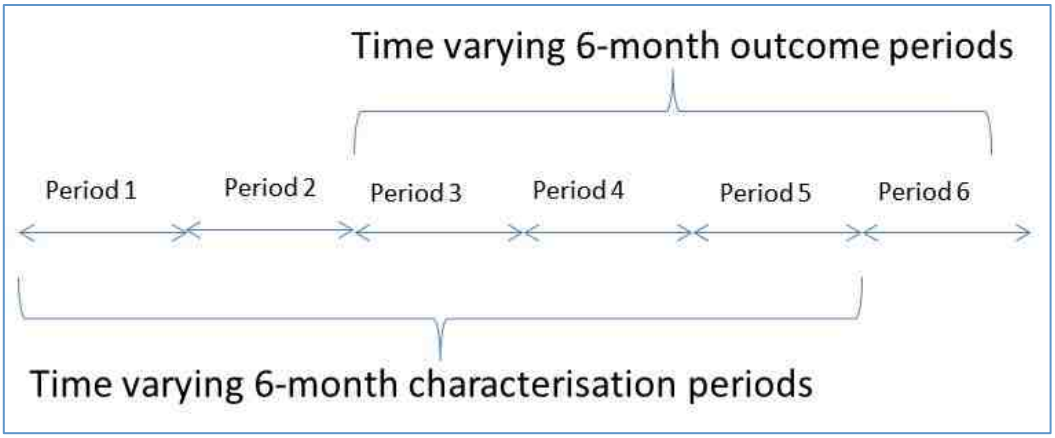
a. **At a population level including prevalent risk factors (e.g. occurring in ≥10% of the population)**
b. **At patient level – a series of risk factor clusters that include rare risk factors (e.g. occurring in <10% of the population)**

(ii) **As modifiable risk factors with greatest power to predict future exacerbations:** these provide opportunity for clinical interventions targeted at reducing future exacerbations (and the associated health and financial costs to the patient and the health service). Modifiable risk factors could include: therapy step-down, reduced adherence, untreated rhinitis and current smoking status. These could all be (at least partially) addressed by optimising therapeutic

management, tailoring prescribing regimens to patient needs to improve adherence, assessing patient perceptions of medication and possible treatment side effects, and supporting lifestyle changes (such as smoking cessation).

4. ***Hierarchical longitudinal analysis***

The modelling from phase 3 will be extended to include risk factors more closely related to outcomes, by splitting the follow-up 3 year period into 6 periods of 6 months each (see figure below). The modeling will consider the outcome rates and events in each of the final 4 periods simultaneously adjusted for exacerbations in the preceding 6 months and 7-12 months, and the other risk factors characterised during the preceding periods. The analysis will also take into account the correlation among patients within practices.



Evaluation 3

Outcome periods = periods 3, 4, 5 and 6

Characterisation periods = periods 1-2, 1-3, 1-4, and 1-5.

METHODS

Code lists

Code lists (using OXMIS, Read and drug codes) have been developed by Research in Real Life Ltd in collaboration with UK clinicians and researchers who have experience of respiratory disease and coding of events within UK primary care. These lists have been iteratively refined over a number of years, informed by experience from their application in other large UK database studies.

The Charlson Comorbidty Index (CCI) has been developed using ICD-9 matching algorithms produced by CliniClue® (the registered Trademark of The Clinical Information Consultancy Ltd).[22]

[22] Clinical Information Consultancy homepage: http://www.cliniclue.com/home

Statistical analysis

Appropriate statistical methods will be used to address the complex interaction analyses that will need to be explored:

- Interaction analysis of treatment, markers of inflammation and treatment adherence;
- The role of treatment pathway on subsequent exacerbations;
- The stability of different (exacerbation-defined) subgroups, i.e. variation in year-to-year exacerbation rates
- Predictors of the very high risk exacerbation subgroup (i.e. those patients experiencing ≥4 exacerbations annually)

All statistical analyses will be carried out using SAS v9.3, SPSS v20 and EXCEL 2007. The statistical methods that will be used, will include (as appropriate):

Phase 1. Autocorrelation plots will be examined to assess seasonality and time dependent relationships in the rate of exacerbations as described in the methods section.

Phase 2 & 3. Univariate (phase 2) and multivariate (phase 3) associations will be estimated using:

(i) Negative binomial regression models: will be used to determine predictors of future risk in terms of severe exacerbation rates over subsequent 1 & 2 years.

(ii) Ordinal logistic regression models: will be used when annual exacerbations are categorised 0, 1 and ≥2.

(iii) Logistic regression models: will be used when severe exacerbations is defined as a binary outcome. Here, population attributable risks will be estimated to provide an estimation of the proportion of "frequent exacerbation" trait that is explained by each statistically significant factor in the multivariate models.

Alternative variable selection techniques shall be considered where appropriate. The risk factor interactions detailed in the methods will be tested within the regression models.

Phase 4. Hierarchical multi-level modelling will be used to estimate associations with exacerbation rates. The appropriate modelling strategy will be informed by the results of phases 1-3. Prior exacerbation rates in the previous 6 months and previous 7-12 months will be considered as risk factors. Otherwise, time-varying risk factors will be considered over all preceding characterisation periods or just the preceding 6 month period where appropriate. The season at the start of the 6 month outcome period will be adjusted for. Appropriate correlation structures will be explored informed by the analysis in phase 1. A random effect will be specified for practice ID to account for the correlation among individuals attending the same GP practice.

Limitations of the study design, data sources and analytical methods

As with all database studies a number of limitations exist such as the need to use proxy measures where explicit data are not available. As 3 years of GP records will

be extracted retrospectively, risk factors for severe exacerbations will be limited to risk factors for severe exacerbations unrelated to mortality. Another limitation of the study is that it will be conducted in a dataset comprising UK practice data only, which may limit its generalizability non-UK asthma 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 (~350), 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.

FUNDING & THE RESEARCH TEAM

The study will be funded through a research grant from the Respiratory Effectiveness Group (REG; www.effectivenessevaluation.org) – a new investigator-led initiative designed to raise the quality and profile of real-life respiratory research. Funding will cover the costs associated with protocol development, analysis, report development, congress abstract development (x1) and manuscript publication (x1).

REG collaborators will form the core of the study group and Research in Real Life Ltd (RiRL) will be contracted to undertake the analysis on behalf of the study collaborators. See **Appendix 4** (or visit the group's website) for more information about the REG initiative.

Research Collaborators

Lead Investigator: Mike Thomas, Professor of Primary Care Research at the University of Southampton.

David Price: Primary Care Respiratory Society UK, Professor of Primary Care Respiratory Medicine, University of Aberdeen, UK; Director Optimum Patient Care Ltd and Research in Real Life Ltd
John Blakey: Liverpool School of Tropical Medicine, Aintree University Hospital, North Mersey HIS, UK
Vibeke Backer: Dept of Respiratory Medicine L, Respiratory Research Unit, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark
Lynn Josephs: Primary Care research, University of Aberdeen
Ian Pavord: Institute for Lung Health, University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, UK
Borislav Dimitrov: Senior Lecturer in Medical Statistics at the University of Southampton
Dirkje Postma: Professor of Pulmonary Medicine at the University of Groningen and the University Medical Center of Groningen
Alberto Papi: Professor of Respiratory Medicine and Director of the Section of Respiratory Diseases of the Department of Clinical And Experimental Medicine of the University of Ferrara at S.Anna University Hospital, Ferrara
Alexandra Dima: Researcher in Health Psychology, Department of Communication Science, University of Amsterdam, The Netherlands
Todor Popov: Professor at Clinical Centre of Allergology in Sofia
Hilary Pinnock: Principal in General Practice, Whitstable Medical Practice, UK; Reader, Allergy and Respiratory Research Group, Centre for Population Health Sciences: GP Section, University of Edinburgh, UK

Iain Small: General Practitioner from Peterhead, Aberdeenshire, UK Chair of the Primary Care Respiratory Society in the UK; Trustee of Asthma UK
Alan Kaplan: Family physician, Ontario, Canada and Chair of the Respiratory Medicine Special Interest Focus Group of the College of Family Physicians of Canada
Cindy Rand: Professor of Medicine, John Hopkins University, USA
Janet Holbrook: Associate Professor of Epidemiology, Johns Hopkins Center for Clinical Trials, USA
Emilio Pizzichini: Head of the Pulmonology Department of the Universidade Federal de Santa Catarina - UFSC, Federal University of Santa Catarina - School of Medicine, Florianópolis, Brazil
Gene Colice: Chest Physician, Pulmonary, Critical Care and Respiratory Services, Washington Hospital Center, and The George Washington University School of Medicine
Sam Walker: Director of Education & Research at Education for Health, UK
Alison Chisholm: Respiratory Effectiveness Group Implementation Manager

STUDY TIMELINE

This study will be funded as part of REG's year 1 funding. The initiative's year began on 1 April 2013 and will run through to 31 March 2014. While study activities will commence during this period, REG acknowledge that the analysis (and dissemination of results) will continue into the second year of the initiative – this is accepted and understood by the study funders.

A more complete timeline will be established once the protocol has been finalised, but it is estimated that analysis work will commence in November 2013 with phases (i)–(iv) completing sequentially over the six months of 2014. There will be no unnecessary delay between completion of the study analysis and publication.

APPENDIX LIST

List of Appendices:

- **APPENDIX 1**: Questionnaire used for optimum patient care's asthma service evaluation
- **APPENDIX 2**: OPCRD data dictionary
- **APPENDIX 3**: Control and Symptom Score Definitions
- **APPENDIX 4**: The respiratory effectiveness group

APPENDIX 1: QUESTIONNAIRE USED FOR OPTIMUM PATIENT CARE'S ASTHMA SERVICE EVALUATION

Asthma Questionnaire

Please take a few minutes to complete the whole questionnaire, following the instructions at the head of each section.

In the last week:	0	1	2	3	4	5	6	7	8	9	10+
How many times have you used your reliever inhaler?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Thinking about the last 7 days (please tick one box for each question):	0	1	2	3	4	5	6	7
How many days has asthma interfered with your normal activities (eg sport, school, work/housework)?	☐	☐	☐	☐	☐	☐	☐	☐
How many nights have you been affected/woken by asthma symptoms (including cough)?	☐	☐	☐	☐	☐	☐	☐	☐
How many days have you experienced asthma symptoms?	☐	☐	☐	☐	☐	☐	☐	☐

In the past 4 weeks, did you:	Yes	No	Unsure
Miss any work, school, or normal daily activity because of your asthma?	☐	☐	☐
Wake up at night because of asthma?	☐	☐	☐
Believe that your asthma was well controlled?	☐	☐	☐
In general, do you use an inhaler for quick relief from asthma symptoms?	☐	☐	☐

If yes, in the past 4 weeks, what was the highest number of puffs in 1 day you took of the inhaler?

☐ 0 ☐ 1 to 4 puffs ☐ 5 to 8 puffs ☐ 9 to 12 puffs ☐ More than 12 puffs

In the last 12 months:	0	1	2	3	4	5	6	7	8	9	10+
How many times have you needed a course of steroid tablets for worsening asthma?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
How many days have you had off work/education because of asthma?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

How many times have you been admitted to hospital with breathing or chest problems? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5+

About smoking:

Which best describes you? ☐ Never smoked ☐ Used to smoke, but don't now ☐ Still smoking

	1-5	6-10	11-15	16-20	21-30	31-40	41-50	50+
If you smoke or used to smoke, how many do you/did you smoke per day?	☐	☐	☐	☐	☐	☐	☐	☐
If you smoke, or used to smoke, how many years have you smoked/did you smoke?	☐	☐	☐	☐	☐	☐	☐	☐

Smoking can make asthma worse - if you still smoke, would you like support from your GP or practice nurse to quit?	Yes	No
	☐	☐

About your nose:

Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold? ☐ No ☐ Occasionally & little bother ☐ Occasionally & quite a bother ☐ Most days but little bother ☐ Most days & a lot of bother

Do any of the following upset your asthma? Tick all that apply. ☐ Colds ☐ Strenuous activity or exercise ☐ Allergies eg cats, dogs, pollen ☐ Cigarette smoke

Please complete other side

Do you have a preventer inhaler (usually brown, orange, red or purple)? ☐ *Yes* ☐ *No, skip to* ***Section B***

Which statement best describes how you take your regular Asthma treatment. Please tick only one box

☐ *I take it every day* ☐ *I take it some days but others I do not* ☐ *I used to take it, but now I do not* ☐ *I take it only when I have symptoms* ☐ *I never take it*

Please tell us how you well you use your preventer inhaler:

"I think my inhaler technique is very poor" ☐ *1* ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐ *6* "I think my inhaler technique is excellent"

About your preventer inhaler:	*Strongly disagree*	*Disagree*	*Not Sure*	*Agree*	*Strongly agree*
I need to take my inhaler(s) regularly for my asthma to be well controlled	☐	☐	☐	☐	☐
I find my inhaler(s) difficult to use	☐	☐	☐	☐	☐
Having to take regular asthma medication worries me	☐	☐	☐	☐	☐
I would prefer to take my asthma medications in a once a day dose	☐	☐	☐	☐	☐

Still about your preventer inhaler:	*Never*	*Rarely*	*Sometimes*	*Often*	*Always*
I use it only when I feel breathless	☐	☐	☐	☐	☐
I avoid using it if I can	☐	☐	☐	☐	☐
I forget to take it	☐	☐	☐	☐	☐
I decide to miss a dose	☐	☐	☐	☐	☐
I choose to take it once a day	☐	☐	☐	☐	☐

When you use your preventer inhaler:	*Yes*	*No*
Do you feel a sensation at the back of the throat?	☐	☐
Do you sometimes feel a need to cough	☐	☐
Do you feel your medication is deposited at the back of your throat?	☐	☐

Questions about preventer inhaler side-effects - please tick yes or no for each one

	Yes	*No*		*Yes*	*No*
Continual sore mouth/throat	☐	☐	Hoarse voice	☐	☐
Oral Thrush	☐	☐	Abnormal Weight Gain	☐	☐
Bruising	☐	☐	Cough	☐	☐

Section B: Have you had your inhalers checked in the last 12 months? ☐ *Yes* ☐ *No*

Have you seen a specialist respiratory doctor or nurse outside the practice? ☐ *In the last year* ☐ *More than a year ago* ☐ *Never*

If you have a peak flow meter, please tell us your reading today:

for example: 4 2 0 ☐ *I don't have a peak flow meter*

In the future, would you be willing to participate in further research? If yes, please return your cover letter with this questionnaire ☐ *Yes* ☐ *No*

Practice Ref:

Survey Ref:

APPENDIX 2: OPCRD DATA DICTIONARY

1. Patient

The **Patient** file contains basic patient demographics, patient registration and practice registration details.

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Practice_ID	Unique practice identifier.
Year_Of_Birth	Patient year of birth in format YYYY
Gender	Patient gender
Status	Patient registration status - (R) – Registered, (L) – Left, (D) - Death
Joined_Date	Date joined practice or date first registered on database
Leaving_Date	Date left practice or date first registered on database
Leaving_Reason	Reason for leaving practice
Post_Code	"Out" part of patient postcode and first character of "in" part of patient post code

2. Clinical

The **Clinical** file contains medical history events. This file contains all the medical history data entered on the GP system, including symptoms, signs and diagnoses. This can be used to identify any clinical diagnoses, and deaths. Patients may have more than one row of data. The data is coded using Read codes, which allows linkage of codes to the medical terms provided.

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Event_Date	Date of event
Read_Code	Five byte read code for event including terminal code if available
Read_Term	Rubric associated with read_code
Numeric_1	First numeric value if stored
Numeric_2	Second numeric value if stored
Text	First 50 characters of any text associated with entry

3. Referral

The **Referral** file provides details of all referrals for the defined patient cohort identified by a medical code indicating the reason for referral. This table contains information involving patient referrals to external care centres (normally to secondary care locations such as hospitals for inpatient or outpatient care).

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Event_Date	Date of event in format dd/mm/yyyy
Read_Code	Five byte read code for event including terminal code if available
Read_Term	Rubric associated with read_code
Referral_Type	Referral type e.g. Outpatient
Referral_To	Organisation referred to

Specialism	Referral by e.g. GP referral
Attendance_Type	Attendance type e.g. First visit, follow up

4. Therapy

The **Therapy** file contains details of all prescriptions on the GP system. This file contains data relating to all prescriptions (for drugs and appliances) issued by the GP. Patients may have more than one row of data. Drug products and appliances are recorded by the GP using the Multilex product code system.

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Event_Date	Date of event in format dd/mm/yyyy
Drug_Code	Coding for drug
Drug_Term	Drug term associated with drug code
Form	Formulation e.g. inhaler, tablets etc
Dosage	Usage instructions
Quantity	The quantity supplied
numberpack	Number of packs prescribed
packsize	The units of quantity supplied. (the preparation)
issue_ty	Type of issue where A = Acute Issue, R = Repeat Issue
strength	Drug strength
numberdays	Treatment days
bnf_code	BNF code

5. Practice

The **Practice** file contains details for practices, including region and collection information.

Field Name	*Content*
PracticeID	Unique OPC practice id
Practice_NHS	Unique NHS practice identifier.
Practice_Name	Name of practice
Practice_Address1	Address line 1
Practice_Address2	Address line 2
Practice_Address3	Address line 3
Practice_Address4	Address line 4
Practice_Postcode	Post Code
Practice_list_size	Total practice list size
Last_Extract_Date	Date when practice last did an extract

6. Asthma Questionnaire Data Collection

The **Asthma Questionnaire Data Collection** file contains the data collected from the questionnaires received from patients participating in the OPC Asthma Review Service. The file provides the original response as well as calculated values derived from the patient responses to the questions. Questions currently being surveyed are the following:

Questions	***Answer Options***
In the last week, how many times have you used your reliever inhaler (usually blue).	0–9; ≥10
In the last 7 days, how many days has asthma interfered with your normal activities?	0–7
In the last 7 days, how many nights have you been affected/woken by asthma symptoms (including cough)?	0–7
In the last 7 days, how many days have you experienced asthma symptoms?	0–7
In the last 4 weeks, did you miss any work, school or normal daily activity because of your asthma?	Yes; No; Unsure
In the last 4 weeks, did you wake up at night because of asthma?	Yes; No; Unsure
In the last 4 weeks, did you believe that your asthma was well controlled?	Yes; No; Unsure
In the last 4 weeks, in general, do you use an inhaler for quick relief from asthma symptoms?	Yes; No; Unsure
If yes, in the past 4 weeks, what was the highest number of puffs in 1 day you took of the inhaler?	0 / 1 to 4 puffs; 5 to 8 puffs; 9 to 12 puffs; More than 12 puffs
In the last 12 months, how many times have you needed a course of steroid tablets for worsening asthma.	0–9; ≥10
In the last 12 months, how many days have you had off work/education because of asthma.	0–9; ≥10
In the last 12 months, how many have you been admitted to hospital with breathing or chest problems?	0–9; ≥10
In the last 12 months, how many time have you been treated in accident and emergency or anywhere other than your GP surgery for your asthma?	0–9; ≥10
About smoking, which best describes you?	1 = Never smoked, 2 = Current Smoker, 3 = Ex-smoker
If you smoke or used to smoke, how many cigarettes do you/did you smoke per day?	1-5; 6-10; 11-15; 16-20; 21-30; 31-40; 41-50; >50
If you smoke, or used to smoke, how many years have you smoked/did you smoke?	1-5; 6-10; 11-15; 16-20; 21-30; 31-40; 41-50; >50
Smoking can make asthma worse - if you still smoke, would you like support from your GP or practice nurse to quit?	Yes / No
Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold?'	No / Occasionally & Little Bother / Occasionally & Quite a Bother / Most days & Little Bother / Most Days & a lot of bother
Do any of the following upset your asthma?	Colds / Strenuous Activity & Exercise / Allergies e.g. cats, dogs, pollen / Cigarette smoke

Thinking about how often you take your regular Asthma treatment during the day:	1 = I always take it exactly at the time prescribed. 2 = I occasionally miss the odd dose. 3 = I often miss or forget to take doses. 4 = I take all once a day- it's easier. 5 = I never take it.
I think my inhaler technique is very poor / I think my inhaler technique is excellent.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I do not need to take my inhaler(s) for my asthma to be well controlled / I need to take my inhalers(s) regularly for my asthma to be well controlled.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I find my inhaler(s) easy to use / I find my inhaler(s) difficult to use.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
Taking regular asthma medication does not worry me / Taking regular asthma medication worries me.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I prefer to take my asthma medications in a twice daily dose / I prefer to take my asthma medications in a once a day dose.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I use it regularly / I use it only when I feel breathless.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never avoid using it if I can / I always avoid using it if I can.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never forget to take it / I always forget to take it.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never decide to miss a dose / I always decide to miss a dose.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never choose to take it once a day / I always choose to take it once a day.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
When using preventer inhaler, do you feel a sensation at the back of the throat?	Yes / No
When using preventer inhaler, do you sometimes feel a need to cough?	Yes / No
When using preventer inhaler, do you feel your medication is deposited at the back of your throat?	Yes / No
Experience any side effects for the preventer inhaler?	Yes / No
Perceived Side Effects: Continual sore throat?	Yes / No
Perceived Side Effects: Hoarse voice?	Yes / No
Perceived Side Effects: Oral Thrush?	Yes / No
Perceived Side Effects: Abnormal Weight Gain?	Yes / No
Perceived Side Effects: Bruising?	Yes / No

Perceived Side Effects: Cough?	Yes / No
Have you had your inhaler technique checked in the last 12 months?	Yes / No
Have you seen a specialist respiratory doctor or nurse outside the practice?	Yes / No
Do you have a peak flow meter?	Yes / No
If you have a peak flow meter, please tell us your reading today?	Value
In the future, would you be willing to participate in further research?	Yes / No
Do you have a preventer inhaler?	Yes / No

APPENDIX 3: EXACERBATION DEFINITIONS

OBJECTIVE PROXY MEASURES FOR EVALUATING MODERATE-TO-SEVERE ASTHMA EXACERBATIONS IN ROUTINE PRIMARY CARE DATASETS

a. Moderate-to-severe exacerbations: based on the ATS/ERS taskforce definition, any of:
(i) Asthma-related:
    a. Hospitalisations (inpatient admissions) OR
    b. A&E attendance OR
(ii) Use of acute oral steroids

b. Extended clinical exacerbation definition: extension of the ATS/ERS exacerbation based on clinical guidance that exacerbations are often recorded as lower respiratory tract infections in routine management:
(i) Asthma-related
    a. Hospitalisations (inpatient admissions) OR
    b. A&E attendance OR
    c. Out-of-hours attendance OR
(ii) Use of acute oral steroids
(iii) Antibiotic prescriptions for lower respiratory tract infections

SUBJECTIVE CONTROL MEASURES – EVALUABLE USING PATIENT QUESTIONNAIRE RESPONSES:

GINA levels of asthma control

A. Assessment of current clinical control (preferably over 4 weeks)			
Characteristic	Controlled (all of the following)	Partly controlled (any present in any week)	Uncontrolled
Daytime symptoms	None (≤2 per week)	More than twice per week	≥3 or more features of partly controlled asthma*†
Limitation of activities	None	Any	
Nocturnal symptoms	None	Any	
Need for rescue / "reliever" mediation	None (≤2 per week)	>2 per week	
Lung function (PEF or FEV_1)‡	Normal	<80% predicted or personal best (if known)	

*Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate
†By definition, an exacerbation in any week makes that an uncontrolled asthma week
‡Without administration of bronchodilator
Lung function is not a reliable test for children 5 years and younger

APPENDIX 4: THE RESPIRATORY EFFECTIVENESS GROUP

The Respiratory Effectiveness Group (REG) is an investigator-led initiative that brings together expert respiratory researchers and advocates to set the agenda and raise the profile of real-life research with the aim of improving and reinforcing the quality of real-life research, and elevating its quality, profile and influence.

Nature of the organisation

The Respiratory Effectiveness Group is registered under the laws of England and Wales as "Respiratory Effectiveness Limited" as a social enterprise company (head office located at: 5a Coles Lane, Oakington, Cambridge, CB24 3BA, United Kingdom, company number: 8354149).

Social Enterprises under the law of England and Wales:

A social enterprise is a business that trades for a social and/or environmental purpose. It must have a clear sense of its 'social mission' and how it plans to achieve it. It must have clear rules about what it does with its profits, reinvesting these to further the 'social mission'.

Funding of the Respiratory Effectiveness Group

The REG will be funded through multiple grants from commercial sponsors. All moneys donated to the group will be provided as unrestricted grants and pooled for communal use. No money provided by any one funder will be ring-fenced for a particular REG activity. The activities carried out by the group will be set by the members of the group and not by the group's funders.

Members of the group receive no direct payment for their time and expertise, but will be reimbursed for reasonable expenses directly incurred in the undertaking of REG-related activities.

Objectives

All REG members will work together to achieve the common goal of: raising the profile of real-life research in: the research and academic, political, regulatory and public arenas by:

- Providing leadership and achieve excellence in real-life research.
- Setting and (where necessary) raising, standards in real-life research.
- Evaluating mechanisms for integrating real-life research appropriately into clinical practice guidelines.
- Evaluating the appropriate incorporation of real-life research findings into clinical practice.
- Providing ethical review and registration of real-life research study protocols.
- Communicating best practice standards in real-life research and the (appropriate) contribution it can make to the evidence base.
- Engaging with authorities (e.g. drug licensing bodies) to ensure real-life research is appropriately incorporated into drug licensing processes and national and international health strategies.
- Working with organizations (guideline bodies, research organizations and beyond) who are committed to the shared-goals of the group.

The initiative's activities will focus on three core areas:

(1) **Research and Academia:** influencing and improving best practice by:
- Conducting high-quality real-life research
- Setting quality standards for real-life research
- Appraising the existing guidelines and their evidence grading
- Validating research outcomes
- Offering expert review and registration of real-life research protocols.
- Undertaking communication activities to educate those new to the field of real-life research of its role and relevance.

(2) **Political:** work alongside national and international government and regulatory bodies to ensure real-life research is appropriately incorporated into the regulatory process and national and international health

(3) **Public:** where appropriate, share meaningful real-life research findings with those affected so as to empower, educate and inform them to take control of their condition and optimize their health outcomes.

Annual activity summary

Each year the REG will undertake: research activities; quality assurance activities; communication and educational activities; collaborative / engagement activities with other organisations, including other respiratory and inter-disciplinary research groups, guideline bodies and regulatory bodies.