REG STUDY PROTOCOL

TITLE:

A PREDICTION MODEL FOR FUTURE EXACERBATION RISK IN CHILDREN

Research Protocol developed by The Respiratory Effectiveness Group

Date: 29 November; **Version:** 1.0

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BACKGROUND & RATIONALE

Asthma attacks in children are common and result in considerable morbidity and occasionally mortality. Additionally, childhood asthma attacks may adversely affect their education, their parents economic productivity and always incur costs to the healthcare system. Remarkably little is understood about factors which predict childhood asthma attacks and much of what is known is derived from relatively small clinical trials in countries other than the UK and the results may not be generalisable. The present analysis will use routinely acquired data collected in primary care in the UK to identify factors associated with asthma attacks in children. Predictive variables will include demographics (the child's age and sex), asthma characteristics (severity, control and past attacks) and physiological measurements (obesity, lung function and blood eosinophil count). Blood and airway eosinophilia are both risk factors for asthma attacks in adults and whilst the latter would be preferable, this is not routinely collected whereas blood eosinophil count is often measured and is used in this analysis.

AIM & OBJECTIVE

The aim of this study is to create a tool to predict which paediatric patients are at risk of future exacerbation.

It is recognised that previous exacerbations are predictive of future exacerbations; and additional specific questions to be answered from the data include:

- What proportion of patients have an exacerbation during the year post-Index Date?
- What proportion of patients with 1 exacerbation in the year prior to Index Date have an exacerbation during the year post-Index Date?
- What proportion of patients with 2 exacerbations in the year prior to Index Date have an exacerbation during the year post-Index Date?

However, a predictive model will also highlight additional "novel" factors predictive of future risk.

STUDY DESIGN & DATASET

Data source

A combined dataset of patients from Clinical Practice Research Datalink (CPRD) and the Optimum Patient Care Research Database (OPCRD) is used for analyses.

CPRD[1], formerly known as the General Practice Research Database (GPRD), is a computerised longitudinal research database containing anonymised medical record data from approximately 650 subscribing UK primary care practices.

OPCRD[2] is a respiratory-focused primary care research database of Optimum Patient Care providing chronic respiratory review services. It contains anonymous, longitudinal data extracted from over 550 UK practices (>800.000 asthma patients). It is approved by Trent

[1] https://www.cprd.com
[2] See http://optimumpatientcare.org/opcrd/

Multi Centre Research Ethics Committee for clinical research use and offers a high-quality data source that is used regularly in clinical, epidemiological and pharmaceutical research.

Both datasets are constructed separately using CPRD and OPCRD data in a patient unidentifiable form with harmonised variables. Previous studies using these combined datasets have shown very limited potential overlap (~2%) in patient records obtained from both databases. Potential duplicate data records are removed from the dataset by matching on a number of variables, such as the year of birth, gender and date of the last blood eosinophil count. In case of potential duplicates, data from CPRD are kept. During this process patients will never become identifiable.

Study Design

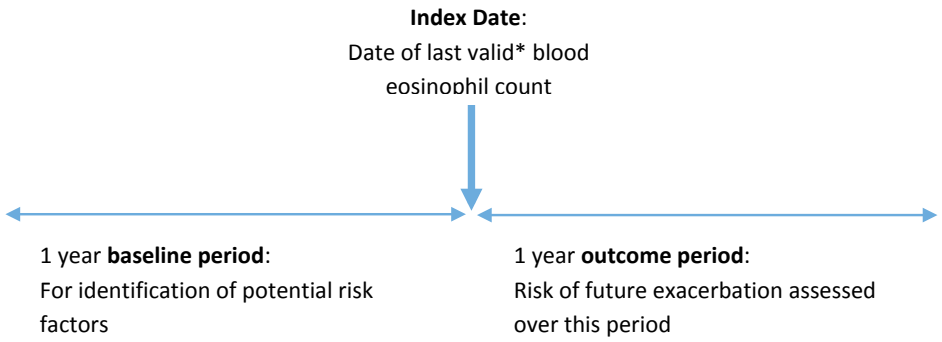

Figure 1: Study Design

Study Period

Data available from 1st Jan 1999 through April 2012 for the CPRD and through December 2012 for the OCRD will be used.

Index event

Index event: Date of the patient's last valid blood eosinophil count.

Baseline & Outcome periods

Baseline period: patients will be characterised over a one-year period immediately prior to IPD for identification of potential asthma exacerbation risk factors
Outcome period: Outcomes will be evaluated in the year immediately following IPD to assess risk of future asthma exacerbations

STUDY POPULATION

Eligibility Criteria

Inclusion criteria

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

- Valid blood eosinophil count expressed as a numeric value ≤5000 blood eosinophils/µl, recorded at least 1 year prior to the end of available data
- Aged 5-12 years at date of last valid blood eosinophil count
- An asthma diagnosis (at any time)
- 2 years of continuous data (one year pre/ one year post date of last valid blood eosinophil count).

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Exclusion criteria

Patients will be excluded if they meet the following criteria:

- Diagnosis of any other chronic respiratory disease

OUTCOMES

Primary outcomes

1. Exacerbations:

An exacerbation is defined as the occurance of the following:

- Respiratory-related hospital attendance / admission AND/OR
- Respiratory-related A&E attendance AND/OR
- An acute oral corticosteroids course

Potential Exacerbation Risk Factors

2. Blood eosinophil count
3. Percent Predicted Peak Flow
4. Number of GP consults for lower respiratory tract infections
5. Acute oral steroid usage
6. Hospital in-patient admissions
7. GINA management step

Exploratory outcomes

8. Demographic and clinical characteristics:
    a. Age
    b. Sex
    c. Height
    d. Weight
    e. BMI
    f. Comorbidities
        i. Allergic and non-allergic rhinitis
        ii. Hay fever diagnosis
        iii. Eczema
    g. Medication prescriptions
        i. NSAIDS
        ii. Paracetamol
    h. History of anaphylaxis

ANALYSIS; VARIABLES & STATISTICAL APPROACH

Analysis

Univariable logistic regression models will be used to identify baseline measures of disease severity, patient demographics and comorbidities predictive of future exacerbations. The dichotomous variable indicating an exacerbation during the outcome period (YES/NO) will be used as the dependent variable with each measure of disease severity, patient demographic and comorbidity as an explanatory variable. Those variables which show an association ($p < 0.05$) with future exacerbation will be entered into a multivariable model and step-wise reduced to produce a final list of non-collinear predictors of one or more future exacerbations. Results will be presented as odds ratios (OR) with 95% confidence intervals (95% CI).

This process will be repeated with 0/1 versus 2+ future exacerbations as the dichotomous dependent variable to produce a list of non-collinear predictors of two or more future exacerbations.

LIMITATIONS OF STUDY DESIGN / ANALYSIS

As with all database studies, a number of limitations exist such as: incomplete data and the need to use proxy measures where explicit data are not available. A further limitation of the OPCRD as a UK primary care database is the limited data available on patients' secondary care contacts (e.g. emergency department attendances, hsoptial admission) and use of other healthcare services (e.g. out of hours, walk-in centres). The limited recording of such data is anticipated to lead to an under-estimate of the true number of exacerbations in the study population.

The data from observational studies should be viewed as one element of the overall evidence base and considered in combination with data from other study designs and is intended as a precursor to a prospective pragmatic trial validation.

DATA DISSEMINATION PLANS

REG is committed to registering all research that it conducts (on the ENCePP e-registry) and to publishing all study findings in order to ensure: (i) transparency of its activities and (ii) so that REG-funded research can be used to inform the research and lay community.

At least one abstract from the study will be submitted to a key international respiratory congress (e.g. the European Respiratory Society, American Thoracic Society or similar) and at least one manuscript will be developed and submitted for to a peer review respiratory journal to disseminate the primary elements of the planned analysis.

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.

Ethics for CPRD data use

STUDY TEAM

Co-Principle Investigators
Steve Turner: Senior Clincial Lectuer, Child Health, University of Aberdeen, Aberdeen, UK

Steering Committee Members
The study steering committee will include members of the REG Child Health Working Group and on-going REG Asthma Risk Predictors study. A full list of the steering committee members is detailed below:

Wanda Phipatanakul: Associate Professor of Pediatrics, Boston Children's Hospital, Boston, MA, USA
Nikolaos G. Papadopoulos: Professor of Allergy and Pediatric Allergy, Center for Pediatrics and Child Health, Institute of Human Development, The University of Manchester

Royal Manchester Children's Hospital, Manchester, UK

Clare Murray: University of Manchester and Royal Manchester Children's Hospital, Manchester, UK

Alan Kaplan: Family Physician Airways Group of Canada and Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada
James Paton: Clinical Reader (Child Health), University of Glasgow, Glasgow, UK
Teoh Oon Hoe: Department of Paediatrics, Respiratory Medicine Service Head & Senior Consultant, KK Women's and Children's Hospital, Singapore, Singapore
Alberto Papi: Head Respiratory Medicine and Research Center on Asthma and COPD University of Ferrara and S. Anna University Hospital, Ferrara, Italy
John Blakey: Senior Clinical Lecturer, Liverpool School of Tropical Medicine
Mike Thomas: Professor of Primary Care Research at the University of Southampton, Southampton, UK
David Price: Professor of Primary Care Respiratory Medicine at the University of Aberdeen, UK
Emilio Pizzichini: Professor of Medicine, Universidade Federal de Santa Catarina, Hospital Universitário – NUPAIVA, Florianópolis, Brazil