Study protocol

Asthma and Type 2 Comorbidities

Real-life Characterisation of Patients with Active Asthma and Type 2 Asthma Comorbidities

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Regeneron contact:
Siddhesh Kamat

Observational & Pragmatic Research Institute

OPRI Pte Ltd
60 Paya Lebar Road
Paya Lebar Square
Level 5, Unit 33 & 34
Singapore
409051

5a Coles Lane
Oakington
Cambridge CB24 3BA
United Kingdom

Phone +65 6802 9724
Web site http://www.opri.sg

Chief Investigator:

Professor David Price, Professor of Primary Care Respiratory Medicine and OPRI Director
Mobile: +44 7787905057
Office number: +44 2081233923
Skype ID: respiratoryresearch
Email: david@opri.sg

Project coordinator:

Victoria Carter, Research & Operations Director
Observational & Pragmatic Research Institute
Office address: 60 Paya Lebar Road, Paya Lebar Square, #05-33/34, Singapore 409051
Direct number: +65 8650 8766
Email: victoria@opri.sg

Study sponsor:

Regeneron
Sanofi

Primary contact

Siddhesh Kamat [siddhesh.kamat@regeneron.com]

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Study aims and objectives	Phase 1 To identify common clusters of T2 type comorbidities in a real world active asthma population. To identify a limited set of comorbidity clusters for further investigation. Phase 2 To describe the overlap between these clusters and between individual comorbidities within the clusters. This will include an investigation of the characteristics of each cluster by comorbidity severity and activity, eosinophil count and age. Patient demography, asthma severity, resource utilisation and costs will be compared within and between selected key clusters.
Country of study	United Kingdom
Author	OPRI Pte Ltd 60 Paya Lebar Road Paya Lebar Square Level 5, Unit 33 & 34 Singapore 409051

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
CCI	Charlson Comorbidity Index
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
FEV_1	Forced Expiratory Flow in one second
GINA	Global Initiative for Asthma
GP	General Practitioner
HES	Hospital Episode Statistics
HRU	Healthcare Resource Utilisation
ICS	Inhaled Corticosteroids
ICU	Intensive Care Unit
IQR	Interquartile range
LABA	Long Acting Beta-Agonists
LAMA	Long-acting Muscarinic Antagonists
LTRA	Leukotriene Receptor Antagonists
OCS	Oral Corticosteroids
OPC	Optimum Patient Care
OPCRD	Optimum Patient Care Research Database
PEF	Peak Expiratory Flow
PSSRU	Personal Social Services Research Unit
QOF	Quality and Outcomes Framework
RDAC	Risk Domain Asthma Control
SABA	Short Acting Beta-Agonists
SD	Standard deviation

1.0 Background

An estimated 334 million people suffer from asthma worldwide.[1] National studies show wide variation in achieving optimal asthma control, varying between 0% to 30%.[2,3] In a recent OPCRD report on over 100,000 UK active asthma patients, 20% were controlled and 60% were partially controlled.[4]

An important molecular mechanism of asthma is type 2 inflammation.[5] Asthma patients frequently suffer from T2 type comorbid conditions such as atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, and nasal polyposis.[6] Of these, allergic rhinitis may be the most common, with estimates of prevalence in asthma patients of 25% to 100%.[7,8] These conditions also frequently occur together in patients with asthma, and are more common in this group than in the wider population: the prevalence of co-morbid chronic rhinosinusitis and nasal polyps, for example, has been estimated at 7% in people with asthma and 4% in general population.[9]

T2 type comorbidities also recognised as important determinants of asthma management and prognosis as these are associated with inadequate disease control, higher health care use, and poor quality of life.[5] Studies from OPRI and others have reported that atopic dermatitis, for example, is associated with more frequent asthma attacks and more persistent asthma in comorbid patients.[10,11]

Because of the common underlying disease process, it has been suggested that successful treatment of one of these conditions might also improve related conditions. This was not demonstrated in a review of intranasal corticosteroids for allergic rhinitis and asthma control [12], but more recent treatments such as Dupilumab have shown promise in patients with moderate to secere atopic dermatitis and in those with persistent asthma. [13,14]

The frequency with which these related conditions co-occur/cluster in patients with asthma in the community has not yet been described, nor has the relationship of these comorbidity clusters with asthma severity, resource utilisation and cost.

2.0 Study aims and objectives

2.1 Study aims

To identify and characterise common clusters of T2-type comorbidities in patients with active asthma.

2.2 Study objectives

Phase 1: The primary objective is to estimate the frequency of each combination/cluster of T2 type comorbidities in a real world active asthma population, and to select, by consensus, a limited set of common comorbidity clusters for further investigation.

Phase 2: The primary objective is to describe the overlap between these clusters and between individual comorbidities within the clusters in terms of patient demography, and asthma severity, resource utilisation and costs.

3.0 Study design

3.1 List of comorbidities of interest

The nine T2-type comorbidities of interest are: atopic dermatitis; allergic rhinitis; chronic rhinosinutis; nasal polyps; urticaria; allergic conjuctivitis; food allergy; eosinophilic oesophagitis; and anaphylaxis.

3.2 Study design

A two-phase historical cross-sectional and cohort study using routine electronic patient records from UK primary care practices. The study period will be 2010-2017 (or the latest available data). It will include patients with active asthma. In Phase 1 the frequency of each combination of comorbidities will be estimated using most recent clinical data available for each eligible patient. In Phase 2, the clinical characteristics and service use in a 1-year period after the date of co-morbidity assessment will be described for a pre-selected set of common comorbidity clusters.

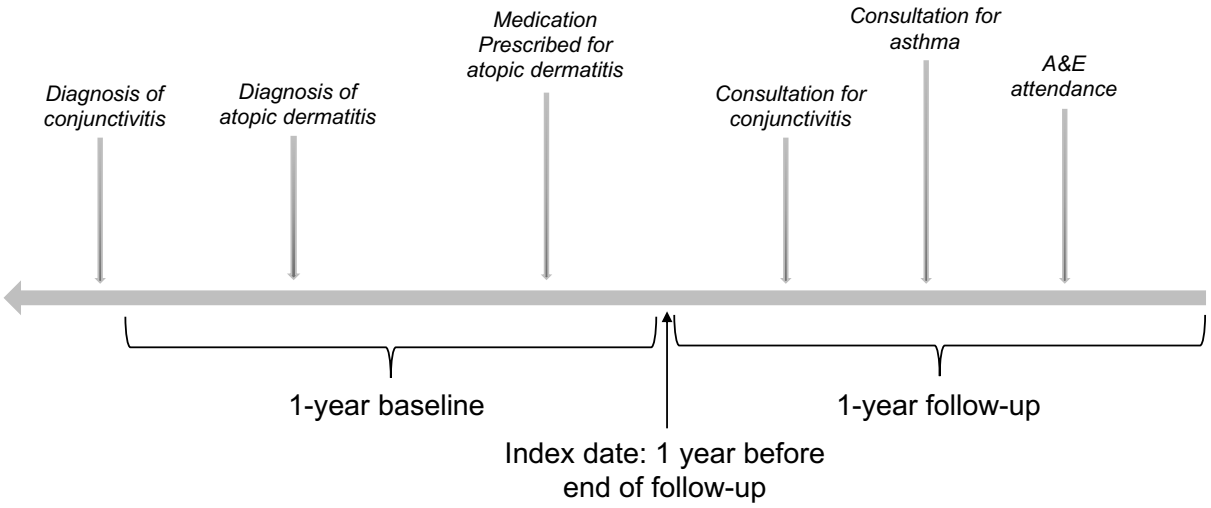

Figure 1: Study design Phase 2

4.0 Study population

4.1 Data sources

Phase 1: The Optimum Patient Care Research Database (OPCRD)

- Contains anonymous, longitudinal medical records for 5.3 million patients from about 700 primary care practices across the UK.
- Includes patient-level diagnostic, clinical and prescribing information.

Phase 2: The OPCRD and the Clinical Practice Research Datalink (CPRD).

- The CPRD includes linked primary and secondary care (HES) data for approximately 300 UK primary care practices.
- The HES records from the CPRD are required to identify secondary care service use and costs, and for some measures of disease severity.

4.2 Inclusion and exclusion criteria

Inclusion criteria

Registered at a participating practice for at least one year prior to their index date and within the study period. In phase 1, the cross-sectional assessment of co-morbidity co-occurrence, the index date for each patient will be the earlier of the following dates: the last data collection from each practice and 6 months before patient deregistration (to any avoid gaps in the clinical data due to late recording of patient deregistrations). For CPRD practices with linked HES data, the index date will be the earliest of the following dates: the last data collection from each practice, 6 months before patient deregistration, date of last HES record. In phase 2, the index date will be one year before the last data collection from each practice and 6 months before patient deregistration, to allow for one year of follow-up.

Patient had active asthma at their index date:

- a diagnosis of asthma at any time before their index date (using QOF Read codes: see Appendix 1); AND
- two or more prescriptions for an asthma medication in the preceding year.

Exclusion criteria

Any other chronic lower respiratory condition recorded at any time (Read coded: see Appendix 2). These are:

- Lung disease due to external agents, other than smoking, such as occupational agents.
- Active COPD (a Read code at any time + medication in the last year of follow-up).
- Bronchiolitis obliterans.
- Pulmonary fibrosis.
- Pulmonary hypertension.
- Cystic fibrosis

5.0 Study variables and study outcome definitions

5.1 Describing demographic and clinical variables

The demographic and clinical characteristics of interest at index date are: gender, age, smoking status, most recent recorded BMI prior to index date, most recent spirometry recorded prior to index date (PEF, FEV_1, FEV_1/FVC ratio), number with severe asthma, GINA step, Risk Domain Asthma Control and Overall Asthma Control, asthma medications in the year prior to index date, blood eosinophil count.

- Smoking status will be categorised as: never smoked; ex-smoker; or current smoker based on the latest recorded Read code prior to the index date.
- Body Mass Index (BMI) will be calculated from height and weight data if available (weight in kg/height in m^2) or taken from the practice recorded BMI value if not.
- The most recently recorded Peak Expiratory Flow (PEF), Forced Expiratory Flow in one second (FEV1) and Forced Vital Capacity (FVC) will be taken from the practice recorded value. FEV1/FVC ratio will be calculated using the last recorded of each of these two values. FEV_1% predicted will also be calculated and reported,
- Severe asthma will be defined according to the ERS/ATS guidelines (Chung, Kian Fan, et al. "International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma." European Respiratory Journal (2013): erj02020-2013).
- We will also report the number of patients meeting the definition of severe asthma used in Regeneron RCTs.
- GINA step will be determined by prescribed medication: see Appendix 4. Highest GINA step (1-5) in the year prior to the index date will be reported.
- Risk Domain Asthma Control (RDAC). Controlled asthma will be defined as the absence of the following in the year prior to the index date: (i) an asthma-related A&E attendance, in-patient admission or out-patient department attendance; (ii) an acute course of oral corticosteroids with evidence of a lower respiratory consultation; and (iii) an antibiotic prescribed with evidence of a lower respiratory consultation.

- Overall Asthma Control. Controlled asthma will be defined as the absence of the following aspects of asthma risk during the baseline year: attainment of RDAC and an average daily dose of ≤200mcg salbutamol / ≤500mcg terbutaline.

- The asthma medications of interest are: ICS, ICS/LABA, SABA, SAMA, LABA, LAMA, LABA/LAMA, LTRA, biologics (where known), and chronic oral corticosteroids (see Appendix 5 for algorithm to distinguish between acute and chronic oral corticosteroid prescribing).

5.2 Identifying comorbidities of interest

The nine T2-type comorbidities of interest (atopic dermatitis; allergic rhinitis; chronic rhinosinutis; nasal polyps; urticaria; allergic conjuctivitis; food allergy; eosinophilic oesophagitis; and anaphylaxis) will be identified by the presence of a Read code for the condition in the patient record. Anaphylaxis will also be identified by the prescription of adrenaline. Appendix 3 lists conditions where there are existing Read code definitions and those which will be developed during the study.

5.3 Categorising comorbidity activity and severity

Many of the comorbidities can be futher characterised as inactive or active, and mild or moderate/severe at the index date using prescribing and primary and secondary consultation data. A comorbidity will be defined as inactive in the year prior to the index date if it was not classified as active. Similarly, a comorbidity will be defined as mild in the year prior to the index date if it was not classified as moderate/severe.

Following a rapid review of the definitions applied by studies using routine patient data and prescribing guidelines, the following definitions were adopted.

Note on medications with more than one indication

The indication for a prescription may not be recorded as the time it is issued and some medications can be indicated for more than one of the comorbidities of interest. Following a review of the approaches used in other published studies, the diagnosis recorded closest in time to the initiation of the medication will be taken as the indication. Similarly, the reason for outpatient consultations is not routinely coded in HES data and individual hospital specialties may treat more than one of the comorbidities of interest (e.g. ENT treating both allergic rhinitis and chronic rhinosinutis). Where this occurs we will attribute the outpatient consultation to the diagnosis recorded closest in time to the secondary care consultation.

Atopic dermatitis

Active: A primary or secondary care consultation in the previous year. Prescription of a topical corticosteroid in the previous year.

Moderate/severe: A primary or secondary care consultation in the previous year. Prescription of a medium- to high-potency topical corticosteroid in the previous year (see Appendix 6 for categorisation of topical corticosteroid preparations).

Allergic Rhinitis

Active: A primary or secondary care consultation in the previous year. Prescription of a nasal corticosteroid in the previous year.

Moderate/severe: A primary or secondary care consultation in the previous year. Three or more nasal corticosteroid in the previous year.

Chronic Rhinosinutis

Active: Always active as this is a chronic condition.

Moderate/severe: A primary or secondary care consultation in the previous year. Three or more nasal corticosteroid prescriptions in the previous year.

Nasal polyps

Active: Always active.

Moderate/severe: A primary or secondary care consultation in the previous year. Three or more nasal corticosteroid in the previous year. Polypectomy at any time.

Urticaria

Active: A primary or secondary care consultation in the previous two years. Prescription of an oral antihistamine in the previous year.

Moderate/severe: A primary or secondary care consultation in the previous year. A double or greater dose of an oral antihistamine at any time prior to the index date.

Allergic Conjunctivitis

Active: A primary or secondary care consultation in the previous year. Prescription of any topical eye drop in the previous year.

Moderate/severe: A primary or secondary care consultation in the previous year. Two or more prescriptions of any topical eye drop in the previous year.

Food Allergy

Active: Always active.

Moderate/severe: A primary care consultation in the previous year. A secondary care consultation in the past two years. A prescription for adrenaline in the past 30 months (adrenaline has an 18-month shelf life). Anaphylaxis at any time.

Eosinophilic oesophagitis

Active: Always active (as long-term treatment required).

Moderate/severe: Always categorised as moderate/severe (differentiation not appropriate).

Anaphylaxis

Active: Always active (there is always a risk of a subsequent episode).

Moderate/severe: A secondary care consultation, ER attendance or hospital admission in the past year. A prescription for adrenaline in the past 30 months (adrenaline has an 18-month shelf life).

Sources

[1] How much of a topical agent should be prescribed for children of different sizes? Andrew A. Nelson, Alicia D. Miller, Alan B. Fleischer, Rajesh Balkrishnan, Steven R. FeldmaJ Dermatolog Treat. 2006; 17(4): 224–228.

[2] UpToDate (https://www.uptodate.com/home).

[3] Rapid reviews to identify comorbidity definitions used in other studies using routine patient data (see Appendices 13 and 14).

[4] Fardet L, Petersen I, Nazareth I. Common Infections in Patients Prescribed Systemic Glucocorticoids in Primary Care: A Population-Based Cohort Study. PLoS Med. 2016; 13(5); e1002024.

[5] Lucendo AJ, Arias Á, Molina-Infante J, Arias-González L. The role of endoscopy in eosinophilic esophagitis: from diagnosis to therapy. Expert Review of Gastroenterology & Hepatology. 2017; 11(12): 1135-1149.

5.4 Quantifying health resource use (HRU) and costs

The following HRU outcomes and associated costs will be tabulated for each of the comorbidity clusters identified in phase 1. These will be for the year prior to the index date. Secondary care resource use and costs will be limited to patients with linked secondary care (HES) data and the most recent HES year. Costs will be reported in 2017 GB pounds.

Primary care

1. Physician office visits:
    a. Number and cost of asthma-related consultations.

2. Number of primary care medication prescriptions:
    a. ICS
    b. ICS/LABA
    c. SABA
    d. SAMA
    e. LABA
    f. LAMA
    g. LABA/LAMA
    h. LTRA
    i. biologics (where known)
    j. chronic oral corticosteroids
    k. antibiotics

3. Total cost of asthma drug prescribing.

4. Total cost of oral corticosteroid and antibiotic prescribing.

5. Total primary care costs (physician office visits + prescribing).

Secondary care

6. Outpatient visits:
    a. Number and cost of asthma-related outpatient visits.

7. Emergency Room attendances:
    a. Number and cost of asthma-related Emergency Room attendances.

8. Inpatient hospital admissions:
    a. Number and cost of asthma-related hospital admissions.

9. Total secondary care costs (outpatient + ER + inpatient).

Combined primary and secondary HRU and costs

11. Total primary and secondary care costs (primary care + secondary care).

6.0 Statistical analysis

6.1 Sample size

Phase 1: Approximately 220000 OPCRD patients with active asthma will be available for inclusion in this phase. Of these, approximately 85000 have moderate to severe asthma (GINA steps 4 & 5).

Phase 2: Approximately 220000 OPCRD patients and 440000 CPRD patients with active asthma will be available for inclusion in this phase (85000 moderate to severe from OPCRD and 170000 moderate to severe from CPRD). Approximately 260000 of the CPRD patients will have linked secondary care data (HES): the HES records are required to identify secondary care service use and costs, and for some measures of disease severity.

6.2 Software used

Stata MP/6 version 15.1.

6.3 CONSORT chart

A CONSORT-type chart, describing the number and proportion of patients retained and excluded at each step of the inclusion/exclusion criteria will be generated for each study phase.

6.4 Demographic and clinical characteristics of patients at index date (phase 1 and 2)

Phase 1: The demographic and clinical characteristics at index date of patients included in the analysis will be tabulated: this will include the number and proportion of patients with each of the comorbidities of interest. For completeness, the number of patients with no comorbidities will also be reported. As it will not be possible to distinguish between inactive and active comorbidity and mild to moderate/severe comorbidity for all comorbidities of interest without linked HES data, this will be reported as the number of patients with active/inactive comorbidity.

Phase 2: A similar set of outputs will be produced for the second phase. In addition, the number and proportion of patients whose comorbidity is inactive, active, mild and

moderate/severe will be tabulated for each comorbidity using the primary care and linked HES data.

Patient characteristics at index date will be reported for the study population using the following conventions:

- Continuous variables will be summarised using descriptive statistics: n (non-missing sample size), percentage of non-missing, mean, standard deviation, median, inter-quartile range (25th and 75th percentile), maximum and minimum.
- For categorical measures, the frequency and percentages (based on the non-missing sample size) of observed levels will be reported.

Comorbidity prevalence will be estimated for each comorbidity cluster by dividing the number of patients in the cluster by the total number of patients eligible for inclusion in the study.

The ratio of observed to expected cases for each comorbidity cluster will be estimated by dividing the observed prevalence of the cluster by the expected prevalence of the cluster (the product of the prevalence of each individual disease in the cluster).

6.5 Identification and selection of comorbidity clusters (phase 1)

There are over 500 possible combinations of the 9 comorbidities of interest. The prevalence of each combination of comorbidities will be tabulated (including patients with no comorbidities) (see mock table in appendix 8). Clusters will be ranked by prevalence. The ratio of observed cases to expected for each cluster and cumulative proportion of population accounted for at each step will be calculated.

Visualisations of the frequency and age distribution of comorbidity in the asthma population will be produced. A table with the source data will accompany each figure. The first figure will chart the frequency of comorbidities in the study population (see illustrative example in appendix 9). The second figure will chart the mean number of comorbidities in the asthma population by age group and gender (appendix 10).

A small set of key comorbidity clusters will then be selected by consensus for further analysis in phase 2. This will be based on their clinical importance, prevalence, observed/expected ratio and cumulative proportion of population included.

6.6 Characterisation of selected comorbidity clusters (phase 2)

The associations between the individual diseases in the selected clusters will be illustrated in graph format (appendix 11). This will show which diseases are often diagnosed together. An edgelist, a list of all disease pairs in the clusters, will be used to calculate the position of each disease in two-dimensional space using a multidimensional scaling procedure.

This will include an investigation of the characteristics of each cluster by comorbidity severity and activity, eosinophil count and age. Patient demography and asthma severity will also be compared within and between these key comorbidity clusters. Associations between specific co-morbidity patterns and disease severity will be estimated using logistic regression, adjusting for confounders.
The list of tables and figures to be produced will be finalised at the beginning of phase 2.

6.7 Healthcare resource utilisation (HRU) and costs (phase 2)

The HRU outcomes and associated costs will be calculated and reported for each of the outcomes of interest in the year prior to the index date (mock table in appendix 12).
Associations between specific co-morbidity patterns and healthcare resource utilisation and costs will be estimated using generalised estimating equations with cluster robust standard errors, log link and gamma distribution, adjusting for confounders.

Secondary care resource use and costs will be limited to patients whose practices have linked secondary care (HES) data.

Prices assigned to primary care consultation costs will be taken from the latest Personal Social Services Research Unit (PSSRU) document (http://www.pssru.ac.uk/project-pages/unit-costs/2017/index.php)

Prices assigned to secondary care costs will be based on the national average hospital costs as found in PSSRU document.

Prices assigned to drugs will be taken from the Dictionary of Medicines and Devices browser (http://dmd.medicines.org.uk/). The electronic British National Formulary (eBNF) and the Medical Index of Medicinal Substances (MIMS) will be used to fill any gaps.

6.8 Confounding handling approach

The multivariable models will be adjusted on variables that are known or show to confound the association of interest. For this we will use both expert opinion and a data driven technique using bias potential.

Expert opinion will decide what set of baseline characteristics will always be adjusted on in the models. Also, expert opinion will decide on the set of candidate confounders to consider in the next step, using bias potential assessment. This assesses the degree to which the observed association between the exposure of interest and the outcome is affected by conditioning on the variable. It measures the relative change in coefficient of the exposure compared to the model without the candidate confounder. Confounder candidates will be introduced into the model iteratively, the one with the highest bias potential first. If the observed change in estimate if more than 2%, the variable is kept in the model, and all remaining candidates are re-evaluated until none of the confounder candidates are left or none cause a change in estimate of more than 2%.

6.9 Sensitivity analyses

It can be expected that the observed prevalence of a co-morbditiy is partly a function of the distribution of the length of the available medical record data, which can vary considerably. We assume that when a patient moves from one GP practice to another, the most relevant morbditiy information remains available in the medical record. To assess to what extent our assumption holds, we will repeat the phase 2 analyses in a subset of patients for whom we have at least 5 years of medical record history available.

7.0 Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu.

The OPCRD is approved by the Health Research Authority for clinical research use, and governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee. We will submit the finalised version of this protocol to ADEPT for approval.

Access to the CPRD for research use follows a similar governance process. We will submit an application and protocol for phase 2 of the study to their Independent Scientific Advisory Committee (ISAC) for approval.

8.0 Data dissemination

It is proposed that initial results be presented in poster and/or oral format at ATS 2019 and ERS/EAACI 2019. One manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine.

9.0 Advisory group

1) Professor Claus Bachert (ENT Specialist), University of Ghent

2) Dr Andrew Menzies-Gow (Respiratory Physician) Royal Brompton & Harefield NHS Foundation Trust, London, UK.

10.0 Research team

Research Organisation:

Observational & Pragmatic Research Institute (OPRI)

Chief Investigator:

David Price, Professor of Primary Care Respiratory Medicine and OPRI Director

Mobile: +44 7787905057

Office number: +44 2081233923

Skype ID: respiratoryresearch

Email: david@opri.sg

Other OPRI team members:

General Manager: Victoria Carter [victoria@opri.sg]

Medical Lead: Janwillem Kocks

Senior Researcher: Jaco Voorham (Lead)

Senior Statistician: Arul Earnest

Junior Researcher: Sarah Burrell

Senior Data Analyst: Derek Skinner

Medical Writer: Antony Hardjojo

Project research lead: Jaco Voorham [jaco@opri.sg]

Study sponsor:

Regeneron

Sanofi

Primary contact

Regeneron: Siddhesh Kamat [siddhesh.kamat@regeneron.com]

Sanofi: Asif Khan [asif.khan@sanofi.com]

11.0 Timelines

Action	Timeline
Contract signature	0
Literature search (comorbidity severity) & proposal	4 weeks (completed)
Proposal sign-off	1 week (completed)
Full Protocol delivery	3 weeks
Protocol sign-off	2 weeks – To be determined by Regeneron
Dataset delivery (OPCRD) + ADEPT approval	2 weeks
Phase 1 analyses	3 weeks
Sign-off on key clusters of interest	2 weeks – To be determined by Regeneron
Dataset delivery (CPRD) + ISAC approval	12-26 weeks (direct purchase from CPRD)
Phase 2a analyses	5 weeks
Phase 2b analyses	3 weeks
Final study report	3 weeks
Study report sign-off	2 weeks – To be determined by Regeneron
Conference abstract 1	ATS 2019
Conference abstract 2	ERS/EAACI 2019
Manuscript	6 weeks

12.0 References

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13.0 APPENDICES

13.1 Appendix 1: Read code lists for asthma (QOF)

See: 160715_Read codes_QOF asthma_v1.0.xlsx

13.2 Appendix 2: Read code lists for other chronic lower respiratory condition

See: 160513_Read code list_Other chronic respiratory disease Dx_v3.0.xlsx and 160219_Read code list_COPD diagnosis_Broad definition_v0.2.xlsx

13.3 Appendix 3: Read code lists for the comorbidities of interest

Existing code lists

Atopic dermatitis: 160129_Read codes_eczema diagnosis_v1.0.xlsx
Allergic rhinitis: 160120_Rhinitis diagnosis_read_codes_v1.0.xlsx
Nasal polyps: 160614_Read code list_Nasal polyps diagnosis_V1.0.xlsx
Anaphylaxis: 160211_Read codes_anaphylactic reactions_v1.0.xlsx

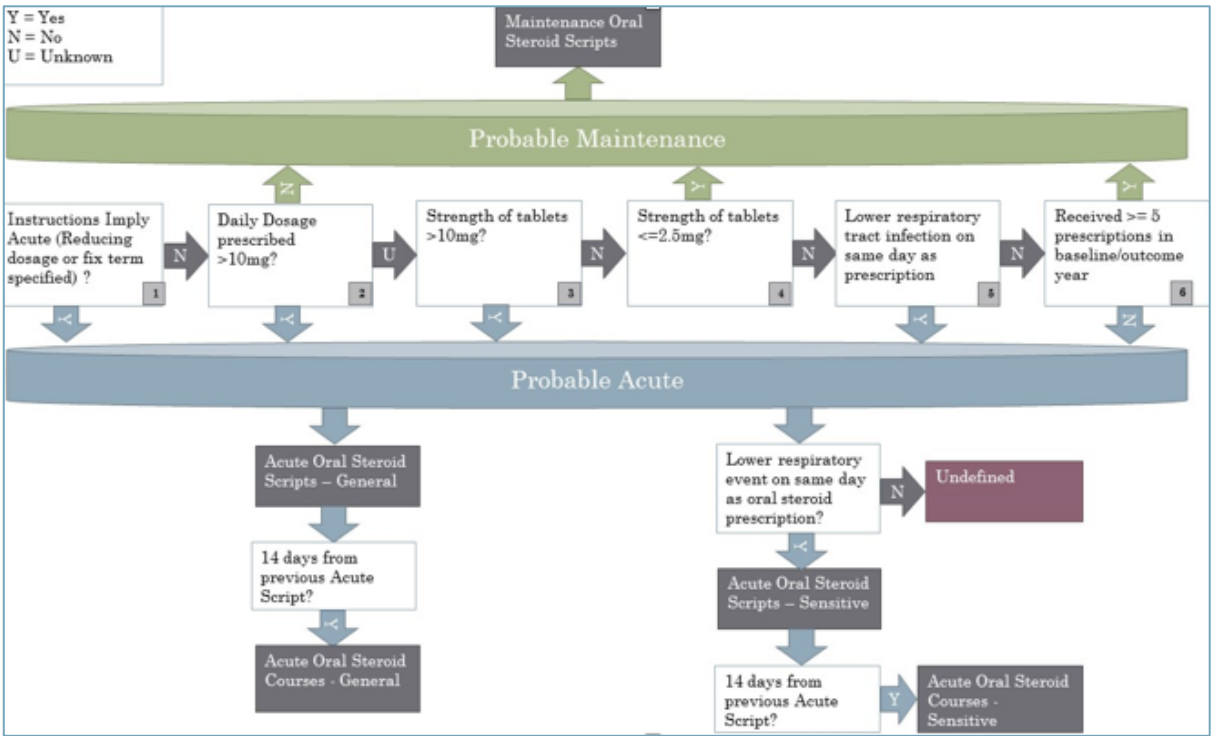
Code lists to be developed

Chronic rhinosinutis
Urticaria
Allergic conjuctivitis
Food allergy
Eosinophilic oesophagitis

13.4 Appendix 4: GINA step definition

GINA Step:	Drug Class Groups:
1	SABA **or** LABA +/- SABA(although discouraged without ICS)
2	Low dose (LD) ICS[1] +/- SABA **or** LTRA +/- SABA **or** THEO +/- SABA **or** LABA + THEO +/- SABA(although discouraged without ICS) **or**
3	LD ICS + LABA +/- SABA (adults) / Medium dose (MD) ICS + LABA +/- SABA (children) **or** MD ICS +/- SABA LD ICS + LTRA +/- SABA **or** LD ICS + THEO +/- SABA **or** LD ICS + LABA + LTRA +/- SABA **or** LD ICS + LABA + THEO +/- SABA **or** LD ICS + LABA + LTRA + THEO +/- SABA **or**
4	MD /High dose (HD) ICS + LABA +/- SABA (adults) **or** HD ICS + LABA +/- SABA (children)
5	MD/HD ICS + LTRA +/- SABA **or** MD/HD ICS + THEO +/- SABA **or** MD/HD ICS + omalizumab **or** ICS + LABA + Maintenance oral steroids +/- SABA **or** ICS + LTRA + Maintenance oral steroids +/- SABA **or** ICS + THEO + Maintenance oral steroids +/- SABA **or** Maintenance oral steroids

13.5 Appendix 5: Algorithm to define acute versus chronic oral corticosteroid prescriptions



13.6 Appendix 6: Classification of topical steroid potency

Potency	Class	Topical corticosteroid	Formulation
Ultra-high	I	Clobetasol propionate	Cream, 0.05%
		Diflorasone diacetate	Ointment, 0.05%
High	II	Amcinonide	Ointment, 0.1%
		Betamethasone dipropionate	Ointment, 0.05%
		Desoximetasone	Cream or ointment, 0.025%
		Fluocinonide	Cream, ointment or gel, 0.05%
		Halcinonide	Cream, 0.1%
	III	Betamethasone dipropionate	Cream, 0.05%
		Betamethasone valerate	Ointment, 0.1%
		Diflorasone diacetate	Cream, 0.05%
		Triamcinolone acetonide	Ointment, 0.1%
Moderate	IV	Desoximetasone	Cream, 0.05%
		Fluocinolone acetonide	Ointment, 0.025%
		Fludroxycortide	Ointment, 0.05%
		Hydrocortisone valerate	Ointment, 0.2%
		Triamcinolone acetonide	Cream, 0.1%
	V	Betamethasone dipropionate	Lotion, 0.02%
		Betamethasone valerate	Cream, 0.1%
		Fluocinolone acetonide	Cream, 0.025%
		Fludroxycortide	Cream, 0.05%
		Hydrocortisone butyrate	Cream, 0.1%
		Hydrocortisone valerate	Cream, 0.2%
		Triamcinolone acetonide	Lotion, 0.1%
Low	VI	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Fluocinolone acetonide	Solution, 0.01%
	VII	Dexamethasone sodium phosphate	Cream, 0.1%
		Hydrocortisone acetate	Cream, 1%
		Methylprednisolone acetate	Cream, 0.25%

Source: WHO Model Prescribing Information: Drugs used in Skin Disease. WHO: Geneva, Switzerland, 1997.

13.7 Appendix 7: Mock table for demographic and clinical variables at index date

	Number of patients
Number of patients eligible for inclusion, n	x
Age (years), mean (SD)	x (x)
Age (years), median (IQR)	x (x)
Male gender, n (%)	x (x)
BMI (kg/m^2), n (%)	x (x)
Non-missing	x (x)
Underweight	x (x)
Normal	x (x)
Overweight	x (x)
Obese	x (x)
Mean (SD)	x (x)
Median (IQR)	x (x)
Smoking status, n (%)	x (x)
Non-missing	x (x)
Non-smoker	x (x)
Current smoker	x (x)
Ex-smoker	x (x)
%predicted PEF	
Non-missing, n (%)	x (x)
Mean (SD)	x (x)
%predicted FEV$_1$	
Non-missing, n (%)	x (x)
Mean (SD)	x (x)
FEV1/FVC ratio	
Non-missing, n (%)	x (x)
Mean (SD)	x (x)
Severe asthma - ERS/ATS definition, n (%)	x(x)
Severe asthma – Regeneron RCT definition, n (%)	x(x)
GINA step	
Non-missing, n (%)	x (x)
Step 1, n(%)	x (x)
Step 2, n(%)	x (x)
Step 3, n(%)	x (x)
Step 4, n(%)	x (x)
Step 5, n(%)	x (x)
Risk Domain Asthma Control, n (%)	x (x)
Overall Asthma Control, n (%)	x (x)
Medication pre-index	x (x)
SABA, n (%)	x (x)
SAMA, n (%)	x (x)
SABA/SAMA, n (%)	x (x)
LABA, n (%)	x (x)
LAMA, n (%)	x (x)
LABA/LAMA, n (%)	x (x)
ICS/LABA, n (%)	x (x)
ICS, n (%)	x (x)
Biologics (where known), n (%)	x (x)
Chronic OCS, n (%)	x (x)
Antibiotics, n (%)	x (x)

13.8 Appendix 8: Mock comorbidity prevalence table

comorbidity									rank	prevalence	obs/exp ratio	number of patients	cum. percentage of pop.
1	2	3	4	5	6	7	8	9					
•									1	20.0%	-	2000	20%
									⋮				
•	•	•				•		•	33	3.5%	1.5	350	54%
									⋮				
	•	•			•		•		154	0.5%	7.3	50	95%
									⋮				
•	•		•	•	•	•		•	270	0.0%	1.0	1	100%

Adapted from: van den Bussche H , Koller D , Kolonko T , et al . Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. BMC Public Health 2011;11:101

13.9 Appendix 9: Mock example of figure illustrating the frequency of comorbidity in the asthma population

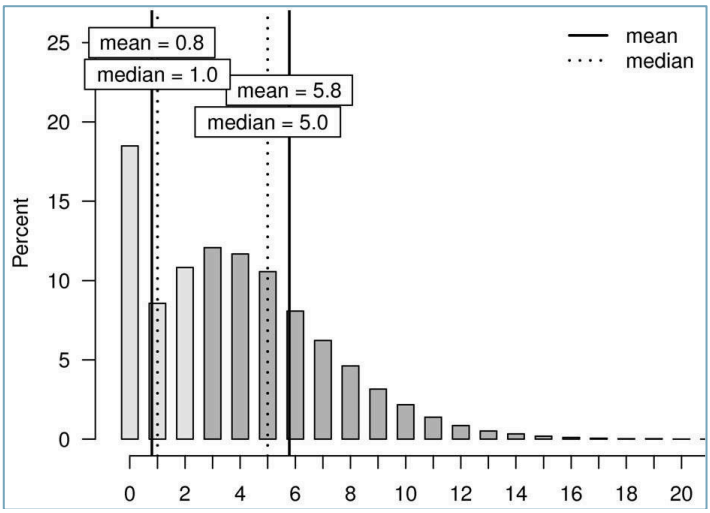


Figure 1
Frequency (in %) of the number of chronic conditions within the list of 46 conditions in the non-multimorbid sample (light grey columns) and the multimorbid sample (dark grey columns) and mean and median for both samples.

Source: van den Bussche H , Koller D , Kolonko T , et al . Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. BMC Public Health 2011;11:101

13.10 Appendix 10: Mock example of figure illustrating the mean number of comorbidities in the asthma population by age group and gender

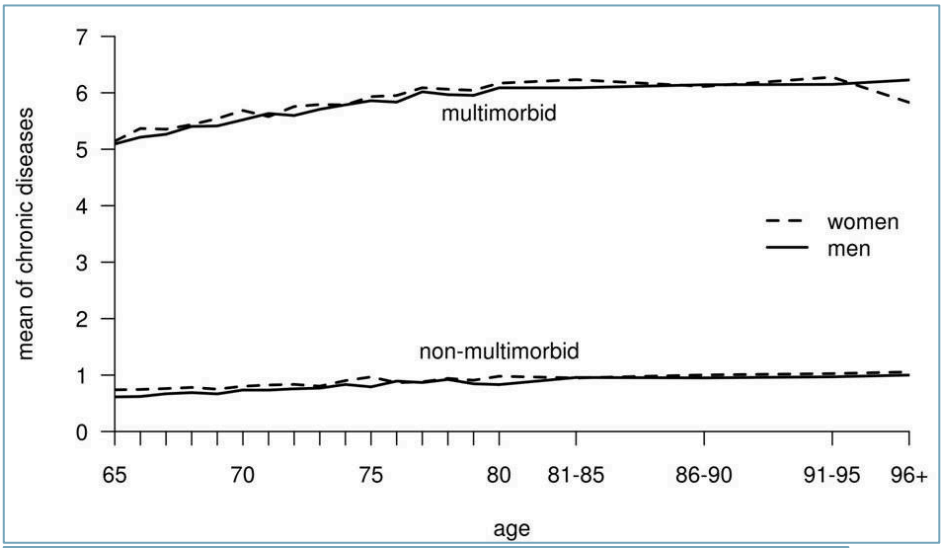


Figure 2
Mean number of chronic conditions according to age and gender in the non-multimorbid and the multimorbid sample. Means were calculated for each year of life until 80. Due to the small number of cases in old age, we generated four age groups for age > 80 years before calculation.

Source: van den Bussche H , Koller D , Kolonko T , et al . Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. BMC Public Health 2011;11:101

13.11 Appendix 11: Mock example of figure illustrating the association between the individual diseases in the selected clusters

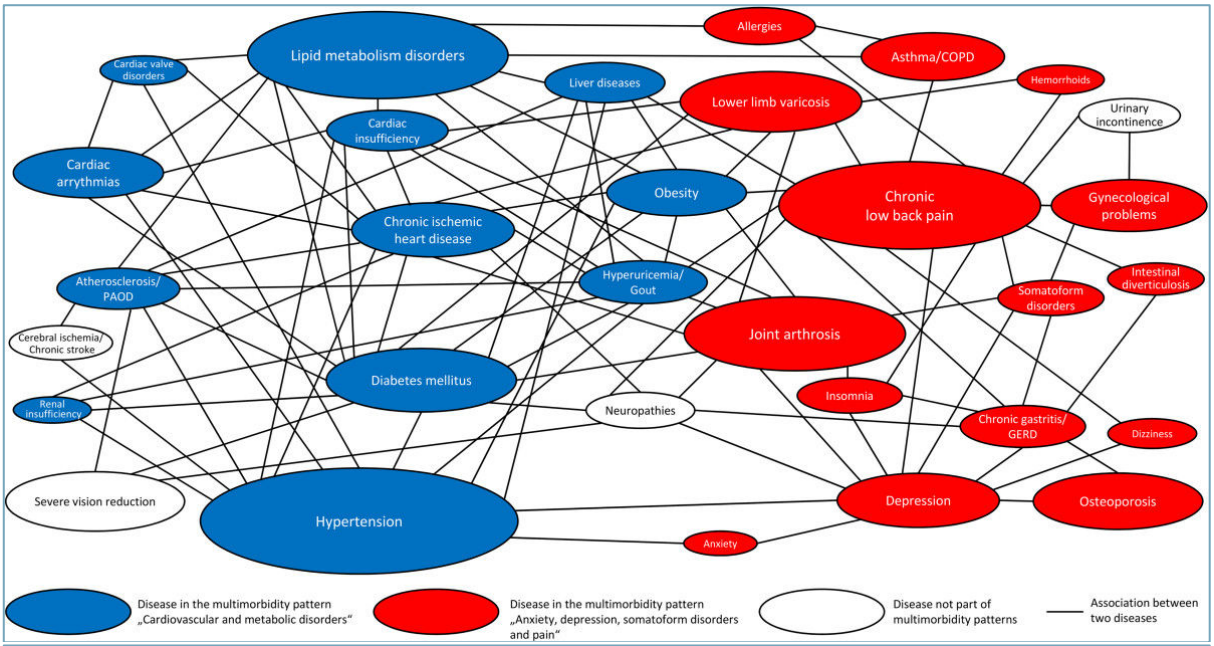


Figure 1
Disease associations in multimorbidity clusters based on triads with a prevalence ≥ 1% and an observed/expected ratio ≥ 2 in the female population with ≥ 3 chronic conditions.

Source: Schäfer I , Kaduszkiewicz H , Wagner HO , et al . Reducing complexity: a visualisation of multimorbidity by combining disease clusters and triads. BMC Public Health 2014;14:1285.

13.12 Appendix 12: Mock healthcare resource utilisation (HRU) and costs table for a single comorbidity cluster

Cluster1: atopic dermatitis and allergic rhinitis	Number of HRU events in year	Annual cost
	Mean (SD)	Mean (SD)
Physician office visits	x (x)	x (x)
Primary care prescribing (asthma)		
ICS	x (x)	x (x)
SABA	x (x)	x (x)
LABA	x (x)	x (x)
⋮	⋮	⋮
Total asthma prescribing cost	-	x (x)
⋮	⋮	⋮
Total primary care costs	-	x (x)
Outpatient visits (asthma-related)	x (x)	x (x)
ER visits (asthma-related)	x (x)	x (x)
Inpatient admissions (asthma-related)	x (x)	x (x)
Total secondary care costs	-	x (x)
Severe exacerbations	x (x)	x (x)
Total primary and secondary care costs	-	x (x)

13.13 Appendix 13: Rapid review of literature to identify comorbidity definitions used in other studies using routine patient data (limited to primary care)

Literature review to identify methods used to categorise the severity of conditions of interest in the Regeneron asthma comorbidities study

Ronan Ryan, Isha Chaudhry
V2 RR20180105

Background

A PubMed search was carried out on the 2-4 Jan 2018 to find published studies which used primary care electronic patient records and mentioned one of the 9 comorbidities of interest.

The aim was to identify definitions of disease severity which could be adopted by the current study.

Methods

The conditions of interest and the PubMed search terms used are listed in Appendix 1-3.

Individual papers were relevant if they described a method for categorising the severity of one or more of the comorbidities of interest which could be operationalised in routine primary care electronic patient records with or without linked secondary care data.

Summary of findings

- **Anaphylaxis:** Patients at high risk of anaphylaxis can be defined as individuals who had one or more adrenaline autoinjector prescriptions in the preceding year. There is no need to require a Read-coded indication as many patients will not have one recorded. Episodes of anaphylaxis can be categorised as mild, moderate or severe if linked secondary care data is available.

- **Allergic rhinitis:** Moderate to severe allergic rhinitis can be defined as the prescription of an intranasal steroid on one or more occasions if the patient also has an earlier Read coded diagnosis.

- **Eczema:** Chronic eczema may be defined as having one or more Read codes for eczema separated by between 90 and 365 days or at least one course of a potent topical steroid. Steroid-refractory chronic eczema may be defined as having a dermatology referral or being prescribed phototherapy, systemic immunomodulators, oral corticosteroids, alitretinoin or acitretin.

- **Chronic rhinosinusitis:** Chronic rhinosinusitis refractory to medical management may be defined as having endoscopic sinus surgery.

Results

The full references for the papers identified as relevant and not relevant are listed in Appendix 4-5.

49 potentially relevant papers were identified. 43 papers were categorised as not relevant as they did not provide a definition of disease severity based on their title, abstract or full-text.

Full-text PDFs were found for 4 of the 5 relevant papers. Two were on anaphylaxis, and there was one each on allergic rhinitis, hand eczema and chronic rhinosinusitis.

1. Diwakar, L., et al. (2017).
Anaphylaxis: Patients were defined as at high risk of anaphylaxis in a study year if they had a prescription for an adrenaline autoinjector in that year. Only half of children prescribed an autoinjector had a relevant Read code for allergy or anaphylaxis. (Data source: THIN)

2. Peng, M. M. and H. Jick (2004).
Anaphylaxis: Cases were identified by Read code and free-text comments. Copies of letters from hospital were requested and reviewed. Anaphylaxis was categorised as mild if was primarily limited to generalised urticaria (angioedema) and did not lead to an emergency department admission or hospitalisation. The illness was categorised as moderate severity if a hospital visit was initiated and the illness was treated with adrenalin. The illness was considered to be severe if there was hypotension or shock that was described as life-threatening. (Data source: GPRD)

3. Price, D. B., et al. (2016).
Allergic rhinitis: The paper reported that intranasal steroids are recommended for moderate to severe allergic rhinitis (Allergic Rhinitis and its Impact on Asthma (ARIA) Guideline). (Data source: OPCRD)

4. Crane, M. M., et al. (2017).
Hand eczema: This study categorised hand eczema into three groups. Simple hand eczema cases were identified as patients with Read coded eczema only. A patient was categorised as having chronic hand eczema if they had additional Read codes 90-365 days after the initial code or if they were prescribed at least one course of a potent topical steroid. The patient was categorised as having steroid-refractory chronic hand eczema if they were referred to a dermatologist, prescribed phototherapy, systemic immunomodulators, oral corticosteroids, alitretinoin or acitretin. (Data source: CPRD)

5. Hopkins, C., et al. (2015).
Chronic rhinosinusitis: Patients with chronic rhinosinusitis refractory to medical management were defined as patients who had endoscopic sinus surgery. (Data source: CPRD)

Appendix 1 Comorbidities of interest

eczema
allergic rhinitis
chronic rhinosinusitis
nasal polyps
urticaria
allergic conjunctivitis
food allergy
eosinophilic oesophagitis
anaphylaxis

Appendix 2 Additional synonyms used in PubMed search

atopic dermatitis
nasal polyposis
conjunctivitis

Appendix 3 Full PubMed search terms

((
gprd[Text Word] OR
general practice research database[Text Word] OR
cprd[Text Word] OR
clinical practice research datalink[Text Word] OR
clinical practice research database[Text Word] OR
qresearch[Text Word] OR
thin database[Text Word] OR
the health improvement network[Text Word] OR
opcrd[Text Word] OR
Optimum Patient Care Research Database[Text Word] OR
ResearchOne[Text Word]
)

OR
((
electronic health records[MeSH Terms] OR
Medical Records Systems, Computerized[MeSH Terms] OR
electronic primary care records[Text Word] OR
electronic patient records[Text Word]
)
AND
(
primary health care[MeSH Terms] OR
primary health care[Text Word] OR
primary care[Text Word]
)))

AND

(
eczema[Text Word] OR
atopic dermatitis[Text Word] OR
allergic rhinitis[Text Word] OR
chronic rhinosinusitis[Text Word] OR
nasal polyps[Text Word] OR
nasal polyposis[Text Word] OR
urticaria[Text Word] OR
allergic conjunctivitis[Text Word] OR
Conjunctivitis[Text Word] OR
Food allergy[Text Word] OR
Eosinophilic oesophagitis[Text Word] OR
anaphylaxis[Text Word]
)

Appendix 4 List of relevant publications identified

Full-text PDF available

1. Diwakar, L., et al. (2017). "Prescription rates of adrenaline auto-injectors for children in UK general practice: a retrospective cohort study." Br J Gen Pract **67**(657): e300-e305.

2. Peng, M. M. and H. Jick (2004). "A population-based study of the incidence, cause, and severity of anaphylaxis in the United Kingdom." Arch Intern Med 164(3): 317-319.

3. Price, D. B., et al. (2016). "UK prescribing practices as proxy markers of unmet need in allergic rhinitis: a retrospective observational study." NPJ Prim Care Respir Med 26: 16033.

4. Crane, M. M., et al. (2017). "Hand eczema and steroid-refractory chronic hand eczema in general practice: prevalence and initial treatment." Br J Dermatol 176(4): 955-964.

Full-text PDF not available

5. Hopkins, C., et al. (2015). "Does time to endoscopic sinus surgery impact outcomes in chronic rhinosinusitis? Retrospective analysis using the UK clinical practice research data." Rhinology 53(1): 18-24.

Appendix 4 List of non-relevant publications identified

1. Abuabara, K., A. M. Magyari, O. Hoffstad, Z. K. Jabbar-Lopez, L. Smeeth, H. C. Williams, J. M. Gelfand, D. J. Margolis and S. M. Langan (2017). "Development and Validation of an Algorithm to Accurately Identify Atopic Eczema Patients in Primary Care Electronic Health Records from the UK." J Invest Dermatol 137(8): 1655-1662.
2. Apter, A. J., J. L. Kinman, W. B. Bilker, M. Herlim, D. J. Margolis, E. Lautenbach, S. Hennessy and B. L. Strom (2006). "Is there cross-reactivity between penicillins and cephalosporins?" Am J Med 119(4): 354.e311-359.
3. Arana, A., C. E. Wentworth, C. Fernandez-Vidaurre, R. G. Schlienger, E. Conde and F. M. Arellano (2010). "Incidence of cancer in the general population and in patients with or without atopic dermatitis in the U.K." Br J Dermatol 163(5): 1036-1043.
4. Arellano, F. M., A. Arana, C. E. Wentworth, C. Fernandez-Vidaurre, R. G. Schlienger and E. Conde (2009). "Lymphoma among patients with atopic dermatitis and/or treated with topical immunosuppressants in the United Kingdom." J Allergy Clin Immunol 123(5): 1111-1116, 1116.e1111-1113.
5. Bremner, S. A., I. M. Carey, S. DeWilde, N. Richards, W. C. Maier, S. R. Hilton, D. P. Strachan and D. G. Cook (2003). "Early-life exposure to antibacterials and the subsequent development of hayfever in childhood in the UK: case-control studies using the General Practice Research Database and the Doctors' Independent Network." Clin Exp Allergy 33(11): 1518-1525.
6. Bremner, S. A., I. M. Carey, S. DeWilde, N. Richards, W. C. Maier, S. R. Hilton, D. P. Strachan and D. G. Cook (2007). "Vaccinations, infections and antibacterials in the first grass pollen season of life and risk of later hayfever." Clin Exp Allergy 37(4): 512-517.
7. Bremner, S. A., I. M. Carey, S. DeWilde, N. Richards, W. C. Maier, S. R. Hilton, D. P. Strachan and D. G. Cook (2008). "Infections presenting for clinical care in early life and later risk of hay fever in two UK birth cohorts." Allergy 63(3): 274-283.
8. Card, T. R., S. M. Langan and T. P. Chu (2016). "Extra-Gastrointestinal Manifestations of Inflammatory Bowel Disease May Be Less Common Than Previously Reported." Dig Dis Sci 61(9): 2619-2626.
9. Cardwell, C. R., D. J. Carson and C. C. Patterson (2008). "No association between routinely recorded infections in early life and subsequent risk of childhood-onset Type 1 diabetes: a matched case-control study using the UK General Practice Research Database." Diabet Med 25(3): 261-267.
10. Carey, I. M., D. G. Cook, S. De Wilde, S. A. Bremner, N. Richards, S. Caine, D. P. Strachan and S. R. Hilton (2003). "Implications of the problem orientated medical record (POMR) for research using electronic GP databases: a comparison of the Doctors Independent Network Database (DIN) and the General Practice Research Database (GPRD)." BMC Fam Pract 4: 14.
11. Carey, I. M., D. G. Cook, S. De Wilde, S. A. Bremner, N. Richards, S. Caine, D. P. Strachan and S. R. Hilton (2004). "Developing a large electronic primary care database (Doctors' Independent Network) for research." Int J Med Inform 73(5): 443-453.
12. Davey, G., P. Sedgwick, W. Maier, G. Visick, D. P. Strachan and H. R. Anderson (2002). "Association between migraine and asthma: matched case-control study." Br J Gen Pract 52(482): 723-727.

13. Dhalwani, N. N., J. West, A. A. Sultan, L. Ban and L. J. Tata (2014). "Women with celiac disease present with fertility problems no more often than women in the general population." Gastroenterology 147(6): 1267-1274.e1261; quiz e1213-1264.
14. Gaitatzis, A., K. Carroll, A. Majeed and W. S. J (2004). "The epidemiology of the comorbidity of epilepsy in the general population." Epilepsia 45(12): 1613-1622.
15. Ghouri, N., J. Hippisley-Cox, J. Newton and A. Sheikh (2008). "Trends in the epidemiology and prescribing of medication for allergic rhinitis in England." J R Soc Med 101(9): 466-472.
16. Gonzalez-Perez, A., Z. Aponte, C. F. Vidaurre and L. A. Rodriguez (2010). "Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review." J Allergy Clin Immunol 125(5): 1098-1104.e1091.
17. Hall, G. C., P. T. G. Davies, M. Y. Karim, M. D. M. Haag and C. O'Leary (2018). "Observational safety study of specific outcomes after trivalent cell culture seasonal influenza vaccination (Optaflu((R))) among adults in THIN database of electronic UK primary healthcare records." Pharmacoepidemiol Drug Saf 27(1): 52-58.
18. Hesdorffer, D. C., L. Ishihara, L. Mynepalli, D. J. Webb, J. Weil and W. A. Hauser (2012). "Epilepsy, suicidality, and psychiatric disorders: a bidirectional association." Ann Neurol 72(2): 184-191.
19. Hollowell, J. (1997). "The General Practice Research Database: quality of morbidity data." Popul Trends(87): 36-40.
20. Lang, K., F. Allen-Ramey, H. Huang, M. Rock, E. Kaufman and M. S. Dykewicz (2016). "Health care resource use and associated costs among patients with seasonal versus perennial allergic rhinitis." Allergy Asthma Proc 37(5): 103-111.
21. McKeever, T. M., S. A. Lewis, C. Smith, J. Collins, H. Heatlie, M. Frischer and R. Hubbard (2001). "Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database." Thorax 56(10): 758-762.
22. McKeever, T. M., S. A. Lewis, C. Smith, J. Collins, H. Heatlie, M. Frischer and R. Hubbard (2002). "Early exposure to infections and antibiotics and the incidence of allergic disease: a birth cohort study with the West Midlands General Practice Research Database." J Allergy Clin Immunol 109(1): 43-50.
23. McKeever, T. M., S. A. Lewis, C. Smith and R. Hubbard (2002). "The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database." Am J Respir Crit Care Med 166(6): 827-832.
24. McKeever, T. M., S. A. Lewis, C. Smith and R. Hubbard (2002). "Mode of delivery and risk of developing allergic disease." J Allergy Clin Immunol 109(5): 800-802.
25. McKeever, T. M., S. A. Lewis, C. Smith and R. Hubbard (2004). "Vaccination and allergic disease: a birth cohort study." Am J Public Health 94(6): 985-989.
26. Meropol, S. B., K. A. Chan, Z. Chen, J. A. Finkelstein, S. Hennessy, E. Lautenbach, R. Platt, S. D. Schech, D. Shatin and J. P. Metlay (2008). "Adverse events associated with prolonged antibiotic use." Pharmacoepidemiol Drug Saf 17(5): 523-532.
27. Mukherjee, M., J. C. Wyatt, C. R. Simpson and A. Sheikh (2016). "Usage of allergy codes in primary care electronic health records: a national evaluation in Scotland." Allergy 71(11): 1594-1602.

28. Olsen, J. R., V. Piguet, J. Gallacher and N. A. Francis (2016). "Molluscum contagiosum and associations with atopic eczema in children: a retrospective longitudinal study in primary care." Br J Gen Pract 66(642): e53-58.
29. Petersen, I. and A. C. Hayward (2007). "Antibacterial prescribing in primary care." J Antimicrob Chemother 60 Suppl 1: i43-47.
30. Price, D., A. M. Wilson, A. Chisholm, A. Rigazio, A. Burden, M. Thomas and C. King (2016). "Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice." J Asthma Allergy 9: 1-12.
31. Punekar, Y. S., A. Ahmad and H. A. Saleh (2011). "Estimating the effect of nasal steroid treatment on repeat polypectomies: survival time analysis using the General Practice Research Database." Rhinology 49(2): 190-194.
32. Punekar, Y. S. and A. Sheikh (2009). "Establishing the sequential progression of multiple allergic diagnoses in a UK birth cohort using the General Practice Research Database." Clin Exp Allergy 39(12): 1889-1895.
33. Rowlands, S., H. Devalia, C. Smith, R. Hubbard and A. Dean (2001). "Otitis externa in UK general practice: a survey using the UK General Practice Research Database." Br J Gen Pract 51(468): 533-538.
34. Sheikh, A., J. Hippisley-Cox, J. Newton and J. Fenty (2008). "Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England." J R Soc Med 101(3): 139-143.
35. Simpson, C. R., J. Newton, J. Hippisley-Cox and A. Sheikh (2008). "Incidence and prevalence of multiple allergic disorders recorded in a national primary care database." J R Soc Med 101(11): 558-563.
36. Simpson, C. R., J. Newton, J. Hippisley-Cox and A. Sheikh (2009). "Trends in the epidemiology and prescribing of medication for eczema in England." J R Soc Med 102(3): 108-117.
37. Sturkenboom, M., A. Nicolosi, L. Cantarutti, S. Mannino, G. Picelli, A. Scamarcia and C. Giaquinto (2005). "Incidence of mucocutaneous reactions in children treated with niflumic acid, other nonsteroidal antiinflammatory drugs, or nonopioid analgesics." Pediatrics 116(1): e26-33.
38. Summers, J. F., D. G. O'Neill, D. B. Church, P. C. Thomson, P. D. McGreevy and D. C. Brodbelt (2015). "Prevalence of disorders recorded in Cavalier King Charles Spaniels attending primary-care veterinary practices in England." Canine Genet Epidemiol 2: 4.
39. Taylor, R. R., E. Sladkevicius, M. Panca, G. Lack and J. F. Guest (2012). "Cost-effectiveness of using an extensively hydrolysed formula compared to an amino acid formula as first-line treatment for cow milk allergy in the UK." Pediatr Allergy Immunol 23(3): 240-249.
40. Vena, G. A., N. Cassano, V. Pegoraro, N. Cataldo, F. Heiman, I. Cricelli, D. Colombo, E. Zagni, C. Cricelli and F. Lapi (2016). "Medication patterns in chronic spontaneous urticaria: results from a nationwide investigation in the primary care setting in Italy." G Ital Dermatol Venereol.
41. Winchester, C. C., T. V. Macfarlane, M. Thomas and D. Price (2009). "Antibiotic prescribing and outcomes of lower respiratory tract infection in UK primary care." Chest 135(5): 1163-1172.
42. Zelig, A., I. Harwayne-Gidansky, A. Gault and J. Wang (2016). "Effect of educational and electronic medical record interventions on food allergy management." Allergy Asthma Proc 37(5): 404-408.

13.14 Appendix 14: Rapid review of literature to identify comorbidity definitions used in other studies using routine patient data (unrestricted)

Literature review to identify methods used to categorise the severity of conditions of interest in the Regeneron asthma comorbidities study (wider search for studies for remaining comorbidities)

Ronan Ryan
V2 RR20180222

Background

A PubMed search was carried out on the 20-22 Feb 2018 to find published studies which used electronic patient records and mentioned one of the 9 comorbidities of interest.

A previous search in January, restricted to primary care electronic patient records, was not able to identify any relevant studies for 5 of the 9 comorbidities of interest (nasal polyps, urticaria, allergic conjunctivitis, food allergy, eosinophilic oesophagitis)

The aim was to identify definitions of disease severity for the remaining 5 comorbidities which could be adopted by the current study.

Methods

The conditions of interest and the PubMed search terms used are listed in Appendix 1-3.

Individual papers were relevant if they described a method for categorising the severity of one or more of the comorbidities of interest which could be operationalised in routine primary care electronic patient records with or without linked secondary care data.

Summary of findings

- **Anaphylaxis (food and other causes):** Food-related anaphylaxis can be identified using a clinician coded record of anaphylaxis: the presence of individual reactions alone (e.g. shortness of breath/urticaria) should not be used to define anaphylaxis. This may be also be applicable to other causes of anaphylaxis.

- **Severity of anaphylaxis:** Moderate to severe anaphylaxis in secondary care can be identified by the presence of respiratory, cardiovascular, gastrointestinal and neurological symptoms. It is unlikely that this level of detail from the hospital record will be routinely entered into the primary care record at a later date: the main diagnosis of an anaphylactic reaction may be the only indication of the event.

- **Identification of disease severity using Read codes alone:** It may not be possible to identify moderate to severe comorbidity using Read codes alone because of their

structure and use in primary care. Additional sources of data should also be use, e.g. prescribing and contacts with secondary care.

Results

The full references for the papers identified as relevant and not relevant are listed in Appendix 4-5.

45 potentially relevant papers were identified. 42 papers were categorised as not relevant as they did not provide a definition of disease severity based on their title, abstract or full-text.

Full-text PDFs were found for the three relevant papers. One was on food allergy/food intolerance, the second was on anaphylaxis but included mention of food intolerance as a cause, and the third was a more general paper on coding of three of the allergies of interest (allergic conjunctivitis, urticarial and food allergy). No relevant papers were found for nasal polyps or eosinophilic oesophagitis.

1. Acker, W., et al. (2017).
Food allergy/intolerance: Patients were classified as having had an anaphylactic reaction to food only if the clinician described the reaction as anaphylactic in the patient record. The recording of hives or shortness of breath alone, for example, would not have been classified as anaphylaxis. (Data source: A single large US healthcare organisation.)

2. Kim, S-Y., et al. (2008).
Food-related anaphylaxis: Moderate anaphylaxis was defined as reactions involving respiratory, cardiovascular, and gastrointestinal symptoms (such as dyspnea, wheezing, vertigo, nausea, vomiting, and abdominal pain); the patient also had to be conscious with systolic blood pressure >90 mmHg. Severe anaphylaxis was defined as reactions involving cyanosis, hypotension, and neurological symptoms with oxygen saturation <92% or systolic blood pressure <90 mmHg. (Data source: a single hospital in South Korea.)

3. Mukherjee, M., et al. (2016).
Allergic conjunctivitis, urticaria and food allergy: This paper described the use of Read clinical codes for 11 allergic-type conditions in general practice, including three others of interest to the current study (anaphylaxis, eczema and rhinitis). The severity of these conditions was not directly addressed, but the authors observed that 10% of the available Read codes were used 95% of the time. Also, for food allergy, anaphylaxis and eczema, the codes used referred to the diagnosis or a personal history of this allergy, suggesting that the severity of the condition was not usually recorded using a specific Read code. No similar data were given for the other conditions of interest. (Data source: 393 Scottish general practices.)

Appendix 1 Comorbidities of interest

nasal polyp
urticaria
allergic conjunctivitis
food allergy
eosinophilic oesophagitis

Appendix 2 Additional synonyms used in PubMed search

nasal polyposis
polyps
"Nasal Polyps"[MeSH Terms]

"Urticaria"[MeSH Terms]

conjunctivitis
"Conjunctivitis, Allergic"[MeSH Terms]

"Food Hypersensitivity"[MeSH Terms]

eosinophilic esophagitis
EoE
allergic oesophagitis
allergic esophagitis
"Eosinophilic Esophagitis"[MeSH Terms]

Appendix 3 Full PubMed search terms

```
(
electronic records[Text Word] OR
electronic patient records[Text Word] OR
electronic health records[MeSH Terms] OR
Medical Records Systems, Computerized[MeSH Terms]
)

AND

(
nasal polyps[Text Word] OR
nasal polyposis[Text Word] OR
"Nasal Polyps"[MeSH Terms] OR

urticaria[Text Word] OR
"Urticaria"[MeSH Terms] OR

allergic conjunctivitis[Text Word] OR
conjunctivitis[Text Word] OR
"Conjunctivitis, Allergic"[MeSH Terms] OR

food allergy[Text Word] OR
"Food Hypersensitivity"[MeSH Terms] OR

eosinophilic oesophagitis[Text Word] OR
eosinophilic esophagitis[Text Word] OR
EoE[Text Word] OR
allergic oesophagitis[Text Word] OR
allergic esophagitis[Text Word] OR
"Eosinophilic Esophagitis"[MeSH Terms]
)
```

Appendix 4 List of relevant publications identified

Full-text PDF available

1. Acker, W. W., et al. (2017). "Prevalence of food allergies and intolerances documented in electronic health records." J Allergy Clin Immunol **140**(6): 1587-1591.e1581.

2. Kim, S. Y., et al. (2018). "Different clinical features of anaphylaxis according to cause and risk factors for severe reactions." Allergol Int **67**(1): 96-102.

3. Mukherjee, M., et al. (2016). "Usage of allergy codes in primary care electronic health records: a national evaluation in Scotland." Allergy **71**(11): 1594-1602.

Appendix 4 List of non-relevant publications identified

1. Agarwal S, Wang J. Prevalence and characteristics of food allergy in urban minority adults. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2014;112(5):476-8.
2. Bell C, Chakravarty A, Gruber S, Heckbert SR, Levenson M, Martin D, et al. Characteristics of study design and elements that may contribute to the success of electronic safety monitoring systems. Pharmacoepidemiology and drug safety. 2014;23(11):1223-5.
3. Bessmertny O, Hatton RC, Gonzalez-Peralta RP. Antiepileptic hypersensitivity syndrome in children. The Annals of pharmacotherapy. 2001;35(5):533-8.
4. Campbell RL, Hagan JB, Manivannan V, Decker WW, Kanthala AR, Bellolio MF, et al. Evaluation of national institute of allergy and infectious diseases/food allergy and anaphylaxis network criteria for the diagnosis of anaphylaxis in emergency department patients. The Journal of allergy and clinical immunology. 2012;129(3):748-52.
5. Eibling D. Making us smart: why the design of clinical decision support systems is so critical. The Laryngoscope. 2008;118(12):2121-4.
6. Epstein RH, St Jacques P, Stockin M, Rothman B, Ehrenfeld JM, Denny JC. Automated identification of drug and food allergies entered using non-standard terminology. Journal of the American Medical Informatics Association : JAMIA. 2013;20(5):962-8.
7. Erlewyn-Lajeunesse M, Dymond S, Slade I, Mansfield HL, Fish R, Jones O, et al. Diagnostic utility of two case definitions for anaphylaxis: a comparison using a retrospective case notes analysis in the UK. Drug safety. 2010;33(1):57-64.
8. Fattinger K, Roos M, Vergeres P, Holenstein C, Kind B, Masche U, et al. Epidemiology of drug exposure and adverse drug reactions in two swiss departments of internal medicine. British journal of clinical pharmacology. 2000;49(2):158-67.
9. Flood EM, Zazzali JL, Devlen J. Demonstrating measurement equivalence of the electronic and paper formats of the Urticaria Patient Daily Diary in patients with chronic idiopathic urticaria. The patient. 2013;6(3):225-31.
10. Garg L, Dauwels J, Earnest A, Leong KP. Tensor-based methods for handling missing data in quality-of-life questionnaires. IEEE journal of biomedical and health informatics. 2014;18(5):1571-80.
11. Goh SH, Soh JY, Loh W, Lee KP, Tan SC, Heng WJK, et al. Cause and Clinical Presentation of Anaphylaxis in Singapore: From Infancy to Old Age. International archives of allergy and immunology. 2018.
12. Gonzalez-Gregori R, Dolores Hernandez Fernandez De Rojas M, Lopez-Salgueiro R, Diaz-Palacios M, Garcia AN. Allergy alerts in electronic health records for hospitalized patients. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2012;109(2):137-40.
13. Hill DA, Dudley JW, Spergel JM. The Prevalence of Eosinophilic Esophagitis in Pediatric Patients with IgE-Mediated Food Allergy. The journal of allergy and clinical immunology In practice. 2017;5(2):369-75.
14. Huerta-Vena A, Gonzalez-de-Olano D, Gonzalez-Mancebo E, Sebastian-Viana T, Lechuga-Suarez LA, Mohedano-Vicente E, et al. Analysis of Allergy Alerts Registered in a Hospital Electronic Health Record System. Journal of investigational allergology & clinical immunology. 2016;26(6):400-2.

15. Iqbal K, Bhargava K, Skov PS, Falkencrone S, Grattan CE. A positive serum basophil histamine release assay is a marker for ciclosporin-responsiveness in patients with chronic spontaneous urticaria. Clinical and translational allergy. 2012;2(1):19.
16. Kim MH, Park CH, Kim DI, Kim KM, Kim HK, Lim KH, et al. Surveillance of contrast-media-induced hypersensitivity reactions using signals from an electronic medical recording system. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2012;108(3):167-71.
17. Lee J, Dierkhising R, Wu TT, Alexander J, Weiler C. Eosinophilic gastrointestinal disorders (EGID) with peripheral eosinophilia: a retrospective review at Mayo Clinic. Digestive diseases and sciences. 2011;56(11):3254-61.
18. Magen E, Waitman DA, Dickstein Y, Davidovich V, Kahan NR. Clinical-laboratory characteristics of ANA-positive chronic idiopathic urticaria. Allergy and asthma proceedings. 2015;36(2):138-44.
19. Mandell BF. Recognizing the unusual: the diagnostic epiphany. Cleveland Clinic journal of medicine. 2011;78(5):277.
20. Meyers A, Wysoker A. The Weight-by-Date chart: A personalized tool for following hospitalized children. Pediatrics. 2001;108(3):821.
21. Moore GE, DeSantis-Kerr AC, Guptill LF, Glickman NW, Lewis HB, Glickman LT. Adverse events after vaccine administration in cats: 2,560 cases (2002-2005). Journal of the American Veterinary Medical Association. 2007;231(1):94-100.
22. Moore GE, Guptill LF, Ward MP, Glickman NW, Faunt KK, Lewis HB, et al. Adverse events diagnosed within three days of vaccine administration in dogs. Journal of the American Veterinary Medical Association. 2005;227(7):1102-8.
23. Moore KM, Duddy A, Lee GM, Velentgas P, Burwen DR, Platt R, et al. Outpatient urticaria diagnosis codes have limited predictive value for same-day influenza vaccine adverse event detection. Journal of clinical epidemiology. 2010;63(4):407-11.
24. Mulder DJ, Hurlbut DJ, Noble AJ, Justinich CJ. Clinical features distinguish eosinophilic and reflux-induced esophagitis. Journal of pediatric gastroenterology and nutrition. 2013;56(3):263-70.
25. Murad A, Katelaris CH. Anaphylaxis audit in a busy metropolitan Emergency Department: a review of real life management compared to best practice. Asia Pacific allergy. 2016;6(1):29-34.
26. O'Connell HM, Chance S, Bowman L. Computerized drug-use evaluation. American journal of hospital pharmacy. 1994;51(3):363-7.
27. Orrico KB. Sources and types of discrepancies between electronic medical records and actual outpatient medication use. Journal of managed care pharmacy : JMCP. 2008;14(7):626-31.
28. Renz-Polster H, David MR, Buist AS, Vollmer WM, O'Connor EA, Frazier EA, et al. Caesarean section delivery and the risk of allergic disorders in childhood. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2005;35(11):1466-72.
29. Robinson M, Greenhawt M, Stukus DR. Factors associated with epinephrine administration for anaphylaxis in children before arrival to the emergency department. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2017;119(2):164-9.

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31. Savidge C, Ewing P, Andrews J, Aucoin D, Lappin MR, Moroff S. Anaplasma phagocytophilum infection of domestic cats: 16 cases from the northeastern USA. Journal of feline medicine and surgery. 2016;18(2):85-91.
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33. Seth S, Khan DA. The Comparative Safety of Multiple Alternative Agents in Refractory Chronic Urticaria Patients. The journal of allergy and clinical immunology In practice. 2017;5(1):165-70 e2.
34. Silverman S, Localio R, Apter AJ. Association between chronic urticaria and self-reported penicillin allergy. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2016;116(4):317-20.
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42. Zelig A, Harwayne-Gidansky I, Gault A, Wang J. Effect of educational and electronic medical record interventions on food allergy management. Allergy and asthma proceedings. 2016;37(5):404-8.