REG STUDY PROTOCOL

LONG TITLE:

ADDITION OF ANTIBIOTICS TO USUAL CARE MANAGEMENT OF ASTHMA EXACERBATIONS: A REAL-LIFE COMPARATIVE EFFECTIVENESS STUDY

SHORT TITLE: ROLE OF ANTIBIOTICS IN ASTHMA EXACERBATION MANAGEMENT

Research Protocol developed by The Respiratory Effectiveness Group

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BACKGROUND & RATIONALE

Asthma exacerbations are major contributors to asthma morbidity and mortality (and related costs). Their management presents a major clinical need that is not adequately met by current approaches. Respiratory viruses (especially rhinovirus) are the most common causes of asthma exacerbations and may be involved in the pathogenesis of chronic asthma in children,[1] but there are other factors can increase the risk/severity of exacerbations. Recently evidence suggests atypical bacterial infections (such as Mycoplasma pneumonia and Chlamydophila) may also contribute to exacerbation severity.[2]

Standard management of asthma exacerbations is the use of bronchodilators and systemic steroids,[3] but there are evidence to suggest (as yet inconclusive) that macrolide antibiotics and the ketolide antibiotic telithromycin may have an effect on asthma exacerbations through their antibacterial and/or anti-inflammatory properties.[2]

A recent randomised controlled (RCT) trial of telithromycin in adult patients (n=278) with acute exacerbations of asthma found a significant reduction in asthma symptoms among patients receiving add-on telithromycin compared with placebo. The mechanism or mechanisms of action was/were not determined.[4]

A second recent open-label randomised study, evaluating the effect of clarithromycin in children (n=40) with acute asthma suggests its use as add-on therapy may offer benefit over standard exacerbation treatment alone. Children in the trial were randomized to receive 15mg/kg of clarithromycin for 21 days in addition to their regular (GINA-guided) exacerbation treatment. Children were followed up with diary cards for 12 weeks; lung function was assessed at entry and at 3 and 12 weeks post exacerbation. Compared with controls, children receiving clarithromycin had an increase in their number of symptom-free days, a reduction in the number and severity of days with loss of control following index episode, and a decrease in the duration of the initial asthma exacerbation. Lung function did not differ between groups.[5]

These RCT findings warrant further exploration in larger more representative adult and paediatric routine care populations.

AIM & OBJECTIVE

The aim of the proposed study is to evaluate the comparative effectiveness of managing asthma exacerbations with oral steroids alone (i.e. usual care) versus combination antibiotics and oral steroids in paediatric and adult asthma populations.

Secondary objectives of the study will be to explore the differential usage and associated outcomes of different classes of antibiotics, as used in this context.

STUDY DESIGN & DATASET

Data source

The Optimum Patient Care Research Database (OPCRD) will be used as the source of data for the study. The OPCRD is a UK research-quality clinical database comprising electronic medical records (EMRs) extracted through the Optimum Patient Care (OPC) Clinical Service. The clinical service involves a combined review of (anonymised) primary care

EMRs and patients' responses to disease-specific questionnaires. The data are used to characterise patients in terms of their demography, disease control and exacerbation history. The review process produces practice and patient-level reports suggesting possible management changes (in line with best practice guidelines) to optimise control and minimise future risk at the lowest possible therapeutic dose.

The anonymised EMRs captured through the OPC service are collected within the OPC Research Database (OPCRD). At the time of writing, the OPCRD contains anonymised, research-quality data for approximately 3 million UK primary care patients who have received ≥1 prescription for obstructive lung disease medication, from more than 525 practices across the UK that subscribe to the OPC Clinical Service Evaluation (see **Appendix 1** for OPCRD Data Dictionary).

Study Design

This will be a prospectively planned comparative effectiveness study drawing on retrospective EMRs from the OPCRD.

Study Period

To minimise temporal effects introduced by potential changes in asthma and asthma exacerbation management practice, the study will consider a recent 10-year evaluation period (1 January 2004–31 December 2014)[1].

Index event

Index event: prescription for oral corticosteroids ± concomitant antibiotic prescribing.

Index prescription date (IPD): date of the patients index event (i.e. date of receipt of their prescription for oral corticosteroids ± antibiotics).

Baseline & Outcome periods

Baseline period: patients will be characterised over a 6-month period[2] immediately prior to IPD.
Outcome period: Outcomes will be evaluated in the weeks immediately following IPD to explore the potential effect of the index event management option on short-term outcomes:

- **Primary outcome:** 12 weeks post IPD[3]
- **Secondary exploratory outcome periods:** 2 weeks post IPD; 6 weeks post IPD, and 26-weeks (6-months) post IPD.

Study Phases

To inform the optimum analysis approach, the study will be divided into two key phases:

Phase I: Event rate characterisation
Mapping the pattern asthma-related (primary) healthcare resource utilisation during the

[1] Or the latest 10-year period for which research quality data are available within the OPCRD
[2] Index date month will be used within statistical modeling to adjust for potential seasonal effects
[3] 12-week outcome period selected as the primary as intended outcomes as the sensitivity of some of the study outcomes may be diminished over shorter periods

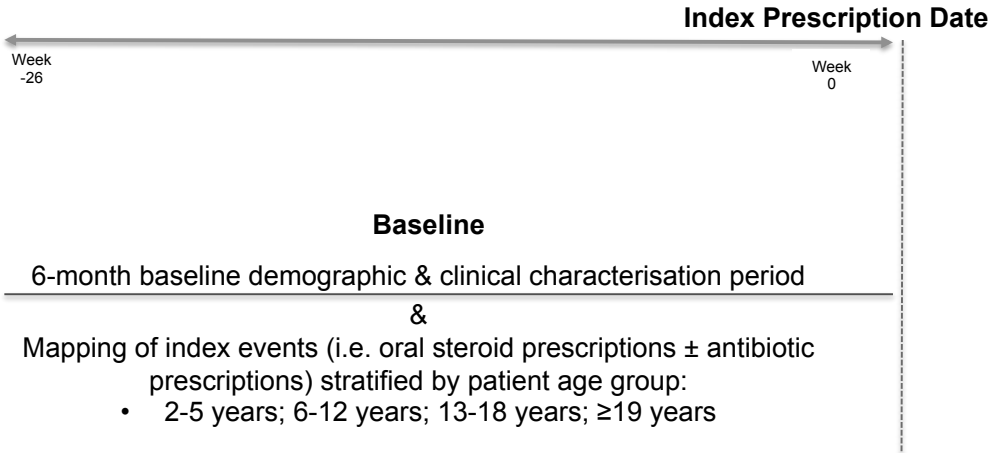
baseline 6-month period. Total event rate and pattern of incidence will be mapped for the following (collectively and independently):

- Primary care consultations coded for asthma / wheeze
- Primary care consultations coded for asthma / wheeze resulting in an antibiotic prescription
- Primary care consultations coded for asthma / wheeze resulting in an oral steroid prescription
- Primary care consultations coded for asthma / wheeze resulting in both an antibiotic and an oral steroid

As event rates are likely to differ depending on the age of the patient (i.e. higher in paediatrics and younger children), the distribution of event rates will be stratified (at the per-patient level) by age, for following age categories:

- 2-5 years
- 6-12 years
- 13-18 years
- ≥19 years

Figure 1. Phase I characterisation schematic



Phase II: Comparative Outcomes

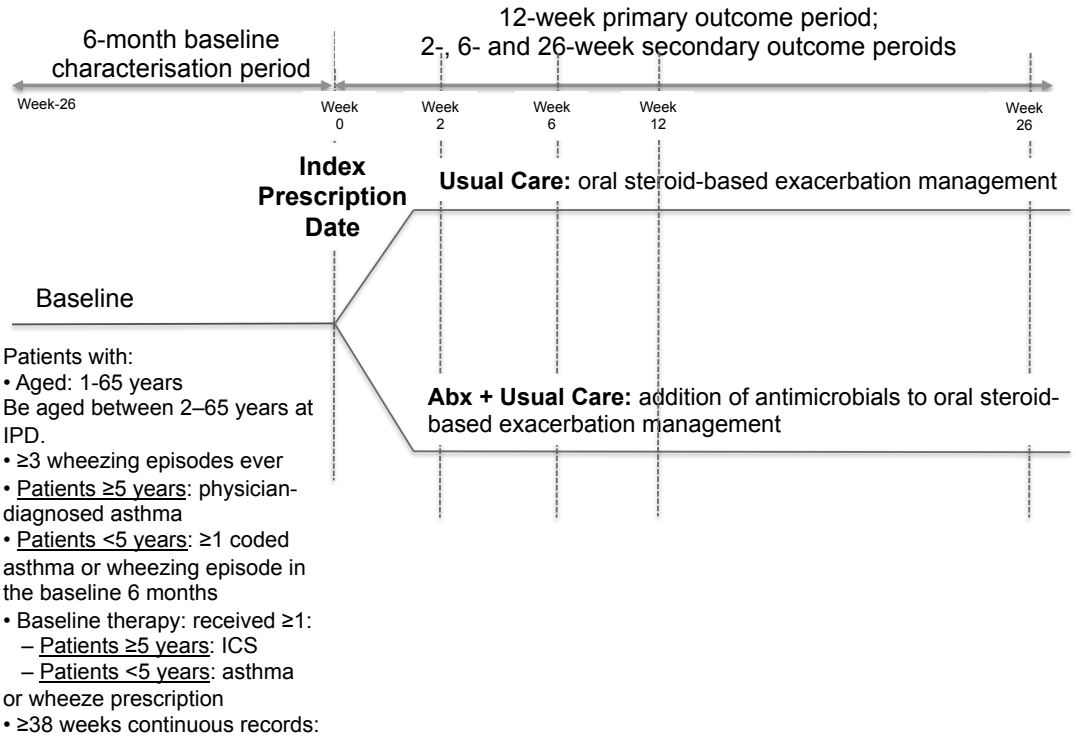
Phase II will be a comparative outcome evaluation of index event management approaches, informed by the pattern of event rates and distributions identified during Phase I. The Phase II analysis approach and statistical analysis plan will, therefore, be developed on completion of Phase I.

Three potential options have been identified:

- Approach 1: a survival analysis considering time to event following the index event, (for all events). This is the approach favoured by the statisticians consulted in the development of the study, but a final decision on the optimum approach will be withheld until the results of Phase I are available
- Approach 2: a repeated measurements analysis
- Approach 3: using each patient as their own control to evaluate different time to next event for patient depending on their index prescription (e.g. comparative time to next event for each patient when prescribed oral steroids only versus oral steroids + antibiotics).

Outcomes will be evaluated separately for adults and paediatric populations, but with specific age stratification thresholds informed by the Phase I and differences within event rates across different paediatric populations.

Figure 2. Phase II comparative effectiveness outcome schematic



STUDY POPULATION

Eligibility Criteria

Inclusion criteria

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

- Be aged between 2–65[i] years at IPD.
- Have had ≥3 wheezing episodes ever
- Have:
  - Patients ≥5 years: physician-diagnosed asthma (i.e. Read code for asthma)
  - Patients <5 years: ≥1 coded asthma or wheezing episode in the baseline 6 months
- Received ≥1:
  - Patients ≥5 years: inhaled corticosteroid (ICS) prescription in the baseline 6 months
  - Patients <5 years: asthma or wheeze prescriptions in the baseline 6 months, where a "wheeze prescription" will be a maintenance/preventer therapy (e.g. ICS, LTRA, ICS/LABA). Releiver therapies (e.g. short-acting bronchodilators) will not be classified as "wheeze prescriptions".
- ≥38 weeks continuous records: ≥26 weeks prior to IPD (baseline 6-months) and ≥12 weeks following IPD (12-week primary outcome).

Exclusion criteria

In order to provide the fullest picture of UK primary care prescribing practice possible, few patients will be excluded. The only exclusion that will be applied will aim to avoid confusion

between index and outcome events associated with asthma and those associated with other chronic comorbidities:

Patients will be excluded if they meet the following criteria:

- Are receiving chronic antibiotics for other chronic respiratory conditions (e.g. cystic fibrosis, PCD, bronchiectasis)
- Are on maintenance oral steroids (for any reason).

OUTCOMES

Primary and secondary outcomes will be evaluated at:

- Primary outcome period: 12 weeks (primary outcome period)
- Secondary outcome periods: 2 weeks, 6 weeks and 26 weeks post index date.

Primary outcomes

1. **Respiratory consultations:**
   - **1a.** Primary care consultations coded for asthma / wheeze
   - **1b.** Primary care consultations coded for asthma / wheeze resulting in an antibiotic prescription
   - **1c.** Primary care consultations coded for asthma / wheeze resulting in an oral steroid prescription
   - **1d.** Primary care consultations coded for asthma / wheeze resulting in both an antibiotic and an oral steroid

N.B. Selection of the primary outcome (e.g. ***number/rate of events*** or ***time to first event*** post IPD) will be will be confirmed following the Phase I characterisation of event rates and final agreement on the most meaningful analysis approach (see Analysis Section, below).

Secondary outcomes

2a. Primary care consultations coded for asthma / wheeze resulting in a prescription for a short-acting bronchodilator (SABA)
2b. Consultation for asthma / wheeze resulting in a SABA
2c. Hospitalisations for lower respiratory complaints
2d. Accident & Emergency (A&E) / Emergency Room (ER) attendance for lower respiratory complaints.

ANALYSIS; VARIABLES & STATISTICAL APPROACH

Analysis

The study poses a number of statistical challenges to ensure minimisation of bias through confounding by severity (e.g. concomitant prescribing of antibiotics and oral steroids cannot be assumed to be a randome prescribing event) while also avoiding selection of an index event that will potentially bias the results (e.g. towards younger populations by selecting the first index event within the dataset as a patients index prescription date).

Matching, often used to minimise potential confounding by severity, will not be possible as it would required matching on multiple events per person.

Three potential options have been identified:

- Approach 1: a repeated measurements analysis
- Approach 2: a survival analysis considering time to event following the index event, (for all events).
- Approach 3: using each patient as their own control to evaluate different time to next event for patient depending on their index prescription (e.g. comparative time to next event for each patient when prescribed oral steroids only versus oral steroids + antibiotics).

Potential counfounders will be managed by appropriate statustical adjustments.

A full statistical analyis plan will be developed by the satistical team on completion of Phase I.

Subgroup analysis

Age: Results will be analysed separately for adult (≥19 years) and paediatric populations (2–18 years) with the Phase I stratification of baseline event frequency by age category (2-4 years; 5-12 years; 13-18 years; ≥19 years) informing age-related matching or stratification requirements for the paediatric analysis.

Antibiotic class: the results will also be stratified by, and compared across, antimicrobial class: beta-lactam; macrolide; other.

Baseline maintenance treatment: with particular focus on any differential effect among patients maanged on ICS therapy during baseline vs ICS/LABA therapy

Smoking status: stratified by current, ex, never smokers.

Variables

VARIABLE	**POINT / PERIOD OF EVALUATION**		
	During baseline	**At index date**	
Demographics			
Age		X	
Sex	X		
Weight	X		
Height	X		
BMI[1]	X		
Smoking status		X	
Clinical features			
Asthma-specific measures (where available)	***Ever (before/during study)***	**During baseline**	**At index date**
Asthma diagnosis	X		
SABA device type		X	X
SABA prescriptions (number); inhaler number		X	X
GP consultations: • All • Coded for asthma • Coded for wheeze • Coded for lower respiratory complaints[2] • Resulting in an oral steroid prescription • Not in an oral steroid prescription • Resulting in an antibiotic prescription		X	X

• Not in an antibiotic prescription			
Out patient department attendances: • All • Coded for asthma • Coded for wheeze • Coded for lower respiratory complaints		X	X
Hospitalisations: • All • Coded for asthma • Coded for wheeze • Coded for lower respiratory complaints			
A&E attendances: • All • Coded for asthma • Coded for wheeze • Coded for lower respiratory complaints			
LABA use		X	X
Add-on asthma therapies		X	X
ICS device type (metered-dose inhaler [MDI], breath-actuated inhaler [BAI] or dry powder inhaler [DPI])			X
Exposure medication possession ratio[2]			X
Spacer use with an ICS MDI during			X
ICS prescriptions			X
ICS inhalers prescribed			X
ICS duration (total pack days)			X
ICS prescription days (actual period)			X
VARIABLE	**POINT / PERIOD OF EVALUATION**		
	Ever (before/during study)	**During baseline**	**At index date**
ICS prescribed dose (most recent)			X
ICS average daily dose (µg in beclometasone equivalents per day)			X
SABA prescriptions		X	X
SABA inhalers prescribed		X	X
Average SABA dosage (average µg taken per day)[3]		X	X
Leukotriene receptor antagonist (LTRA) average daily dose (µg/day)			X
Acute respiratory events	***Ever (before/during study)***	**During baseline**	**At index date**
Hospitalisations (inpatient admissions) coded for: • asthma • wheeze • lower respiratory complaint		X	X
Asthma-related or A&E (i.e. ER) attendance coded for: • asthma • wheeze • lower respiratory complaint		X	X
Acute courses of oral corticosteroids[4] • asthma code • wheeze code • lower respiratory code		X	X
Antibiotic prescriptions with: • asthma code		X	X

• wheeze code • lower respiratory code			
Acute respiratory events (continued)	***Ever (before/during study)***	**During baseline**	**At index date**
Class of antimicrobial prescribed at index date		X	X
Eczema: • Coded diagnosis • Topical steroid prescriptions ≥1 • Coded diagnosis + topical steroid prescriptions	X	X	X
Rhinitis diagnosis ± prescriptions for • Coded diagnosis • Nasal steroids prescriptions ≥1 • Coded diagnosis + nasal steroids prescriptions ≥1	X	X	X
Anaphylaxis diagnosis		X	X
Diabetes diagnosis	X	X	X
Cardiovascular disease diagnosis	X		
Iscahemic Heart Disease diagnosis	X		
Depression & Anxiety • Coded diagnosis • ≥1 prescription for A&D • Coded diagnosis + prescriptions	X		
GERD • Coded diagnosis • ≥1 prescription for GERD • Coded diagnosis + prescriptions	X	X	
VARIABLE	**POINT / PERIOD OF EVALUATION**		
	Ever (before/during study)	**During baseline**	**At index date**
Charleson Comorbidity Index			
Paracetamol prescribed (yes/no)		X	X
NSAIDs prescribed (yes/no)		X	X
Blood eosinophil count[5]		X	X
Oral candidiasis: • Coded diagnosis • ≥1 prescription for antifungals • Coded diagnosis + prescriptions		X	

Variable definitions

1: BMI: defined as the ratio of weight (kg) to squared height (m^2) recorded closest to the end of each study year, and categorised as 'underweight'; 'normal weight'; 'overweight' and 'obese'

2: Refers to any of the following: (a) lower respiratory Read codes (including asthma, COPD and **3:** LRTI Read codes); (b) asthma/COPD review codes excl. any monitoring letter codes; (c) lung function and/or asthma monitoring; or (d) any additional respiratory examinations, referrals, chest x-rays or events.

3: Calculated as follows for the whole baseline period: (total pack days / baseline period in days) x 100; total pack days = sum of number days per pack; number days per pack = number of actuations per pack / number of actuations per day.

500 µg of terbutaline are considered equivalent to 200 µg of the other SABAs.

4: Defined as: (a) all courses that are definitely not maintenance therapy; and/or (b) all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed); and/or (c) all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions. Maintenance therapy is defined as prescriptions with daily dosing instructions of ≤10mg prednisolone or prescriptions for 1mg or 2.5mg prednisolone tablets where daily dosing instructions are not available.

5: counts ($x10^9$/L), at any time before or within each study year and categorised as high/normal thresholds to be informed by the study steering committee

LIMITATIONS OF STUDY DESIGN / ANALYSIS

As with all database studies a number of limitations existed, such as: incomplete data and the need to use proxy measures where explicit data are not available.

The proposed Phase I characterisation of event rate will inform selection of the most robust analysis approach based on incidence patterns within the baseline data. The proposed subset analyses (and senstivities within the outcome definitions) will further test the robustness of the findings (or consistency across) more tightly-defined subgroups.

Subject to the final analysis approach selected, differences between comparator arms will be addressed using statistical methods (matching and/or statistical adjustments), however it will not be possible to account for all confounders in this way and some residual confounders of potential clinical relevance may remain.

For these reasons, the data from this observatonal study should be viewed as one element of the overall evidence base and considered in combination with data from other study designs, e.g. pragmatic trials and randomized controlled trials (RCTs).

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.

STUDY TEAM

Co-Principle Investigators

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

Steering Committee Members

The study steering committee will include REG Chairman (David Price), 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
Steve Turner: Senior Clincial Lectuer, Child Health, University of Aberdeen, Aberdeen, 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

Research
Data analysis and statistical support will be contracted from Research in Real Life Limited – lead researcher **Anjan Nibber**.

Proposal Development & Project Management Oversight
Alison Chisholm: REG Chief Scientific Officer

Patient involvement
At the time of writing, there are no patient experts or advocates involved in the planning and/or review of this study.

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4. Johnston SL, Blasi F, Black PN, Martin RJ, Farrell DJ, Nieman RB; TELICAST Investigators. The effect of telithromycin in acute exacerbations of asthma. *N Engl J Med*. 2006;354:1589-600.
5. Koutsoubari I, Papaevangelou V, Konstantinou GN, Makrinioti H, Xepapadaki P, Kafetzis D, Papadopoulos NG. Effect of clarithromycin on acute asthma exacerbations in children: an open randomized study. *Pediatr Allergy Immunol*. 2012;23:385-90.

APPENDIX

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

[i] Patients aged ≥60 will be include only if they are non-smokers