REG STUDY PROTOCOL

LONG TITLE:

IDENTIFYING OPPORTUNITIES FOR EARLIER DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS IN ROUTINE CARE IN THE UK: A RETROSPECTIVE CLINICAL COHORT STUDY

SHORT TITLE:

OPPORTUNITIES FOR EARLIER IPF DIAGNOSIS

Research Protocol developed by The Respiratory Effectiveness Group

CONTENTS PAGE

BACKGROUND & RATIONALE

Idiopathic pulmonary fibrosis (IPF) is the most common and lethal of the idiopathic interstitial pneumonias. It is estimated to affect between 14–43 people per 100,000, most commonly occurring in those over the age of 50.[1,2,3]

The disease appears to be driven by abnormal/dysfunctional alveolar epithelial cells that promote fibroblast recruitment and proliferation. The result is scarring of the lung, irreversible loss of function and decreased oxygen to the major organs of the body.[4,5] It has an associated 5-year survival of approximately 20%.[6]

Until recently, treatment options for patients with IPF have been limited, primarily focusing on symptom management and palliation. Yet growing understanding of the pathogenesis of the disease over the last two decades has resulted in the development of novel compounds targeted at the mechanisms underlying the disease pathobiology. Indeed in 2014, the European Medicines Association (EMA) in Europe and Food and Drug Administration (FDA) in the USA approved two "first-in-class" compounds (pirfenidone and nintedanib) for the management of IPF.

Both drugs have pleiotropic mechanisms of action and have been shown to slow disease progression and lung function decline in IPF patients with mild to moderate functional impairment. There are also data to suggest they reduce the risk of acute exacerbations, which can lead to hospitalisation and death.[7]

Although this marks an important step forward for IPF management, without the potential to reverse the disease, with the arrival of these therapies places increased emphasis on the need for earlier identification and diagnosis to optimise the potential treatment benefits.

At this time, knowledge is limited of the pathway to a diagnosis of IPF. In absolute terms, IPF is a rare condition that affects only a very small number of patients. Clinicians working in general practice may only come across one or two cases in their medical careers. As such, it is likely that patients presenting in primary care with symptoms of IPF may be misdiagnosed and that there may be a delay in their IPF diagnosis.

In the UK, all patients who ultimately receive a diagnosis of IPF will have first presented in the primary care setting. Thus by carrying out a historical review of the primary care records for patient in the years preceding their IPF diagnosis, it should be possible to identify common patterns (trends) in healthcare resource utilization (HRU) and identify potential "red flags" to support decision support tools to aid earlier diagnosis.

AIMS & OBJECTIVE

With a view to identifying potential opportunities for earlier referral to specialists and (ultimately) earlier diagnosis of IPF, this study aims to:

(i) Evaluate patients' patterns of HRU in the years preceding their IPF diagnosis.
(ii) Characterise the clinical features of patients at the time of their IPF diagnosis.

STUDY DESIGN & DATASET

Study Design

The study will be a prospectively planned, historical follow-up study using electronic medical records and linked questionnaire data from the Optimum Patient Care Research Database (OPCRD).

Data source

The OPCRD is a quality-controlled, longitudinal, primary-care respiratory focused database containing anonymous data from general practices in the UK.

The data are collected via the Optimum Patient Care (OPC) Clinical Service Evaluation, which involves a combined review of clinical records and patients' responses to disease-specific questionnaires (see **Appendix 1** for the full COPD and asthma questionnaires). The data are curated in the Optimum Patient Care Research Database (OPCRD), with electronic medical records (EMRs) linked to patient-reported data (where available) via a unique patient identifier.

At the time of writing, the OPCRD contains anonymised, research-quality data for over 2.5 million UK patients from move than 525 practices across the UK that subscribe to the OPC Clinical Service Evaluation. A full data dictionary for the OPCRD is detailed in **Appendix 1**.

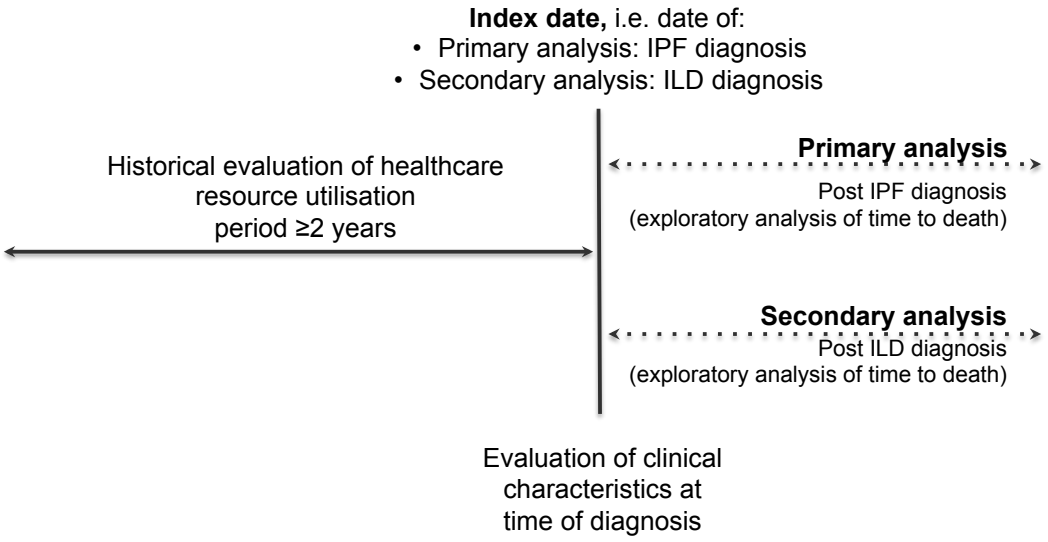
Study Period

The study period will include the 45-year period (1970–2015) coincident with the migration of UK patient records from paper to electronic format. At a practice level, to avoid use of retrospectively entered routine consultation data, only routine data recorded after the date the practice began to use full electronic medical records will be included.

Evaluation Period

The evaluation period will consist of:

- An index date at which patients receive their IPF diagnosis (see **Appendix 2** for a full code list)
- Characterisation period: ≥2 years continuous EMR immediately preceding the index date



STUDY POPULATION

Eligibility Criteria

Inclusion criteria

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

- Have a diagnostic (Read code) for IPF (see **Appendix 3** for full code list)
- Diagnosed with IPF between 1990 and 2015.
- Have a minimum of 2 years continuous clinical records in the years immediately preceding their index diagnosis
- Aged 40 years or older at index date

Exclusion Criteria

No additional exclusion criteria will be applied to ensure the study population includes the broadly heterogeneous patient population treated in routine primary care in the UK.

OUTCOMES

Longitudinal patterns of healthcare resource utilization

To evaluate common patterns and potential increasing trends in HRU in patients diagnosed with IPF, the following will be evaluated over the 25 years (and in 5-year categories: 0–5 years; 6–10 years, 11–15 years, 16–20 years and 21–25 years) preceding their diagnosis:

1. **Consultations:**
   - **a)** Lower respiratory[1] (LR) consultations
   - **b)** LR Consultation resulting in a course of antibiotic drugs (on the same day)
   - **c)** LR Consultation resulting in a course of oral steroids (on the same day)

2. **Hospitalisations (in-patient attendances) with a code for a:**
   - **a)** All
   - **b)** LR complaint on the same day
   - **c)** LR complaint within the following 7 days

3. **Out patient visits with a code for a:**
   - **a)** LR complaint on the same day
   - **b)** LR complaint within the following 7 days

4. **Accident & Emergency (A&E) attendances coded for a:**
   - **a)** LR complaint on the same day
   - **b)** LR complaint within the following 7 days

5. **Chest X-ray / radiology**

[1] Where a lower respiratory complaint code includes lower respiratory tract infections (such as bronchitis, tracheitis, and pneumonia, which might need antibiotic treatment), non-infective lower respiratory conditions (such as asbestosis and chronic respiratory failure), and respiratory symptoms (such as breathlessness, hyperventilation, cough, and wheezing).

Potential misdiagnosis

a) COPD:
- Physician-diagnosed COPD
- Duration of comorbid COPD (i.e. years between COPD and IPF diagnosis)

b) Asthma:
- Physician-diagnosed asthma
- Duration of comorbid asthma (i.e. years between asthma and IPF diagnosis)

c) Chronic respiratory conditions other than asthma and COPD:
- Physician-diagnosis
- Duration of comorbid condition (i.e. years between diagnosis and IPF diagnosis)

Clinical characterisation at time of diagnosis

Patients will be characterized as follows in order to:

(a) Evaluate the extent to which patients diagnosed with IPF within the OPCRD are representative, of those commonly treated by specialists
(b) Identify potential differential diagnoses
(c) Identify common traits and potential triggers for earlier specialist referral.

1. Demographic & lifestyle factors (at or closest to index date):

a) Sex
b) Age
c) Height
d) Weight
e) Body mass index, (BMI)
f) Smoking status.

2. Comorbidities:

Respiratory

a) COPD: presence of comorbid COPD; duration of comorbid COPD
b) Asthma: presence of comorbid asthma; duration of comorbid asthma
c) Chronic respiratory conditions other than asthma and COPD: presence of comorbid condition; duration of condition

Other

d) Allergy (eczema, allergic or non-allergic rhinitis)
e) Nasal polyps
f) Diabetes mellitus
g) Gastroesophageal reflux disease (GERD)
h) Ischemic heart disease (IHD),
i) Heart failure
j) Anxiety/depression
k) Charlson Comorbidity Index.

3. Respiratory pharmacotherapy in the year preceding index date:

a) Prescriptions for SABA: Total prescribed dose; Total number of inhalers prescribed
b) Prescriptions for LABA: Total prescribed dose; Total number of inhalers prescribed
c) Prescriptions for LAMA: Total prescribed dose; Total number of inhalers prescribed

d) Prescriptions for ICS[2]: Total prescribed dose; Total number of inhalers prescribed
e) Prescriptions for LTRA: Total prescribed dose; Total number of inhalers prescribed
f) Prescriptions for ICS/LABA: Total equivalent prescribed ICS dose; Total equivalent LABA dose; Total number of inhalers prescribed

4. **Symptom severity:**

a) modified Medical Research Council (mMRC) dyspnea score[3] [closest to index date]
b) COPD assessment test (CAT) score[3] [closest to index date]
c) Number of COPD exacerbations in previous year (see **Appendix 3** for full definition)
d) Number of COPD exacerbations in previous year (see **Appendix 3** for full definition)

5. **Spirometry:**
   a) FEV1 (% predicted)
   b) FEV1/FVC ratio.
   c) GOLD Category (where relevant)

6. **Blood eosinophilia** (≥0.5 x 10^9/ L).

Exploratory Outcome

Among the subset of patients with outcome data and a death record within their clinical records, **survival time** (i.e. time from IPF diagnosis to death – all cause and respiratory-related) will be evaluated and compared with average (median, IQR) IPF survival times observed in clinical practice.

The survival analysis will also aim to explore potential associations between pre-diagnosis HRU patterns and time between diagnosis and death.

ANALYSIS

The period over which trends in HRU (and missed opportunities for diagnosing IPF) will be evaluated will be informed by the duration of continuous clinical records available within the study population, once extracted.

The full statistical approach will be outlined in the statistical analysis plan (SAP) and will be approved by the lead investigator before the study commences. Provisionally:

- The analysis will assess changes in HRU over the 25-year period (1990–2015), and in 5-year increments (0–5 years; 6–10 years, 11–15 years, 16–20 years and 21–25 years)
- Summary statistics will be used to characterise patients at time of IPF diagnosis:
  - For variables measured on the interval or ratio scale, summary statistics produced will be:
    - Sample size (n)
    - Percentage non missing
    - Mean
    - Variance/standard deviation
    - Range (minimum- maximum)
    - Median
    - Inter-quantile range (25th and 75th percentile)

[2] Beclomethasone dipropionate- (BDP-) equivalent dose
[3] Where available (i.e. in the subgroup of patients with questionnaire responses)

  - For categorical variable the summary statistics will include:
    - Sample size (n)
    - Range (if applicable)
    - Count and percentage by category (distribution)
- Statistically significant results will be defined as $p<0.05$ and trends as $0.05 \leq p < 0.10$.
- Suitable tests (e.g. F tests, t tests, $\chi 2$ tests) and models (e.g. linear models) will be used, as appropriate, to explore the interaction between different clinical characteristics and features (e.g. year, age) of diagnosis.
- The number and percentage of patients with missed opportunities for diagnosis will be evaluated by year before diagnosis (1–20 years before) and in 5-year bands before diagnosis.
- Generalised linear models will be utilised to explore how missed opportunities to diagnose IPF have changed from 1990 to 2015.

LIMITATIONS OF STUDY DESIGN / ANALYSIS

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

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

DATA DISSEMINATION PLANS

REG is committed to registering all research that it conducts (e.g. in the ENCePP or clincialtrials.gov registries) 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

Lead investigator: Luca Richeldi, National Institute for Health Research, Southampton Respiratory Biomedical Research Unit, University of Southampton, Southampton, United Kingdom

David Price: Professor of Primary Care Respiratory Medicine, University of Aberdeen, Aberdeen, UK; Owner of Optimum Patient Care Ltd and Chairman of the Respiratory Effectiveness Group

Carlo Vancheri: "Regional Centre for Rare Lung Diseases", Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Christopher Ryerson: Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; Department of Medicine, University of California San Francisco, San Francisco, California, USA.

Ian Glaspole: Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Melbourne, Australia

Kevin Flaherty: Dept of Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

Vincent Cottin: National Reference Centre for Rare Pulmonary Diseases, Department of Respiratory Medicine, Claude Bernard Lyon University, Lyon, France

Toby Maher: National Institute for Health Research (NIHR) Clinician Scientist and ... Physician on the Interstitial Lung Disease Unit, Royal Brompton Hospital

Alison Chisholm: Chief Scientific Officer of the Respiratory Effectiveness Group, Cambridge, UK

TIMELINE

The study will take approximately 18 weeks (4.5 months) from ethical approval through to final report delivery; manuscript submission approximately 3 months following the steering committee's approval of the final study report. Definitive timelines will be agreed at the point of study initiation.

Action	Timeline
ADEPT approval for data use	2 weeks
Data extraction	2 weeks
Analysis	4 weeks
Report writing (incl internal review)	2 weeks
Steering committee review	2 weeks
Analysis	2 weeks
Final report writing (incl internal review)	2 weeks
Steering committee review	2 weeks
First draft of manuscript	12 weeks from final report

BUDGET SUMMARY

Activity	GBP
Project Management	5,000
Legal and finance	2,000
Protocol development	4,000
Data extraction	12,000
Baseline analysis	6,000
Report writing – initial draft (slides)	4,000
Steering committee**/REG review I and revisions	1,000
Outcome analysis	5,000
Report writing – final (slides, Word doc, other)	3,000
Steering committee**/REG review and revisions	1,000
Abstract writing	1,000
Abstract submission to 1 x Congress	1,000
Poster / Slide preparation	3,000
Internal review of submission and revisions	2,000
Travel and accommodation to Congress for PI	5,000
First draft of manuscript	12,000
Revisions	1,000
Liaison with publishers, authors, further revisions	2,000
Internal review	2,000
Submission to journal	2,000
Publication fee	5,000
Open Access fee	3,000
Total Budget	**82,000.00**

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3. American Thoracic Society. Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. Am J Respir Crit Care Med. 2000;161:646–664.
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5. Richeldi L, et al. Design of the INPULSIS® Trials: Two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis. *Respir Med*. 2014;108:1023-30.
6. European Respiratory Society. ERS White Book: Interstitial Lung Disease. Available online at: http://www.erswhitebook.org/chapters/interstitial-lung-diseases/ (last accessed 19 August 2015)
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APPENDIX 1

OPCRD data dictionary & questionnaires

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

APPENDIX 2

IPF Code List

[Full code list in development]

Read Code	Read Term
H563.	Idiopath.fibrosing alveolitis
H563.11	Hamman - Rich syndrome
H563.12	Crypt fibrosing alveolitis
H5632	Pulmonary fibrosis
H5630	Alveolar capillary block
H5631	Diffuse pulmonary fibrosis
H563z	Idiopath.fibrosing alveol.NOS

APPENDIX 3

Exacerbation definitions & hospitalisation definitions

Asthma exacerbation definition based on the ATS/ERS Position Statement

An exacerbation is defined as an occurrence[4] of the following:

1. Asthma-related[5]:
   a. Hospital admissions OR
   b. A&E attendance; OR
2. An acute[6] course of oral steroids.

Asthma exacerbation definition based on the ATS/ERS Position Statement (SENSITIVITY DEFINITION)

An exacerbation is defined as an occurrence of the following:

1. Asthma-related:
   a. Hospital admissions OR
   b. A&E attendance; OR
2. An acute course of oral steroids with lower respiratory consultation[7].

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[4] Where ≥1 oral steroid course / hospitalisation occurs within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

[5] **Asthma-Related Hospitalisations:** consists of either a definite Asthma Emergency Attendance or a definite Asthma Hospital Admission; OR a generic hospitalisation read code which has been recorded on the same day as a **Lower Respiratory Consultation** Error! Bookmark not defined.**5** (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test).

[6] Acute oral steroid use associated with asthma exacerbation treatment will be defined as:

- all courses that are definitely not maintenance therapy, and/or
- all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
- all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

where "maintenance therapy" is defined as: daily dosing instructions of <=10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.

[7] **Lower Respiratory Consultations -** consist of the following:

a) Lower Respiratory read codes (including Asthma, COPD and LRTI read codes);
b) Asthma/COPD review codes excl. any monitoring letter codes;
c) Lung function and/or asthma monitoring
d) Any additional respiratory examinations, referrals, chest x-rays or events.

Moderate/Severe COPD Exacerbations

Where an exacerbation is defined as an occurrence[8] of:

1. COPD-related[9]: Unscheduled hospital admission / A&E attendance; OR
2. An acute[10] course of oral steroids; OR
3. Antibiotics prescribed with lower respiratory consultation[11].

Moderate/Severe COPD Exacerbations – sensitivity definition

Where an exacerbation is defined as an occurrence[8] of:

1. COPD-related[9]: Unscheduled hospital admission / A&E attendance; OR
2. An acute[10] course of oral steroids with lower respiratory consultation[11]; OR
3. Antibiotics prescribed with lower respiratory consultation[11].

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[8]Where ≥1 oral steroid course / hospitalisation / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

[9]**COPD-related Hospitalisations:** consist of either a definite COPD Emergency Attendance or a definite COPD Hospital Admission; OR a generic hospitalisation read code which has been recorded on the same day as a **Lower Respiratory Consultation**[11] (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test).

[10] Acute oral steroid use associated with COPD exacerbation treatment will be defined as:

- all courses that are definitely not maintenance therapy, and/or
- all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
- all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

where “maintenance therapy” is defined as: daily dosing instructions of <=10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.

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d) Any additional respiratory examinations, referrals, chest x-rays, or events.