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TITLE: Lifetime prevalence of Type 2 comorbidities in patients with COPD – especially those with higher eosinophilic counts

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADEPT	Anonymised Data Ethics and protocol transparency
BEC	Blood eosinophil counts
BMI	Body mass index
CCL5	C-C Motif Chemokine Ligand 5
COPD	Chronic obstructive pulmonary disease
CRS	Chronic rhinosinusitis
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
ICS	Inhaled Cortico-Steroid
IL	Interleukin
IQR	Interquartile range
NHS	National Health Service
PR	Prevalence rate
OPCRD	Optimum and Pragmatic Research Institute
OPRI	Observational and Pragmatic Research Institute
RA index	Rheumatoid arthritis- index
RECORD	Reporting of studies Conducted using Observational Routinely collected Data
REC	Research Ethics Committee
REG	Respiratory Effectiveness Group
SABA	Short-acting beta-2 agonist
SNOMED CT	Systematized Nomenclature of Medicine – Clinical Term
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SMD	Standardised mean difference
SD	Standard deviation
T2	Type 2
UK	United Kingdom

1. BACKGROUND & RATIONALE

Chronic obstructive pulmonary disease (COPD) and asthma are complex (1), heterogeneous (1,2) and among the most prevalent chronic respiratory conditions, considered as distinct entities. Emerging evidence suggests a significant overlap between the two, particularly in relation to their inflammatory pathways. Asthma is primarily linked to Type 2 (T2) inflammation, characterized by elevated eosinophils, increased fractional exhaled nitric oxide (FeNO), and cytokines activation (IL-4, IL-5, and IL-13) (3). Traditionally seen as neutrophil-driven disease, caused by smoking, COPD also includes a subset (10-40%), with elevated blood eosinophil counts—resembling asthma (4,5). These patients show Type 2-transcriptome signatures and a higher risk of exacerbations driven by T2 cytokines including IL-4, IL-5, IL-13, and CCL5, highlighting shared inflammatory pathway and potential common treatment.

Sustained T2 inflammation in COPD can contribute to airway remodeling, mucus hypersecretion, and structural changes that worsen disease severity (6). Despite the recognition of its potential role, significant gaps are still present in understanding the impact of T2 inflammation on comorbidities and clinical outcomes in COPD (3). Blood Eosinophil Count (BEC) has emerged as a potential biomarker for guiding treatment decisions, particularly in predicting responses to Inhaled Corticosteroid (ICS) therapy. Although ICS are commonly used in COPD to reduce exacerbations, their effectiveness is limited to a subset of patients, and they are associated with risks such as an increased likelihood of pneumonia. By using BEC to show patients most likely to benefit from ICS, treatment outcomes can be refined, while minimizing unnecessary risks. A sputum eosinophil threshold of 3% and/or blood eosinophils ≥300/μL has often been suggested to define eosinophilic airway inflammation in COPD (7). However, some COPD patients show a persistent eosinophilic phenotype – while others show transient eosinophilia during exacerbations.

For example, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study proved that 37.4% of COPD patients shown persistent eosinophilia, highlighting its relevance as a tool for precision medicine (8). However, the clinical application of BEC in COPD faces several challenges, including variability over time due to factors such as infections, medications, comorbidities, and malignancies. Despite these challenges, BEC remains a promising tool for finding subgroups of COPD patients who may receive help from targeted therapies.

Further research is needed to clarify the prevalence and clustering of T2 inflammation in COPD, as well as its therapeutic implications.

Investigating the prevalence of blood eosinophil-associated airway diseases such as allergic rhinitis, chronic rhinosinusitis, and atopic dermatitis, in COPD patients compared with asthma, is essential to better understand their role in inflammation and to refine treatment approaches based on eosinophilic phenotype.

This protocol adheres to the RECORD (Reporting of studies Conducted using Observational Routinely collected Data) checklist, ensuring transparency, rigor, and completeness in reporting observational studies using routinely collected health data (9). The RECORD guidelines extend the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, addressing unique challenges related to study design, data sources, patient selection, bias, and data linkage in observational research.

2. STUDY AIMS AND OBJECTIVES

2.1. Study aims

2.1.1. Primary

- Compare the lifetime prevalence of Type 2 comorbidities (allergic rhinitis, nasal polyps, atopic dermatitis and eczema, chronic rhinosinusitis with or without polyps, ulcerative colitis, eosinophil esophagitis) between the COPD-only patients (without asthma history) and asthma-only patients.
- Stratify the study population based on blood eosinophil count categories to examine trends in T2 comorbidities within COPD-only and asthma-only groups.

2.1.2. Secondary

- Compare the lifetime prevalence of T2-related comorbidities (e.g., allergic rhinitis, nasal polyps, atopic dermatitis) among COPD-only patients (without asthma history) and those with COPD-asthma-comorbid patients.
- Perform sensitivity analyses to address the rounding biases in blood eosinophil counts, ensuring correct categorisation.

2.1.3. Exploratory

- To analyse the prevalence rates separately by age, sex and ethnicity to understand the potential differences in the comorbidity patterns.

3. STUDY DESIGN

This is a historical observational study using electronic health records from the Optimum Patient Care Research Database (OPCRD) UK. This is a collaborative study between the University of Exeter (UK) and OPRI.

3.1. Study period

The study will include OPCRD practices found using the Rheumatoid arthritis (RA)-index, which flags the highest quality practices for research. The study period will span from the start of the data until present (24/03/2025). The RA index aims to identify GP sites contributing to OPCRD which have better data recording practices.

4. STUDY POPULATION

4.1. Data sources

The data for this study will be obtained from the Optimum Patient Care Research Database (OPCRD) (http://opcrd.co.uk), a comprehensive repository of anonymized, routinely collected patient-level health records. OPCRD holds diagnostic, clinical, laboratory results and prescription data for over 24 million patients across 1,000 primary care practices across England, Scotland, Wales and Northern Ireland, representing approximately 35% of the total UK population. OPCRD has received ethical approval for the use of anonymized data in research from the National Health Service (NHS) Health Research Authority, under the Research Ethics Committee (REC) reference: 15/EM/0150. Prior to data extraction and analysis, the study protocol will be sent for review and approval by the Anonymized Data Ethics and Protocols Transparency (ADEPT) Committee (protocol reference: ADEPT0923). ADEPT is an independent expert panel, including regulatory authorities, commissioned by the Respiratory Effectiveness Group (REG) (www.effectivenessevaluation.org), to oversee research using OPCRD data and ensure adherence to ethical standards.

This study is being designed and documented before data extraction in alignment with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidelines. It will be formally registered with ENCePP under an assigned registration number (XXX). The study will be conducted in compliance with Good Clinical Practice (GCP) and the Declaration of Helsinki. As this is a retrospective study using the anonymized data, individual patients' consent is not required.

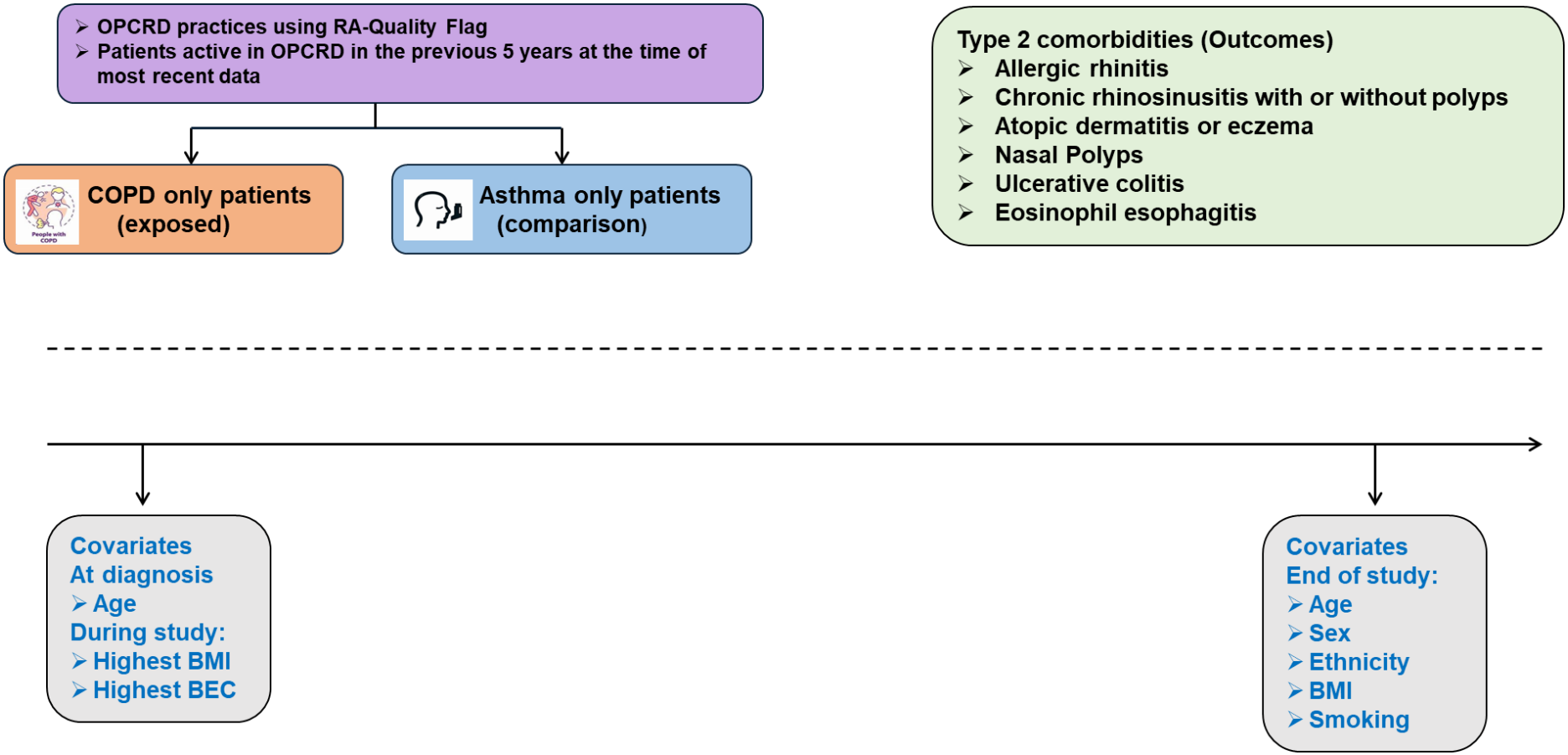

Figure 1: Conceptual figure of lifetime prevalence of type 2 comorbidities comparing the COPD-patients with asthma patients. COPD: chronic obstructive pulmonary disease, RA: rheumatoid arthritis, BMI: Body Mass Index, BEC: Blood eosinophil counts.

4.2. Eligibility criteria

4.2.1. Inclusion criteria

- Any patient with a COPD or asthma diagnosis at any time from patients active in OPCRD in the previous 5 years at the time of the most recent data in OPCRD with their complete demographic medical and lifestyle history.

All these patients will be extracted from OPCRD practices using the RA-index.

4.2.2. Exclusion criteria

- Patients with history of cystic fibrosis will be excluded from the study due to different disease pathology.
- Excluding those who are less than 5 years old at the end of study period.

5. STUDY VARIABLES AND STUDY OUTCOME DEFINITIONS

5.1. Exposure

5.1.1. COPD-only patients

- Patients with a confirmed COPD diagnosis (FEV1/FVC ratio < 70%) + no COPD resolved code
- COPD diagnosis code + last COPD diagnosis date after last COPD resolved date
- No asthma diagnosis ever

5.1.2. Asthma only patients

- Patients with asthma regardless of FEV1/FVC < 70% but no recorded history of COPD (at any time, previous or concurrent).
- Asthma diagnosis based on clinical records (Read/SNOMED CT codes).
    - Asthma diagnosis code present + no asthma resolved code or
    - Asthma diagnosis code + last asthma diagnosis date is after the last asthma resolved date
    - No COPD diagnosis code ever.

5.1.3. COPD + active asthma comorbid

- Coded asthma or COPD reviews per QOF
- COPD diagnosis code + no COPD resolved code and
- Asthma diagnosis code + no asthma resolved code
- Coded asthma or COPD review in last year

5.1.4. COPD cohort with previous/concurrent asthma (messy group)

- COPD diagnosis code and
- Asthma diagnosis code ever
- Asthma/COPD maintenance prescriptions in the last year.

5.2. Outcomes

The outcomes of interest are T2-related comorbidities including

- allergic rhinitis,
- atopic dermatitis and eczema,
- chronic rhinosinusitis (CRS) with or without polyps.
- nasal polyps,
- eosinophilic esophagitis,
- ulcerative colitis

These conditions will be identified using validated Read codes, and SNOMED CT codes recorded within the OPCRD dataset, ensuring consistency and accuracy in diagnosis classification. By examining these outcomes, this study will provide a detailed assessment of the relationship between T2 inflammation, eosinophil levels, and the burden of comorbidities in individuals with COPD and asthma.

5.3. Covariates

5.3.1. Demographics

i) **Age:** Age will be measured at two-time points

- Age will be measured at two-time points age at diagnosis (to show the age-differences across the three groups)
- age at the end of study period the last recorded instance of COPD within the dataset:
  - Below 9
  - 10-19,
  - 20-29,
  - 30-39,
  - 40-49,
  - 50-59,
  - 60-69,
  - 70-79,
  - 80-and above.

ii) **Gender and ethnicity** are time-invariant covariates measured at the end of study

- men and
- women,

iii) Ethnicity categorized as:

- European (includes groups like white British, Irish, and other European origins),
- Black (includes black Africans, Black Caribbean, and other black background),
- Asian (includes Asian Indian, Pakistani, Bangladeshi, Chinese, and other South Asian and East Asian backgrounds),
- missing (not reported/recorded) will be measured at the end of study.

5.3.2. Lifestyle factors

i) **BMI** will be measured as highest ever recorded and the latest entries as a continuous variable and
categorical variable defined as:

- <18.5: underweight
- 18.5-24.9: healthy weight
- 25-29.9: overweight
- >=30: obese

ii) **Smoking** is a major risk factor especially for COPD and will be measured as a latest entry and categorized as

- current smoker
- ex-smoker and
- never smoker
- missing.

6. STRATIFICATION BY BLOOD EOSINOPHIL LEVELS

Blood eosinophil levels have become an important biomarker in both COPD and asthma, influencing disease severity, exacerbation risk, and treatment response. In this study, blood eosinophil levels will be treated as a stratification variable, rather than an exposure, to examine its association with T2-related comorbidities such as allergic rhinitis, eosinophilic esophagitis, and atopic dermatitis.

6.1. Stratification Categories

Patients will be stratified based on their highest ever recorded eosinophil count at any point during their medical history. The eosinophil count will be categorized into the following groups:

- 0–100 cells/μL
- 101–200 cells/μL
- 201–300 cells/μL
- 301–400 cells/μL
- 401–500 cells/μL
- >501 cells/μL
- Missing

These categories align with earlier research on blood eosinophils and disease burden, ensuring comparability with existing literature (22).

6.2. Purpose of Stratification

Stratifying patients by eosinophil levels will allow the study to assess how different levels of eosinophils correlate with the presence and severity of T2-related comorbidities.

Demographics and anthropometrics	
Age	Age in years at: ➢ COPD-diagnosis and asthma-diagnosis ➢ End of the study period expressed as mean ± standard deviation and/or median with interquartile range. This is to be described as a continuous variable and categorical variable as: ➢ below 9 ➢ 10-19 years ➢ 20-29 years ➢ 30-39 years ➢ 40-49 years ➢ 50-59 years ➢ 60-69 years ➢ 70-79 years ➢ 80-89 years ➢ Above 90 years; it is analyzed as categorical variable.
Sex	Female or male
Body Mass Index (BMI)	Defined as the ratio of weight (kg) to squared height (m^2) closest to the index date. This is to be described as both a continuous and categorical variable, with the following categories: ➢ Underweight (BMI < 18.5) ➢ Normal weight (BMI 18.5 to <25) ➢ Overweight (BMI 25 to <30) ➢ Obese (BMI 30 and over) It is analysed as categorical variable.
Smoking status	The status prior to and closest to the study end date and the latest records will be used. This will be analysed and described as categories, with the following categories: ➢ Current ➢ Ex-smoker ➢ Non-smoker ➢ Passive
Ethnicity	This will be analysed and described as categories, with the following categories: ➢ European ➢ Black ➢ Asian ➢ Mixed/others ➢ Unknown
Blood eosinophil count	This refers to the highest blood eosinophils at any time during their medical history. This is to be analysed and described as categorical variable, with the following categories: ➢ 0–100 cells/μL ➢ 101–200 cells/μL ➢ 201–300 cells/μL ➢ 301–400 cells/μL ➢ 401–500 cells/μL ➢ >501 cells/μL ➢ Missing

STATISTICAL ANALYSIS

Table 1: Patient flow

Patient Flow	Number of patients
OPCRD	29,536,599
RA Practices (RA Index=1 indicating high quality recording)	21,768,098
Asthma or COPD diagnosis ever	2,723,690
Active in the last 5 years (visit recorded in the last 5 years)	1,597,607
No diagnosis record of cystic fibrosis	1,596,894
Age at least 5 and less than 95 at end of study period (24th March 2025)	1,437,410
Date anomalies	1,413,805
GROUP 1: Asthma only ➢ Asthma diagnosis code + no asthma resolved code **or** ➢ Asthma diagnosis code + last asthma diagnosis date after last asthma resolved date **and** ➢ No COPD diagnosis code ever	1,156,757
GROUP 2: COPD only ➢ COPD diagnosis code + no COPD resolved code **or** ➢ COPD diagnosis code + last COPD diagnosis date after last COPD resolved date **and** ➢ No Asthma diagnosis code ever	181,139
COPD based on dx codes and confirmed spirometry values	122,846
COPD only with missing spirometry values	58,293
GROUP 3: COPD & Asthma ➢ COPD diagnosis code + no COPD resolved code **and** ➢ Asthma diagnosis code + no Asthma resolved code **and** ➢ Asthma/COPD diagnosis code or Asthma/COPD/Respiratory review code or maintenance prescriptions in the last year	70,416
GROUP 4: COPD & Asthma (messy) ➢ COPD diagnosis code **and** ➢ Asthma diagnosis code **and** ➢ Asthma/COPD diagnosis code or Asthma/COPD/Respiratory review code or maintenance prescriptions in the last year	5,493
Count	1,413,805

7.2. Sample size

The primary goal of this study is to compare the prevalence of Type 2 inflammation-related comorbidities, including atopic dermatitis and eczema, allergic rhinitis, CRS with or without nasal polyps, nasal polyps, eosinophilic esophagitis, and ulcerative colitis in COPD and asthma patients. The sample size for each outcome was calculated using a two-sample test of proportions, since we are comparing the prevalence rates between COPD and asthma patients. To estimate the difference in proportions for each outcome, we used 99% power and a significance level of 0.05. Based on earlier studies, the prevalence of chronic rhinosinusitis (CRS) was 48% in COPD patients (10) and 50% in asthma patients (11), thus the required sample size per group was 32,921. For atopic dermatitis, the prevalence was 25% in asthma and 14% in COPD, so the required sample size per group was 4,080(10,12). For allergic rhinitis, the prevalence was 35% in COPD and 55% in asthma, with a required sample size of 321 patients per group (12). The highest sample size requirement is for CRS (i.e., 32,921 per group). Therefore, to ensure adequate power for detecting significant differences across all outcomes, the study will need to recruit 32,921 COPD patients and 32,921 asthma patients, which will be sufficient to meet the sample size requirements for all outcomes, including CRS, the most demanding outcome. The highest required sample size is for CRS, which is 32,921 participants per group. Given the available feasibility counts for both COPD and asthma patients, recruitment will be possible, and the study will be powered to detect statistically significant differences across all outcomes with 99% power and a 0.05 alpha level.

7.3. Analytical methods

7.3.1. Descriptive analysis

- Descriptive statistics (e.g., means, standard deviations, medians, and interquartile ranges) will be used to summarize the baseline characteristics of the study population, including blood eosinophil levels (stratified into categories of:0–100,
- 101–200,
- 201–300,
- 301–400,
- 401–500,
- >501 cells/μL,
- Missing

These descriptive measures will allow for an overview of the distribution of eosinophil levels across the COPD and asthma patient groups, as well as the characteristics of patients in different eosinophil strata.

7.3.2. Lifetime prevalence of Type 2-related comorbidities

The lifetime prevalence of Type 2-related comorbidities (e.g., allergic rhinitis, atopic dermatitis and eczema, CRS with or without polyp or eosinophilic esophagitis, atopic dermatitis) will be calculated for each study cohort (COPD only, asthma only, COPD-asthma comorbid and COPD-asthma messy group) by determining the number of patients who have been diagnosed with specific Type 2-related comorbidity recorded in their medical records at any time before or during the study period, up until the end of follow-up (24/03/2025). The prevalence will be expressed as the number of patients with a comorbidity divided by the total population at risk in each cohort.

Primary comparison: The prevalence of Type-2-related comorbidities will be compared between COPD-only, with asthma-only reference group. The COPD-asthma comorbid group will also be compared separately to the asthma-only reference group. PRs greater than 1.0 indicate a higher prevalence of Type 2-related comorbidities in COPD-only or COPD-asthma patients compared to asthma-only, while PRs less than 1.0 indicate a lower prevalence.

Eosinophil stratification: The analysis will be further stratified by eosinophil count categories

- 0–100
- 101–200
- 201–300
- 301–400
- 401–500
- >501 cells/μL

Within each eosinophil category, prevalence ratios will be calculated for COPD-only and COPD-asthma comorbid groups compared to asthma-only.

The lifetime prevalence will be analysed using a log-binomial model or Poisson regression model with robust variance if there are convergence problems with the log-binomial model. These approaches are preferred over logistic regression for estimating prevalence ratios in observational studies with binary outcomes (13). Unadjusted prevalence will be compared across groups (COPD only, asthma only, COPD-asthma comorbid), with stratification by eosinophil levels. The asthma-only group will serve as the reference category for prevalence ratio (PR) calculations.

7. SOFTWARE

A combination of SQL Management Studio and Stata v15.1 (12) will be used for this analysis.

8. REGULATORY AND ETHICAL COMPLIANCE

This work requires ADEPT approval for use of OPCRD data.

9. DATA DISSEMINATION

The work will be published in a peer-reviewed journal.

10. TIMELINES

Action	Timeline
Protocol finalised	2/04/2025
Protocol sign-off by Directors,	2/04/2025
Dataset Creation	31/03/2025
Baseline characteristics (demographics)	14/04/2025
ADEPT (if OPCRD or ISAR data is used) approval	23/10/2025
Full Results Slide deck	28/04/2025
Final study report	15/05/2025
Study report sign-off+ sent	15/05/2025; then extra analysis was done and sent off 01/09/2025
Conference abstract	
Publication	

11. VERSION HISTORY

Version	Date	Authors
1.0	04/02/2025	Sent to Shelly
1.1	26/02/2025	Revised based Professor Halpin
1.2	02/04/2025	Revised again after OPRI meeting
2.0	12/03/2025-14/04/2025	➢ Baseline table and main results discussed in the external meeting ➢ This involved major changes to the cohort ➢ Revise the whole data-extraction considering top RA-practices
2.1	15/05/2025	Final report sent
2.2	01/09/2025	More analyses were included and sent off the report again

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