PROTOCOL CHECKLIST

Required area	Included in protocol?	If no, reason for omission
Study investigator team	X	
Roles, responsibilities and resources	X	
Funding statement	X	
Objective, specific aims	X	
Background and rationale	X	
Study design	X	
Study population	X	
Selection of comparison group(s) or controls	X	
Exposures, outcomes and covariates	X	
Data analysis and sample size	X	No sample size as health economics study
Approvals and registration	X	
Limitations of the study design, data sources and analytic methods	X	
Plans for disseminating and communicating study results, including proposed authorship	X	

REG STUDY PROTOCOL

Title: A global evaluation of the economic impact of time to initiation of biologic treatment of severe asthma patients

Version: 2
REG Project code (if available): REG-RES2028
Date: 03/010/2024

Research Protocol developed by Graham Lough and Brett McQueen in collaboration with the REG Cost Effectiveness Working Group.

CONTENTS PAGE

1. INVESTIGATION TEAM

Principle investigator(s)

Name: Dr. Brett McQueen
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REG research lead

Name: Graham Lough
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Steering committee involvement

The steering committee will be responsible for oversight of the study, providing comment on the protocol, final report and dissemination materials.

Name	Organisation
Job van Boven	University of Groningen | RUG
Wenjia Chen	National University of Singapore
David Price	Observational & Pragmatic Research Institute (OPRI)
Julia Slejko	University of Maryland School of Pharmacy

Patient involvement

No patients or advocates were involved in the planning and/or review of this study.

2. ROLES, RESPONSIBILITIES AND RESOURCES

Study phase	Responsibility	Estimated REG time requirement	Estimated PI time requirement	Proposed timeline
Funding and contracts	REG CEO	5 days	1 day	Month 1
Project management	REG	40 days		Throughout
Protocol development & data request	REG researcher with input from PI and steering committee sign-off	36 days	2 days	Month 1
Data provision	ISAR	-	-	Month 2
Data analysis	REG researcher with PI oversight	84 days	30 days	Month 3-9
Final report	REG researcher with input from PI and steering committee sign-off	35 days	3 days	Month 9-10
Conference abstract/ presentation	REG researcher/PI	9 days	1 day	Dependent on conference schedule
Manuscript writing & submission	REG researcher with input from PI and steering committee sign-off	49 days	2 days	Month 11-12
Total		**258 days**	**39 days**	

3. FUNDING STATEMENT

This project will be funded by AstraZeneca.

4. AIM & OBJECTIVE

1. Evaluate global and national-level cost-effectiveness:
   - Assess the cost-effectiveness of initiating biologic treatment early in severe asthma patients at both the global and national level.
   - Compare this to delayed initiation, considering direct and indirect costs at a global / country-specific level.
2. Explore cross-country variations:
   - Investigate variations in early biologic initiation effectiveness across different countries.
   - Identify factors contributing to these variations and potential implications for national healthcare strategies.
3. Quantify cumulative national disease burden:
   - Quantify and compare the cumulative disease burden in severe asthma patients at the national level with early biologic initiation versus later initiation.
   - Explore long-term health outcomes, including exacerbation rates, hospitalizations, and quality-adjusted life years (QALYs), tailored to each country's context.

5. BACKGROUND & RATIONALE

In the UK, approximately 1 million people are treated for 'difficult-to-control' asthma[1,2]. Difficult-to-control asthma are patients who do not respond to standard therapy and thus their disease remains poorly controlled or uncontrolled[3]. Of those with difficult-to-control asthma, an estimated 200,000 people in the UK have 'severe' asthma[1,2]. Patients with severe asthma have uncontrolled disease despite confirmed adherence to tailored effective treatment provided by evidence-based guidelines, requiring further treatment to increase disease control[4]. The Global Initiative for Asthma (GINA) recommends the consideration, on a case-by-case basis, of biological treatment for severe asthma patients on GINA step 5[5]. Patients are defined as step 5 retrospectively, where treatment or step down of treatment fails to adequately control their disease after at least 2–3 months and the 'level of treatment required to control symptoms and exacerbations'[6]. Use of biologics has been shown to improve patient quality of life, reduce exacerbations, improve disease outcomes and limit hospitalisations[7,8].

Patients with severe asthma may have poor disease control due to factors beyond the effectiveness of their inhaler therapy, such as poor inhaler technique[9], poor adherence to medication[10] and comorbidities[11]. Regardless of reasons for poor disease control, there are implications for use of higher healthcare resources, and therefore, increased costs, than that of the general asthma population[12]. It has been found that approximately 25% of severe asthma patients have ≥4 exacerbations per year[13]. The costs associated with exacerbations in severe asthma patients is high[14]. However, in selected patient populations, the use of biologics to treat severe asthma can be cost-effective in reducing disease burden and reduction in inhaled medication use[15,16], including the use of maintenance oral corticosteroids (OCS)[7]. OCS have been found to be overprescribed, leading to potentially ineffective disease control in severe asthma patients who do not benefit and may be more suitable for biologic

therapy[17,18]. Reducing the use of regular OCS has been shown to reduce direct costs associated with the disease[19].

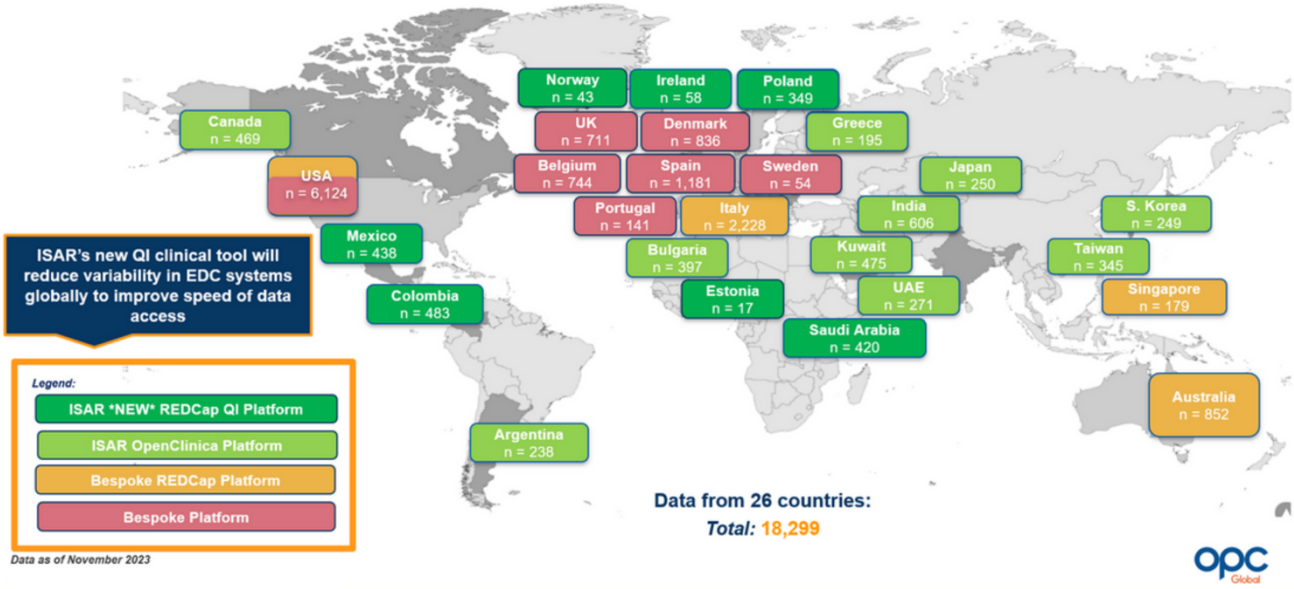
This study aims to identify the effect of time to initiation of biologic treatment of severe asthma patients on lifetime cost and disease burden at both global and national levels.

6. DATA SOURCE, STUDY DESIGN AND METHODOLOGY

Data Source

Historical electronic medical records (EMRs) from the International Severe Asthma Registry (ISAR) will be used. The ISAR database encompasses data from over 18,000 patients across 26 countries (*Figure 1*)[20]. Data from ISAR[21] will be used to identify relevant clinical information at the national level associated with biologic initiation and disease burden and calculate parameters for the economic model.

Figure 1: Location of ISAR data



Study Design

This study will proceed through a systematic two-step process: (i) identification of biologic initiation and its clinical implications using the ISAR database and (ii) development of economic models to understand the cost-effectiveness of early versus late or non-initiation.

1. Calculation of national-level estimates:
   - Utilise retrospective ISAR and other published data to derive national-level estimates for model parameters and inputs.
2. Development of cumulative national disease burden:
   - Utilize a validated economic model[22] to generate and estimate scenarios comparing earlier biologic initiation versus later initiation.
3. Cross-country comparison

- Explore factors contributing to observed variation between countries, including differences in healthcare infrastructure, treatment accessibility, or patient demographics.

7. STUDY POPULATION

For descriptive characterisation

Inclusion criteria

- Participants must have a minimum of ≥1 year of continuous medical records following the period in which they meet the criteria for potentially severe asthma.

8. MEASURES

Primary outcome period: No specified period.

Primary outcome(s)

Identification of the cost-effectiveness of time to initiation of biologics (i.e., against country-specific or commonly cited cost-effectiveness thresholds) within real-world setting scenarios and prediction of the effect on disease burden and associated costs at the national level.

Secondary outcome(s)

Comparison between countries, evaluating the potential economic repercussions associated with delayed initiation of biologic therapy in severe asthma patients.

Covariates (as identified in ISAR feasibility report)

Demographics:

- Country residence
- Age at enrolment DOB / visit date
- Age of asthma onset (inc. months)
- Sex (Male, Female)
- Ethnicity (Caucasian, South-East Asian, North East Asian, African, Mixed, Other, Unknown)

Clinical:

Type of asthma (e.g., allergic / eosinophilic) – Inferred from multiple variables within ISAR:

- Eosinophils & Sputum Data:
  - Highest blood eosinophil count (including unit, percentage, and date)
  - Highest sputum eosinophil count (including date)
  - Blood eosinophil count during exacerbation
- Allergens:
  - Environmental allergen test performed
  - Serum allergen test result
  - Skin prick test result
- Clinical Indicators of Atopy:
- Indication of allergic rhinitis, chronic rhinosinusitis, eczema, and nasal polyps
- Relevant comorbidities
- Current atopic disease
- IgE Levels:
  - IgE counts within the last year
- FeNO (Fractional exhaled Nitric Oxide) Test:
  - FeNO test result
- Clinical Management and History:
  - Patient's asthma symptoms' onset age
  - History of asthma medication/treatment switch
  - Biologic therapy

Date of first biologic treatment:

- Biologic initiation is a specific visit option, recording visits that fall on the same date as first biologic initiation

Changes to biologic treatment:

- "Was the patient switched from any previous therapy to a biologic during baseline..." and "Please specify the reason for switch in patient's asthma medication/treatment" are collected variables that directly relate to changes in biologic treatment.

Date of first Asthma diagnosis:

- As above

Asthma-related mortality:

- Inferred

EQ-5D/QOL Score

- Partially Inferred. Not directly collected.
- Descriptive System: 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, indicating severity of problems (e.g., no problems, some problems, severe problems).
- EQ Visual Analogue Scale (EQ VAS): endpoints labelled 'Best imaginable health state' to 'Worst imaginable health state'.
- ACT/ACQ control scores (by visit), regression analysis / mapping[23] to infer EQ-5D from these scores.

- Comorbidity data for depression and anxiety (among others) as standard
- Activity limitation within 4 weeks of any visit

Biologic Treatment Response:

- Inferred from clinical outcomes post-biologic initiation
- Date of first biologic treatment, day of termination / switch
- Biologic (medication) type.
- Asthma Control level
- Spirometry data i.e., Pre-SABA FEV_1 and Post-SABA FEV_1
- Exacerbation count(s), date(s), and type
- Safety events (e.g. cancer, serious infection, anaphylaxis)
- Biomarker data (e.g., BEC and FeNO)

Adverse Events:

- Asthma related hospital admission (date, type)
- Total A&E visits since last visit
- Steroid related AE's
- Total number of hospital visits
- Total number of invasive ventilation either ever or since last visit.

BMI

GINA STEP

- Inclusion criteria accept GINA 4 uncontrolled OR GINA 5, derived from core patient information variables.

Healthcare utilisation:

From date of meeting GINA step 5 criteria: Exacerbations / hospitalizations per patient for asthma/respiratory causes:

Baseline visit: GINA step 5

- Persistent symptoms throughout the day (related to control score)
- Significant airflow limitation on lung function tests (spirometry data)
- Reliance on high-dose ICS/LABA combination therapy or oral corticosteroids (medication type)
- Frequent exacerbations requiring oral corticosteroids, hospitalizations, or ER visits (exacerbation type and date(s))
- Impact on daily life and quality of life (Control score(s))
- Presence of comorbid conditions

Number of exacerbations

Annualised exacerbation rate

Number of emergency department visits

- "Total Numeric of A&E attendances for asthma within the last year (visit 1/pre-visit 1) or since the last visit (follow-up)?"

Number of hospitalisations

- "Total Numeric of hospital admissions for asthma within the last year (visit 1/pre-visit 1) or since the last visit (follow-up)"

Total duration of hospitalisation - inferred

Medication

Number of days of OCS
- Start / end date of therapy

OCS dose
- Frequency, label dose, total daily dose, duration

ECONOMIC DATA

Direct medical costs

- Treatment regimen, clinical evaluation and unit cost for each treatment for each country
- Unit costs related to healthcare utilisation / management of exacerbations for each country

Indirect medical costs

- Productivity loss (work-days lost)
- Excess cost of disease

Unit costs for treatments and healthcare utilization will be determined based on national guidelines, local healthcare systems, and available literature.

9. DATA ANALYSIS AND STATISTICS

Using the data outlined above from the ISAR database, descriptive statistics, rates and ratios will be calculated for each parameter / input as required in the validated Markov model[22]. The model is a standardised approach to modelling asthma as a function of day-to-day symptoms and risks for severe events (described below). A standardised global model and a national model for each country in the study will be produced. Each model includes three total health states and 3 substates within the exacerbation state:

1. Asthma non-exacerbation state (i.e., day-to-day asthma symptoms, controlled, partially controlled, uncontrolled))
2. Asthma exacerbation state (including three mutually exclusive subcategories:
    a. Asthma-related event that requires an OCS burst
    b. Asthma-related emergency department visit
    c. Asthma-related hospitalization
3. Death (including asthma-related mortality and other cause mortality)

Health states are defined by two-week cycles, consistent with evidence on durations of exacerbations for asthma-related events. Asthma-related mortality is indirectly modeled through the asthma-related hospitalization substate. In previous work, the model has been validated to produce equivalent asthma-related morality to national government-reported statistics.

Model output

Model outcomes include lifetime total drug and non-drug health care costs, life years (LY) gained, quality-adjusted life years (QALYs) gained, equal value of life years (evLY) gained, and treatment response.

These will be compared between countries of early and late initiation. Variations in treatment guidelines, reimbursement mechanisms and healthcare infrastructure will be identified across countries. We will explore uncertainty in our findings through one-way and multi-way sensitivity analyses. Moreover, we plan to explore a number of "break-even" analyses that inform the appropriate time to initiate biologics.

Analysis will be conducted using R software (https://www.r-project.org/).

Sample size calculation

This a health economic study and therefore there is no required sample size for this study.

10. APPROVALS & REGISTRATION

This study protocol will be submitted to the Anonymised Data Ethics Protocols and Transparency (ADEPT) Committee for approval to sanction the use of the ISAR for the purposes of the proposed study. The study will be registered with European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

11. LIMITATIONS OF STUDY DESIGN / ANALYSIS

Specify any inherent limitations in the planned study design:

As with all registry-based studies, several limitations must be acknowledged:

- *Incomplete or Missing Data*: Registry data may contain gaps or missing information. In such cases, random forest alogirithm may be used to impute missing data. Where this is not appropriate, proxy measures (e.g., area-level deprivation indices or income brackets) may be necessary, which could introduce some bias. Sensitivity analyses will help assess the robustness of results when using such proxies.
- *Data Heterogeneity*: Data from different countries and healthcare systems can vary in depth and consistency. This lack of uniformity complicates cross-country comparisons. Standardising data definitions and adjusting for differences in clinical practice will help improve comparability.
- *Data Completeness and Quality*: The quality and completeness of economic outcomes (e.g., direct medical costs) may differ across sites, especially when using historical data. This can be mitigated by excluding sites with incomplete data or conducting sensitivity analyses to assess how these gaps influence results.

- *Generalisability of Results*: The ISAR population, while extensive, may not represent the global severe asthma population fully. Differences in patient demographics and healthcare practices between ISAR countries and those not included could limit generalisability. Caution will be needed when extrapolating findings to non-ISAR countries.
- *Need for Stratification or Sensitivity Analyses*: Heterogeneity across sites and countries will require stratification or sensitivity analyses to ensure the robustness of the economic models. Stratification by region, healthcare system, and treatment access will help contextualise the findings and account for variability.
- *Cross-Country Comparisons*: Comparing the economic impact of biologic treatments across countries is complicated by healthcare system differences, such as treatment costs and reimbursement policies. To ensure valid comparisons, adjustments e.g., purchasing power parity (PPP) or currency standardisation will be applied to normalise costs across countries.

12. DATA DISSEMINATION PLANS

At least one abstract arising from this study will be presented at a key respiratory conference (e.g. the European Respiratory Society or American Thoracic Society or similar) and a manuscript will be submitted to a peer-reviewed journal.

The PI and REG researcher will be lead authors on the manuscript and the steering committee will be co-authors if they meet the ICMJE authorship ICMJE criteria: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

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