Study Protocol

ENLIGHTEN: Assessment of quality improvement on long-term oral corticosteroid use in the International Severe Asthma Registry

Date:
06/10/2025

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TITLE	**ENLIGHTEN: Assessment of quality improvement on long-term oral corticosteroid use in the International Severe Asthma Registry**
Subtitle	
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Study aims and objectives	The overarching aim of this study is to assess changes in LTOCS use before and after the introduction of a quality improvement programme. We will also investigate the factors driving change. The specific objectives are to: **Primary Objective:** To assess the proportion of specialist-treated patients remaining on long-term oral corticosteroids (LTOCS) before and after the progressive roll-out of the ISAR quality improvement initiative. We will conduct several secondary analyses to explore how differences in outcome definition, study design and statistical methods impact our findings. **Exploratory Objective 1**: To explore the potential drivers of LTOCS change before and after the quality improvement initiative including changes in initial presentation (e.g. LTOCS use), asthma treatments (e.g. biologic therapy) and other factors. **Exploratory objective 2**: To explore the magnitude and drivers of country-specific differences in LTOCS change before and after the quality improvement initiative.

Table of Contents

Countries of study	All countries/sites contributing to the ISAR initiative who have consented for their data to be used in research
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List Of Abbreviations

Abbreviation or special term	Explanation
ADEPT	Anonymised Data Ethics & Protocol Transparency
HCRU	Healthcare resource utilisation
IgE	Immunoglobin E
IL-4	Interleukin-4
IL-5	Interleukin-5
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
ITS	Interrupted-time series
LTOCS	Long-term oral corticosteroids
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
QI	Quality improvement
TSLP	Thymic Stromal Lymphopoietin

1. Background

Quality improvement (QI) within the healthcare setting drives improved patient experiences and outcomes achieved through a process of systematic change[1]. These improvements extend to electronic health records as data are increasingly used to judge whether high-quality care is being provided to patients, often through an investigation of both process (e.g. data accuracy and completeness) and clinical outcomes (e.g. better control of symptoms)[2].

The International Severe Asthma Registry (ISAR) was established in 2017 as a collaborative initiative aiming to improve asthma patient care and outcomes worldwide. It has since expanded into the largest real-world evidence data resource for severe asthma, representing a comprehensive, standardised, globally-sourced dataset which enables the tracking of asthma care and outcomes[3 4]. At the forefront of ISAR's original (and continuing) mission was an aim to reduce long-term oral corticosteroid (LTOCS) exposure.[5] Use of LTOCS in the management of severe asthma remains widespread[6] despite the associated increased risk of various adverse outcomes at cumulative lifetime dosages of as little as 0.5-1g[7-9].The burden of OCS-related comorbidity is significant in severe asthma patients, with 68% recording at least one such comorbidity including obesity (42%), hypertension (23%), dyslipidaemia (16%), osteoporosis (13%), diabetes (12%), and coronary heart disease (9%)[10]. The needs for OCS stewardship have been reflected in the most recent Global Initiative for Asthma (GINA) recommendation to prescribe OCS only when clinically justified, at the lowest effective dose and as a last resort, prioritising the use of alternative treatment strategies including targeted biologics[11-13].

The increasing availability of biologic therapies targeting various steps in of the inflammatory pathway including immunoglobulin E (IgE), interleukin (IL)-4Rα, IL-5/IL-5Ra and thymic stromal lymphopoietin (TSLP), has been transformative for the severe asthma treatment landscape. Their use in concert with phenotyping by readily available biomarkers has been a breakthrough for precision personalisation of asthma care, enabling a reduction of exacerbation rates, healthcare resource utilisation (HCRU) and reliance on LTOCS[14]. However, despite compelling evidence of OCS-related harm and the wider availability of effective steroid-sparing therapies, OCS burden and weaning practices still vary substantially both within and between countries[15 16]. Due to its reach, ISAR offers a unique opportunity to impact treatment practices and to set a new standard for LTOCS stewardship globally.

A quality improvement initiative was introduced across ISAR in 2024 with the explicit aim of reducing LTOCS use within all contributing centres. The underlying intervention is inherently multifactorial and is described in further detail within Appendix 1 and Appendix 2. It comprised a constellation of engagements with ISAR collaborators including deployment of LTOCS focused dashboards, providing country-level feedback, presentation of aggregate findings at international conferences and the provision of an electronic data capture tool. In addition to these specific activities, several research articles published by ISAR highlighting the ongoing OCS burden in severe asthma and the opportunities for practice change are likely to have impacted LTOCS use within participating centres and beyond. This includes publications pertaining to phenotyping (BRISAR[17]; EMBER[18]), the impact of exacerbation on lung function decline[19], profiling of biologic initiators (GLITTER I[20]) and impact of initiation (GLITTER II[5]), comparison of alternative biologic classes in patients eligible for multiple (FIRE[21]), comorbidity burden with LTOCS and the impact of biologics on this (PRISM I[22] and PRISM II[23]), impact of pre-biologic impairment or phenotype on response outcomes (BEAM[24], IGNITE[25]), definitions and predictors of biologic response and remission (FULL BEAM response[26] and FULL BEAM remission[27]), heterogeneity in biologic response (LUMINANT[28]), impact of biologics on LTOCS use (SOLAR I[29]) and associated systemic adverse outcomes (SOLAR II[30]), and pre-biologic characterisation of associations between LTOCS use and both biomarker profile and disease burden (STAR[31]). We hypothesise that the QI initiative could have affected LTOCS use in a number of ways including a reduction in the severity of patients attending severe asthma centres, increased biologic prescribing and more aggressive LTOCS weaning among patients treated within biologics.

This study investigates changes in LTOCS use among countries contributing data to the International Severe Asthma Register (ISAR) before and after the introduction of a quality improvement programme.

2. Study Aims and Objectives

2.1. Study Aims

The overarching aim of this study is to assess changes in LTOCS use before and after the introduction of a quality improvement programme. We will also address the factors driving change.

2.2. Study Objectives

Primary objective: To assess the proportion of specialist-treated patients remaining on long-term oral corticosteroids (LTOCS) before and after the progressive roll-out of the ISAR quality improvement initiative. We will conduct several secondary analyses to explore how differences in outcome definition, study design and statistical methods impact our findings.

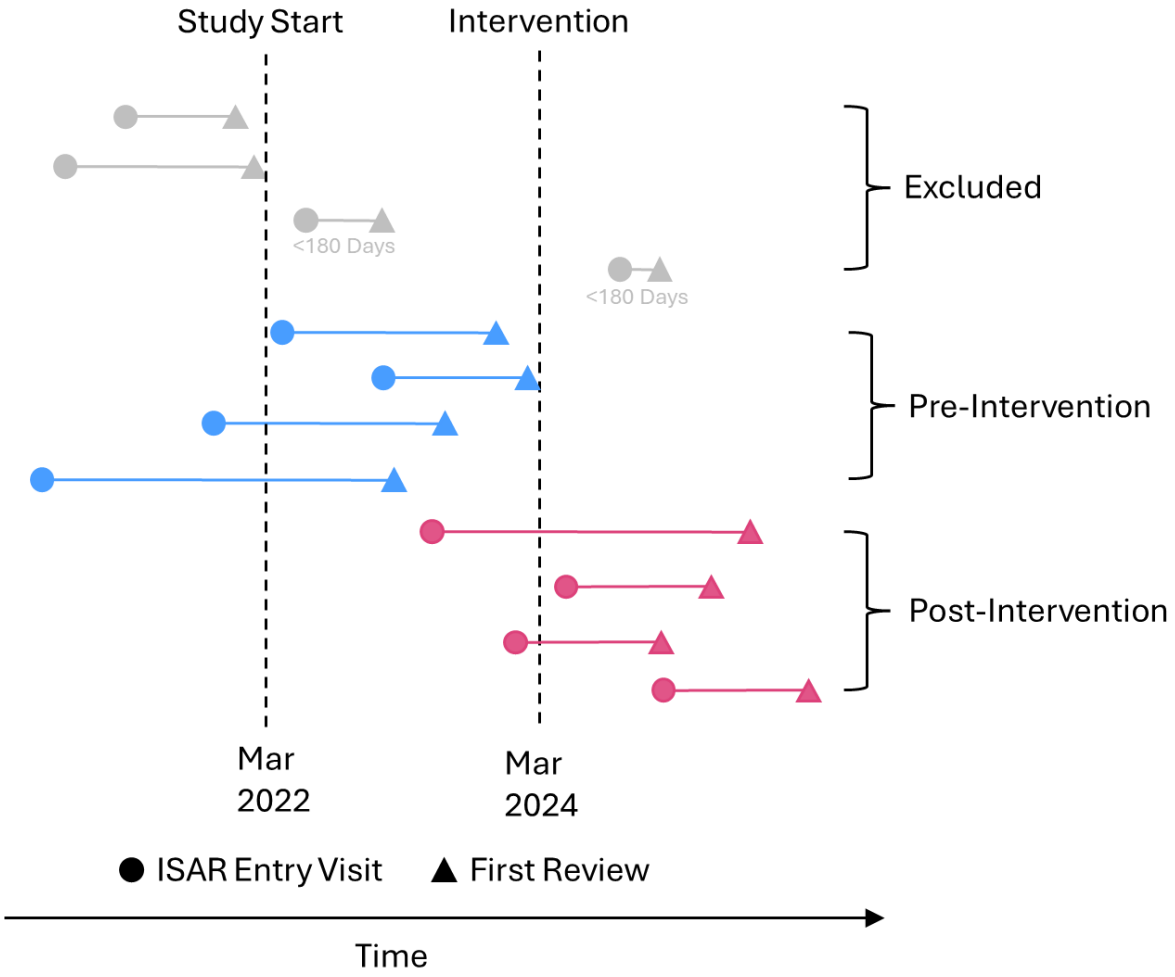
Exploratory objective 1: To explore the potential patient-level drivers of LTOCS change before and after the quality improvement initiative including changes in initial presentation (e.g. LTOCS use), asthma treatments (e.g. biologic therapy) and other factors.

Exploratory objective 2: To explore the magnitude and drivers of country-specific differences in LTOCS change before and after the quality improvement initiative.

3. Study Design

This is a single-arm retrospective cohort study using all patient data from countries participating in the ISAR quality improvement initiative. Patients entered the study at the time of their ISAR entry visit. Patients left the study at their first review, which was defined as the visit closest to their first annual review date (365 days after the ISAR entry visit). Visits which occurred less than 180 days after the ISAR entry visit were excluded, as were those with a first review visit prior to 1st March 2022. The study design is summarised in the figure below:

Figure 1: Study design schematic. Circles represent ISAR entry visit and triangles represent first review (follow-up visit closest to 365 days after ISAR entry visit). First reviews occurring less than 180 days after the ISAR entry visit were excluded, as were those with a first review prior to 1st March 2022.



4. Study Population

4.1. Data Sources

This study uses data on eligible patients from countries participating in the ISAR quality improvement initiative.

4.2. Inclusion and Exclusion Criteria

Inclusion Criteria

- Patient meets criteria for severe asthma as per ISAR inclusion criteria[4]:
  - On Global Initiative for Asthma (GINA 2021) Step 5 (8)
  - Uncontrolled on GINA Step 4, at least one of the following:

- poor symptom control: asthma control questionnaire ACQ>1.5, ACT<20 or “not well controlled" by National Education and Prevention Program [NAEPP]/GINA guidelines
- airflow limitation: after appropriate bronchodilator withhold Forced expiratory volume in 1 second (FEV1) <80% predicted (in the face of reduced FEV1/forced vital capacity [FVC] defined as less than the lower limit of normal)
- serious exacerbations: at least one hospitalisation in the previous year or intensive care unit (ICU) stay or mechanical ventilation ever
- frequent exacerbations: two or more bursts of systemic corticosteroids (>3 days each) in the previous year

- Have data on LTOCS utilisation recorded at both their ISAR entry visit and first review visit.

Exclusion Criteria

- First review visit prior to 1st March 2022
- First review less than 180 days after the ISAR entry visit

5. Study Variables and Study Outcome Definitions

Outcomes

For all objectives, the primary outcome will be LTOCS use (yes/no) at the first review visit. First review visits are defined as those closest to 12 months after the ISAR entry visit. First review visits which occurred less than 180 days after the patients’ ISAR entry visit were excluded.

Exposures

The implementation date of the QI programme was March 2024, hence any patients with a first review after this date were assigned to the post-intervention group. The pre-intervention period was defined as the two years prior to implementation and included patients with a first review between 1st March 2022 and 28th February 2024. This two-year period was selected to enable estimation of practice directly prior to the implementation of the QI programme, while providing a sufficient number of patients to accurately estimate study parameters. The study design is summarised in Figure 1 and full details of the QI programme are provided within Appendix 1 and Appendix 2Appendix 1Appendix 2.

Covariates

Patient age, sex, country and time to first review will be included in all models to account for potential confounding.

6. Statistical Analysis

6.1. Sample Size

Feasibility analysis suggests that around 10% of patients within the ISAR dataset are recieving LTOCS at their first review. Sample size calculations based on a test for two independent proportions suggest that a total of 2882 patients (1921 pre-intervention, 961 post-intervention) would be required assuming:

- Statistical power of 80% at an alpha level of 0.05
- Allocation ratio of 2:1 in the pre-intervention vs post-intervention arm (approximately proportional to the amount of follow-up time currently available in each arm)
- A relative decrease of 30% in LTOCS use would be clinically significant (i.e. from 10% to 7%).

Feasibility analysis suggests these requirements would be met with the current ISAR dataset. Additional data is being added continuously which will enable a fuller investigation of secondary analyses including an assessment of inter-country differences.

6.2. Software

This project will use Stata statistical software (v19) and SQL Server Management Studio (v20)

6.3. Statistical methods for each objective

All analyses will be conducted under a complete case framework including only observations with complete data for all study variables. Two-tailed hypothesis tests will be conducted and Type-I error rates set at 5%.

Objective 1: **To assess the proportion of specialist-treated patients remaining on long-term oral corticosteroids (LTOCS) before and after the implementation of the quality improvement initiative.**

We will calculate counts and percentages of patients on LTOCS at first review and display these graphically using bar charts. 95% confidence intervals will be calculated using the binomial distribution. We will assess the impact of the quality improvement programme using logistic regression:

$$\text{logit}(P) = \beta_0 + \beta_1 D_i + \beta_j X_{ji}$$

Where P is the probability of receiving LTOCS at first review, D is study intervention period (0=pre-intervention, 1=post-intervention) and β_j represents other study covariates. β_0 is the average log-odds at when all other covariates are zero, β_1 represents the effect of the intervention and β_j represents the effect of other study covariates.

Models will include covariates for age, sex and time between first ISAR visit and first review to prevent residual confounding. We will include fixed effects for country to allow pre-intervention LTOCS use to vary and will include country-level interaction-terms with intervention (β_1) to allow its effect to vary.[32] To allow the robust estimation of country-specific effects, countries with less than 30 patients in both the pre- and post-intervention period will be combined into an 'Other' category. To increase the interpretability of our results, we will calculate adjusted predictions which represent the proportion of patients using LTOCS at first review in both the pre- and post-intervention period, assuming other covariates remain constant.

Secondary and sensitivity analyses

1. **Outcome definition:**
    a. It is recognised that some patients may continue receiving low-dose LTOCS treatment, despite adequate asthma control, due to adrenal insufficiency. Therefore, we will conduct a sensitivity analysis exploring low-dose LTOCS use (≤5mg) as the outcome.
    b. We will categorise LTOCS dose, and present pre- and post-intervention distributions for each country
    c. If sufficient data is available, we will repeat our analysis using outcomes collected at the second and third review visit to examine the longer-term impact of the intervention.

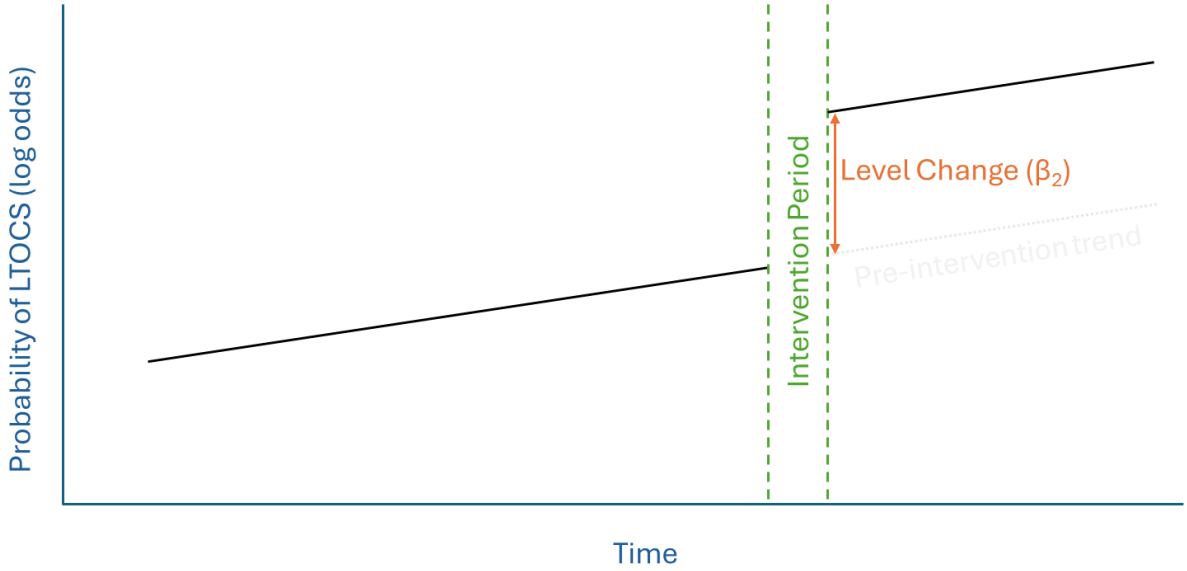
2. **Intervention period:** LTOCS reduction has been a long-standing aim of ISAR. Although the quality improvement initiative led to specific actions related to this aim, it is possible that the primary analysis has not fully captured wider ISAR activities taking

place prior to 1st March 2024. Consequently, we will repeat our analysis investigating earlier implementation dates 6-months (1st September 2023) and 12-months (1st March 2023) prior to the date used in the primary analysis.

3. **Implementation period:** In the primary analysis, we have assumed an immediate effect of the intervention, however in practice it may have taken some time before changes in outcomes were observed. Consequently, we repeated our analysis with 3-month (1st March 2024 to 31st May 2024) and 6-month (1st March 2024 to 31st August 2024) implementation periods. Patients with a first review occurring during the implementation period will be excluded from the analysis.

4. **Interrupted time series analysis:** To adjust for wider secular trends in LTOCS use we will conduct an interrupted-time series (ITS) analysis to assess the impact of the quality improvement programme[32]. Typically, an ITS analysis allows the measurement of an interventions effect on both the change in level and trend of an outcome. Change in level corresponds to the sudden change in LTOCS use immediately after the intervention. A change in trend corresponds to difference in the time-trend between the pre-intervention and post-intervention periods and is modelled statistically with an interaction term. However, estimation of these interactions requires large sample sizes, and simulation studies have demonstrated insufficient power given the likely size of the study dataset. Furthermore, we observed that attempting to model a change in trend during our analysis would adversely affect our ability to detect changes in level. Consequently, we will conduct a modified ITS analysis which assumes that the pre-intervention slope was maintained after the introduction of the intervention.

Figure 2: Schematic presentation of ITS analysis



The analysis will use a segmented logistic regression model:

$$logit\ (P) = \beta_0 + \beta_1 T_i + \beta_2 D_i + \beta_j X_{ji}$$

Where P is the probability of being on LTOCS at first review, T is time since study start, D is study intervention period (0=pre-intervention, 1=post-intervention) and β_j represents other study covariates. β_0 is the average log-odds at when all other covariates are zero, β_1 is the time-trend in the pre-intervention period, β_2 is the level change after the introduction of the intervention and β_j represents the effect of other study covariates.

Models will include covariates for age, sex and time between initial visit and first review to prevent residual confounding. We will adjust for country using fixed-effects and will include a country-level interaction-terms with time (β_1) to allow LTOCS utilisation trends to vary by country.[32]

5. **Time-to-event analysis:** To provide comparability between the pre- and post-intervention period, our primary analysis is based on data collected at the first review. However, it is recognised that some patients will have substantial data collected after their first review which may span across the introduction of the QI programme. To fully utilise this data, we will conduct a separate time-to-event analysis with patients entering at the study at the time of ISAR entry visit and leaving the study at the earliest date of: a) cessation of LTOCS, b) loss to follow-up within ISAR, c) last ISAR visit. The outcome will be time to LTOCS cessation, and the intervention will be treated as a

time-varying covariate meaning patients can contribute data to both the pre- and post-intervention time periods. Our initial analysis will assume an immediate effect of the intervention (i.e. on 1st March 2024) however we will conduct additional analyses using 3- and 6-month lag periods. Analyses will be restricted to patients receiving LTOCS at their ISAR entry visit. Descriptive analyses will be conducted using Kaplan-Mier plots and modelling will be conducted using Cox regression models including potential confounders such as age, sex, country and LTOCS dose. The effect of the intervention will be assessed using the hazard ratio for the post-intervention period with associated 95% confidence intervals.

Exploratory Objective 1: To explore the potential drivers of LTOCS change before and after the quality improvement initiative

We will explore the potential drivers of LTOCS prescribing before and after the quality improvement initiative.

a) Changes in LTOCS use at the first ISAR visit: We will calculate counts and percentages of patients presenting with LTOCS at the ISAR entry visit in the pre- and post-intervention periods and display these graphically using bar charts. 95% confidence intervals will be calculated using the binomial distribution.

b) Changes in biologic use: Among patients receiving LTOCS at their ISAR entry visit, we will calculate counts and percentages of patients prescribed biologic therapy prior to their first review and display these graphically, using bar charts. 95% confidence intervals will be calculated using the binomial distribution.

c) Practice changes unrelated to LTOCS at the ISAR entry visit or biologic utilisation: We will repeat our logistic regression analysis including LTOCS use (at baseline) and biologic use (prior to first review) as additional model covariates. If differences between the pre- and post-intervention time-periods persist, it suggests that other unrelated factors (e.g. changes in LTOCS weaning practices) may be partially driving any observed differences.

Exploratory Objective 2: To explore the magnitude of drivers of country-specific differences in LTOCS change before and after the quality improvement initiative.

We will explore country differences in the effect of the QI programme using a likelihood ratio test. We will rank countries from highest to lowest effect (based on the adjusted country-specific effect estimate) and describe their engagement with elements of the QI initiative such as attendance at country meetings and utilisation of tools including REDCap cloud and the OCS risk calculator. After reviewing the available data, we will define a composite measure of QI engagement and will quantify the association between this and the country-specific effect using the Spearman's correlation coefficient.

7. Regulatory and Ethical Compliance

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

ISAR is approved by the Health Research Authority for clinical research use and governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee. We will submit the finalised version of this protocol to the ADEPT committee (https://www.regresearchnetwork.org/adept-committee/) for approval.

All sites enter into a regulatory agreement in compliance with the specific data transfer laws and legislation pertaining to each country and its relevant ethical boards and organisations. Further, all data extracted from sites is de-identified in the form of anonymised patient IDs. The data will be retrieved by Optimal Patient Care/Observational & Pragmatic Research Institute data analysts and utilised as an anonymised dataset to perform the analysis according to protocol. This study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

8. Data Dissemination

Publications:

The findings will be submitted for publication in peer-reviewed journals.

Conferences:

Results will also be presented at relevant medical and scientific conferences, through abstract presentations and/or discussions.

Authorship:

Authorship will be determined in accordance with the ISAR authorship policy as outline in the ISAR publication charter, which has been approved by the ISAR steering committee. Authorship will recognise significant contributions to the study's conception, analysis, and writing.

9. Project management group and wider steering committee group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee (ISC).

The project management group for this project will be led by Professor David Price. Other members of the project management group are listed below.

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60	Saraid Cerda Reyes	Mexico
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83	Tavleen Kaur Jaggi	Singapore
84	Mariko Siyue Koh	Singapore
85	Esther Ann	South korea
86	Chin Kook Rhee	South Korea
87	Borja G. Cosio	Spain
88	Luis Perez-de-Llano	Spain
89	Yi-Han Hsiao	Taiwan
90	Diahn-Warng Perng	Taiwan
91	Ming-Ju Tsai	Taiwan
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93	Laila Salameh	United Arab Emirates
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10. Research Team

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11. Timelines

Action	Timeline
Protocol delivery to steering group	January 2025
Protocol sign-off	February 2025, update August 2025
Dataset delivery + ADEPT approval	February 2025, update August 2025
Preliminary results	September 2025
Final study report	October 2026
Study report sign-off	November 2026
Manuscript	December 2026

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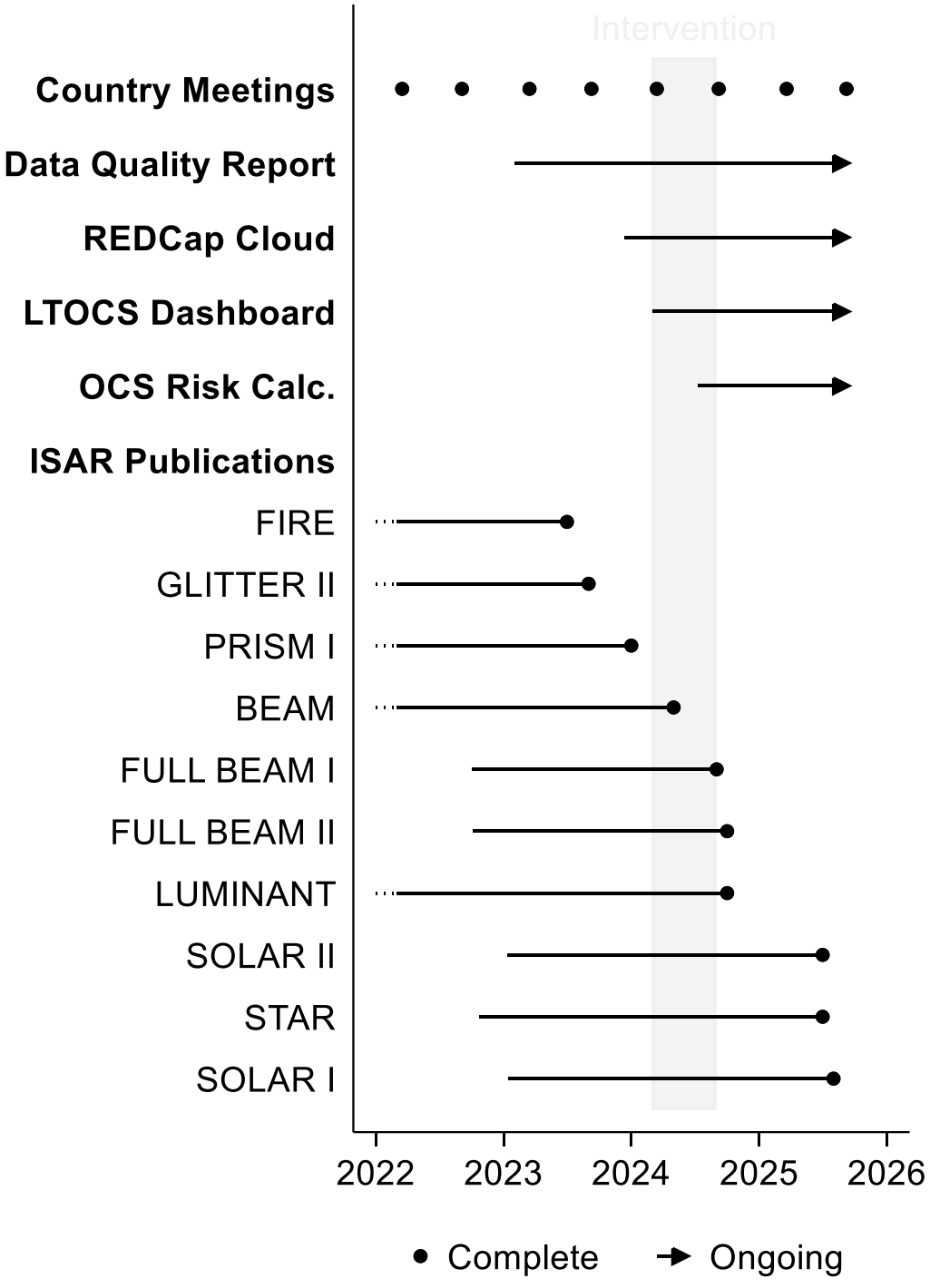
13. Appendices

Appendix 1: Components and timing of intervention



[a] Dotted line represents activities starting prior to January 2022. ISAR publications are limited to those relevant to the QI programme, start date is time of protocol approval and end date is time of publication

Appendix 2: Description of intervention component and relevance to LTOCS use

Component	Description	QI Domain[a]			
		Data	Burden	Biologics	Other
Country Meetings	• Country-level meetings focussed on data quality and quality improvement • All-country meetings showcasing ISAR research and sharing best practice • Specific focus on LTOCS during the intervention period	✓	✓	✓	✓
Data Quality Report	• Highlights issues with LTOCS data completion • Facilitates LTOCS dashboard and other local analyses	✓			
REDCap Cloud	• Streamlined data capture tool • Supports high-quality data capture around LTOCS use • Facilitates LTOCS dashboard and other local analyses	✓			
LTOCS Dashboard	• Provides country-level feedback on LTOCS trends • Enables intra-country benchmarking and comparison to global trends • Highlights issues with LTOCS data completion	✓	✓		
OCS Risk Calc.	• Models risk of morbidities by OCS prescription frequency • Designed for use by patients and clinicians • Requires input of basic demographic and clinical information • Outputs risk of morbidity for different OCS treatment strategies		✓		
ISAR Publications					
FIRE	• Explored comparative effectiveness of anti-IL5 and anti-IgE biologics in patients eligible for both • Reported that in dual-eligible patients, anti-IL5(R) medications are superior in reducing LTOCS			✓*	
GLITTER II	• Explored the impact of biologic initiation on asthma outcomes • Reported that biologic initiation was associated with a substantial reduction in LTOCS use			✓	
PRISM I	• Explored the prevalence and pattern of comorbidities in adults with severe asthma • Reported LTOCS use was associated with a greater likelihood of OCS-related comorbidities		✓		
BEAM	• Explored the impact of pre-biologic impairment on meeting domain-specific biologic responder definitions • Reported that biologic treatment allowed withdrawal of LTOCS and highlighted greater OCS-sparing among anti-IL5(R) treated patients			✓*	
FULL BEAM I	• Explored definitions and correlates of biologic response			✓	

	• Highlighted the ability of biologic treatment to reduce LTOCS use			
FULL BEAM II	• Estimated the proportion of patients meeting various definitions of clinical remission • Demonstrated OCS-sparing benefits of biologics • Highlighted LTOCS use as an important barrier to clinical remission		✓	✓
LUMINANT	• Investigated different measures of response among biologic treated populations • Demonstrated OCS-sparing benefits of biologics		✓	
SOLAR II	• Compared the risk of new-onset OCS-related adverse outcomes between biologic initiators and non-initiates • Reported that biologic initiators had decreased rate of developing OCS-related adverse outcomes		✓	✓
STAR	• Explored the effect of OCS use prior to biologic initiation on asthma phenotype • Reported that LTOCS use was associated with greater disease severity	✓		
SOLAR I	• Examined the efficacy of biologic initiation on total OCS exposure • Demonstrated higher rates of total OCS reduction when compared to non-initiators		✓	

[a] Data: Improves LTOCS data quality. Burden: highlights ongoing use of LTOCS, opportunities for reductions (e.g. benchmarking) and impact of LTOCS on asthma burden. Biologics Highlights steroid sparing effect of biologics (* suggests differences by biologic class).