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# Individualised risk prediction model for exacerbations in patients with severe asthma: protocol for a multicentre real-world risk modelling study

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## ABSTRACT

**Introduction** Severe asthma is associated with a disproportionally high disease burden, including the risk of severe exacerbations. Accurate prediction of the risk of severe exacerbations may enable clinicians to tailor treatment plans to an individual patient. This study aims to develop and validate a novel risk prediction model for severe exacerbations in patients with severe asthma, and to examine the potential clinical utility of this tool.

**Methods and analysis** The target population is patients aged 18 years or older with severe asthma. Based on the data from the International Severe Asthma Registry (n=8925), a prediction model will be developed using a penalised, zero-inflated count model that predicts the rate or risk of exacerbation in the next 12 months. The risk prediction tool will be externally validated among patients with physician-assessed severe asthma in an international observational cohort, the NOVEL observational longiTudinal studY (n=1652). Validation will include examining model calibration (ie, the agreement between observed and predicted rates), model discrimination (ie, the extent to which the model can distinguish between high-risk and low-risk individuals) and the clinical utility at a range of risk thresholds.

**Ethics and dissemination** This study has obtained ethics approval from the Institutional Review Board of National University of Singapore (NUS-IRB-2021-877), the Anonymised Data Ethics and Protocol Transparency Committee (ADEPT1924) and the University of British Columbia (H22-01737). Results will be published in an international peer-reviewed journal.

**Trial registration number** European Union electronic Register of Post-Authorisation Studies, EU PAS Register (EUPAS46088).

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A robust and generalisable risk prediction model for exacerbation in patients with severe asthma will be developed and validated in two international, well-characterised cohorts.
⇒ Candidate predictors will be shortlisted from a comprehensive list of commonly recorded patient and clinical characteristics in severe asthma by surveying 70 investigators and care providers with expertise in severe asthma.
⇒ Advanced statistical approaches will be employed to develop a clinically applicable, parsimonious model, with adjustment for dynamic treatment switching during follow-up.
⇒ Potential limitations include the inconsistent inclusion/exclusion criteria within and between the two cohorts and protocol variability across countries.

## INTRODUCTION

Asthma is a common chronic respiratory disease affecting more than 330 million people worldwide.[1] Five to ten per cent of asthma patients have severe or refractory asthma, which is defined by the European Respiratory Society (ERS) and American Thoracic Society (ATS) as being difficult to control despite maximal doses of inhaled therapies.[2–4] A major feature of the natural course of asthma is exacerbations (also known as lung attacks).[5] Exacerbations, defined broadly as symptomatic episodes that are beyond the day-to-day variability of symptoms, are a major source of the burden especially in patients with severe asthma.[6] Of particular relevance to disease management are severe exacerbations that require treatment with oral systemic corticosteroids (OCS), and at times require inpatient care. Even small cumulative doses of OCS are associated with an increased risk of severe comorbidities.[7 8] In the past decade, a number of advanced therapeutic antibodies ('biologics') have shown efficacy in improving asthma symptoms and reducing the risk of severe exacerbations and dependence on OCS.[9–15] However, biologics are among the most expensive medications, costing US$10 000–US$30 000 per year.[16]

Current clinical guidelines for the management of severe asthma are based on the

average treatment effect elicited from clinical trials, or in subsets defined by single markers such as blood eosinophil count.[17–19] This approach may result in inefficient treatment strategies given the low external validity of these trial findings by excluding majority of 'real-life' patients due to the stringent inclusion and exclusion criteria.[17] The efficiency of severe asthma management and cost-effectiveness of advanced treatments may be greatly improved with robust multivariate risk prediction. In addition to improving the predictability of exacerbations, communicating numerical risks of outcomes has been shown to empower patients by helping them better understand the consequence of treatment decisions and facilitating shared decision-making.[20]

To date, the applicability and generalisability of existing prediction tools for severe asthma are limited. In a review of 24 prediction models for asthma exacerbations published before April 2017, a history of health service use, respiratory symptoms and lung function were the most commonly retained predictors in the models. Notable variation was observed in outcome definitions for exacerbations (eg, risk, rate and timing of exacerbation). However, none of those prediction models were considered suitable for immediate application in clinical practice due to the use of suboptimal methods and single geographical settings resulting in miscalibration and limited transportability.[21] Patients with severe asthma may particularly benefit from precision risk stratification to inform advanced therapies. Moreover, in recent years, several new prediction tools with the inclusion of biomarkers and/or the use of machine-learning algorithms on large-scale electronic medical records or health administrative data (including medication use and laboratory results) have been proposed.[22–27] However, there is no validated risk-scoring tool for patients with severe asthma.

Based on two global observational cohorts, our study aims to develop and externally validate an individualised prediction model for the risk of severe exacerbations in patients with severe asthma. The secondary objective is to assess the clinical utility of this prediction model over a plausible range of risk thresholds for classifying patients at high exacerbation risk.

## DATA, METHODS AND ANALYSIS

Figure 1 presents the schematic illustration of the study design. This prediction modelling study will follow the general steps laid out in the Prediction model Risk Of Bias and Assessment Tool (PROBAST).[28] We plan to start data analysis on 30 March 2023. We will also adhere to the Transparent Reporting of a multivariable prediction model of Individual Prognosis Or Diagnosis statement for disseminating the results.[29]

### Sources of data

#### Derivation data

To derive the prediction equations, we will extract data from a large international observational cohort of patients with severe asthma, namely the International Severe Asthma Registry (ISAR, https://isaregistries.org/).[30] The details of this registry have been described elsewhere.[31] In summary, ISAR (2015–2021) includes data from Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, South Korea, Saudi Arabia, Spain, Taiwan, United Arab Emirates, UK and USA. ISAR collects a rich source of real-life, longitudinal data on demographics, health behaviours, asthma symptoms and treatment, lung function, type 2 inflammation biomarkers, comorbidities, health services use and health outcomes, such as exacerbations, of patients who are diagnosed with severe, uncontrolled asthma.[30] A summary of how each registry diagnoses asthma and categorises severe asthma is provided in online supplemental appendix table 1; the definitions are broadly consistent with the ERS/ATS definition of severe asthma.[2] Namely, asthma is considered severe if achieving symptom control requires treatment with high-dose combination therapy of inhaled corticosteroids (ICS) and long-acting beta2-agonist (LABA), with or without additional controller medications (including biologic therapy), or asthma that remains uncontrolled despite medium/high dose ICS+LABA.[2] At the time of submitting this work, the ISAR dataset provides a total sample of 12 427 patients with severe asthma, among whom 8352 patients (67.2%) were above 18 years of age and have follow-up data, and contributed to 2178 severe exacerbations in the first year of follow-up (table 1).

#### Validation data

We will use data from the subgroup of patients with physician-assessed severe asthma from the NOVEL observational longiTudinal studY (NOVELTY).[32] NOVELTY (2016–2021) is an international study in North and South America, Europe and the Asia-Pacific region, in which patients underwent clinical assessments and received standard medical care as determined by their treating physician. NOVELTY is a global prospective cohort study

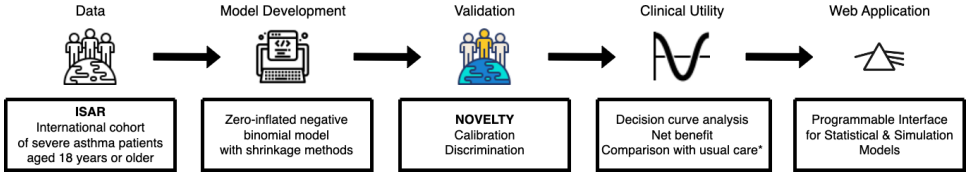


**Figure 1** Schematic illustration of the study design. ISAR, International Severe Asthma Registry; NOVELTY, NOVEL observational longiTudinal studY.

Table 1 Summary of randomised controlled trial datasets for development and validation of a risk prediction tool

| Dataset | Purpose | Patients with severe asthma (n) | Severe exacerbations in first 12 months of follow-up (n)* |
|---|---|---|---|
| ISAR | Development | 8352 | 2178 |
| NOVELTY | Validation | 1652 | 798 |

*Severe exacerbation is defined in both ISAR and NOVELTY as a worsening of asthma which required oral corticosteroid for at least 3 days, hospitalisation or emergency room visit requiring oral corticosteroids.
ISAR, International Severe Asthma Registry; NOVELTY, NOVEL observational longiTudinal studY.

of 11 243 patients with a diagnosis, or suspected diagnosis, of asthma and/or chronic obstructive pulmonary disease (COPD) across 18 countries for 3 years, with an additional 2-year extension study at participating sites.[32 33] NOVELTY collects a rich set of patient data including spirometry measurements, medication usage, sociodemographics and health services use. The validation dataset contains 1652 patients with physician-assessed severe asthma, for whom there were 798 severe exacerbations in the first year of follow-up (table 1). Of note, different from ISAR, NOVELTY identified patients with asthma by the diagnostic labelling provided by the treating physician, and asthma severity as assessed by the treating physician (mild/moderate/severe), in order to reflect the realities of community care for asthma. The primary validation analysis will accordingly be based on these patients with physician-assessed severe asthma. We will apply the definition used in ISAR in a sensitivity analysis.

## Target population

The prediction tool will be developed for patients aged 18 years or older with a clinical diagnosis of severe asthma.

## Index date

For both the ISAR registry and NOVELTY study, the index date of a patient is defined as the date of baseline visit to the asthma clinic to join the study.

## Outcome variables

The primary outcome is the risk of the occurrence of ≥1 severe exacerbations within the first 365 days after the index assessment. The secondary outcome is the annual rate of severe exacerbations within the same time period. In line with the ATS/ERS definition,[34] we define a severe exacerbation as a worsening of asthma which required OCS for at least 3 days, hospitalisation or emergency room (ER) visit requiring systemic corticosteroids. The 365-day time horizon was considered the most relevant by key opinion leaders surveyed as part of this study due to its alignment with current guidelines. As well, such a time horizon will average out the effect of seasonal variation.

The model will predict the 365-day risk and rate of severe exacerbations as if the patient remains on their current treatment (eg, for a patient on biologic therapy, the risk and rate will pertain to the continuous use of the biologic for the next 12 months). We consider this definition to be the most pertinent for clinical use. As the model will be developed using real-world data, treatment status might change over time (although this will be in a small proportion of patients given the follow-up time is only 12 months). Following the PROBAST recommendation to minimise the risk of prediction bias,[28] all age-qualified participants of ISAR and NOVELTY with any follow-up data on the outcome will be included in the analysis, and the impact of changes in treatment will be modelled using appropriate statistical methods (details are provided in the Statistical analysis section).

## Predictors

From the baseline data collected in ISAR (the development dataset), we have identified 52 commonly recorded patient characteristics that were consistently assessed (the full list is provided in online supplemental appendix table 2). These characteristics fell into the following broad categories: sociodemographic, history of exacerbations in previous 12 months, pulmonary function tests and biomarkers, medication use and comorbidities. All variables are measured at index date or in the immediate 12-month period before the index date.

From the list of candidate predictors, this analysis will exclude variables which are not captured in both development and validation datasets, those that are not available in certain countries (eg, some comorbidities which were not part of an ISAR standard list of 15 core comorbidities, nor reported in the form of free text), and those with a large proportion of missing data.[28]

From this list, a short list of candidate predictors will be determined through expert knowledge elicitation on the clinical relevance to asthma management and the availability of such predictors in a typical care setting.[28] An online survey has been developed to rate these 52 variables, based on a 1 (a not recommended predictor) to 5 (a strongly recommended predictor) scale, to create a shorter list of clinically relevant predictors. The survey will be circulated to the Scientific Committees of ISAR and NOVELTY, as well as the Respiratory Effectiveness Group (https://www.regresearchnetwork.org/the-reg-team/), totalling over 70 key opinion leaders in severe asthma care and management. We will rank the variables based on their average recommendation score, and will remove the variables that receive low relevance/feasibility score to generate a short list of candidate predictors.

In the next step, we will evaluate the correlation matrix of predictors to identify highly colinear ones. Among colinear predictors, we will retain the one with the highest ranking by the experts and will remove the others. Finally, we will apply regularisation-based machine learning algorithm to further achieve model sparsity by removing non-essential predictors from the remaining variables (details

are provided in the Statistical analysis section). These steps are taken to optimise study power, improve model parsimony and enhance clinical usability of the final scoring tool.[28 35–37]

### Outliers and missing data

Predictors with systematically missing values in the development or validation samples will be removed from the analysis. Extreme values will be examined case by case with clinicians, flagged as outliers if such values are deemed infeasible in practice, and recoded as missing values (so that these will be imputed along with other missing values).[38] For predictors that will remain in the final list, following expert recommendation,[28] a robust machine learning-based non-parametric algorithm (MissForest) will be performed to impute variables with missing data.[39] The random forest approach outperforms traditional and deep-learning-based approaches under a diverse set of circumstances in which missingness occurs.[40]

### Statistical analysis

All statistical analyses will be performed using SAS, V.9.4 and R, V.4.2.2.

#### Model derivation

We will use the final set of predictors to develop a zero-inflated negative binomial regression model to predict individualised rate of severe exacerbation in the next 12 months in patients with severe asthma.[41] The zero-inflated component captures the potential excess number of patients who will have no severe exacerbations in the following 12 months.[41] This model allows flexible prediction of severe exacerbation count, from which the risk of ≥1 severe exacerbation (the primary prediction endpoint) can be calculated. In the meantime, the prediction model is flexible enough to also produce predicted rates (secondary prediction endpoint).

The risk of having ≥1 severe exacerbation in the next 12 months will be obtained as:

$$\text{predicted risk} = 1 - \left[P_0 + \left(1 - P_0\right) P(Y = 0)\right]$$

where $P_0$ is the probability of not experiencing any events from the zero-inflated component and P(Y=0) is the probability of having zero exacerbation in the next 12 months from the count component of the model. Of note, due to the scarcity of death events in severe asthma (<3%),[42] the competing risk of death will not be considered.

Because ignoring treatment changes during follow-up may bias the associations between the rest of predictors and the outcome, this prediction model will include the treatment effect of biologics.[19] We will apply marginal structural modelling, in particular inverse-probability-of-treatment weighting at baseline and over the follow-up period, to create a pseudo-population in which baseline treatment remains constant over time.[43] Calculating such inverse probabilities requires specifying a causal model for treatment selection and outcome, and our previous work has identified confounding factors for the association between biologic use and severe exacerbations in the ISAR data, and has successfully recovered treatment effect from this observational study that is compatible with results from clinical trials.[44]

#### External validation

For external validation (NOVELTY), following published guidelines and best practices,[45] we will examine model calibration (ie, the agreement between observed and predicted outputs) and discrimination (ie, the extent to which the model can distinguish between high-risk and low-risk individuals). In NOVELTY, a severe asthma exacerbation will be defined as a physician-reported exacerbation that was treated with OCS and/or required an ER visit or hospitalisation; validation will be performed using severe exacerbations from the first 12 months of follow-up. We will apply the same inverse-probability-of-treatment weighting to remove the confounding effect of treatment with biologics, as explained in the derivation sample. Calibration is assessed by comparing observed and predicted 12-month risk of severe exacerbation per decile in calibration plots across risk groups (eg, sex groups), in terms of the difference in means of prediction versus observation ('calibration-in-the-large') and the 'calibration slope' of which a value smaller than 1 indicates more extreme prediction: low prediction too low and high prediction too high. Discrimination will be assessed by calculating receiver operating characteristic curves and the area under the curve that are related to the predicted risk of having prespecified number of severe exacerbations in the following 12 months.

#### Clinical utility assessment

Furthermore, the clinical utility of the risk prediction tool will be examined via conducting a decision curve analysis (DCA) as part of the external validation using the NOLVETY data.[46] Medical decision-making often entails specifying a risk threshold above which the patient can be considered high-risk (eg, for escalation of treatment such as biologic therapy). At each level of risk threshold, DCA calculates a clinical 'net benefit' for the risk prediction model compared with default strategies of treating all or no patients.[46] Net benefit is calculated as $\frac{\text{True Positives}}{N} - \frac{\text{False Positives}}{N}\left(\frac{p_t}{1-p_t}\right)$, where $N$ is the number of patients and $p_t$ is the minimum 1-year risk of severe exacerbation at which treatment escalation is warranted (ie, 'risk threshold'). We will compare the net benefit of our final model to treat patients with three alternatives: (1) treating no one, (2) treating all and (3) using binary classification into type 2 (vs non-type 2) asthma per the GINA 2022[47] criteria for evidence of type 2 inflammation (≥150/µL blood eosinophils or ≥20 ppb FeNO or ≥2% sputum eosinophils).[2 47] We will examine the net benefit across the entire range of thresholds (0–1) but will also determine a plausible range for risk thresholds of interest for biologic therapy from the clinical experts.

### Implementation

Once validated and piloted, the analysis code will be made publicly available. The code implementing the model will be publicly available in popular statistical programming environments (R, Stats, SAS). We will also host the model on the Programmable Interface for Statistical & Simulation Models, a web-based application programming interface platform that will enable remote risk prediction suitable for implementation as web application and incorporation of the model into electronic health records.[48]

### Patient and public involvement

This study will be based on retrospective, real-world cohorts of patients with severe asthma. We will retrieve archived patient-level data from these cohorts, but we will not directly recruit patient for prospective follow-up or involve public to the current study.

### Strengths, limitations and implications

This proposed study aims to develop and externally validate a statistical scoring tool that predicts the risk and frequency of severe exacerbation in the next 12 months in patients with severe asthma, and to assess the clinical usefulness of this prediction tool in guiding escalation of asthma treatment. To improve model generalisability,[45] we will independently derive and validate the model in two large 'real-world' cohorts of patients with asthma, for which study characteristics, predictors and outcomes were collected from routine care or healthcare registries in over 20 countries. To improve user trust and credibility, this prediction tool will include predictors based on the overall ranking of clinical of clinical relevance and feasibility by internationally renowned clinical experts. Advanced statistical methods will be applied to control for overfitting and collinearity, optimise prediction accuracy, and clinical relevance. Once validated and piloted, this prediction model will be implemented into an e-health tool to support clinical decision-making in routine care of patients with severe asthma.

Despite the prevalence of asthma and the urgency to optimally treat patients with severe asthma in a cost-effective manner, as far as we are aware, there is no externally validated risk prediction tool for exacerbations in severe asthma. In recent years, several complex machine-learning models have been developed, all based on electronic health records from local settings that cover an exhaustive list of comorbidity, medication use and occasionally lab test results, to predict asthma exacerbations and admissions in the general asthma population.[25–27 49] Given the model complexity and data availability issues, those models are hardly generalisable to patients with severe asthma or general asthma patients in other routine care settings. Recently, a proof-of-concept prototype scoring tool has been developed to stratify exacerbation risk in the general asthma population based on blood eosinophil count and FeNO,[50] which demonstrated the potential to quantify the excess risk of asthma attacks in type-2 high asthma and reduction of risk with anti-inflammatory or biologic therapy.[22]

The major potential utility of this proposed prediction tool would be to triage referral and support treatment decisions. For instance, this tool could supply predictions to triage referrals of high-risk patients to a specialist, or to aid shared decision-making for initiating biologics in patients on maximal inhaled therapies. The decision to initiate such therapies is often a consequential one for both patients and healthcare systems, and a risk-based approach has the potential to significantly improve its efficiency, in particular to shorten the decision time to perform clinical assessment and subsequently initiate the treatment. In patients with atrial fibrillation, quantitative risk prediction improved shared decision-making and patients' satisfaction with their chosen treatment, subsequently leading to greater adherence to therapies.[20] By relying on well-established variables that may be routinely collected in electronic health records, the proposed model can become an easy-to-use tool in outpatient settings. As such, our proposed work may be a practical step towards precision medicine and digital health in the context of asthma, one of the most common chronic conditions worldwide.

A major strength of our study is the reliance on two large, community-based yet well-characterised severe asthma cohorts for development and validation. Because of strict inclusion criteria, asthma efficacy trials are usually focused on a small, relative homogenous subgroup of patients who are enriched for the health event of interest.[51 52] Thus, characteristics, predictors and outcomes in efficacy trials often have narrow distributions, which limit the generalisability of a trial-data-based prediction algorithm. The use of real-world data may improve the generalisability of our proposed prediction model. Meanwhile, local (eg, national severe asthma registries) are often too small to enable the development of robust clinical prediction models. The feasibility of our approach has been enhanced by two international collaborative efforts. Both the ISAR and NOVELTY studies have applied a rigorous standard for variable recording and patient follow-up, enabling sophisticated comparative effectiveness research or phenotype classification.[31 32]

This proposed study has several limitations. First, the number of adolescent participants were both limited in ISAR and NOVELTY and thus this age group was excluded from our analysis. Second, we are unable to impute missing data not at random, in particular when a predictor is not available in all participating centres. Fortunately, both datasets have recorded a core list of variables across all settings, which are well-established predictors of asthma-related adverse events and include criteria for biologic initiation. Third, the inclusion and exclusion criteria for severe asthma differ across countries in the ISAR registry; further in the NOVELTY study, severe asthma was defined by physician assessment. Likewise, some predictors may not be consistently measured across all participating centres within each study. Fourth, in addition to country variation in case and outcome definitions, there may be global and temporal variations in the risk of severe exacerbations. For instance, while histories of asthma-related ER attendances, hospitalisations

or use of invasive ventilations can be strong predictors of future severe exacerbations, there are great variations between countries and over time in health system and policy factors that may affect health resource use, and risk can be modified temporally by environmental factors such as weather, allergen exposure and viral infections. Given the potential bias of risk prediction due to country effects, we will conduct a follow-up analysis to investigate the extent of country variation in exacerbation rates. If the effects are found to be substantial, we will provide guidelines for updating the prediction model to local settings. Last but not least, the clinical adoption of such a risk prediction tool to real-life practice requires a more thorough economic evaluation on cost-effective intervention strategies following the risk prediction, and piloting in clinical practice.

To conclude, we hypothesise that commonly collected patient characteristics and biomarkers can be used to predict the individualised risk of clinically significant exacerbations in patients with severe asthma, and we propose to develop, validate and assess the clinical utility of a novel individualised risk prediction model for severe exacerbations in real-world international severe asthma populations.

## ETHICS AND DISSEMINATION

This study has obtained ethics approval from the Institutional Review Board of National University of Singapore (NUS-IRB-2021-877), the Anonymised Data Ethics and Protocol Transparency Committee (ADEPT1924) and the University of British Columbia (H22-01737).

Results will be presented at international conferences and published in international peer-reviewed journals. The prediction tool will be made publicly available via a web application.

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**Contributors** WC, MS, CPY, TYL and RR contributed to study conceptualisation and design. WC, MS, DBP, RB, CJ and MSK acquired data for analysis. TYL and WC wrote the first draft of protocol. DBP, RB, CJ and MSK provided critical clinical input in study design. WC obtained the study funding. CPY and RR contributed to administrative, technical or logistic support. All authors critically revised the protocol and approved the submitted version.

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**Competing interests** DBP has advisory board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma, Novartis; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, Thermofisher; funding for patient enrolment or completion of research from Novartis; stock/stock options from AKL Research and Development which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology; is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment; and was an expert witness for GlaxoSmithKline, outside the submitted work. RB reports grants and personal fees from AstraZeneca, grants from Genentech, grants and personal fees from Health Research Council NZ, personal fees from Cipla, personal fees from Avillion, outside the submitted work. MSK reports grants and personal fees from Astra-Zeneca, personal fees from GlaxoSmithKline, personal fees from Sanofi, personal fees from Novartis, outside the submitted work.

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# Development, validation, and clinical utility assessment of an individualised risk prediction model for exacerbations in patients with severe asthma: study protocol

## Supplemental materials

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**Appendix Table 1. A summary of how each ISAR registry diagnosed asthma and categorized severe asthma**

| Country | Diagnostic criteria for asthma | Severe Asthma Definition |
|---|---|---|
| **Argentina** | • Bronchodilator response (BDR) > 200mL and/or > 12% of FEV1 baseline<br>• FEV1 variability > 12% (between two FEV1 values measured within 2 months of each other) | • Lack of asthma control despite regular treatment with the combination of highest dose ICS and LABA<br>• Or asthma that becomes uncontrolled when highest doses are reduced |
| **Australia** | • Variable airflow obstruction demonstrated within the last 10 years (any of the following).<br>• Bronchodilator response (BDR) > 200mL and/or > 12% of FEV1 baseline<br>• Airway hyper-responsiveness (AHR) in response to any standard challenge agent e.g. methacholine, histamine, hypertonic saline, mannitol, adenosine monophosphate, exercise<br>• Peak flow variability > 12% when monitored over at least 1 week<br>• FEV1 variability > 12% (between two FEV1 values measured within 2 months of each other) | • Confirmed Asthma Diagnosis with variable airflow obstruction<br>• Maximal ICS Therapy with 2nd Controller<br>• Optimized asthma management skills (inhaler technique, adherence, education, written asthma action plan)<br>• Poor asthma control with 1 or more of the following:<br>• Poor symptom control: ACQ6 consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)<br>• Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year<br>• Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year; or<br>• Persistent airflow limitation: FEV1 < 80% predicted (in the face of reduced FEV1/FVC) following a withhold of short and long-acting bronchodilators (i.e. PRE-bronchodilator). |
| **Bulgaria** | • GINA and ERS confirmed asthma diagnosis.[1] | • As per ISAR protocol criteria for including asthmatics in the registry – ATS/ERS definition for severe asthma |
| **Canada** | • GINA confirmed asthma diagnosis.[1] | • Uncontrolled asthma despite a combination of high dose ICS and an additional controller, review of inhaler technique and adherence and appropriate treatment of comorbidities |
| **Colombia** | • GINA confirmed asthma diagnosis.[1] | • Aged ≥18 years<br>• On GINA Step 5 or asthma uncontrolled on GINA Step 4.<br>Uncontrolled defined as: |

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| | | (a). Poor symptom control: ACQ consistently>1.5, ACT<20 (or ‘‘not well controlled’’ by NAEPP/GINA guidelines)<br>(b). Severe exacerbations: at least one hospitalization, ICU stay or mechanical ventilation due to asthma exacerbation in the previous year<br>(c) Frequent exacerbations: two or more bursts of systemic CS (>3days each) in the previous year |
| **Denmark** | • GINA confirmed asthma diagnosis.[1] | • Severe asthma, defined as asthma requiring either at least 1600 micrograms of budesonide equivalent ICS plus a second controller (LABA, LAMA, or LTRA) or use of OCS at least 50% of the year |
| **Greece** | • GINA confirmed asthma diagnosis.[1] | • Aged >12years<br>• Diagnosis of severe asthma according to ERS/ATS criteria<br>• Patients not controlled on GINA 4 treatment with the combination of high dose of ICS and LABA<br>• Patients experiencing ≥2 asthma exacerbations (requiring systemic corticosteroids)<br>• Patients requiring Continuous or frequent treatment with OCS to achieve asthma control and reduce symptoms and exacerbations |
| **India** | • GINA confirmed asthma diagnosis.[1] | • Patients 18 years or older<br>• Patients in receiving treatment according to GINA Step 5 or uncontrolled in Step<br><br>Uncontrolled defined as: (a) Having Severe asthma symptoms AND/OR<br>(b) Frequent severe asthma exacerbations requiring systemic corticosteroids<br><br>**Severe asthma symptoms (ERS/ATS Guidelines):** (a) Poor symptom control where Asthma Control Questionnaire |

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| | | consistently >1.5, Asthma Control Test <20 (b) Airflow limitation: FEV1 < 80% predicted (in the face of reduced FEV1/FVC following a withhold of short and long-acting bronchodilators, i.e. Pre-bronchodilator) (c) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the in the previous year<br><br>**Frequent severe asthma exacerbations requiring systemic corticosteroids (ERS/ATS Guidelines):** Two or more bursts of systemic Corticosteroids (>3 days course each) in the previous year |
| **Ireland** | • GINA confirmed asthma diagnosis.[1] | • Aged ≥18 years<br>• On GINA Step 5 or asthma uncontrolled on GINA Step 4.<br>Uncontrolled defined as:<br>(a).Poor symptom control: ACQ consistently>1.5, ACT<20 (or ‘‘not well controlled’’ by NAEPP/GINA guidelines)<br>(b).Airflow limitation: after appropriate bronchodilator withhold FEV1<80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)<br>(c).Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year<br>(d) Frequent exacerbation : two or more bursts of systemic CS (>3days each) in the previous year |
| **Italy** | • GINA confirmed asthma diagnosis.[1] | • Aged >12 years<br>• Diagnosis of severe asthma according to ERS/ATS criteria (as for UK registry above)[4]<br>• Lack of asthma control despite regular treatment with the combination of high dose ICS and LABA |
| **Japan** | • GINA confirmed asthma diagnosis.[1] | • Aged ≥18 years<br>• On GINA Step 5 or asthma uncontrolled on GINA Step 4. |

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| | | • Uncontrolled defined as remaining severe asthma symptoms, frequent severe exacerbations required, systemic corticosteroids |
| **Kuwait** | • GINA confirmed asthma diagnosis[1] | • Patients not controlled on GINA step 4-5 treatment in the previous year<br>• Uncontrolled defined as ACT score <20 or prebronchodilator $FEV_1$ <80% predicted<br>• With the following criteria:<br>  ○ ≥2 exacerbations requiring course of systemic corticosteroids<br>  ○ ≥2 exacerbations requiring A&E visit or 1 hospital admission, or ICU admission<br>• Airflow limitation: Post bronchodilator $FEV_1$ <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal) |
| **Mexico** | • GINA confirmed asthma diagnosis, or when not fully reaching the spirometric cut-offs for reversibility: clinical symptoms and elevated FeNO. | • Aged ≥18 years<br>• On GINA Step 5 or asthma uncontrolled on GINA Step 4.<br>Uncontrolled defined as <u>any of the below</u>:<br>  ○ Poor symptom control: ACQ consistently>1.5, ACT<20 (or ''not well controlled'' by NAEPP/GINA guidelines)<br>  ○ Severe exacerbations: at least one hospitalization, ICU stay or mechanical ventilation due to asthma exacerbation in the previous year<br>• Frequent exacerbations: two or more bursts of systemic CS (>3days each) in the previous year |
| **Poland** | • GINA confirmed asthma diagnosis [1] | • The need to use high doses of inhaled glucocorticosteroids (> 1000 mcg of beclometasone dipropionate daily in adults and children aged 12 years and over, in children aged 6-11 years> 400mcg or other inhaled glucocorticosteroid in a dose equivalent according to current guidelines The Global Initiative for Asthma (GINA)) in combination with another |

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| | | asthma control drug (long-acting β-2 adrenergic agonist, leukotriene modifier, long-acting muscarinic receptor blocker).<br>• Two or more episodes of exacerbation per year requiring the use of systemic corticosteroids or increasing their dose in adults and children aged 12 years and above who use them chronically; in children 6-11 years of age - two or more episodes of exacerbation a year despite the use of inhaled glucocorticosteroids.<br><br>And meeting at least 2 of the following criteria:<br>• Symptoms of uncontrolled asthma (lack of asthma control in the asthma control questionnaire ACQ> 1.5 points),<br>• Hospitalization within the last 12 months due to exacerbation of asthma,<br>• An asthma attack that may have been life-threatening in the past,<br>• Persistent airway obstruction (forced expiratory volume in one second FEV1 <80% predicted or daily variation in peak expiratory flow PEF> 30%),<br>• Deterioration of quality of life due to asthma (mean score on the miniAQLQ quality of life control test in patients with asthma <5.0 points in adults and children aged 12 and over or PAQLQ <5.0 points in children 6-11 years of age. |
| **Portugal** | • GINA confirmed asthma diagnosis.[1] | • Lack of asthma control despite maintenance treatment with GINA step 4-5 treatment in the previous year<br>• Uncontrolled asthma defined as:<br>  ○ poor symptom control (considering cutoff values for ACT and CARAT), or<br>  ○ ≥2 severe exacerbations (need for ≥3 days course of systemic corticosteroids) in the previous year, or<br>  ○ ≥1 hospitalisation, ICU stay or mechanical ventilation in the previous year, or |

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| | | • $FEV_1$ <80% predicted after bronchodilation (coupled with $FEV_1$/FVC <70%) |
| **Saudi Arabia** | • GINA confirmed asthma diagnosis.[1] | • Aged ≥18 years<br>• On GINA Step 5 or asthma uncontrolled on GINA Step 4.<br>• Uncontrolled asthma defined as remaining severe asthma symptoms ACT<20, frequent severe exacerbations requiring ER visit or short course of steroids, patient on daily systemic corticosteroids |
| **South Korea** | • GINA confirmed asthma diagnosis[1] | • Patients NOT controlled continuously on GINA Step 4 treatment<br>• Patients controlled on GINA Step 4 treatment, but who meets the following criteria:<br>o ≥1 urgent care visit (emergency room or unscheduled out-patient department visit)<br>o ≥3 courses of systemic corticosteroid/year<br>o Immediate asthma deterioration after 25% reduction of ICS/OCS<br>• History of near fatal asthma attack |
| **Spain** | • GEMA confirmed diagnosis | • Aged ≥18 years<br>• Lack of asthma control despite maintenance treatment with a combination of high dose ICS and LABA<br>• Uncontrolled asthma defined as:<br>o poor symptom control (ACQ ≥1.5 or ACT < 20), or<br>o ≥2 severe exacerbations (need for ≥3 days course of systemic corticosteroids) in the previous year, or<br>o ≥1 hospitalisation, ICU stay or mechanical ventilation in the previous year, or<br>o $FEV_1$ <80% predicted after bronchodilation (coupled with $FEV_1$/FVC <70%) |
| **Taiwan** | • | • Aged ≥20 years<br>• Patients in receiving treatment according to GINA Step 5 or uncontrolled in Step 4 according to GINA 2017 guideline.<br>• Uncontrolled is defined as |

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| | | (a). Poor symptom control: ACQ consistently>1.5, ACT<20 (or ‘‘not well controlled’’ by NAEPP/GINA guidelines)<br>(b). Airflow limitation: after appropriate bronchodilator withhold FEV1<80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)<br>(c). Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year<br>(d). Frequent exacerbation: two or more bursts of systemic CS (>3 days each) in the previous year |
| **United Arab Emirates** | • GINA confirmed asthma diagnosis.[1] | • Aged ≥18 years<br>• On GINA Step 5 or asthma uncontrolled on GINA Step 4.<br>• Uncontrolled asthma defined as:<br>o poor symptom control (ACT < 20), or<br>o ≥2 severe exacerbations (need for ≥3 days course of systemic corticosteroids) in the previous year, or<br>o ≥1 hospitalisation, ICU stay or mechanical ventilation in the previous year, or<br>• $FEV_1$ <80% predicted after bronchodilation (coupled with $FEV_1$/FVC <70%)<br>• Uncontrolled asthma despite a combination of high dose ICS and an additional controller, review of inhaler technique and adherence and appropriate treatment of comorbidities. |
| **UK** | • NICE or BTS/SIGN Guidelines[2,3] | • Diagnosis of severe asthma according to ERS/ATS criteria[4]<br>o Requires treatment with guideline suggested medications for GINA steps 4-5 asthma for the previous year or systemic corticosteroids for ≥50% of the previous year to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy<br>• Uncontrolled asthma defined as: |

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| | | ○ Poor symptom control: ACQ consistent ≥1.5, ACT< 20 or 'not well controlled' by NAEPP/GINA guidelines<br>○ Frequent severe exacerbations: ≥2 bursts of systemic corticosteroids (≥3 days each) in the previous year<br>○ Serious exacerbations: ≥1 hospitalisation, ICU stay or mechanical ventilation in the previous year<br>○ Airflow limitation: after appropriate bronchodilator withhold $FEV_1$ <80% predicted (in the face of reduced $FEV_1$/FVC defined as less than the lower limit of normal)<br>• At least one of the following:<br>○ An event of acute severe asthma which is life threatening, requiring invasive ventilation within the last 10 years<br>○ Continuous or frequent treatment with OCS<br>○ Fixed airflow obstruction, with a post-bronchodilator $FEV_1$ <70% of predicted normal<br>• Referred as an adolescent transition patient from a paediatric severe asthma service |
| **USA** | • ATS confirmed asthma diagnosis[4] | • Aged ≥18 years<br>○ On GINA Step 5 or asthma uncontrolled on GINA Step 4<br>○ Uncontrolled defined as ACT score <20 or prebronchodilator $FEV_1$ <80% predicted |

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; A&E: Accident & Emergency; AHR: airway hyper-responsiveness; ATS: American Thoracic Society; BG: Bulgaria; BTS: British Thoracic Society; CN: Canada; DK: Denmark; ERS: European Respiratory Society; ES: Spain; $FEV_1$: forced expiratory volume in 1 second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; GR: Greece; ICS: inhaled corticosteroid; ICU: Intensive Care Unit; ISAR: International Severe Asthma Registry; IT: Italy; JP: Japan; KW: Kuwait; LABA: long-acting $\beta_2$-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; NAEPP: National Asthma

Education and Prevention Programme; NICE: National Institute for Clinical Excellence; OCS: oral corticosteroid; pMDI: pressurised metered dose inhaler; SK: South Korea.

* GINA confirmed asthma diagnosis with confirmed variable airflow obstruction current or historical within 10 years[1]:

- Bronchodilator response > 200 mL or >12% (post-bronchodilator $FEV_1$ following administration of 400 µg salbutamol, pMDI with spacer after 10 mins AND/OR
- AHR in response to any standard challenge agent (e.g. methacholine, histamine, hypertonic saline, mannitol, adenosine monophosphate, exercise) AND/OR
- Peak flow variability > 12% over at least 1 week AND/OR $FEV_1$ variability >12% within 2 months

Reference GEMA 4.0: Guía Española para el manejo del asma (Spanish Guideline for Asthma Management). Plaza Moral V; Comité Ejecutivo de GEMA. [GEMA(4.0). Guidelines for Asthma Management. Arch Bronconeumol. 2015 Jan;51 Suppl 1:2-54. doi: 10.1016/S0300-2896(15)32812-X. Diagnostic criteria: Asthma symptoms plus: positive bronchodilator response, or PEF variability, or exhaled nitric oxide > 50 ppb, or bronchial hyperresponsiveness, or complete reversion of bronchial obstruction after an oral corticosteroid test.

**Appendix Table 2. Full list of ISAR variables that will be considered as potential predictors in the online survey**

| Group | Variable | Definition |
|---|---|---|
| **Patient characteristics** | Age | Age of the patient. |
| | Sex | Gender of the patient. |
| | Ethnicity | Which ethnic group does the patient belong to? |
| | Smoking Status | Whether the patient has ever smoked. |
| | BMI | Basal Metabollic Index (BMI) = Weight (kg)/(Height (m))^2 of the patient. |
| | Asthma Control | Defined and categorized by GINA 2022 assessment of asthma symptom control, Asthma Control Test, or Asthma control questionnaire |
| | Duration of Asthma | Time duration of the affliction (Age - Asthma onset age). |
| **Timing** | Season | The country-wise prevalent season during the index month. |
| **Pulmonary function tests** | Pre FEV1 | Pre-bronchodilator measure of forced expiratory volume at 1 second (FEV1) |
| | Pre-FVC | Pre-bronchodilator measure of forced vital capacity (FVC) |
| | Pre FEV1/FVC ratio | Pre-bronchodilator ratio of FEV1 and FVC. |
| | Post FEV1 | Post-bronchodilator FEV1 measure. |
| | Post-FVC | Post-bronchodilator FVC measure. |
| | Post FEV1/FVC ratio | Post-bronchodilator ratio of FEV1 and FVC. |
| | Fractional Exhaled Nitric Oxide (FeNO) | Fraction Exhaled Nitric Oxide Test result. |
| **Biomarkers** | Baseline Eosinophil Counts (BEC) | Highest blood eosinophils count in last year. |
| | IgE count | Total serum IgE count within the last year. |
| | Composite Eosinophilic Gradient | Calculated based on biologics use, eosinophil counts & FeNO results [50]. |
| **Positive allergen tests** | Serum specific IgE test to allergens | Whether the patient has tested positive to any of a number of serum Allergen Test of Grass Mix, Weed Mix , Mould Mix , Dust Mite, Cat, Dog , Trees, Aspergillus, Food Mix, Animal Mix, Asperillus, Other<br>• Categorised as positive reaction if >0.7kU/L |

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| | Skin prick test to allergens | Whether the patient has tested positive to Skin prick test tp house dust mite, animal dander (cat, dog), pollen (tree, grass) and moulds (Aspergillus).<br>● Categorised as positive reaction if >4 mm is wheal diameter |
| **Health services use** | Exacerbations | Total number of exacerbations occurring in the last year |
| | Total ER visits | Total asthma-related Emergency Room (ER) visits in the past year |
| | Total Hospital visits | Total asthma-related cases of hospitalisation within the past year |
| | Invasive Ventilation | Total number of invasive ventilations within the past year |
| | Medication adherence | Whether the patient has evidence of poor medical adherence |
| **OCS use** | Long-term OCS | Whether the patient takes long-term/maintenance oral corticosteroids (OCS) |
| **Other medication use (all patients were required to be taking medium or high dose ICS/LABA)** | LAMA | Whether the patient takes long-acting muscarinic antagonists (LAMA) |
| | LABA/LAMA | Whether the patient takes a combination therapy of long-acting beta-agonist (LABA) and LAMA |
| | Macrolide | Whether the patient takes long-term macrolide |
| | Steroid sparing | Whether the patient takes steroid sparing drugs such as xxx |
| **Comorbidities** | Allergic rhinitis | Did this patient have a positive diagnosis of allergic rhinitis as of or prior to baseline visit? |
| | Chronic rhinosinusitis | Did this patient have a positive diagnosis of Chronic rhinosinusitis of or prior to baseline visit? |
| | Nasal polyps | Did this patient have a positive diagnosis of Nasal polyps of or prior to baseline visit? |
| | Eczema | Did this patient have a positive diagnosis of Eczema of or prior to baseline visit? |
| | GERD | Did this patient have a positive diagnosis of GERD of or prior to baseline visit? |
| | Bronchiectasis | Did this patient have a positive diagnosis of Bronchiectasis of or prior to baseline visit? |
| | COPD | Did this patient have a positive diagnosis of COPD of or prior to baseline visit? |
| | Anxiety | Did this patient have a positive diagnosis of Anxiety of or prior to baseline visit? |
| | Depression | Did this patient have a positive diagnosis of Depression of or prior to baseline visit? |
| | Dysfuctional breathing | Did this patient have a positive diagnosis of Dysfuctional breathing of or prior to baseline visit? |
| | Hypertension | Did this patient have a positive diagnosis of Hypertension of or prior to baseline visit? |

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| | Pneumonia | Did this patient have a positive diagnosis of Pneumonia of or prior to baseline visit? |
| | Cataract | Did this patient have a positive diagnosis of Cataract of or prior to baseline visit? |
| | Glaucoma | Did this patient have a positive diagnosis of Glaucoma of or prior to baseline visit? |
| | Renal Failure | Did this patient have a positive diagnosis of Renal Failure of or prior to baseline visit? |
| | Heart failure | Did this patient have a positive diagnosis of Heart failure of or prior to baseline visit? |
| | IHD | Did this patient have a positive diagnosis of IHD of or prior to baseline visit? |
| | Embolism | Did this patient have a positive diagnosis of Embolism of or prior to baseline visit? |
| | Peptic Ulcer | Did this patient have a positive diagnosis of Peptic Ulcer of or prior to baseline visit? |
| | Type II Diabetes | Did this patient have a positive diagnosis of Type II Diabetes of or prior to baseline visit? |
| | Sleep Apnea | Did this patient have a positive diagnosis Sleep Apnea of or prior to baseline visit? |
| | Stroke | Did this patient have a positive diagnosis of Stroke of or prior to baseline visit? |
| | Obesity. | Did this patient have a positive diagnosis of Obesity. of or prior to baseline visit? |