PAGE Study: Summary of a study protocol to estimate the prevalence of severe asthma in Spain using big-data methods

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Abstract

**Background:** The proposal and the initiative to conduct the Prevalence of Severe Asthma in Hospital Units in Spain (PAGE) study arises from the perspective of widespread implementation of electronic medical records and the limited data available on the prevalence of severe asthma in hospitals in our setting.

**Objectives:** The primary objective is to determine the prevalence of severe asthma in the outpatient departments of allergy and pneumology services in Spain. Secondary objectives include describing the most prevalent characteristics and phenotypes of severe asthma, evaluating the selection criteria for receiving approved biological treatments for this disease, and estimating resource consumption. Furthermore, taking advantage of the incorporation of digital technology and new data collection sources, which allow the reuse of information stored in electronic medical records (Big Data), the use of one of these tools (Savana) has been integrated into the study.

**Methods:** The PAGE study is designed as a multicenter, non-experimental, observational, cross-sectional study in a first phase, and prospective in a second phase, controlled, population-based, with a two-stage selection of subjects by random sampling. The research will be carried out in 40 hospitals, following a criterion of convenience, which assumes the geographical representativeness of Spain.

**Results:** This manuscript describes the study design and protocol.

**Conclusions:** Our study design is robust to avoid bias and to allow establishing the prevalence of patients with severe asthma in Spanish hospitals. It is the first to incorporate new tools that can help in routine clinical practice and research, such as big data analysis software, and to evaluate its reliability and efficiency.

**Key words:** Severe Asthma, Big data, Prevalence, Hospital, Machine learning.
Resumen

Antecedentes: La propuesta y la iniciativa de realizar el estudio Prevalencia del Asma Grave en las Unidades Hospitalarias de España (PAGE) surge desde la perspectiva de una implantación generalizada de la historia clínica electrónica y de los escasos datos disponibles sobre la prevalencia del asma grave en los hospitales de nuestro entorno.

Objetivos: el objetivo principal es determinar la prevalencia de asma grave en las consultas externas de los servicios de alergia y neumología en España. Como objetivos secundarios, se incluyen describir las características y fenotipos más prevalentes del asma grave, evaluar los criterios de selección para recibir los tratamientos biológicos aprobados para esta enfermedad y estimar el consumo de recursos. Además, aprovechando la incorporación de la tecnología digital y las nuevas fuentes de recogida de datos, que permiten la reutilización de la información almacenada en las historias clínicas electrónicas (Big Data), se ha integrado en el estudio la utilización de una de estas herramientas (Savana).

Métodos: El estudio PAGE está diseñado como un estudio multicéntrico, no experimental, observacional, transversal en una primera fase, y prospectivo en una segunda fase, controlado, basado en la población, con una selección de sujetos en dos etapas por muestreo aleatorio. La investigación se llevará a cabo en 40 hospitales, de acuerdo con un criterio de conveniencia, que asuma la representatividad geográfica de España.

Resultados: El presente manuscrito describe el diseño y protocolo del estudio.

Conclusiones: nuestro diseño del estudio es robusto para evitar sesgos y permitir establecer la prevalencia de pacientes con asma grave en los hospitales españoles. Es el primero en incorporar nuevas herramientas que pueden ayudar en la práctica clínica habitual y en la investigación, como un gran software de análisis de datos, y en evaluar su fiabilidad y eficiencia.

Palabras clave: Asma grave, Big data, Prevalencia, Hospital, Inteligencia artificial.
Introduction

Asthma is one of the most common chronic diseases worldwide. According to the World Health Organization (WHO), it is estimated that there are currently more than 358 million patients with asthma[1,2], with a widespread but heterogeneous distribution in all countries, irrespective of the degree of development [3].

Its prevalence varies widely even within a single country. In Spain, the mean prevalence of asthma is 5% in the general adult population and 10% in children [4-7]. The existing evidence is more limited regarding the prevalence of severe uncontrolled asthma. In Spain, data are only available from a study conducted in hospital asthma units where a prevalence of 3.9% was estimated in adults with asthma and 8.8%7 in children with asthma [8].

Under Global Initiative for Asthma (GINA) recommendations [1], the paradigm in asthma management involves five treatment steps, where according to the level of asthma control, treatment is adjusted in a continuous cycle based on the patient’s asthma control. Data is currently available showing that asthma control is an achievable goal with the treatment armamentarium [9]. However, when the available results are analyzed, it is shown that asthma is not controlled, with different nuances, in a significant proportion of cases [10,11], a situation that has been attributed to many causes, including poor adherence to therapy [12], coexisting comorbidities or exposure to aggravating factors [13-15]. This lack of control leads to a high resource consumption [16-18], and determines that asthma is considered a true public health problem.

Both GINA and the European Respiratory Society (ERS)/ American Thoracic Society (ATS) consensus on the definition, evaluation and treatment of severe
asthma, define this type of asthma as the one that requires treatment with high doses of inhaled corticosteroids (ICS) in addition to a second maintenance treatment (and/or systemic glucocorticoids) (GINA step 4 or 5) to prevent it from being “uncontrolled”, or that it remains “uncontrolled” despite this treatment [17]. This same definition has been adopted by other subsequent guidelines such as the Consensus on severe uncontrolled asthma published by the Spanish Society of Pneumology and Chest Surgery (SEPAR) and adapted to our setting [18]. However, although both documents adequately define the steps for labelling patients as having poorly controlled severe asthma, the reality is that many patients originally classified as having moderate or severe asthma, either did not have asthma or had milder manifestations of uncontrolled asthma [17,18].

The proposal and the initiative to conduct the Prevalence of Severe Asthma in Hospital Units in Spain (PAGE) study arises from the perspective of a widespread implementation of the electronic medical record and the scant data available on the prevalence of severe asthma in hospitals in our setting, the primary objective of which is to determine the prevalence of severe asthma in the outpatient clinics of allergy and pulmonology departments in Spain. As secondary objectives, it will seek to describe the characteristics and most prevalent phenotypes of severe asthma, to evaluate the selection criteria for receiving biologic therapies approved for this disease, and to estimate resource consumption. In addition, taking advantage of the incorporation of digital technology and new data collection sources, which allow for reuse of information stored in electronic medical records (big data) [19,20], another objective was to incorporate and use one of these tools in this study (Savana).
The big data concept refers to the processing of large volumes of data by developing mathematical algorithms, in order to establish relationships between data (structured, unstructured and semi-structured) and to determine behavioral patterns that predict trends for improving decision-making. Analysis of big data using traditional methods would take too long and would be very expensive to upload them to a relational database for analysis, and few studies have analyzed this technology in patients with asthma [19-26]. Savana is able to analyze and interpret the plain free text contained in electronic medical records, regardless of the electronic system in which they operate, in order to conduct predictive analyses without the use of classical statistical methods, and to compare them with the descriptive analysis of prevalence and the prospective analysis of the course of patients in the first part of the study, which will be considered the gold standard against which the tool will be compared.

A Scientific Committee consisting of four pulmonologists, two allergists and an epidemiologist has been formed for preparing and advising about the study. This study will be conducted in accordance with the criteria established in Order SAS/3470/2009 of 16 December, establishing the guidelines for post-authorisation observational studies with medicinal products for human use [Notification/submission to the responsible regulatory authorities, Ethics Committees (CREC) and/or Competent Authorities (CA)] will be done as stipulated by Spanish law (Order SAS/3470/2009 for observational studies). The study will be conducted in accordance with the protocol and standard operating procedures (SOPs) that ensure compliance with Good Clinical Practice (GCP) guidelines as described in the ICH Good Clinical Practice
guidelines (1996) [27]. To maintain patient confidentiality, demographic data that could identify the patient (initials, date of birth) will not be collected.

Methodology

Design

The PAGE study is designed as a multicenter, non-experimental, observational study, cross-sectional in a first phase, and prospective in a second phase, controlled, population-based, with a 2-stage subject selection by random sampling. The research will be conducted at 40 national hospitals (Figure 1), according to a criterion of convenience, which assumes geographic representativeness in Spain.

Study objectives:

Study objectives are defined in table 1.

Selection of participants:

First stage, population random sampling. The principal investigator (PI) at each site will create an internal confidential list of all patients diagnosed with asthma at their site through the diagnostic coding systems of their hospital. Patients will be identified with a consecutive number known only by the investigator, who will provide the total number of patients included to the person responsible for statistical analysis. The statistician will provide then, a list of 80 random numbers per site. Each investigator, in the order established in the randomized list, will diagnose consecutively the severity of asthma (mild-moderate or severe) in the electronic case report form (eCRF) of 40 patients in order to respond to the prevalence of severe asthma.
Second stage, random sampling. From the list of 40 patients in the previous phase, after a new randomisation, 12 patients per site will be selected, who will be classified into two cohorts in a 2 to 1 ratio with regard to severity (severe asthma, non-severe asthma).

Cohort A. Patients with severe asthma who meet the inclusion criteria and none of the exclusion criteria.

Cohort B. Patients with non-severe asthma who meet the inclusion criteria and none of the exclusion criteria.

In both cohorts, individuals who refuse to participate in the follow-up phase will be replaced by the following patient in the randomisation list until the required sample size is achieved.

The data of each patient, including demographic data, asthma characteristics, comorbidities, treatment and laboratory tests, as recorded in the patient’s medical record (source document), will be recorded in the eCRF. No patient identifiable information will be collected; a unique patient number will be automatically assigned by the eCRF once the investigator or designated authorised person creates the patient file.

Eligibility criteria

Inclusion criteria:

Cohort A: Patients diagnosed with severe asthma according to GINA and ATS/ERS criteria, aged ≥18 years, who sign the relevant informed consent.

Cohort B: Patients with non-severe asthma according to GINA criteria, aged ≥18 years, who sign the relevant informed consent.

Both groups of patients will be recruited over a period of 3 months. A subsequent follow-up of 12 months will be performed, according to standard
clinical practice (second phase), collecting information at 3 visits (baseline, 6 and 12 months).

**Sample size**

For the primary objective, to assess the prevalence of patients with severe asthma treated in the allergy and pneumology units of Spanish hospitals, considering a maximum inaccuracy estimate of 2% in the prevalence of severe asthma, an asymptotic two-sided 95% confidence interval, and assuming a 20% prevalence of severe asthma and an average of 40 diagnoses per site, it is necessary to diagnose 1600 asthmatic patients. The prevalence of severe asthma below the expected value, will provide lower values of inaccuracy. For the secondary objectives, a total sample of 320 patients with severe asthma guarantees a maximum inaccuracy of 5% in the estimation of the percentages derived from the binary variables, provided that these are less than 30%, which implies a minimum of 8 patients with severe asthma per site. Cohort B includes 160 patients with non-severe asthma, representing an average of 4 patients per site.

**Data collection**

Primary and secondary data will be collected during 3 visits (baseline, 6 and 12 months). The source documents and medical records containing sociodemographic and clinical data, diagnosis, treatment and laboratory tests, and medical records and data provided directly by the patients during each visit will be recorded. The Patient Reported Outcomes (PROs) will be completed by paper questionnaires and recorded by the investigators in the eCRF specially designed for the study, located at (https://ines.emea.research.quintilesims.com/MR/adm/), using a 128-bit SSL
protocol for web communication, which ensures confidentiality between the servers and the investigator's computer, encrypting all the results sent and will be the source of information from which the data obtained from the study will be analyzed.

The data included in the medical record are protected by the Personal Data Protection Act [., so they will be anonymized at each site by the person responsible for the information before being sent to Savana. In addition, Savana has a specific data processing that includes adding false information in each patient, in order to be able to reuse clinical information without conflicting with the necessary data privacy [29].

**Variables and procedures**

After agreeing to participate in the study and signing the informed consent, follow-up and collection of variables and study procedures will be performed at 3 visits (baseline, 6 and 12 months) according to standard clinical practice and without any therapeutic intervention. Variables related to data from participating hospitals and study subjects will be collected.

At the baseline visit, sociodemographic and background data will be collected; age, ethnic group (Caucasian/Latin/African/Asian/Other/Unknown), educational level, occupational status, housing, smoking, physical examination, body mass index (BMI), diagnosis of respiratory diseases, asthma severity (table 2), age at asthma onset, associated comorbidities, allergies, clinically relevant exacerbations in the previous year and current treatment, score on asthma control test (ACT)[29], follow-up laboratory tests, spirometry, bronchodilator test, complete blood count, basic biochemistry with IgE levels, and coagulation laboratory parameters. A health-related quality of life questionnaire will be
administered at each visit, the Saint George’s Respiratory Questionnaire (SGRQ) [30,31], ACT [29], and Morisky-Green treatment adherence questionnaire [32]. Spirometry will be performed with a bronchodilator test according to American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations [33], using the reference values for the Mediterranean population [34]. Slow and forced maneuvers will be repeated 15-30 minutes after inhalation of 400 μg albuterol, considering a positive bronchodilator test when an increase in FVC or FEV1 greater than 200 mL and greater than 12% from baseline is recorded. The measurement of fractional exhaled nitric oxide (FeNO) will be perform with the equipment of each site before spirometry and bronchodilator test, following the ATS/ERS guidelines [35].

In addition, data will be collected on eosinophilia in sputum, if performed (otherwise in blood), and skin test results in patients for whom this data and healthcare resource utilization were available, assessed using the information collected at each study visit over the previous 6 months. Direct costs: a) number of scheduled visits (primary care, allergy, pulmonology, other specialist); b) number of unscheduled visits and reason for the visit; c) number of emergency room visits related to asthma; d) number of tests performed due to severe asthma (pulmonary function, biomarkers, laboratory tests, chest X-ray or CT); e) hospital admissions to ward or Intensive Care Unit (ICU) for asthma-related reasons in the past 6 months; d) referrals to other specialists. Indirect costs: total number of work days lost due to asthma in the past 6 months.

**Statistical analysis**

Primary objective:
Meta binary variable analysis (prevalence) according to a fixed effect model with inverse variance weighting. In case of heterogeneity, a random effects model will be used. In case of significant heterogeneity and I-square >50%, exploratory post hoc analysis of subgroups or meta regression will be done according to the characteristics of the sites.

Secondary objectives:

Univariate and standard bivariate descriptive analysis will be performed for categorical, binary, or continuous variables; relative frequencies and mean 95% CI estimates; Student’s t and Wilcoxon tests for comparisons of two means; Z-test for comparing two proportions; chi-square test to check the independence of qualitative variables, as well as logistic binary multiple regression models to identify differential factors related to the diagnosis of severe asthma; and mixed models for longitudinal data analysis. Descriptive measures of prediction reliability will also be performed: specificity, sensitivity, predictive values for positive and negative values; probability ratios and logistic binary multiple regression models to check for relevant factors related to the prediction of clinical events.

To analyze the substudy objectives, it will be determined whether the point of prevalence estimated by the tool Savana is included in the 95% CI of the prevalence provided by monitoring. Formal comparisons will be made between tool and clinician predictions. Descriptive measures of prediction reliability will be used: specificity of sensitivity, predictive values for positive and negative results, and probability ratios, as compared to clinical prediction regarding the clinical course of patients with severe asthma.
In general, a 5% significance level and two-sided tests will be considered. There will be no special considerations for other types of data. There will be no transformation of variables. There will be no new variables created by transformations as this is not a confirmatory study, but a descriptive and hypothesis-generating study. There will be no intermediate analysis. Global alpha adjustments are not expected by multiple comparisons or subgroup analysis.

**Implications for PAGE study design**

Based on the primary objective of determining the prevalence of severe asthma in allergy and pneumology units using population and random sampling to assess the objectives of the substudy, anonymized data will be collected from the 40 participating sites to obtain the prevalence and prediction of the course of patients with severe asthma, which will be compared to the results obtained in the prospective study. Savana has developed a free text analysis tool (as natural language) capable of meaningful interpretation of the content included in electronic medical records, regardless of the electronic system in which they operate as long as they are available in free text. The program allows for reusing the information included in the electronic medical records so that a randomized sample of patients from the site is not required, as all patients with the inclusion criteria will be detected and included in the study. When large numbers of patients are available, more appropriate techniques will be applied to big data processing. All available data will be used to generate the model that best represents patient outcome. The population will be separated into a training sample and a validation sample to avoid over-training of the model. The model will combine a set of artificial intelligence techniques, which cannot be
defined in advance but will combine from machine learning techniques (machine learning) to deep learning [36-43]. Deep and/or recurrent neuronal networks may be used as a guide.

The system is based on processing of a large amount of information (big data), so the impact of random errors is minimized. In the clinical area, it is used as a support tool and aids in medical decision-making. The development of this new technology has been possible and has run in parallel to progressive electronic medical record implementation in our country.

Discussion

Asthma is a common disease, frequent across all ages, and with a prevalence of approximately 5% to 10% in Western countries [4,7]. However, the prevalence of patients with severe asthma is poorly understood, perhaps due to limited consensus in the international community to define severity, which has limited study results. Asthma severity is known to have a disproportionate effect on both quality of life and costs associated with its treatment [44-49].

Epidemiological studies based on postal surveys have shown that the proportion of patients with severe asthma ranges from 18% to 29% of patients with asthma [50-54]. These estimates are potentially partial because patients with more severe disease may be more likely to participate in epidemiologic studies involving respiratory disease. Results from previous studies suggest that people with severe asthma represent the largest health economic burden due to increased risk of hospitalizations, emergency department visits, loss of lung function, and low quality of life [45,46]. Therefore, it is recommended that this vulnerable group of patients be evaluated and treated by respiratory specialists, but it is unclear whether this recommendation is followed. Although
Asthma is a clinical diagnosis made by physicians based on the typical symptoms and clinical examination, many of these prevalence studies have been conducted with postal or telephone surveys completed by patients or using prescription databases.

In the recent European Respiratory Society American Thoracic Society guidelines [17], the definition of severe asthma was unified in order to adequately classify this type of patients and prevent the heterogeneity of definitions existing to date. In Spain, there is only one study in adults that analyses the prevalence of severe asthma seen in the pulmonology and allergy departments, estimating it to be 3.9% [8]. The data available in the pediatric population estimates the prevalence of severe asthma to be 8.8% [7]. All these studies have their limitations; they define asthma severity based on clinical criteria and control different from GINA recommendations, since their design was before 2006, which is when GINA publishes the criteria for good asthma control; and the definition of severe asthma was different from that proposed by the ATS/ERS consensus, since the study design was prior to it. In our study, patient selection was carried out by searching the computer systems of each hospital based on key words that included the word asthma or the coding of admission diagnoses in the diagnosis section. The search was general, not limited to allergy or pulmonology departments. The selection period of the search covered from the first computer records to the start of the study. Therefore, patient randomization was very robust, avoiding selection bias, in order to optimize the prevalence of patients with severe asthma.

The quality of the data obtained in other prevalence studies is also questionable, since most studies involving a very large population sample are
based on postal or telephone surveys, not confirming the diagnosis of asthma with objective measures [10,55]. In our study, in the first part of the study analyzing the prevalence of patients with severe asthma, we subsequently verified in the medical record the severity of the patients according to the ATS/ERS consensus criteria [17], to define patients with severe asthma. In addition, in a second phase, 8 patients with severe asthma and 4 patients with “non-severe” asthma per site were selected to follow-up and analyze the secondary objectives of the study. For this reason, we believe that our study has a robust design in terms of avoiding patient selection bias and in the quality of the data provided.

Another potential disadvantage of other prevalence studies is that they have a cross-sectional design, so they only provide a snapshot of the different symptoms and signs of severity and their degree of overlap, without determining the dynamics of the disease and aging. However, although patients may enter and exit the “severity phenotypes” defined over time, the overall prevalence of severity in the population is unlikely to change. Therefore, in our study, a sample of patients initially analyzed was followed up for one year.

**Study limitations**

Although this is a prospective study with three follow-up visits, some of the study variables were collected by review of the medical record, such as the use of resources for asthma, so the absence of some data may provide information and recall biases that may interfere with the results, though most of them may be verified. The limitation of the retrospective part of a study may be reduced in this case as the sample is randomly selected per site. In addition, there is likely to be heterogeneity related to how each site determines the list of all its
asthmatic patients and the source (database) from which this list comes from. As well, it can be found that patients forgot to complete the health-related quality of life (HRQoL) questionnaires, or asthma control test (ACT), which could interfere with the results related to these variables. However, our study is the first one, in our country, to examine the contributions of large-scale asthma data analysis (big data) in Spain at this scale. This section is part of a substudy to analyze the reliability and feasibility of big data using as a comparator (gold standard) conventional analysis of the patient sample followed for one year. This will be done using a computer program specifically designed for medical data analysis called Savana. Twenty of the sites participating in the study will install this software, which performs a comprehensive analysis of all medical records entered into the electronic medical record system. Based on search criteria, Savana is intended to be able to provide the prevalence of patients with asthma, the prevalence by severity, and its results are correlated to the secondary objectives of the study.

In conclusion, our study design is robust in order to avoid bias and allow the prevalence of patients with severe asthma in Spanish hospitals to be established. It is the first to incorporate new tools that may help in routine clinical practice and research, such as big data analysis software, and to evaluate its reliability and efficiency.

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**Conflict of interest**

MGSH and DBC are employees of GSK. CA has no relevant interests to disclosure. CM has no relevant interests to disclosure. SQ has no relevant
interests to disclosure. FJAG has no relevant interests to disclosure. VC has no relevant interests to disclosure. JS has no relevant interests to disclosure. CAS has participated in speaking activities, advisory committees and consultancies during the period 2015-2019 sponsored by: AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, ALK Mundipharma, Novartis, Pfizer, SEPAR and NEUMOMADRID. CAS declares not receiving ever, directly or indirectly, funding from the tobacco industry or its affiliates.

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References


Figure. Study Design

**SELECTION PHASE**
1. IPs generate an internal list of all asthma patients seen in their sites since there is electronic medical record encoded by diagnosis
2. Patients must be codified with a consecutive number
3. The list will be sent to the study statistician
4. Each PI will receive a randomized list of asthma patients
5. PIs will include patients consecutively in each cohort who fulfill the eligibility criteria once the patient signs the informed consent

**COHORT A**
Severe Asthma patients

**COHORT B**
Non-severe asthma patients

**BASELINE VISIT**
Informed consent
Screen potential participants by inclusion and exclusion criteria, obtain history, document.
Sociodemographic variables
Asthma variables
Treatment and management
Questionnaires:
- Morisky-Green
- ACT
- SGRQ

**VISIT AT 6 MONTHS**
Asthma variables
Treatment and management
Questionnaires:
- Morisky-Green
- ACT
- SGRQ

**VISIT AT 12 MONTHS**
Asthma variables
Treatment and management
Questionnaires:
- Morisky-Green
- ACT
- SGRQ
Table 1. PAGE Study Objectives

Primary
To estimate the prevalence of patients with severe asthma seen in the outpatient clinics of allergy and pneumology departments of Spanish hospitals.

Secondary
1. To describe the sociodemographic and clinical characteristics of patients with severe asthma and compare them to patients with non-severe asthma (except drug treatment).
2. To estimate the prevalence of the different phenotypes of severe asthma.
3. To describe patients who meet the eligibility criteria for biologic therapy for severe asthma.
4. To assess the course of patients with severe asthma as compared to patients with non-severe asthma at 6 and 12 months.
5. To assess the impact of severe asthma compared to non-severe asthma on patients in terms of health-related quality of life (HRQoL).
6. To measure the use of healthcare resources in patients with severe asthma in terms of direct and indirect resources and compare them to patients with non-severe asthma.
7. To establish a prediction of the course of patients with severe and non-severe asthma at 6 and 12 months, based on the experience and knowledge of the investigator, and to compare the results with monitoring (secondary objective 5).
8. To establish the determinants used by clinicians to establish predictions of patient outcome (objective 8).
Substudy Objectives

Substudy Objectives: The substudy will compare the results obtained using this software installed at 20 sites with the results obtained by the traditional observational study. There will be a descriptive use (substudy objective 1) and a predictive use of the tool (substudy objectives 2 and 3). The substudy objectives to be measured are:

1. To verify if the prevalence of severe asthma calculated from the aggregate information collected through this specific software is similar to the prevalence of severe asthma obtained in the observational study through monitoring, which will be the gold standard for this comparison.

2. To compare the prediction of the course of patients at 6 and 12 months based on collection of aggregate information collected in the 5 years prior to the study with the prediction made by the clinician of this same course. This will only provide descriptive information; no formal comparisons will be made between the prediction of the clinician and the tool.

3. To compare the prediction of the tool on the course of patients with severe asthma at 6 and 12 months with the results obtained by monitoring in the observational study. The gold standard will be the information collected by monitoring. The tool will be compared to “real data”. Further details on secondary objective comparisons can be found in Section 5 “Considerations for Statistical Analysis”.

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### Table 2. GINA Classification of Asthma Severity

<table>
<thead>
<tr>
<th>STEP</th>
<th>Symptoms/Day</th>
<th>Symptoms/Night</th>
<th>PEF or FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>PEF variability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>Intermittent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 1 time a week</td>
<td>&lt;/= 2 times a</td>
<td>&gt;/= 80%</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic and</td>
<td>month</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>normal PEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>between attacks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Mild Persistent</td>
<td>&gt; 2 times a</td>
<td>&gt;/= 80%</td>
<td>20-30%</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 time a week but</td>
<td>month</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 1 time a day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Attacks may affect</td>
<td>&gt; 2 times a</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>activity</td>
<td>month</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Moderate Persistent</td>
<td>Daily</td>
<td>&gt; 1 time a week</td>
<td>60%-80%</td>
</tr>
<tr>
<td></td>
<td>Attacks affect</td>
<td>&gt; 1 time a</td>
<td></td>
<td>&gt; 30%</td>
</tr>
<tr>
<td></td>
<td>activity</td>
<td>week</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Severe Persistent</td>
<td>Continuous</td>
<td>Frequent</td>
<td>&lt;= 60%</td>
</tr>
<tr>
<td></td>
<td>Limited physical</td>
<td></td>
<td></td>
<td>&gt; 30%</td>
</tr>
<tr>
<td></td>
<td>activity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PEF, Peak Expiratory Flow; FEV<sub>1</sub>, Forced Expiratory Volume in the first second.

- The presence of one of the features of severity is sufficient to place a patient in that category.
- Patients at any level of severity—even intermittent asthma—can have severe attacks.