NCT06811155 STUDY PROTOCOL

PROTOCOL CODE	
FULL TITLE	*Non-Interventional, descriptive, cross-sectional and unicentric study to describe the clinical management in asthmatic patients attended in the influential area of Hospital Universitario Virgen de la Victoria, Málaga*
ABBREVIATED TITLE	
FINAL PROTOCOL APPROVED	
SPONSORSHIP	Hospital Universitario Virgen de la Victoria, Málaga.
CONTRIBUTING AUTHORS	

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PROTOCOL SYNOPSIS

Protocol Code	
Abbreviated Title	
Rationale	Asthma is a heterogenic chronic disease that affects more than 300 million people worldwide, which it's characterized by acute symptomatic episodes of varying severity, including intermittently inflammation and narrowing of the airways in the lungs. The prevalence in Spain it is estimated to be around 5%, according to the European Community Respiratory Survey (ECRHS) and seems to be increased due to a higher rate of asthma diagnosis[1]. In this condition there's substantial proportion of patients with a poor disease control, which conducts to an important negative impact in their health-related quality of life (HRQoL) and the need to use health care resources[3,4]. During the past decades multiple clinical practice guidelines, such as the international Global Initiative for Asthma (GINA) and national guidelines as Guía Española para el Manejo del Asma (GEMA) have been launched with the aim of improving quality of care in patients with asthma and reduce the high public burden associated to this disease. However, several studies have concluded that high proportion of patients remain uncontrolled[10], being in Spain estimated around 50%[12], and there's direct evidence of poor adherence to the guideline's recommendations for asthma management[3]. In terms of costs, it's estimated that around 70% of total disease cost is determined to this poor control and management[14]. An adequately disease management according to guideline's recommendations would result in a better disease control and a reduction of associated costs[15, 16, 17].
Objectives (Primary, Secondary)	**Primary objective:** 1. Describe the clinical management in asthmatic patients in the influential area of Hospital Universitario Virgen de la Victoria according to the assistance quality indicators established by GEMA guidelines (Appendix 1), which are the following: • Diagnostic confirmation by spirometry with test bronchodilator. The diagnostic confirmation of the patients with asthma is done with spirometry and bronchodilator test as an objective measure of functional impairment.

	• Sensitization study in allergic asthma. To patients with suspicion of allergic asthma should be performed a study of possible sensitization to different allergens. • Smoking cessation. It is recommended smoking cessation to smokers with asthma. • Educational plan in patients with asthma. Patients with asthma must follow a basic education program (formed by: knowledge about their illness, about their treatment, action plan and inhalation technique, documented in writing) as part of their treatment. • Treatment of choice in persistent asthma. The treatment of choice in persistent asthma includes inhaled glucocorticoid (IGC) used daily. In some justified cases, alternative treatment with leukotriene receptor antagonists can be considered. • Asthma treatment in pregnant women. In asthma maintenance treatment in pregnant woman is recommended to keep the commonly used drugs (agonists β2-adrenergic and inhaled glucocorticoids). • Periodic follow-up of patients. Necessity to make periodic monitoring of patients, even if they have not suffered exacerbations, through scheduled medical visits. • Periodic record of exacerbations. The specific assessment of exacerbations is evaluated periodically. **Secondary objectives:** 1. To describe the sociodemographic and clinical characteristics of the study population. 2. To describe the treatment patterns (maintenance treatment, reliever treatment, type of treatment) during the last year. 3. To describe the disease control level in the study population. 4. To describe the use of resources (emergency visit, Primary care visits, specialist visits) during the last year. 5. To describe the number of patients with discontinuation of SABA within the last year and the potential impact on disease control level and use of resources. For descriptive purposes, an analysis of the objectives will be made based on the

	level of disease control.
Study Design	Cross-sectional cohort, non-interventional, descriptive and unicentric
Study Population and Sampling Methods	It is planned that a total of 300 patients with asthma will be included in the study. - Target enrollment/ sample size: 300 patients approximately. - Anticipated rate of enrollment: 6 months. - Estimated study start date: September - Estimated study completion date: March
Data Source	Patient's electronical medical chart
Data Analysis Methods	Data analysis will be performed using SAS Enterprise Guide Version 7.1 and a statistical analysis plan will be designed and agreed before the data analysis initiation. All the analyzes will be performed by descriptive statistical methods of all the variables separately. The quantitative data will be described by the following statistical parameters: number of valid patients (N valid), number of missing data (N missing), mean, SD, median, minimum, maximum and according to the distribution of the analyzed variable, quartiles will also be presented (percentiles 25 and 75). The qualitative data will be presented through the length-frequency distributions (absolute and relative). For both cases, the following will be specified: number of observations (N) and number of missing data (N missing).
Sample Size and Power	In order to estimate a proportion of 50% (maximum variability), with a margin of error of +/- 6 percentage points and a confidence level of 95%, a sample size 267 patients will be required. Assuming 10% of patients with non-available data from the medical records, total sample size must be 300 patients. The study sample size must allow the estimation of dichotomic variables and to determine the percentage of compliance of each quality care indicator established by the GEMA guidelines. This percentage will allow to establish the degree of compliance of each group of indicators in the site.
Limitations	Cross-sectional study, missing data in clinical records

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ABBREVIATIONS

ACT	Asthma Control Test
BMI	Body Mass Index
DMP	Data Management Plan
ED	Emergency Department
ECRHS	European Community Respiratory Survey
eCRF	Electronic Case Report Form
GCP	Good Clinial Practice
GDPR	General Data Protection Regulation
GEMA	Guía Española para el Manejo del Asma
GINA	Global Initiative for Astma
HRQoL	Health-Related Quality of Life
IC	Informed Consent
ICH	International Conference on Harmonisation
IEC	International Ethics Committee
IGC	Inhaled glucocorticoid
IRB	International Review Board
OCS	Oral Corticoids
PBD	Post Bronchodilator
SAP	Statistical Analysis Plan

1. INTRODUCTION/BACKGROUND

Asthma is a heterogenic chronic disease characterized by acute symptomatic episodes of varying severity, including intermittently inflammation and narrowing of the airways in the lungs. The prevalence of this disease is high as affects more than 300 million people worldwide, which varies by country. In Spain, the prevalence it is estimated to be around 5%, ranged between 1% in Huelva and 4,7% in Albacete, according with the European Community Respiratory Survey (ECRHS), and seems to be increased due to a higher rate of asthma diagnosis[1].

It's important to note that in this condition there is a substantial proportion of patients with inadequate control of their disease, which conducts to a higher morbidity and mortality[2]. The poor disease control is associated to an important negative impact in patient's health-related quality of life (HRQoL), causing them daily activity impairment, loss of work productivity and the need of using unscheduled doctor visits and hospital services[3, 4]. The direct and indirect costs in patients with a poor disease control represents an important proportion of the total cost of asthma, which it's estimated to be around 1-2% of the total public healthcare resources in developed countries, especially in patients with severe-persistent asthma[4, 5].

The facts previously exposed turns this disease into a major public health problem due to its high prevalence within all age and sex groups and the high proportion of uncontrolled patients, which causes a high health burden to the National Health System, and which affects directly on the affected patients, as well as their families and the society[6].

For this reason, during the past decades multiple clinical practice guidelines have been designed to improve the quality of care in patients with asthma and to reduce the high public burden associated to this disease[7]. International guidelines such as the Global Initiative for Asthma (GINA) and national guidelines as Guía Española para el Manejo del Asma (GEMA) in Spain, both of them stating that a good disease control can be achieved by most of asthma

patients, were launched to increase the technical training of health professionals in order to reach a better disease management and conduct to a better quality of life in these patients [8, 9].

Specifically, GEMA guidelines also includes a tool to assess the level of assistance quality care through 8 indicators covering 4 dimensions: diagnose, non-pharmacological treatment, pharmacological treatment, monitoring.

However, since guidelines have been launched, there's still evidence of high proportion of patients with poorly disease control and large impact in patient's health-related quality of life[10]. Despite the availability of therapeutic recommendations through guidelines, clinical studies have shown that there's poor adherence to guidelines goals[3]. The Asthma Insight and Reality surveys, which were performed in several regions worldwide, concluded that all participating countries didn't met GINA goals. Specifically, in Central and Eastern Europe, the results showed a high proportion of asthma population who described physical activity limitations (68,2%) and acute symptoms during the previous 4 weeks (74%). Regarding disease monitoring, it' important to note that the results demonstrated that a 36,2% of asthmatic patients had never performed a lung function test[11]. A recent study conducted in Spain and Italy also evidenced a generally poor disease control, with around 50% of participant patients being considered uncontrolled[12], and that strategies were needed to improve the management of this disease as it was concluded in a study performed in Spain to assess the disease control according to GINA criteria[13].

In terms of costs, it's estimated that around 70% of the total cost of the disease is determined by this poor control and management[14]. An adequately disease management based in a higher use of preventive anti-inflammatory medication, a better education in asthma patients and an accurately follow of the recommendations of guidelines would result in a greater disease control and in a reduction of associated costs[15, 16, 17].

This evidence raises the need to determine the assistance quality care in asthma population in the influential area of Hospital Universitario Virgen de la Victoria through the assistance quality

care indicators established by GEMA guidelines. The aim of this study is to obtain clinical data that allow to assess assistance quality degree in order to find improvement opportunities to achieve a better control of asthmatic patients within this influential area.

2. OBJECTIVES

2.1. Primary objective:

- To describe the clinical management in asthmatic patients in the influential area of Hospital Universitario Virgen de la Victoria according to the assistant quality indicators established by GEMA guidelines (Appendix 1), which are the following:
    - Diagnostic confirmation by spirometry with test bronchodilator. The diagnostic confirmation of the patients with asthma is done with spirometry and bronchodilator test as an objective measure of functional impairment.
    - Sensitization study in allergic asthma. To patients with suspicion of allergic asthma should be performed a study of possible sensitization to different allergens.
    - Smoking cessation. It is recommended smoking cessation to smokers with asthma.
    - Educational plan in patients with asthma. Patients with asthma must follow a basic education program (formed by: knowledge about their illness, about their treatment, action plan and inhalation technique, documented in writing) as part of their treatment.
    - Treatment of choice in persistent asthma. The treatment of choice in persistent asthma includes inhaled glucocorticoid (IGC) used daily. In some justified cases, alternative treatment with leukotriene receptor antagonists can be considered.
    - Asthma treatment in pregnant women. In asthma maintenance treatment in pregnant woman is recommended to keep the commonly used drugs (agonists β2-adrenergic and inhaled glucocorticoids).
    - Periodic follow-up of patients. Necessity to make periodic monitoring of patients, even if they have not suffered exacerbations, through scheduled medical visits.

- Periodic record of exacerbations. The specific assessment of exacerbations is evaluated periodically.

2.2. Secondary objectives:

- To describe the sociodemographic and clinical characteristics of the study population.
- To describe the treatment patterns (maintenance treatment, reliever treatment, type of treatment) during the last year.
- To describe the disease control level in the study population.
- To describe the use of resources (emergency visit, Primary care visits, specialist visits) during the last year.
- To describe the number of patients with discontinuation of SABA within the last year and the potential impact on disease control level and use of resources.

For descriptive purposes, an analysis of the objectives will be made based on the level of disease control.

3. RESEARCH METHODOLOGY

3.1. Study Design

A non-Interventional, descriptive, cross-sectional and unicentric study, has been designed and will be conducted in a Spanish hospital of Málaga. The design of the study imposes an only visit to be performed to obtain the patient's signed IC and after signing it (if patient agreed to participate in the study), to perform an Asthma Control Test (ACT) (Appendix 2). Except for this study visit, the rest of study will be based on electronic medical chart review of approximately 300 asthma patients belonging the influential area of Hospital Universitario Virgen de la Victoria. This chart review will be performed by the site investigator or collaborators.

The data collection is stated in 6 months, and during this period the investigators will identify and randomly include the patients who meet selection criteria to avoid bias during patient's

inclusion. The observational period will be conformed of 12 months, and the patient's data will be collected or documented in an electronic case report form (eCRF), which will automatically create or assign an identification numerical code to every patient the moment it's created in the electronic platform. This system guarantees the anonymization of each patient included in the study as no identifiable information won't be able to be captured.

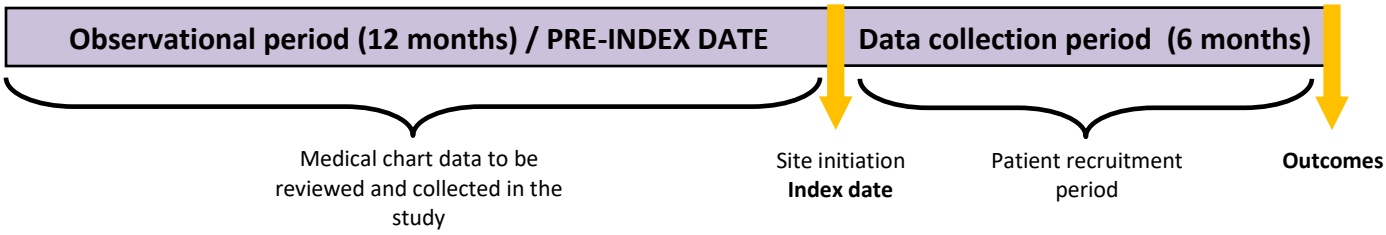

Figure 1. Overall Study design

3.2. Study Population

The study will be performed in Hospital Virgen de la Victoria, which it's the reference hospital that usually attends the asthma population of its influential area. Only patients that meet the eligibility criteria will be included in the study, and it is planned that a total estimation of 300 patients with asthma diagnose will be included in it. The whole patients will be recruited by the site investigator and collaborators, who will conduct the subject's medical chart review. Before the patient's study inclusion, the investigator team must have been obtained the signed informed consent (appendix 3) of each patient recruited and according to ICH GCP and to local legal requirements.

- Target enrollment/ sample size: 300 patients.
- Anticipated rate of enrollment: 6 months.
- Estimated study start date: September 2020
- Estimated study completion date: March 2020.

3.2.1. Eligibility Criteria

All the inclusion and exclusion criteria will be reviewed by the site investigator and collaborators to ensure that the patient is eligible to be included in the study. In order to be eligible to participate in this study, prior to the inclusion, every subject must meet the following selection criteria:

3.2.1.1. Inclusion Criteria

1. Patient with written informed consent prior to participation.
2. Patient female or male ≥ 18 years of age
3. Patient with asthma diagnosis more than one year before the study inclusion
4. Clinical data available at least 1 year before the study inclusion in the electronic medical records.

3.2.1.2. Exclusion Criteria

1. Patient's participation in any clinical trial during the year prior to the index date for data collection.

3.2.2. Sampling

An estimation of 300 asthma patients belonging to the influential area of the Hospital Universitario Virgen de la Victoria will be enrolled.

3.3. Data Source / Data Collection

The data source represents the information contained in original electronic medical documents and records (source documents) that will be necessary for the study. Primary and secondary endpoints will be collected from the patient's source documents, which will be the subject's medical chart. All the study data must be obtained from the source documents.

During the 6 months of data collection period, the study variable will be gathered in an electronic case report form (eCRF), especially designed for the study and where each investigator will access through a personal user account, which will be created once the investigator assigns a personal password during the first access to the eCRF. Is responsibility of the investigator to collect all the study variables in the eCRF, from which the study data will be analyzed.

Given the possible unavailability of certain variables, there will be the possibility in the eCRF to select the unavailability of the variables in the medical records. In order to avoid missing and/or mistaken data, it will include filters and programmable edits that will give feedback when data is missing, out or range or illogical. A data management plan (DMP) will be developed to describe all processes and specifications for data handling.

The investigator/institution will facilitate study-related monitoring, audits, IRB/IEC reviews and regulatory inspection(s), providing direct access to all related source data and source documents.

3.3.1. Endpoints

3.3.1.1. Primary Endpoint

1. The primary endpoint of this study is the asthma management of the study population according to GEMA healthcare quality indicators previously defined. For this assessment, it will be determined the following calculations:

    I. Percentage of asthmatic patients diagnosed using spirometry and bronchodilator (PBD) test.
    II. Percentage of patients with a diagnosed history of suspected allergic asthma included in a sensitization study with different allergens.
    III. Percentage of asthmatic smokers with documented recommendations for smoking cessation.

IV. Percentage of patients included in an educational plan.
V. Percentage of patients in treatment for persistent asthma* receiving inhaled glucocorticoids (ICS).
VI. Percentage of pregnant women (if applicable) with asthma who maintain their treatment plan based on B2-adrenergic agonists and inhaled corticosteroids among the total pregnant asthmatic women recruited in the study.
VII. Percentage of scheduled monitoring visits per patient and per year during the previous year among asthmatic patients with asthma monitored per year.
VIII. Percentage of asthmatic patients with evaluation and documentation of exacerbations.

** Persistent asthma can have asthma symptoms on more than 2 days per week and nighttime awakenings once or twice each month.*

3.3.1.2. Secondary Endpoint(s)

- Demographic characteristics.
  - Age
  - Gender: male, female.
  - Ethnicity: Caucasian / Hispanic / African / Asian / Other / Unkown
  - Weight (kg) and height (cm): BMI autocalculated by the eCRF.
  - Pregnancy status (yes/no)
  - Smoking status (current smoker, ex-smoker*, non-smoker)

    **It will be considered that the patient is ex-smoker since the 6 months of non-smoking.*

- Clinical characteristics:
  - Age at asthma diagnosis
  - Spirometry and bronchodilator test at diagnose
  - Patient's derivation: primary care / specialized healthcare

- Asthma severity degree according to GEMA guidelines: Mild intermittent, Mild persistent, Moderate persistent and Severe persistent.
- Asthma disease control level according to:
    - Clinical criteria (number of SABA canisters retired from the pharmacy in the previous year, number of OCS retired from the pharmacy in the previous year, number of emergency service visits in the previous year, number of unscheduled primary care visits in the previous year).
    - Asthma Control Test (ACT) (most recent value available): No / Yes, specify score: ACT ≥ 20 points (controlled) / ACT less than 20 uncontrolled.
- History of allergic asthma (or suspected): No / Yes.
- Sensitization to allergen study (for those patients with a diagnosed history of suspected allergic asthma).
- Registration of asthma education programs performed (last asthma education program performed by the patient): year when it was performed.
- Current asthma therapeutic level according to GEMA stepwise therapy (at patient's inclusion date): Step 1 / Step 2 / Step 3 / Step 4 / Step 5 / Step 6.
- Comorbidities (at patient's inclusion date) according to Charlson Comorbidity Index (autocalculated). A list of diseases will be displayed in order to be selected those the patient suffers at the inclusion date. The Charlson Comorbidity index score will be autocalculated automatically by the eCRF.
- Maintenance/long-term and reliever treatment prescribed for asthma (at inclusion date): type (SABA, LABA, GCI, LTRA, Biologic, immunomodulator, others), initiation date, end date or if its ongoing. Maintenance/long-term and reliever treatment prescribed for asthma in pregnant women (at inclusion date): type (SABA, LABA, GCI, LTRA,

Biologic, immunomodulator, others), initiation date and end date or if its ongoing.

- Record of scheduled monitoring asthma visits in the last year (the year prior since the patient's inclusion date): register confirmation and number of scheduled visits performed.
- History of asthma exacerbations during the last year (the year prior since the patient's inclusion date): register confirmation and number of asthma exacerbations.
- Use of health resources during the last year (the year prior since the patient's inclusion date): visits to emergency department (ED), visits to primary health care department, visits to specialist.
    - Nº of emergency department (ED) and hospitalization visits related to an asthma diagnosis code in the last year since the date of study inclusion.
        - Treatment prescribed at discharge: type (SABA, OCS, LABA, GCI, LTRA, Biologic, immunomodulator, others).
    - Nº of primary health care department visits related to an asthma diagnosis performed during the last year since the date of study inclusion (scheduled and unexpected),
    - Nº of specialist (allergology, physiotherapy, others) visits related to an asthma diagnosis performed during the last year since the date of study inclusion.

- Nº of oral corticosteroids (OCS) prescriptions in the last year (prior year since the patient's inclusion date).

3.4. Sample Size / Power Calculations

To estimate a proportion of 50% (maximum variability), with a margin of error of +/- 6 percentage points and a confidence level of 95%, a sample size 267 patients will be required.

Assuming 10% of patients with non-available data from the medical records, total sample size must be 300 patients.

The study sample size must allow the estimation of dichotomic variables and to determine the percentage of compliance of each quality care indicator established by the GEMA guidelines. This percentage will allow to establish the degree of compliance of each group of indicators in the site.

The study sample size must allow the estimation of dichotomic variables and to determine the percentage of compliance of each quality care indicator established by the GEMA guidelines. This percentage will allow to establish the degree of compliance of each group of indicators in the site.

Since the primary objective includes a large number of parameters and a descriptive analysis will be done, the sample size (N) has been calculated based on statistical criteria, using the criterion of maximum indeterminacy, when the percentage of one category in a categorical variable is expected to be around 50%. To estimate a proportion of 50%, with a margin of error of +/- 6 percentage points and a confidence level of 95%, a sample size 267 patients will be required. Assuming 10% of patients with non-available data from the medical records, total sample size must be 300 patients.

3.5. Hypotheses

Given that the primary objective aims to obtain an estimation for a population parameter, there is no need for a hypothesis contrast.

4. DATA ANALYSIS CONSIDERATIONS

Data analysis will be performed using SAS Enterprise Guide Version 7.15, and a statistical analysis plan will be designed and agreed before the data analysis initiation.

All the analyzes will be performed by descriptive statistical methods of all the variables separately. All the patients participating in the study who met the eligibility criteria will be included in the study population.

The quantitative data will be described by the following statistical parameters: number of valid patients (N valid), number of missing data (N missing), mean, standard deviation, median, inter-quartile range, minimum and maximum will also be presented.

The qualitative data will be presented through the length-frequency distributions (absolute and relative). For both cases, the following will be specified: number of observations (N) and number of missing data (N missing).

Primary objective:

To analyze the primary objectives, it will be assessed the percentage of compliance of each asthma quality care indicator established by GEMA guidelines (GEMA 4.4, Guía Española para el Manejo del Asma):

GROUP I. Diagnosis

- Diagnostic confirmation by spirometry and bronchodilator test. To know the compliance of this indicator, it will be calculated the percentage of asthmatic patients diagnosed using spirometry and bronchodilator test will be determined:

  Nº patients diagnosed with asthma using spirometry x 100 / nº patients diagnosed with asthma

- Sensitization study in allergic asthma. To know the compliance of this indicator, it will be calculated the percentage of patients with a diagnosed history of suspected allergic asthma included in a sensitization study with different allergens:

  Nº of patients with a diagnosed history of suspected allergic asthma included in a sensitization study with different allergens x 100 / nº patients diagnosed with asthma (and diagnosed history of suspected allergic asthma?)

GROUP II. Non-pharmacological treatment

- Smoking cessation. To know the compliance of this indicator, it will be calculated the percentage of asthmatic smokers with documented recommendations for smoking cessation:

Nº of asthmatic smokers with a documented recommendation for smoking cessation x 100 / nº asthmatic smokers

- Educational plan for patients with asthma. To know the compliance of this indicator, it will be calculated the percentage of patients included in an educational plan:

  Nº of patients with asthma included in an educational plan x 100 / Nº of patients with asthma

GRUPO III. Pharmacological treatment

- Treatment of choice for persistent asthma. To know the compliance of this indicator, it will be calculated the percentage of patients in treatment for persistent asthma who are receiving inhaled glucocorticoids (ICS):

  Nº of patients in treatment for persistent asthma receiving inhaled glucocorticoids (at patient's inclusion date) x 100 / Nº of patients in treatment for persistent asthma

- Treatment for asthma in pregnant women. To determine the compliance of this indicator, it will be calculated the percentage of pregnant women (if applicable) with asthma who maintain their treatment plan based on B2-adrenergic agonists and inhaled corticosteroids among the total pregnant asthmatic women recruited in the study:

  Nº of pregnant women with asthma patients who maintain their treatment plan based on β2-adrenergic agonists and inhaled corticosteroids x 100 / Nº of pregnant women receiving asthma maintenance treatment

GRUPO IV. Monitoring

- Periodic monitoring of patients. To determine the compliance of this indicator, it will be calculated the percentage of scheduled monitoring visits per patient and per year during the previous year among asthmatic patients with asthma monitored per year:

  Nº of scheduled (not unexpected) monitoring visits per patient and per year x 100 / Nº of patients with asthma monitored per year.

- Periodic monitoring of exacerbations. To determine the compliance of this indicator, it will be calculated the percentage of asthmatic patients with evaluation and documentation of exacerbations:

  Nº of patients with asthma with evaluation and documentation of exacerbations during the last year x 100 / Nº of patients with asthma

The interpretation of the result will be subject to the subsequent Statistical Analysis Plan (SAP) which will be determine whether an interpretation of the results obtained will be made or if it will be based on a descriptive definition thereof.

In order to describe the secondary endpoint, the following measures will be described:

- Sociodemographic and clinical characteristics: A descriptive analysis will be performed of the patient's sociodemographic and clinical characteristics collected.
- Treatment patterns: To evaluate this endpoint it will be performed a treatment description of the long-term treatment and the reliever therapy (if applicable).
- To describe the disease control level in the study population. A descriptive analysis will be performed of the disease control level.
- Use of assistance health resources (secondary objective 3): resource use will be evaluated as number of visits performed by the patient the prior year to the inclusion date:
  - Emergency department (ED) linked to asthma.
  - Hospitalizations linked to asthma.
  - Primary care visits (scheduled and unexpected) linked to asthma.
  - Specialist visits (allergists, pulmonologists, etc.) linked to asthma.
- To describe the number of patients with discontinuation of SABA within the last year: It will be described the number of patients with SABA discontinuation during the prior year of the study inclusion date.
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5. LIMITATIONS

As this is a study based on the usual clinical practice and given the real-world nature of the data, the main limitation is the availability of study variables in the subject's medical charts.

6. STUDY CONDUCT, MANAGEMENT & ETHICS

6.1. Ethics Committee/IRB Approval

This non-interventional study will be initiated once all required legal documentation has been reviewed and approved by the Independent Ethics Committee (IEC) and it will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GCP) and any local regulations.

The appointed CRO or the Site Study Responsible will submit required documents to the IEC, such as period updated during the study progress, the notification of study ending, the summary of the study results, as well as any relevant amendment.

6.2. Informed Consent

Prior to patient participation in the study, written informed consent will be needed from each patient (or the patient's legally accepted representative).

The collection of patient's Informed Consent will be performed in accordance with the IRB/ERC requirements, applicable laws and regulations (General Data Protection Regulation (GDPR) (EU) 2016/679) and Sponsor requirements

6.3. Data Protection

The patient's data will be collected or documented in an electronic case report form (eCRF), specially designed for the study, which will automatically create or assign the identification numerical code to every patient the moment it's created in the platform. All the individual

patient medical information is considered confidential, and its confidentiality will be guaranteed as no subject's personal information will be captured during the study.

The eCRF will be the source of information of the study and whose information will be analyzed. The eCRF is a web-based application accessible on any computer with an Internet connection. The 128 bit SSL protocol will be used for Web communications, ensuring confidentiality of communications between servers and the investigator's computer by encrypting all the results sent (a "secure connection").
The e-CRF will allow defining filters in collected variables in order to avoid mistakes, as well as to obtain statistics about the main outcomes in real time. The e-CRF will include specific logic checks and filters for collected variables in an effort to minimize errors in data entry. The e-CRF will also allow the study team to obtain statistics on recruitment and e-CRF completion progression in 'real-time'. The web application is developed with the following technology:

- ASP.NET
- RDBMS SQL SERVER
- SSL (128bits)
- WEB server O.S. Windows

The SSL technology implemented guarantees that all data transferred to the CRO database server will be encrypted and protected from external attacks. An audit trail process will assure the control of every movement made to the data stored. Information registered for every value stored in the database includes: the event date, responsible party, variable, old value, new value, and the type of action taken (creation, updating or deleting). This audit process provides an additional security mechanism for stored data and may also be useful in answering data entry questions by site personnel.

Furthermore, a data Management Plan (DMP), will be also developed to detail how data will be handled. Active ingredients entered into the database will be coded using ATC codes. Medical history/current medical conditions will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

It will be paid special attention to data protection, which will be guaranteed according to the applicable laws and regulations (General Data Protection Regulation (GDPR) (EU) 2016/679) and the corresponding local regulations (*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*), that will be fully respected during the whole study.

6.4. Personally Identifiable Information (PII)

The individual patient medical information is considered confidential for all purposes and it's disclosure to third parties is prohibited with the exceptions indicated below. To guarantee patient's confidentiality, all the data entered in the eCRF during the data collection will be previously anonymized and dissociated as the patient included in the study will be automatically assigned to an identification numerical code the moment when it's created within the eCRF. The study database will never contain any personal data that could identify the patient, so it will remain always protected.

Only in special cases when it might be necessary to know the patient's identification, the sponsor must follow the confidentiality standards according to the local regulations; *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*.

Regarding study results publication, the rights of the investigator and the sponsor with this respect will be described in the study contract. As general rule, no results of the study will be published before the end of the clinical study report.
The clinical study report will be submitted to national health authorities and the corresponding international ethics committee. The results of the study may be also published.

Through the signature of this protocol, the investigator guarantees the sponsor that all the information disposed by the sponsor will remain confidential.

6.5. Adverse Event (AE), Pregnancy Exposure, and Incident Reporting

This is a non-interventional study in which no drug will be studied nor administered, so systematic collection of adverse events does not apply. If any adverse event had occurred during the retrospective period of the study, they should have already been notified as dictated by national regulation "Real Decreto 577/2013, de 26 de julio por el que se regula la farmacovigilancia de medicamentos de uso humano".

If any of the patients included in the study presented an adverse reaction during the study visit, the duty of the investigator will be to act in accordance with the guidelines of the aforementioned regulation and proceed to notify and send it as quickly as possible to the competent body of pharmacovigilance (www.notificaRAM.es), in this case of the autonomous community of Andalusia.

6.5.1. Definitions of adverse events

Adverse reaction: An adverse reaction is defined as any response to a medicinal product which is noxious and unintended, and that takes place at doses used that are normally applied in humans for the prophylaxis, diagnosis or treatment of diseases, or for the restoration, correction or modification of physiological functions.

Serious adverse event or serious suspected adverse reaction: an adverse event or suspected adverse reaction is considered "serious" if it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7. EXTERNAL INVOLVEMENT

7.1. Third Party Supplier

IQVIA Information

7.2. External Expert/Health Care Professionals (Consultants & Research PIs)

APPENDIX 1. Quality assistance indicators – GEMA Guidelines

INDICATOR GROUPS	INDICATOR	CALCULATION
I. Diagnosis	**1. Diagnostic confirmation by spirometry with bronchodilator test**. Diagnostic confirmation of patients with asthma is performed with spirometry and bronchodilator test as an objective measure of functional involvement.	Number of patients with asthma with spirometry performed x100/number of patients diagnosed with asthma.
	2. Sensitization study in allergic asthma. Patients with suspected allergic asthma should be screened for possible sensitizations to different allergens.	Number of patients diagnosed with a history suggestive of allergic asthma with a sensitization study performed to different allergens x100/number of patients diagnosed with asthma.
II. Non-pharmacological treatment	**3. Smoking cessation.** Smoking cessation is recommended in smoking patients with asthma.	Number of asthma patients with smoking and registered dishabituation recommendation x100/asthma patients with smoking.
	4. Educational plan for patients with asthma. Patients with asthma should follow a basic education program (consisting of: knowledge about their disease, about its treatment, action plan and inhalation technique, written document) as part of their treatment.	No. of asthma patients with asthma education program x100/no. of asthma patients.
III. Pharmacological treatment	**5. Treatment of choice in persistent asthma.** The treatment of choice in persistent asthma includes inhaled glucocorticoid (ICG) used daily. In some justified cases, leukotriene receptor antagonists may be considered as an alternative treatment.	Number of patients on control treatment for persistent asthma receiving GCI x 100/number of patients on control treatment for persistent asthma.
	6. Treatment of asthma in pregnant women. In the maintenance treatment of asthma in pregnant women, it is recommended to maintain the drugs usually used (β2-adrenergic agonists and inhaled glucocorticoids).	No. of women with asthma who maintain their usual treatment (β2-adrenergic agonists and inhaled glucocorticoids) in pregnancy x100/number of pregnant women with asthma on maintenance treatment.
IV. Follow-up	**7. Periodic follow-up of patients.** Need for regular follow-up of patients, even if they have not had exacerbations, through scheduled medical visits.	Number of scheduled (non-unplanned) follow-up visits per patient per year x100/number of asthma patients followed up per year.
	8. Periodic recording of exacerbations. The specific assessment of exacerbations is evaluated periodically.	Number of asthma patients in whom exacerbations have been evaluated and documented x100/number of asthma patients.

APPENDIX 2. Asthma Control Test (ACT™)

https://www.asthmacontroltest.com/en-gb/welcome/

APPENDIX 3. Patient Information Sheet and Informed Consent Form

PATIENT INFORMATION SHEET

Study title: "*Observational, descriptive, cross-sectional and single-center study to describe the clinical management in asthmatic patients in the area of influence of the Virgen de la Victoria University Hospital in Malaga*"

Introduction

A research study is being carried out at this health centre and you are invited to participate. The study has been approved by the corresponding Research Ethics Committee and the Spanish Agency for Medicines and Health Products and will be carried out in accordance with current legislation, Royal Legislative Decree 1/2015 approving the revised text of the Law on guarantees and rational use of medicines and medical devices.

Your participation is voluntary and will be confirmed, if you so choose, with your signature at the end of this document. In this respect, you can change your decision and withdraw your consent to participate at any time, without giving any reasons and without affecting your health care. The intention is that you receive adequate and sufficient information so that you can assess and decide whether or not you want to participate in this study. To do this, read this fact sheet carefully and your study doctor will answer any questions you may have.

Why is this study going to be carried out?

The main objective of this study is to describe the clinical management of asthmatic patients in the area of influence of the Virgen de la Victoria University Hospital, i.e. all health centers whose reference hospital is said hospital, according to the quality-of-care indicators established by the Spanish Guide for the Management of Asthma (GEMA).

How will the study be conducted?

The study consists of a single visit, in which you will be offered to participate in this study. Once you have consented to participate in the study and the selection criteria for participation in the study have been confirmed, information will be collected from your medical history of a demographic nature (age, gender, ethnicity, smoking habit, height and weight) and also related to your

asthma disease (age at diagnosis, spirometric diagnostic data, degree of severity, current treatment, history of exacerbations, etc.)

You will also be asked to take a test to assess your level of asthma control (Asthma Control Test - ACTTM) at your study visit, which consists of a 5-question test that will take you less than 5 minutes to complete. Except for this test, all the information will be completed by the investigating physician based on the data available in the patient's medical record, without the study protocol requiring determinations and tests that were not previously carried out and that are not part of the usual routine regardless of whether you participated in the study or not.

What will I have to do in this study, how long will I be in the studio?

Your participation in this study will last only the time of this scheduled visit and in which you will perform the Asthma Control Test, mentioned above.

Potential Benefits

You may not personally benefit from your participation in this study, but it may provide new information that will benefit other patients and be useful to the medical-scientific community for the treatment of asthma.

What happens to my personal data? In accordance with current data protection regulations (Organic Law 3/2018, of 5 December, on the Protection of Personal Data and Guarantee of Digital Rights (LOPD) and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (GDPR), You expressly consent to the inclusion of the data from your medical history, as well as those resulting from your participation in the study in a personal data file under the responsibility of the centre. Access to your personal information will be restricted to the study doctor and his collaborators, health authorities, the Clinical Research Ethics Committee and the monitors, auditors and other personnel authorized by the sponsor, who will be subject to the duty of secrecy inherent to their profession, when necessary, to verify the data and procedures of the study. but always maintaining the confidentiality of these in accordance with current legislation.

The data collected in the study will be identified by a code and only your study doctor and collaborators will be able to relate this data to you and your medical history. Therefore, your identity will not be revealed to any person except in case of medical emergency or legal requirement in the terms indicated above.

INFORMED CONSENT

Patient Number: _____

My signature on this informed consent form means that:

- I have read the information sheet that has been given to me and I have understood the information provided.
- I understand that I am being asked if I wish to participate in an observational study that has been designed to describe the clinical management of asthmatic patients in the area of influence of the Virgen de la Victoria University Hospital in accordance with the quality-of-care indicators established by the Spanish Guide for the Management of Asthma (GEMA).
- I have received enough information about the study
- I have been able to ask questions about the study, receiving complete and satisfactory answers to all my questions.
- I understand that my participation is voluntary.
- I understand that I can withdraw from the study:
    - When I want
    - Without having to explain
    - Without this having an impact on my medical care.

I freely consent to participate in the study and consent to the access and use of my data under the conditions detailed in the information sheet.

_____	_____	_____
Name and surname of the study participant	**Signature of consent of the study participant**	**Date**
_____	_____	_____
Name and surname of the doctor in the study who obtains consent	**Signature of consent of the doctor in the study who obtains consent**	**Date**

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