RSAR Registry Protocol

D-code: D3250R00040

Tracking number: ESR-17-13479

Version 1.2

Date 18.07.2018 г.

Russian Severe Asthma Registry: Protocol

Content

List of abbreviations

BA – Bronchial asthma
RSAR – Russian severe asthma registry
SA - severe bronchial asthma
GINA - Global Initiative for asthma (Global Strategy for Asthma Management and Prevention)
eCRF - electronic case report form
ICS - inhaled glucocorticosteroids
LABA - long acting β-agonists
LAMA – long-acting antimuscarinic agents
COPD - chronic obstructive pulmonary disease
EDS - electronic data logging system
LLC "RSMI" - Limited Liability Company "Regional United System of Medical Informatization"
SNOMED CT - the dictionary of the systematized nomenclature of medical clinical terms
IHTSDO - organization for the development of international health terminology
RAACI - Russian Association of Allergology and Clinical Immunology
QMS - Quality Management System
SOP - standard operating procedure
NEC - National Ethics Committee
RRS - Russian Respiratory Society
CBD - The central database
IPF - idiopathic pulmonary fibrosis
EMC - emergency medical care
Treatment and prophylactic institution
ACQ-5 - Asthma Control Questionnaire (questionnaire for asthma control, 5-question version)
ACT - Asthma Control Test (Asthma Control Test)
OCS - oral corticosteroids
LTRA - a leukotriene receptor antagonist

RESPONSIBLE PARTIES

1. Limited liability company "Regional United Medical Informatization System" (LLC "RSMI") within the framework of the project of the Russian Severe Asthma Registry (RSAR) takes responsibilities to develop and implement software for the work of physicians-investigators within the RSAR creating a database of patients with severe bronchial asthma (SA) on the territory of the Russian Federation on an already existing software company product, named "Medical online platform ROSMED.INFO" protected according to the current legislation of Russian Federation.
2. The limited liability company "Regional United Medical Informatization System" within the framework of the project RSAR assumes the responsibility to perform the functions of a personal data operator of physicians and patients participating in the study.
3. Limited liability company "Regional United Medical Informatization System" within the RSAR project assumes the responsibility for management and administration, including information and technical support, of the project during the whole period of the study.
4. NPO "Russian Respiratory Society" within the project of RSAR assumes the obligation to contribute to the development of indicators of the Electronic Database, to supervise the development of principles and parameters of patient questioning, to create reference materials for patients and/or their legal representatives, to supervise the development of CRF, repeat/monitoring visits and other clinical parameters, correlating with the issues of prophylaxis, management, dynamic clinical monitoring of the health status and rehabilitation process of patients with severe asthma, but not limited to these areas of activity.
5. Russian Association of Allergology and Clinical Immunology (RAACI) within the project of RSAR assumes the obligation to contribute to the development of indicators of the Electronic Database, to supervise the development of principles and parameters of patient questioning, to create reference materials for patients and/or their legal representatives, to supervise the development of CRF, repeat/monitoring visits and other clinical parameters, correlating with the issues of prophylaxis, management, dynamic clinical monitoring of the health status and rehabilitation process of patients with severe asthma, but not limited to these areas of activity.

PROJECT DELIVERY COLLABORATORS

LLC RSMI specializes in conducting medical observational non-interventional prospective multicenter studies.

LLC "RSMI" owns the patented Russian software product "Medical online platform ROSMED.INFO", which serves as a base for development and maintenance of observational studies (registries) on various nosologies, including severe asthma.

NPO "Russian Respiratory Society" (IPO "RRS") is a non-profit public organization that unites on a physician of various specialties engaged in the management of patients with various pulmonological diseases. Among the members of the NPO "RRS" there are leading Russian opinion leaders, the main freelance specialists of the Ministry of Health of the Russian Federation,

the main non-staff regional specialists in the field of respiratory / allergic diseases, who possess extensive experience in development and conductance of clinical trials. The activities of NPO RRS focus on the establishment of best practices and standards in pulmonology, aimed on improvement of the quality of research in real practice for all stakeholders, including patients, clinical practice specialists, representatives of the pharmacological industry and law enforcement / regulatory bodies.

RSAR CORE STEERING COMMITTEE

Russian research working groups are a network of researchers working together to identify unsatisfied research objectives through non-randomized controlled trials and to implement high-quality academic research in this field. The main members of the RSAR Steering Committee jointly conduct the expertise, using scientific data and experience working with databases and research, forming the necessary elements of the work for the initiative group of the Registry (RSAR).

RSAR Steering Committee is headed by Belevsky AS, MD, professor of the pulmonology department of the Higher Educational Institution of Higher Professional Education "Russian National Research Medical University named after N.I. Pirogov "of the Ministry of Health, Chairman of the Moscow branch of the Russian Respiratory Society, President of the Russian Respiratory Society, President of the Association of Russian-Speaking Experts in Respiratory Medicine and Nenasheva N M, MD, professor of the Federal state budget educational institution of post-graduate professional education Russian medical academy of continuous professional education.

Below are the names of the main experts, council members who will take part in the implementation of the Registry (RSAR).

Responsible position within the register	**Organization name**	**Person name**
Chief Scientific Curator	Higher Educational Institution of Higher Professional Education "Russian National Research Medical University named after N.I. Pirogov "of the Ministry of Health	Belevsky Andrey Stanislavovitch
Chief Scientific Curator	Federal state budget educational institution of post-graduate professional education Russian medical academy of continuous professional education	Nenasheva Natalya Mikhailovna
Scientific adviser	FSBO "Research Institute of Pulmonology of FMBA of the Russian Federation"	Avdeev Sergey Nikolaevitch
Scientific adviser	Higher Educational Institution of Higher Professional Education	Aisanov Zaurbek Ramazanovitch

	"Russian National Research Medical University named after N.I. Pirogov "of the Ministry of Health	
Scientific adviser	Scientific Research Institute of Pulmonology of the First St. Petersburg State Medical University named after academician I.P. Pavlov	Titova Olga Nikolaevna
Scientific adviser	Department of pulmonology of Federal State Budget Institution of Higher Education “North-West State Medical University named by I.I. Mechnikov” of Ministry of Health of the Russian Federation	Emelyanov Alexander Viktorovich
Scientific adviser	FSBO SSC Institute of Immunology of FMBA of Russia	Ilyina Natalia Ivanovna
Scientific adviser	FSBO SSC Institute of Immunology of FMBA of Russia	Kurbacheva Oksana Mikhailovna
Scientific adviser	Federal State Funded Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University under the Ministry of Health of the Russian Federation (I.M. Sechenov First MSMU)	Geppe Natalia Anatolievna
Scientific adviser	Federal State Funded Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University under the Ministry of Health of the Russian Federation (I.M.	Malakhov Alexander Borisovich

	Sechenov First MSMU)	

PROTOCOL SYNOPSIS

The Russian registry of patients with severe asthma to collect anonymous long-term evidence.

The Russian Severe Asthma Registry is a Russian initiative to collect anonymous long-term evidence for patients with severe asthma in Russia. The RSAR initiative is realized under the efforts of the Interregional Public Organization "Russian Respiratory Society" and LLC "RSMI" with the sponsorship of "AstraZeneca Pharmaceuticals" LLC.

The developed RSAR electronic database is a Russian software product that meets the current requirements of the Russian legislation in the field of working with personal data and the implementation of similar observational studies.

Participating researchers also agree to grant access and share anonymous data at the patient level as part of the work to implement the RSAR initiative. Participants will provide high-quality data for the development of data sets for research, approved by the Russian Respiratory Society (RPO), which has priority in owning and implementation in scientific field of the gained data. Based on ethical, legal and regulatory authorizations, anonymous data will be collected in the Central Database (CDB) on respiratory diseases (referred to here as the RSAR database) to create sets of important data and the necessary analysis. CDB is part of the software "Medical online platform ROSMED.INFO".

MILESTONES

Period 01/2018 – 12/2018		
Invitation of physicians-investigators to the project, the initiation of the RSAR work	03/2018	
Project working group formation of curators, sponsors, medical experts		
Programming of the individual patient case report form (child (from 12 years) and adult versions)		
The beginning of filling in eCRF by the physicians-investigators	03/2018	
Project management, filling of eCRF by investigators	03/2018-12/2018	
Organization of the database and user's personal information protection	03/2018-12/2018	
Data base administration	03/2018-12/2018	
Data entry in CRF by investigators	03/2018-12/2018	
Analytic report	07/2018 and 12/2018	
Period 01/2019 – 12/2019		
Project management, filling of eCRF by investigators	01/2019-12/2019	
Organization of the database and user's personal information protection	01/2019-12/2019	
Data base administration	01/2019-12/2019	
Data entry in eCRF by investigators	01/2019-12/2019	
Analytic report	06/2019 and 12/2019	
Period 01/2020 – 12/2020		
Project management, filling of eCRF by investigators	01/2020-12/2020	
Organization of the database and user's personal information protection	01/2020-12/2020	
Data base administration	01/2020-12/2020	
Data entry in eCRF by investigators	01/2020-12/2020	
Analytic report	06/2020 and 12/2020	
Period 01/2021 – 12/2021		
Project management, filling of eCRF by investigators	01/2021-12/2021	

Organization of the database and user's personal information protection	01/2021-12/2021	
Data base administration	01/2021-12/2021	
Data entry in eCRF by investigators	01/2021-12/2021	
Analytic report	06/2021 and 12/2021	
Period 01/2022 – 12/2022		
Project management, filling of eCRF by investigators	01/2022-12/2022	
Organization of the database and user's personal information protection	01/2022-12/2022	
Data base administration	01/2022-12/2022	
Data entry in eCRF by investigators	01/2022-11/2022	
Analytic report	06/2022 and 12/2022	
	Total taking into account all receipts	

1.0. BACKGROUND & RATIONALE

1.1. BACKGROUND

Severe asthma

BA is a heterogeneous disease characterized by chronic inflammation of the upper respiratory tract. BA affects 5-15% of people worldwide and its prevalence has increased in the last decade [1]. Asthma management to achieve optimal control and prevention of exacerbations using a step approach in pharmacotherapy is detailed in national and international guidelines [2]. Nevertheless, the question of precise statistical data on the true incidence of severe asthma remains open. In the study "NIKA" [19], an assessment of the level of asthma control in 1,000 patients from 26 outpatient clinics in 12 cities of the Russian Federation was carried out. The level of control was assessed clinically and using specialized questionnaires ACQ-5 and ACT. As a reference method of assessment, the evaluation of symptoms and spirometry parameters were performed in accordance with the GINA criteria. In general, controlled BA was noted in 23% of patients, partial control and uncontrolled asthma - in 35% and 42%, respectively. When diagnosing the level of control, physicians made mistakes in 49% of cases. The use of the ACQ-5 and ACT tests produced a higher and approximately comparable quality of the control evaluation (64% and 60% of

adequate assessments), but the ACT had a systematic error in overestimating the level of control of asthma compared to the GINA criteria. Despite the availability and use of preventive treatment, the costs associated with asthma are increasing, and affect both individuals and health facilities. Regardless of the improved understanding of the nature of the disease, the factors that affect the loss of control are still unclear and largely remain hypothetical. Part of the difficulties lies in determining the severity of asthma, assessing its symptoms and their intensity.

The program of the study of severe asthma revealed various subgroups of severe asthma on the basis of changing clinical manifestations, pathophysiological mechanisms and biomarkers [4)]. In this study, 438 patients with asthma were studied. The authors found that patients with severe asthma tend to be older with a longer illness, daytime symptoms, intensive use of emergency therapy, sinusitis and pneumonia. Despite the fact that lung function was reduced in these patients, most patients had reversibility of bronchial obstruction after taking the bronchodilator [4]. A better understanding of the mechanisms of BA should make an obvious improve in patients' management.

Biomarkers and phenotypes in SA management prognosis of treatment response.

Patients with BA of mild to moderate severity can control symptoms with increasing doses of inhaled glucocorticosteroids (ICS) in combination with long-acting β-agonists (LABA) or leukotriene antagonists. In patients with more severe asthma and frequent exacerbations, this treatment may not be sufficient to control symptoms and prevent exacerbations. Despite the growing range of medicines and improved design of inhalers and patient care, deaths continue to increase due to asthma, with an increase of 17% between 2014 and 2015 only in Great Britain [6]. The novel methods of treatment can help to fight this tendency. However, new therapies are often expensive, and there is a need to identify patients who can get the most benefit from such treatment.

Biomarkers assessment now is an important tool used to achieve optimal management of patients with BA, especially, SA. Biomarkers can be used to study the function of organs or other health parameters [7], providing information on the severity of the disease and the predicted outcomes of treatment, as well as on choosing the most effective treatment for particular patients.

For example, patients with severe BA and significant eosinophilia have a greater risk of exacerbating [8]. Eosinophils can affect the mucous of the upper respiratory tract, provoking epithelial damage and changes in the structure of the upper respiratory tract in asthma, thus affecting the severity of the disease. Studies have shown that peripheral blood eosinophilia can be used as a biomarker to predict the effectiveness of anti-IL-5 therapy in the prevention of exacerbations [9, 10, 11]. Recent data suggest that other variables, as like eosinophils, can predict asthma exacerbations. These include local eosinophilia, as well as nasal polyps and concomitant diseases, including diabetes mellitus [12].

Like the number of eosinophils, an increase in the exhaled nitric oxide fraction (FeNO) helps to predict the exacerbations of asthma (13). An increase in FeNO is considered a clinical biomarker of inflammation. Nevertheless, the values of FeNO are affected by many associated

factors, including tobacco smoking, obesity and the use of glucocorticosteroids [7]. There is a need for a better understanding of when FeNO plays the role of a biomarker in BA. In particular, a combination of data on FeNO and eosinophils of blood can help in predicting who will benefit greatly from the biological therapy. Moreover, a significant proportion of patients with asthma also have an allergic sensitization. The presence of allergen-specific IgE along with exposure to the allergen are known risk factors for the severity of asthma, which along with the content of FeNO and eosinophils of blood allows to predict the response to treatment against IgE [7].

Identification of biomarkers can improve understanding of the phenotype of severe asthma. This progress in understanding the characteristics of the disease can lead to improved management of SA patients.

Given the new opportunities in prevention, diagnosis and treatment, the study of the epidemiology and clinical features of the course of severe asthma is an urgent task of modern medicine. The creation of the first Russian Severe Asthma Registry will serve to monitor and evaluate the efficacy, safety of prescribing therapy for patients with severe asthma, to isolate BA phenotypes and to unite regional specialists in the fight against this disease.

1.2. Rationale.

The development of the Russian Severe Asthma Registry is aimed on supervising current problems that can be encountered when using separate registries for this nosology. Standardization of data collection will help to streamline interoperable sources of data on severe asthma across Russia, as well as to establish an accurate process for researchers to gain access to the Registry, which will collect data and use them in SA patient's management. Data on biomarkers such as FeNO, eosinophils, and IgE will be an important resource in the RSAR, helping to identify patients who are more likely to respond to biological agents.

An example of a successfully implemented observational study is the National Register of Patients with Idiopathic Pulmonary Fibrosis in the Russian Federation, a prospective observational study of idiopathic pulmonary fibrosis (IPF) in the Russian Federation, which was initiated in 2016 by the Russian Respiratory Society in conjunction with the Regional United Medical Informatization System. This innovative project was developed to study the features of epidemiology and the course of IPF, classified as rare diseases (ICD-10 code J84.1 - idiopathic pulmonary fibrosis) in the Russian Federation. It allows to obtain accurate epidemiological data on this nosology, to cooperate specialists from various specialties: pulmonologists, morphologists, radiation diagnostics specialists, and other experts at the federal and regional levels to improve the diagnosis and management of IPF. The Registry allows to achieve significant improvement in the physician's awareness about IPF and to reveal their interest in this problem. So, on the 01.09.2017, 185 doctors from 58 regions of the Russian Federation take part in the Registry, of which:

- 25 major freelance specialists-pulmonologists of the Ministry of Health of the Russian Federation;
- 57 scientists (professors, MD, PhD);

• 51 head of profile departments of state federal, regional and city health care institutions.

The registry improved the detection of IPF: currently there are 519 patients in, while there are total number of about 1000 IPF patients according to epidemiology in the Russian Federation. About 35% of patients in the IPF Registry are of working age. The functioning of the IPF Registry led to an improvement in the quality of medical care for patients with IPF. Within the framework of IPF Registry, 236 online consultations / opinions of federal or regional experts were conducted. During the work of the IPF Registry, the number of patients receiving specific antifibrotic therapy, which is the treatment of choice, has increased according to current recommendations: 97% of patients (59 of 61) receive nintedanib, registered in Russia with indication IPF. The IPF Registry is of high scientific and practical value and of great social significance for the diagnosis and treatment of this life-threatening disease.

The development of the Russian Severe Asthma Registry (RSAR) with a planned number of patients (CRFs) of 7,000 involving researchers from more than 30 cities has the potential to become an important Russian platform to research and a get a better understanding of the heterogeneity of the BA. the same as the rationale for proper use and monitoring the impact of BA treatment with new drugs.

2.0. OBJECTIVES

The RSAR objective is to develop a single automated system for monitoring the SA patient's management in Russia, to evaluate the efficacy and safety of pharmacotherapy prescriptions for patients with severe asthma, to determine the phenotypes of severe asthma, and to unite regional specialists in the fight against this disease.

2.1. Primary Objective(s)

The key objective of establishing the RSAR initiative is to:

- Percentage of patients with severe asthma according **frequency of exacerbations** (1, 2, ≥3 exacerbations) at the time of study enrollment;

2.2. **Secondary Objective(s)**

For the overall sample and by subgroups as appropriate, the secondary objectives are to:

- Percentage of patients with severe asthma according **frequency of exacerbations** (1, 2, ≥3 exacerbations) at the 1 year of follow-up;
- Percentage of patients with severe asthma according frequency of exacerbations (1, 2, ≥3 exacerbations) at the 2 year of follow-up;
- Percentage of patients with severe asthma according frequency of exacerbations (1, 2, ≥3 exacerbations) at the 3 year of follow-up;
- Percentage of patients with severe asthma according frequency of exacerbations (1, 2, ≥3 exacerbations) at the 4 year of follow-up;

- Percentage of patients with severe asthma according **concomitant diseases** (number of observations, the mean value, the standard deviation) at the time of study enrollment;
- Percentage of patients with severe asthma according concomitant diseases (number of observations, the mean value, the standard deviation) at the 1year of follow-up;
- Percentage of patients with severe asthma according concomitant diseases (number of observations, the mean value, the standard deviation) at the 2 year of follow-up;
- Percentage of patients with severe asthma according concomitant diseases (number of observations, the mean value, the standard deviation) at the 3 year of follow-up;
- Percentage of patients with severe asthma according concomitant diseases (number of observations, the mean value, the standard deviation) at the 4 year of follow-up;
- Percentage of patients with severe asthma according to parameters: **age** (the mean value, the standard deviation) at the time of study enrollment;
- Percentage of patients with severe asthma according to parameters: **sex** at the time of study enrollment;
- Percentage of patients with severe asthma with different phenotypes in terms of parameters: **IgE (IU/ml)** (the mean value, the standard deviation, the minimum value, median, maximum value) at the time of enrollment;
- Percentage of patients with severe asthma with different phenotypes in terms of parameters: IgE (IU/ml) (the mean value, the standard deviation, the minimum value, median, maximum value) at the 1years of follow-up;
- Percentage of patients with severe asthma with different phenotypes in terms of parameters: IgE (IU/ml) (the mean value, the standard deviation, the minimum value, median, maximum value) at the 2 years of follow-up;
- Percentage of patients with severe asthma with different phenotypes in terms of parameters: IgE (IU/ml) (the mean value, the standard deviation, the minimum value, median, maximum value) at the 3 years of follow-up;
- Percentage of patients with severe asthma with different phenotypes in terms of parameters: IgE (IU/ml) (the mean value, the standard deviation, the minimum value, median, maximum value) at the 4years of follow-up;
- Percentage of patients with severe asthma with different phenotypes in terms of **eosinophil levels in absolute values** in complete blood count (number of observations, the mean value, the standard deviation, the minimum value, median, maximum value) at the time of enrollment;
- Percentage of patients with severe asthma with different phenotypes in terms of eosinophil levels in absolute values in complete blood count (number of observations, the mean value, the standard deviation, the minimum value, median, maximum value) at the 1 year of follow-up;
- Percentage of patients with severe asthma with different phenotypes in terms of eosinophil levels in absolute values in complete blood count (number of observations, the mean value, the standard deviation, the minimum value, median, maximum value) at the 2 year of follow-up;

- Percentage of patients with severe asthma with different phenotypes in terms of eosinophil levels in absolute values in complete blood count (number of observations, the mean value, the standard deviation, the minimum value, median, maximum value) at the 3 year of follow-up;
- Percentage of patients with severe asthma with different phenotypes in terms of eosinophil levels in absolute values in complete blood count (number of observations, the mean value, the standard deviation, the minimum value, median, maximum value) at the 4 year of follow-up;
- Percentage of patients with severe asthma in the parameters: **of body mass index (kg/m^2),** at the time of study enrollment;
- Percentage of patients with severe asthma in the parameters: **of smoking (smoker's index (pack-years)** at the time of study enrollment;
- Percentage of patients with severe asthma in the parameters: **of professional history** at the time of study enrollment;
- Percentage of patients with severe asthma in the parameters: **of family history** at the time of study enrollment;
- Parameters of **FEV_1 (liters, percentage of predicted)** (the mean value, the standard deviation) **before** bronchodilator in patients with severe asthma at the time of study enrollment;
- Parameters of **FVC** (liters, percentage of predicted) (the mean value, the standard deviation) **before** bronchodilator in patients with severe asthma at the time of study enrollment;
- Parameters of **FEV_1** (liters, percentage of predicted) (the mean value, the standard deviation) **post** bronchodilator in patients with severe asthma at the time of study enrollment;
- Parameters of **FVC** (liters, percentage of predicted) (the mean value, the standard deviation) **post** bronchodilator in patients with severe asthma at the time of study enrollment;
- Parameters of **FEV_1** (liters, percentage of predicted) (the mean value, the standard deviation) **before** bronchodilator in patients with severe asthma at the 1 year of follow-up;
- Parameters of FVC (liters, percentage of predicted) (the mean value, the standard deviation) before bronchodilator in patients with severe asthma at the 1year of follow-up;
- Parameters of FEV_1 (liters, percentage of predicted) (the mean value, the standard deviation) post bronchodilator in patients with severe asthma at the 1 year of follow-up;
- Parameters of FVC (liters, percentage of predicted) (the mean value, the standard deviation) post bronchodilator in patients with severe asthma at the 1year of follow-up;
- Parameters of FEV_1 (liters, percentage of predicted) (the mean value, the standard deviation) before bronchodilator in patients with severe asthma at the 2 year of follow-up;
- Parameters of FVC (liters, percentage of predicted) (the mean value, the standard deviation) before bronchodilator in patients with severe asthma at the 2year of follow-up;

- Parameters of FEV_1 (liters, percentage of predicted) (the mean value, the standard deviation) post bronchodilator in patients with severe asthma at the 2 year of follow-up;
- Parameters of FVC (liters, percentage of predicted) (the mean value, the standard deviation) post bronchodilator in patients with severe asthma at the 2year of follow-up;
- Parameters of FEV_1 (liters, percentage of predicted) (the mean value, the standard deviation) before bronchodilator in patients with severe asthma at the 3 year of follow-up;
- Parameters of FVC (liters, percentage of predicted) (the mean value, the standard deviation) before bronchodilator in patients with severe asthma at the 3year of follow-up;
- Parameters of FEV_1 (liters, percentage of predicted) (the mean value, the standard deviation) post bronchodilator in patients with severe asthma at the 3 year of follow-up;
- Parameters of FVC (liters, percentage of predicted) (the mean value, the standard deviation) post bronchodilator in patients with severe asthma at the 3year of follow-up;
- Parameters of FEV_1 (liters, percentage of predicted) (the mean value, the standard deviation) before bronchodilator in patients with severe asthma at the 4 year of follow-up;
- Parameters of FVC (liters, percentage of predicted) (the mean value, the standard deviation) before bronchodilator in patients with severe asthma at the 4 year of follow-up;
- Parameters of FEV_1 (liters, percentage of predicted) (the mean value, the standard deviation) post bronchodilator in patients with severe asthma at the 4 year of follow-up;
- Parameters of FVC (liters, percentage of predicted) (the mean value, the standard deviation) post bronchodilator in patients with severe asthma at the 4 year of follow-up;
- ;
- Percentage of patients with uncontrolled severe asthma based on the analysis of the questionnaire **ACQ-6** at the time of study enrollment;
- Percentage of patients with uncontrolled severe asthma based on the analysis of the questionnaire ACQ-6 at the 1 year of follow-up;
- Percentage of patients with uncontrolled severe asthma based on the analysis of the questionnaire ACQ-6 at the 2 year of follow-up;
- Percentage of patients with uncontrolled severe asthma based on the analysis of the questionnaire ACQ-6 at the 3 year of follow-up;
- Percentage of patients with uncontrolled severe asthma based on the analysis of the questionnaire ACQ-6 at the 4 year of follow-up;
- **Mean number of exacerbations** (the mean value, the standard deviation) **requiring medical attention** (outpatient prescription of systemic corticosteroids) in patients with severe asthma at the time of study enrollment;
- Mean number of exacerbations (the mean value, the standard deviation) requiring medical attention (outpatient prescription of systemic corticosteroids) in patients with severe asthma at the 1year of follow-up;
- Mean number of exacerbations (the mean value, the standard deviation) requiring medical attention (outpatient prescription of systemic corticosteroids) in patients with severe asthma at the 2 year of follow-up;

- Mean number of exacerbations (the mean value, the standard deviation) requiring medical attention (outpatient prescription of systemic corticosteroids) in patients with severe asthma at the 3 year of follow-up;
- Mean number of exacerbations (the mean value, the standard deviation) requiring medical attention (outpatient prescription of systemic corticosteroids) in patients with severe asthma at the 4 year of follow-up;
- **Mean number of hospitalizations** (the mean value, the standard deviation) in patients with severe asthma at the time of inclusion in the study;
- Mean number of hospitalizations (the mean value, the standard deviation) in patients with severe asthma at the time of inclusion in the 1 year of follow-up;
- Mean number of hospitalizations (the mean value, the standard deviation) in patients with severe asthma at the time of inclusion in the 2 year of follow-up;
- Mean number of hospitalizations (the mean value, the standard deviation) in patients with severe asthma at the time of inclusion in the 3 year of follow-up;
- Mean number of hospitalizations (the mean value, the standard deviation) in patients with severe asthma at the time of inclusion in the 4 year of follow-up;
- **Percentage of patients with severe asthma** (the mean value, the standard deviation) taking high doses of **ICS/LABA, ICS/LABA+LAMA as maintenance therapy, biologics** at the time of study enrollment;
- Percentage of patients with severe asthma (the mean value, the standard deviation) taking high doses of ICS/LABA, ICS/LABA+LAMA as maintenance therapy, biologics at the 1 year of follow-up;
- Percentage of patients with severe asthma (the mean value, the standard deviation) taking high doses of ICS/LABA, ICS/LABA+LAMA as maintenance therapy, biologics at the 2 year of follow-up;
- Percentage of patients with severe asthma (the mean value, the standard deviation) taking high doses of ICS/LABA, ICS/LABA+LAMA as maintenance therapy, biologics at the 3 year of follow-up;
- Percentage of patients with severe asthma (the mean value, the standard deviation) taking high doses of ICS/LABA, ICS/LABA+LAMA as maintenance therapy, biologics at the 4 year of follow-up;
- **Percentage of patients with severe asthma** (the mean value, the standard deviation) **taking OCS as a maintenance therapy** at the time of study enrollment;
- Percentage of patients with severe asthma (the mean value, the standard deviation) taking OCS as a maintenance therapy at the 1 year of follow-up;
- Percentage of patients with severe asthma (the mean value, the standard deviation) taking OCS as a maintenance therapy at the 2 year of follow-up;
- Percentage of patients with severe asthma (the mean value, the standard deviation) taking OCS as a maintenance therapy at the 3 year of follow-up;
- Percentage of patients with severe asthma (the mean value, the standard deviation) taking OCS as a maintenance therapy at the 4 year of follow-up;

- **Percentage of patients with severe asthma** (the mean value, the standard deviation) **who have been changed therapy** (step up, step down by GINA) to 1 year of follow-up;
- Percentage of patients with severe asthma (the mean value, the standard deviation) who have been changed therapy (step up, step down by GINA) to 3 year of follow-up;
- Percentage of patients with severe asthma (the mean value, the standard deviation) who have been changed therapy (step up, step down by GINA) to 4 year of follow-up;
- **Percentage of patients with severe asthma who called for emergency medical care** for asthma (number of observations, the mean value, the standard deviation, median) at the 1 year of follow-up;
- Percentage of patients with severe asthma who called for emergency medical care for asthma (number of observations, the mean value, the standard deviation, median) at the 2 year of follow-up;
- Percentage of patients with severe asthma who called for emergency medical care for asthma (number of observations, the mean value, the standard deviation, median) at the 3 year of follow-up;
- Percentage of patients with severe asthma who called for emergency medical care for asthma (number of observations, the mean value, the standard deviation, median) at the 4 year of follow-up;
- **Percentage of patients with severe asthma who had disability sheets for asthma** (number of observations, the mean value, the standard deviation, median) at the 1year of follow-up;
- Percentage of patients with severe asthma who had disability sheets for asthma (number of observations, the mean value, the standard deviation, median) at the 2 year of follow-up;
- Percentage of patients with severe asthma who had disability sheets for asthma (number of observations, the mean value, the standard deviation, median) at the 3year of follow-up;
- Percentage of patients with severe asthma who had disability sheets for asthma (number of observations, the mean value, the standard deviation, median) at the 4 year of follow-up;

3.0. METHODOLOGY

3.1. Registry Design

The Russian Severe Asthma Registry is a prospective multicenter, non-interventional observational study for patients with severe bronchial asthma (SA).

All patients included in the RSAR platform will be periodically observed during routine visits to the hospital with a follow-up of up to five years.

In the RSAR conductance there is no provision for any intervention in routine clinical practice, including the use of the study therapy / treatment methods or special research methods. From the day the project begins, the physician will collect data on all patients with SA who have visit as outpatient or hospitalized patient and who meet the inclusion criteria for in this study.

The study includes a retrospective part - an analysis of the medical records of patients available at the time of their inclusion in the study.

Patients with a confirmed diagnosis of SA (according to inclusion criteria) will be included in the study sequentially and observed for 5 years.

The period of patient's inclusion - from 03.2018 till 11.2022.

The observation period is from 03.2018 till 11.2022.

The approximate period of the Registry work is from 03.2018 to 12.2022.

The target sample size is up to 7,000 patients with SA over a period of 5 years.

3.2. Draft Cities Initiation

The participation of cities and recruitment of patients in the RSAR is expected:

Period, years	**Number of participating cities (health facilities)**	**Number of SA patients CRFs**
03.2018-12.2018	30 (100 health facilities)	2000
01.2019-12.2019	30 (100 health facilities))	2000
01.2020-12.2020	30 (100 health facilities))	1000
01.2021-12.2021	30 (100 health facilities)	1000

01.2022-11.2022	30 (100 health facilities))	1000

3.3 Data Collection

The main data source within the RSAR will be an electronic database of patients developed on the basis of the "Medical online platform ROSMED.INFO", which is the own development of LLC "RSMI".

The attending physicians of patients with SA will enter information online in the electronic database. As investigation centers will be used health facilities of federal and regional levels, which include specialized pulmonological and allergic departments. These centers have the opportunity to include the largest number of patients with SA in the study, and they also have extensive experience in the management and monitoring of such patients. The total number of health facilities is 100. The centers participating in the study will collect data on all patients diagnosed with SA who have signed written informed consent to participate in the study. Data collection will be carried out on a regular basis during routine patient visits to a doctor or in case of hospitalization. In the work period of this project, no special additional procedures for collecting information will be used. The information will be collected from outpatient cards and / or case histories, based on data received by the physician during routine examination of the patient. Visitors of www.rosmed.info site can not participate in the RSAR study without first being invited by the attending physician.

3.4. Patient Population

Patients receiving step 4 and 5 treatment (according to GINA, 2017) in accordance with the uncontrolled asthma severity (J.45) in health facilities in accordance with local regulatory / ethical requirements. The goal is to include up to 7,000 patients in RSAR throughout Russia during the entire study period.

Signed informed consent will be collected from patients in order to use data in accordance with RF legislation, and to gain approval of the RSAR study by the Independent Interdisciplinary Ethical Review Committee of the Clinical Studies (Committee) - (http://ethicuni.ru).

The role of the Committee is to verify and approve the scientific significance of research objectives. The purpose of the Committee is to ensure that the research database is clinically appropriate and continues to bring real benefits to patients, public health and health organization system.

The study will collect the following data on patients with SA:

- Personal data.
- Patient demographics.

- Anamnesis of the disease, including previous exacerbations, allergic status and current status monitoring.
- Concomitant diseases, including atopic dermatitis, allergic and non-allergic rhinitis, chronic rhinosinusitis with or without polyps.
- Medications prescribed for the treatment of asthma, including data on patient adherence to prescribed treatment, where applicable and assessment of the inhalation technique.
- Treatment outcomes, including asthma control status (control of GINA 2017), quality of life and professional history.
- Spirometry data.
- Biomarkers (blood eosinophils, sputum eosinophils, IgE, and FeNO, where possible).
- Patient's basic therapy, including use of OCS and biological agents.
- The economic burden of asthma in patients (disability sheets, ambulance calls, etc.).
- Evaluation of the frequency and severity of BA exacerbations.

The data including these estimates will be entered into the electronic database of RSAR for storage and subsequent impersonal analytics. Data from any existing registries of patients with severe asthma may also be entered.

For compatibility, the existing data will be sorted in accordance with the standard data collection fields / codes established by the RSAR monitoring group.

3.5. Inclusion Criteria

- Patients aged 12 years or older.
  Patients with confirmed diagnosis of severe asthma.
- Patients receiving treatment according to GINA step 5 or uncontrolled for 4 step. Uncontrolled patients are defined as having symptoms of severe asthma[1] or frequent exacerbations[2].
  Signed informed consent.

[1] Severe symptoms of BA (Guideline of European Respiratory Society (ERS)/American Thoracic Society (ATS)) (2):
(a) BA with uncontrolled symptoms; ACT< 20, ACQ >1,5;
(b Limited air-flow rate, for example: FEV1 <80 % of the norm (along with FEV1/FES at the lower limit of the norm or less) after wash-out period from the bronchodilators;
(c) Severe exacerbation and hospitalization, being in the ICU or on the mechanical ventilation of lungs over the past year.

[2] Frequent severe exacerbations of BA (guidelines ERS/ATS) (2):
Frequent severe exacerbations of BA (2 or more courses of systemic glucocorticoids over the past year).

3.6. Exclusion Criteria

- Intermittent, mild, moderate BA, before verification of the diagnosis.
- COPD.
- Diseases of the respiratory system, such as tuberculosis, sarcoidosis, IPF, lung cancer.
- Vasculitis, systemic connective tissue diseases.
- Neoplasm.
- Written refusal of the patient to participate in the study after signing an informed consent.

3.7. Registry Follow-up

Since the study is in the form of a Registry - non-interventional observational study - there is no planned intervention in the common clinical practice of patient management, the number of follow-up visits will be based on existing recommendations and protocols for managing patients with asthma in the Russian Federation and the patient's needs. It is assumed that the patient will visit health facilities once in 3 months. The frequency of visits depends on the initial level of control of asthma in the patient, the response to treatment.

3.8. Consent Procedures

Participants will be provided with full information about the planned study, their rights and opportunities, after which it will be offered to sign the informed consent, which is a prerequisite for the patient's participation in the Registry.

4.0. DATABASE

4.1. Data Acquisition

With each physician-investigator a civil law agreement will be concluded that regulates the work of the physician within the framework of the project. A cooperation agreement will be concluded between the project technical executor, LLC RSMI, and the supervising organization of the IPO RRS, which will ensure the right of IPO RRS to legally own the accumulated database on patients with severe asthma.

4.2. Data Management

Data from patients with SA will be entered into the electronic CRF by physicians-investigators within a limited time after receiving the diagnostic / consultation results. The CRF is an integrated part of the Universal Medical Complex of Medical Organization and Informatization for the collection, dynamic clinical and epidemiological surveillance and analysis of data in the

remote access mode "ROSMED.INFO", quality control and reliability of the information entered will be checked online by the project manager of LLC " RSMI" within the framework of existing SOPs and quality management standards.

The data of SA patients CRFs will be stored electronically in a secure database, with an obligatory database backup procedure, as well as with a preliminary assessment of the security threats for their elimination (RSMI regulatory document - "Security Threat Model").

Backup information is stored on the servers (databases, data catalogs on file servers, general catalogs of departments and departments).

In parallel, the data will be copied on paper carriers, their storage will be carried out in water and fireproof safes.

Instructions for the operation of the data manager of the RSAR include the full procedure for working with personal data and are available for audit.

A separate data management plan describes all the functions, processes and specifications for data collection, retrieval, sending, cleaning and validation. Electronic CRFs will include a programmed version for instant feedback, if data are not available, go beyond acceptable limits, are illogical and potentially erroneous. This minimizes general data entry errors. A collaborative manual data validation process will be conducted based on plan parameters. In the electronic research data recording system (EDS), special requests will be generated, requiring further explanations.

High data quality standards will be maintained, the processes and procedures used systematically will ensure the highest possible accuracy of the data submitted for analysis. The data quality will be improved through a series of programmed checks to automatically detect abnormal data or data beyond the specified limits. All data modifications will be registered in the audit log.

4.3. Registry Coding

The project work group consisting of representatives of the supervising organization and technical specialists of RSMI LLC will agree on a standardized set of basic and long-term indicators, and will hold regular meetings to ensure long-term expert input through the development, expansion of the register and the achievement of research objectives.

The technical executor of the project, LLC RSMI, should provide the opportunity, if necessary, to convert the accumulated database into a format that corresponds to the standardized clinical codes and terms contained in the dictionary of the systematized nomenclature of medical clinical terms (SNOMED CT), which allows to recognize the clinical sequence of ICD and read the encoding, which will be able to present the data at the detailed level required for the purpose of coding the register. SNOMED CT was developed by the International Health Terminology Organization (IHTSDO), and is currently available in English and Spanish versions.

4.4. Statistics analysis

Primary and secondary statistical indicators will be presented using descriptive statistics methods. Qualitative variables will be presented in the form of incidence and percentage. The quantitative variables will be represented by numerical values, standard deviation indicators, minima and maxima, median and interquartile range. The frequency and severity of adverse events / reactions will be documented according to the Medical Dictionary of Regulatory Terminology, version 16.1.

When analyzing the outcome of the disease among patients on therapy (drug), statistical analysis will be performed in a subgroup of newly identified patients. Evaluation of the outcome of SA can be determined by achieving a sufficient number of patients in a subgroup of newly identified patients and patients undergoing therapy (SA). The lack of comparison between groups of patients is due to the inaccuracy of these therapies in the history and treatment approaches.

In the course of the analysis, the standard statistical characteristics of morbidity, prevalence of the disease (SA) and their dependence on the basic demographic indicators (sex, age) will be assessed.

The statistical analysis of the endpoints will be performed for patients with a diagnosis period of no more than 6 months from the date of inclusion in the register (a subgroup of newly identified patients) and also when the required amount of statistical data is collected within the register database.

The analysis will use standard methods of descriptive, frequency, logistic statistical analysis.

Hypotheses of the study. The main goal of the study is to obtain statistical estimates of the target epidemiological characteristics, formally asking questions about hypotheses of the study in this case is not applicable. After receiving the estimates, they are expected to be compared with similar ones, known in the foreign and domestic literature and official statistics.

Within the Registry, measures should be taken to collect data on the maximum number of patients within the claimed sample. In the absence of information within the fields of the individual registration card, the validating authority should separate information on the statuses "negative value", "no data", "not investigated".

The data of patients dropped out of the register during the observation will be analyzed and used to calculate the primary points, if the number of completed visits allows, the data can be used to analyze part of the parameters of the observation period. The initial characteristics of patients dropped out of the register before its completion will be compared with the characteristics of patients with a fully completed observation period, taking into account the proportionality of the data (the number of "dropped out" patients).

4.5. Main analysis.

The aggregate statistics for continuous variables will include the number of observations (N), the mean value, the standard deviation (SD), the minimum value, Q1 (25th percentile), median, Q3 (75th percentile), maximum value, interquartile range. Tables of categorical variables will represent all possible categories and will display the number of observations for each category, as well as percentages. Precision for percent is one decimal point, if the denominator is less than 100 (in all columns), in this case, percentages are indicated by integers. In general, the percentages will be calculated based on the total number of patients in the analyzed population, regardless of

whether they have missing values or not. The category "Missing" will be displayed when at least one patient falls into this category. The CRF contains several nested questions (that is, questions that require more detailed information only in a subset of patients with a specific value for another question, "if yes" questions); for these variables, percentages will be based on patients with a corresponding value for a higher-level issue, rather than using all patients in the population as reference values.

4.6. Further analysis

In the case of the availability of data on patient, which are observed in parallel in other registries, it is necessary to perform an analysis for this group separately from the rest of the patients. In the event of a discrepancy between the indicators of other registers and this study, the latter is determinative.

4.7. Quality control

The Analytical Working Group and the Technical Operator and the Personal Data Operator will check the data for completeness and correctness, inform the local executors about probable errors and omissions in the data when filling CRFs by the doctors. Obvious corrections will be made at the level of administrators and managers of the system who are employees of LLC "RSMI" with notification to the curators of the register.

The Quality Management System (QMS) of RSMI LLC standardizes the procedures for creating and maintaining patient databases on the basis of a universal software package for medical organization and information for the collection, dynamic clinical and epidemiological surveillance and analysis of data in remote access mode ROSMED.INFO. QMS ensures the fulfillment of the customer's requirements and the conformity of the processes and their results with the legislation of the Russian Federation.

LLC "RSMI" guarantees the availability of personnel, production environment and appropriate infrastructure for the implementation of QMS.

LLC "RSMI" within the framework of the QMS ensures that the organization's knowledge base, the level of sufficient competence of the employees involved in the work process and their awareness of the standards of the quality management system are adequate to the work objectives and objectives.

LLC "RSMI" guarantees the availability of functioning internal and external communications that ensure the operation of the quality management system. The QMS of the organization regulates the analysis of requirements related to the company's products and services. QMS LLC RSMI includes all stages of development and maintenance of the software product and databases, including the stages of statistical processing of the results obtained through the integrated online statistical processing module.

4.8. Limitations of study methods.

The following errors must be taken into account when planning methods for recruiting patients and their follow-up observation:

- Wrong information;
- Incorrect inclusion of the patient in the study;
- Errors in the periods of entering information;
- Removal of the patient at the stage of the beginning of the period of dynamic observation.

In order to reduce the likelihood of these errors within the QMS (quality management system), it is planned to conduct audits for compliance of the RSAR data with the study protocol, the requirements of the study organizers and the legislation of the Russian Federation. The program includes built-in internal validation tools for the entered data. To minimize the risks of mistaken inclusion of patients, the process of registration of patients in the study will be extremely consistent. All patients who meet the inclusion criteria, regardless of location (research base) will necessarily be included in the RSAR. Patients participating in interventional clinical trials will not be included. For the entire population entered in the RSAR, the initial characteristics (primary endpoints) will be examined and analyzed. At each base included in the study, a patient screening log will be kept, including information on the field, age, date of birth, the date of diagnosis of AE of serious gravity, the reason for including the patient / reason for not including the patient in the register, the date of signing the informed consent form for participation in the research, reasons for refusing to participate in the register.

The study monitors will have the opportunity to check the sequence of patients' inclusion in the study. The investigators and organizers of the RSAR will make every effort to minimize unreasonable drop-out of patients from the register, within which regular contact will be made with the patient / his legal representative, in case of dropout, the cause will necessarily be established (with documentary evidence, about death). A signal for an emergency contact with the patient / legal representative will be the miss of another planned visit within the framework of the visit. The contact form and its result will be registered in accordance with the established procedure (SOP LLC RSMI).

In order to minimize the dropout of patients, the following efforts will be made:

- Work with databases where patients are recruited;
- Minimizing the difficulties of participation in the register for patients;
- Constant contact of the researcher with the patient.

To study the effects of dropping out of patients during the observation process, parameters such as the number of patients left in% and the reasons for their departure will be summarized and analyzed. Population characteristics will be summarized for the retired patients, compared with the characteristics of patients who have reached the end of the observation period. The period of time for which the patient has left the observation ahead of schedule will be studied and analyzed.

To exclude the shift in the periods of entering information in the form of the patient's IRC, questions of a clarifying character will be present, with reference to a certain frequency of the event, a time interval, etc.

5. 0. Other aspects of the study

5.1. Data quality assurance

The quality assurance guarantee will cover the following areas:
- guarantee of data quality assurance;
- guarantee of quality assurance of all procedures that are relevant to the RSAR;
- guarantee of software quality assurance and computer systems.

In order to guarantee the quality of the data, measures will be taken to prevent, detect and correct the following types of errors:
- Interpretation or coding errors;
- errors in data entry, accuracy of their transfer and transformation;
- semantic errors;

Activities (steps) to ensure the quality of information will include:
- trainings (training of those responsible for collecting information);
- checking the completeness of the information provided (the presence of an immediate feedback mechanism with the clinical center, where patients are included in the study and observed);
- checking consistency of data (comparing data from different centers and at different time intervals);
- local audit in each center (checking of the screening logs, procedures, data samples);
- special audits (for the centers that cause the greatest fear of inaccurate information entry and are characterized by the greatest number of errors);

In order to ensure the quality of all data on the register, the following will be done:
1. Appointment of the person responsible for the quality of the data in each center included in the study;
2. Scheduled audits of data quality;
3. Activities to maintain and improve the level of competence of staff;
4. Checks security systems and data integrity;
5. Guarantee of the validity of computer systems and software, their compliance with quality and safety standards, compliance with the legislation of the Russian Federation;
6. Information Systems Security Plan;
7. Differentiation of access rights to the patient / legal representative, physician, system administrator, database operator.

Quality assurance of audit can be carried out by representatives of the organizer of the register, and also other authorized regulating bodies. The quality control auditor has access to all medical records related to the research, the researcher's medical files, correspondence and documentation, informed consent of this study.

5.2. Data registration

CRFs for individual patients will be provided to the curators of the project on paper

and in digital form.

RSAR will consist of a two-level collection of standardized data, as described below:

- A list of the main variables (defined by the process within the Medical online platform ROSMED.INFO): it will consist of approximately 100 basic variables.

- Extended variable list: this will make all variables useful for scientific research and maximum data collection and create an optimal list of variables. Long-term variables will be collected through standardized joint modules. The name of several: asthma control (ACQ6), a professional history questionnaire, concomitant diseases, a history of vaccinations and biomarkers of severe asthma.

5.3. Data ownership

Based on the results of the study, biostatistical analyzes (customized) of the RSAR data obtained on an annual basis and interim reports every six months will be compiled.

A number of publications are planned on the basis of the statistical analysis of the research data, the authors' team, the internal editing and review procedures will be decided within the working group on the publication policy. The timing of publications and their content will be regulated by the steering committee, the curators of the study.

The rights to intellectual property belong to the Interregional Public Organization "Russian Respiratory Society".

5.4. Data access and subordination

To begin work of RSAR, it is necessary to obtain approval from the independent ethical committee (NEC).

To gain NEC approval it is necessary to provide following documents:

1. The study protocol.
2. Patient's voluntary informed consent form and Information form for the patient.
3. Biography of scientific curators / experts.
4. Documents confirming the legality of the collection, storage and processing of personal data of participants (doctors and researchers).
5. List of clinical centers participating in the study.
6. Public contract-offer (User agreement), documentation in the framework of the policy regarding the organization and processing of personal data.
7. Case Report Form (eCRF).

8. Documentation that confirms the agreement between the supervising organization and the technical contractor of the project for joint work.

The initiation of the work of the Registry is possible only in case all the necessary legal documents are available, and the NEC approves it in accordance with Russian and international legal norms. The same situation applies to the mechanism for introducing changes and amendments.

To participate in the study, the patient/legal representative must sign an informed consent for participation in the study.

Each signature must be dated personally by the signer and retained for the duration of the study, as well as the form of informed consent and any other documents relevant to the patient. A copy of the signed informed consent, as well as any other additional information about the patient, must be provided directly to the patient or his legal representative.

The patient should be informed that his personal data will be used in accordance with Federal Law No. 152 "On Personal Data". The patient should also be explained the level of disclosure within the framework of possible audits by the organizers, curators, research sponsors and technical support parties.

Identification and authentication measures should ensure that unique characteristic (identifier) will be performed to access objects and access objects, a comparison of the identifier presented by the subject (object) with a list of assigned identifiers will be made to verify that the identifier presented to the subject is authentic (authenticated).

Access control measures should provide management of rights and privileges of access subjects, delineate access of access subjects to access objects based on the set of access control rules established in the information system, and ensure compliance monitoring of these rules.

Measures to protect computer personal data carriers (means of processing (storing) personal data, removable computer personal data carriers) should exclude the possibility of unauthorized access to computer media and personal data stored on them, as well as unauthorized use of removable personal data carriers.

Measures to register security events should ensure the collection, recording, storage and protection of information on security events in the information system, as well as the ability to view and analyze information about and respond to such events.

Anti-virus protection measures must ensure that computer programs or other computer information is detected in the information system for unauthorized destruction, blocking, modification, copying of computer information or neutralizing information protection means, as well as responding to the detection of these programs and information.

Measures to control (analyze) the protection of personal data should ensure that the level of protection of personal data processed in the information system is monitored by carrying out systematic measures to analyze the security of the information system and to test the operation of the personal data protection system.

Measures to protect the virtualization environment should prevent unauthorized access to and manipulate personal data processed in the virtual infrastructure and / or virtual infrastructure components, including virtual infrastructure management tools, virtual machine monitor (hypervisor), storage system (including the storage of images of virtual infrastructure), data networks through elements of a virtual or physical infrastructure, guest operating systems, virtual containers, the system and the replication network, terminal and virtual devices, as well as the backup system and the copies it creates.
Measures for the protection of technical means must exclude unauthorized access to stationary facilities that process personal data, facilities that support the operation of the information system (hereinafter means of operation), and to the premises in which they are permanently located, the protection of technical means from external influences, and also the protection of personal data presented in the form of informative electrical signals and physical fields.
Measures to protect the information system, its facilities, communication systems and data transmission should ensure the protection of personal data in the interaction of the information system or its individual segments with other information systems and information and telecommunications networks through the application of the architecture of the information system and design solutions aimed at ensuring the safety of personal data.
Measures to manage the configuration of the information system and personal data protection systems should provide management of changes in the configuration of the information system and personal data protection system, analyze the potential impact of the planned changes on the security of personal data, and document these changes.
These measures to ensure the security of personal data are implemented in the system of personal data protection for all objects and entities of access at the hardware, system, application and network levels, as well as in the environment of virtualization and cloud technologies.
When using information security tools certified in accordance with the requirements of information security in the informatization system of personal data "Rosmed.info" to ensure the 3 levels of protection of personal data, the following should be applied:
• Means of computer technology no lower than Class 5;
• Intrusion detection systems and anti-virus protection tools of at least Class 4 protection;
• Internetwork screens of at least 3 protection classes.

6. Adverse events/reactions data collection and report

6.1 Definitions

6.1.1 Definition of adverse event (AE).

Adverse event (AE) is any untoward change in state of health of patient or clinical investigation/trial subject administered a pharmaceutical/studied product and which does not necessarily have to have a causal relationship with this treatment. AE can be any unfavorable symptom (for example, nausea, chest pain), sign (for example, tachycardia, enlarged liver) or abnormal examination result (for example, abnormal laboratory finding, change in ECG), the time

of occurrence of which does not exclude causal relationship with the use of a pharmaceutical product, whether or not related to the use of a pharmaceutical product.
The term AE is used to indicate both serious and non serious adverse events.
The data on special situation should also be collected and reported: the use of a pharmaceutical product during pregnancy or lactation (whether the pregnancy outcome is known or not), lack of treatment efficacy, overdose, abuse, misuse, off-label use, suicidal attempt or completed suicide, suspected drug interaction and suspected infectious agent transmission.

6.1.2 Definition of serious adverse event (SAE).

Serious adverse event is AE, that occurs at any stage of the trial (i.e. introductory stage, observation stage) and meets one or more of the following criteria:

- Results in death;
- Is life-threatening (in this context, a reaction can be defined as life-threatening if it places the patient at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is any other clinically significant medical event, that can be menacing to the patient or requires medical treatment to prevent the previously-mentioned conditions. The compliance of AE with the criteria of seriousness can be determined using medical and scientific consideration.

Any suspected unintentional transmission of an infectious agent is also defined as SAE and may be subject to express reporting in some countries. An infectious agent is any microorganism, virus or infectious particle (for example, a prion protein that is a carrier of transmissible spongiform encephalopathy), regardless of pathogenicity.

6.1.3 Definition of adverse reaction (AR)

Adverse reaction (AR) is AE, related to the use of pharmaceutical/studied product and implying at least probable interrelation with the use of suspected pharmaceutical/studied product.
Adverse reaction may occur by use of the pharmaceutical product in accordance with instructions for medical use or not in accordance with it, and also by impact, associated with the occupation.

6.2 Adverse events data collection

In view of the non-interventional nature of this study, active collection of safety data will not be performed. It applies to collection of both primary safety data – (directly from patients) and secondary data (analysis of patient's medical records, available at the time of their enrolment into the trial), in which the safety of prescribed drug therapy with glucocorticoids is being studied.

Nevertheless, if during the visit of the patient the investigator finds out
the AE, occurred in this trial and on the background of the pharmaceutical product intake, it is necessary to ascertain whether there is or there is not a cause-effect relationship with the pharmaceutical product, collect and report information in accordance with regulatory requirements and timing for pharmacovigilance in the postmarketing period for spontaneous report.
For each adverse event it is necessary to record the following variables:

- a term for describing of the adverse event;
- date of occurrence and completion of the adverse event;
- severity of the adverse event;
- compliance of the adverse event with the criteria of seriousness;
- the investigator's assessment of the existence of a cause-effect relationship between the adverse event and the use of a pharmaceutical product (yes
- or not);
- Measures, taken in relation to the pharmaceutical product;
- The outcome.

It is extremely important, that all the staff, participating in the trial, are
familiar with the contents of this section. The principal investigator is
responsible for ensuring that all the staff, involved in the trial, are familiarized with the spontaneous report processing procedures (the term spontaneous report implies voluntary transfer by a health worker or the consumer to the Regulatory Authority, holder of the registration certificate), as well as with national regulatory requirements for pharmacovigilance in Russia.

Adverse events assessment
All AE (both serious and non serious), spontaneously reported by patients oridentified by the investigator, will be assessed for the presence or absence
of causal relationship with pharmaceutical product and should be recorded and evaluated in accordance with the following definitions:
Degree of severity
To estimate the severity of AE concerning its intensity, the following three-level scale will be used:

- Mild: the presence of signs or symptoms that do not affect daily activities.
- Medium: the event is of sufficient intensity to affect daily activities.
- Severe: impossibility to work or perform daily activities (unacceptable event).

Important! The severity of events is not the equivalent of seriousness and is used to describe the intensity of an event (for example, a strong headache may not be of a serious clinical significance) *.

* See the seriousness criteria in the SAE definition or the item is defined by criteria in section 6.1.2.

Causality Assessment between the medicinal product and Adverse Event

The investigator necessarily assesses the relationship between the use of the pharmaceutical product and the occurrence of each adverse event by answering "yes" or "no" to the question:
"Do you think that there is a reasonable probability that this event could be caused by the therapy used (for the drug in the glucocorticoid therapy)?».

6.3 Reporting on the adverse events

6.3.1 Reporting on the adverse events spontaneous reports

Monitoring of safety will be performed according to local pharmacovigilance requirements, applicable in standard medical practice on the territory of the Russian Federation.
If one of the investigators becomes aware of AE, which is estimated to have a causal relationship with the pharmaceutical product of AstraZeneca company, information on such AE should be collected and recorded in the primary documentation and in the form of an AE report (which is part of the eCRF).
All AR and serious adverse reaction (SAR), including fatal events, should be collected and the information should be transmitted in accordance with regulatory requirements and timing for pharmacovigilance in the postmarketing period for spontaneous report.
If the causal relationship is estimated as doubtful in the report (AE or SAE), that report should be included in the final report.
Information about all adverse events should be summarized and represented in the final clinical trail report.

6.3.2 Recording of spontaneous the adverse events

When recording adverse events, identified in the trial, it is necessary to be guided by the following principles: the investigator should report on adverse events by the
pharmacovigilance procedures according to local regulatory requirements.
Method of presenting information on AR/SNR, obtained in the spontaneous reporting:

1. In writing to the Federal Service for Surveillance in Healthcare by contacting: Russian Federation, 109074, Moscow, Slavyanskaya pl., 4, p. 1 At the same time, it is necessary to use a special form located at:

http://www.roszdravnadzor.ru/i/upload/files/1308641445.19876-26263.doc

2. To the relevant pharmaceutical company, i.e. company, in whose name

a registration certificate of the pharmaceutical product has been issued, according to local regulatory requirements.

7. Publication Plan

Dissemination plan for research results and communications on the results obtained. The results of the study, annual reports will be compiled.
A number of publications are planned on the basis of the statistical analysis of the research data, the authors' team, the internal editing and review procedures will be decided within the working group on the publication policy. The timing of publications and their content will be regulated by the Core Steering Committee, the curators of the study.
Intellectual property rights belong to the executors of the project:

1) Interregional Public Organization "Russian Respiratory Society".
2) Russian Association of Allergology and Clinical Immunology.

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9. APPENDIX: Main variables

	Category	**Variable's Fields Names**	**Response options (if appliable)**
1	Inclusion Criteria	Is the patient suffering from uncontrolled asthma and taking medium-to-high doses of ICS? Please check one of the following: 1. At the stage 5 GINA 2. (a) Uncontrolled in Stage 4: There are symptoms of severe asthma 2. (b) Uncontrolled in stage 4: there are exacerbations requiring OCS	No/Yes
2	Inclusion Criteria	The patient meets the criteria for the inclusion in RSAR	No/Yes
3	Detailed description of the patient	Visit date	DD / MM / YYYY
4	Detailed description of the patient	Date of Birth Age at the moment of examination	DD / MM / YYYY Full age (calculated automatically)
5	Detailed description of the patient	Gender	Male/female
6	Detailed description of the patient	Race	Caucasian / Southeast Asian / Northeast Asian / African / Mixed / Other
7	Detailed description of	ΠΠΙΤ	Decimal number (calculated automatically)

	the patient		
8	Detailed description of the patient	BMI	Decimal number (calculated automatically)
9	Detailed description of the patient	Height	Decimal number
10	Detailed description of the patient	Weight	Decimal number
11	Detailed description of the patient	Was the bronchial thermoplastics given to the patient?	No/Yes
12	Occupation	What is the current patient's occupation?	Free text entry
	Occupation	Occupational risks	- at the moment; - in anamnesis.
13	Anamnesis	What is current smoking status of a patient?	Never smoked / Former smoker / Currently smokers
14	Anamnesis	-Number of cigarettes smoked daily? (if marked "ex-smoker", "currently smokes")	Number
15	Anamnesis	-Years of smoking? (please indicate the period of time during which the patient smoked continuously)	Number
16	Anamnesis	-Pack-Years	Number (calculated automatically)
17	Anamnesis	-Years, passed after you quit smoking? (please specify the time period from which the patient stopped smoking)	Number

18	Anamnesis	At what age did the symptoms of asthma start to appear in the patient? Full years or months, if <1 year	Number
19	Anamnesis	Number of exacerbations requiring treatment with systemic glucocorticosteroids in the last 12 months?	Number
20	Anamnesis	The total number of episodes of invasive pulmonary ventilation?	Number
21	Anamnesis	Total number of ambulance calls due to asthma in the last 12 months?	Number
22	Anamnesis	Total number of hospitalizations due to asthma in the last 12 months?	Number
23	Anamnesis	Indicate the number disability episodes in the last 12 months (for BA).	Number
24	Significant concomitant diseases	Atopic dermatitis Atopic disease: yes, if atopic dermatitis is noted	Never / in the past / currently
25	Significant concomitant diseases	Allergic rhinitis Atopic disease: yes, if allergic rhinitis is noted	Never / in the past / currently
26	Significant concomitant diseases	Non-allergic rhinitis	Never / in the past / currently
27	Significant concomitant diseases	Chronic rhinosinusitis with polyps	Never / in the past / currently
28	Significant concomitant diseases	Chronic rhinosinusitis without polyps	Never / in the past / currently

29	Treatment of significant concomitant diseases	Atopic dermatitis Allergic rhinitis Non-allergic rhinitis Chronic rhinosinusitis with polyps Chronic rhinosinusitis without polyps	Indicate treatment of significant concomitant diseases
30	Significant concomitant diseases	Indicate concomitant diseases in the patient	obesity, - Type 2 diabetes, - Arterial hypertension, - IHD, - COPD, - CHF, - CRF; other.
31	Treatment of significant concomitant diseases	obesity, - Type 2 diabetes, - AH, - IHD, - COPD, - CHF, - CRF; other.	Indicate treatment of significant concomitant diseases
32	Blood/ sputum	What was the largest number of eosinophils of blood (over the last year)?	Decimal number
33	Blood/ sputum	- Date of the maximal number of eosinophils of blood (for the last year)	DD / MM / YYYY

34	Blood/ sputum	-Was the greatest number of eosinophils of blood recorded during exacerbation?	No/Yes
35	Blood/ sputum	What was the maximal number of eosinophils of the blood? (for the last year and beyond the exacerbation)	Decimal number
36	Blood/ sputum	Date of the maximal number of eosinophils of blood (for the last year and without exacerbation)	DD / MM / YYYY
37	Blood/ sputum	Current (last) value of eosinophils	Decimal number
38	Blood/ sputum	-Last date of eosinophils measurement	DD / MM / YYYY
39	Blood/ sputum	What was the maximal number of eosinophils in sputum (over the last year)? (in percentages)	Decimal number
40	Blood/ sputum	- Date of the maximal number of eosinophils of blood (for the last year)	DD / MM / YYYY
41	Blood/ sputum	What is the current IgE value (last)?	Decimal number
42	Blood/ sputum	- Date of current IgE measurement (latest)	DD / MM / YYYY
43	Blood/ sputum	Was the patient's periostin level measured?	- Yes; - No;
45	Diagnostics	Was chest radiography performed?	Normal/ Abnormal/Was not performed
46	Diagnostics	Was chest computer tomography performed?	Normal/ Abnormal/Was not performed
47	Diagnostics	-Date of chest computer tomography	DD / MM / YYYY
48	Diagnostics	Was densitometry done?	No/Yes
49	Diagnostics	Date of densitometry	DD / MM / YYYY

50	Lung function	FEV1 before broncholytic	Decimal number
51	Lung function	FEV1 after broncholytic	Decimal number
52	Lung function	Functional Vital capacity before broncholytic	Decimal number
53	Lung function	Functional Vital capacity after broncholytic	Decimal number
54	Lung function	Prognosed FEV1	Decimal number (calculated automatically)
55	Lung function	FEV1 before broncholytics (% of prognosed)	Decimal number (calculated automatically)
56	Lung function	FEV1 after broncholytics (% of prognosed)	Decimal number (calculated automatically)
57	Lung function	Prognosed FVC	Decimal number (calculated automatically)
58	Lung function	FVC before broncholytics (% of prognosed)	Decimal number (calculated automatically)
59	Lung function	FVC after broncholytics (% of prognosed)	Decimal number (calculated automatically)
60	Lung function	The ratio of FEV1 / FVC before bronchodilator	Decimal number (calculated automatically)
61	Lung function	The ratio of FEV1 / FVC after bronchodilator	Decimal number (calculated automatically)
62	Lung function	Spirometry	DD / MM / YYYY
63	Lung function	Was the test for methacholine PC20 / histamine/exercise performed?	No/Yes
64	Lung function	-Date of PC20 test	DD / MM / YYYY
65	Lung function	- PC20 result	Decimal number (calculated automatically)
66	Lung function	An exhaled nitric oxide test was performed?	No/Yes

67	Lung function	- Date of analysis for expired nitric oxide	DD / MM / YYYY
68	Lung function	- Results of the analysis for expired nitric oxide	Decimal number (calculated automatically)
69	Allergic tests (ALL)	Was the environmental allergens test performed?	Determination of specific IgE in blood/Scarification test/Was not done
70	Allergic tests (determination of specific IgE in blood)	- Date of determination of specific IgE in blood	DD / MM / YYYY
71	Allergic tests (determination of specific IgE in blood)	- Was specific IgE in blood positive for year-round allergens?	No/Yes
72	Allergic tests (determination of specific IgE in blood)	+ Indicate the year-round allergens to which specific IgE in blood was positive (select all applicable)	Dust mite (eg D. Pteronyssinus) / cat's hair / mixture of molds / dog hair / aspergillus / other (please specify)
73	Allergic tests (determination of specific IgE in blood)	- Was specific IgE in blood positive for seasonal allergens?	No/Yes
74	Allergic tests (determination of specific IgE in blood)	+ Indicate the seasonal allergens to which specific IgE in blood was positive (select all applicable)	Trees pollen Weeds pollen Grasses pollen
75	Allergic tests (Scarification test (ST))	-ST date	DD / MM / YYYY
76	Allergic tests (Scarification test (ST))	- Was the ST positive for year-round allergens?	No/Yes

77	Allergic tests (Scarification test (ST))	Indicate year-round allergens (for ST) (select all applicable)	Dust mite (eg D. Pteronyssinus) / cat's hair / mixture of molds / dog hair / aspergillus / other (please specify)
78	Allergic tests (Scarification test (ST))	- Was the ST positive for seasonal allergens?	No/Yes
79	Allergic tests (Scarification test (ST))	+ Indicate the seasonal allergens to which the ST was positive (select all applicable)	Trees pollen Weeds pollen Grasses pollen
80	Asthma symptom control	Do patients experience symptoms during the day? (more than twice a week)	No/Yes
81	Asthma symptom control	Does the patient have any limitation of physical activity due to asthma? For what period of time?	No/Yes
82	Asthma symptom control	Does patient awake For what period of time?	No/Yes
83	Asthma symptom control	Does patient need to use asthma symptom relief drugs more than 2 a week?	No/Yes
84	Asthma symptom control	Is the patient's lung function (PEF or FEV1) < 80% of prognosed or best per sonal result (if known)?	No/Yes
85	Drugs to manage asthma	Does patient use currently oral GCS?	No/Yes – Dose - Duration of use - Registered adverse

			effects of OCS
86	Drugs to manage asthma	Did patient use OCS earlier?	No/Yes – Dose - Duration of use - Registered adverse effects of OCS
87	Drugs to manage asthma	-Date of OCS use start	DD / MM / YYYY
88	Drugs to manage asthma	Does patient use currently combined therapy (ICS+LABA)? (please, select from the list)	No budesonide + formoterol fluticasone furoate + vilantherol fluticasone propionate + salmeterol beclomethasone + formoterol other
89	Drugs to manage asthma	Does the patient currently take ICS + LABA as a fixed or free combination?	- Fixed combination - Free combination
90	Drugs to manage asthma	- Date of onset of combined ICS+LABA therapy	DD / MM / YYYY

91	Drugs to manage asthma	Is the patient currently taking ICS (only)? (please select from the list)	No triamcinolone acetonide mometasone furoate fluticasone propionate fluticasone furoate ciclesonide flunysonide budesonide beclomethasone other
92	Drugs to manage asthma	- Date of start / end of ICS intake	DD / MM / YYYY
93	Drugs to manage asthma	Is the patient currently taking LABA (only)? (please select from the list)	No formoterol salmeterol indacaterol olodaterol other
94	Drugs to manage asthma	- Date of start / end of LABA intake	DD / MM / YYYY
95	Drugs to manage asthma	Is the patient currently taking LAMA (only)? (please select from the list)	No aclidinium tiotropium umeclidinium glycopyrronium

			other
96	Drugs to manage asthma	- Date of start / end of LAMA intake	DD / MM / YYYY
97	Inhalation technique assessment.	Appropriate Inappropriate (if so, the next question) Crucial mistakes Present Absent	
98	Drugs to manage asthma	Is the patient currently taking theophylline? (please select from the list)	No theophylline aminophylline other
99	Drugs to manage asthma	- Date of start / end of theophylline intake	DD / MM / YYYY
100	Drugs to manage asthma	Is the patient currently receiving a leukotriene receptor antagonist (LTRA)? (please select from the list)	No zafirlukast montelukast other
101	Drugs to manage asthma	- Date of start / end of LTRA intake	DD / MM / YYYY
102	Drugs to manage	Is the patient currently receiving treatment targeted on	No/Yes

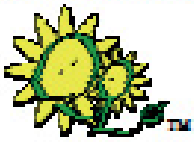
	asthma	immunoglobulin E (Anti-IgE)? (omalizumab is prescribed)	
103	Drugs to manage asthma	Date of start / end of Anti-IgE intake?	DD / MM / YYYY
104	Drugs to manage asthma	Is the patient currently receiving treatment targeted on IL-5 (Anti-IL-5)? (please select from the list)	No reslisumab mepolizumab benalizumab dupilumab (?) tezepelumab (?) other (new biotechnological preparations will be added after approval and start of use in Russia)
105	Drugs to manage asthma	Date of start / end of Anti-IL5 intake?	DD / MM / YYYY
106	Drugs to manage asthma	Does the patient currently receive antibiotic treatment with the macrolide group? (please select from the list)	No azithromycin clarithromycin erythromycin roxithromycin fidaxomycin telithromycin other
107	Drugs to manage	Date of start / end of macrolide	DD / MM / YYYY

	asthma	intake?	
108	Compliance	Is there a non-compliance with the treatment regimen?	No Yes: - dosage; - frequency of reception; - absence of all prescribed medications; - other
109	Management plan	Are there other factors affecting the symptoms of severe asthma?	- "interruptions" in state preferential drug provision; - Other
110	Management plan	Current patient management plan? (Select all that apply)	-Discharged for outpatient treatment of asthma -Current optimization of treatment - Prescription of biological therapy (specific drugs can be found in the list of active medicines) -Bronchial thermoplastics -Supporting oral glucocorticosteroids -Other (please specify)
111	Management plan	Recommendations on asthma therapy (drug (s), dose, regimen) at the current visit:	5 rows to enter - - - - -

112	Management plan	Supposed date of next visit	A reminder for the doctor and patient: - For two weeks, - for 1 week, - for 1 day.
113		What are the sources of preparations for baseline therapy in the patient?	- Self-acquisition; - State preferential drug provision: 1) Federal 2) Regional 4) In hospital drug provision 5) High technology medical care; 6) Territorial programs; 7) Other.
114	Tolerability	Do patients have AE due to the therapy for asthma?	-Indicate the suspected drug. -Fill in the AE registration form (at each visit and the form on AE should be attached to the company's drugs: 1) symbicort turbuhaler (budesonide + formoterol) 2) pulmicort suspension (budesonide)
115	Tolerability	Did the patient take part in randomized clinical trials to study monoclonal antibodies use?	- No - YES: Name of study?

ОПРОСНИК ПО КОНТРОЛЮ СИМПТОМОВ АСТМЫ (ACQ)

RUSSIAN VERSION
(QUESTIONS 1 – 6 ONLY: QUESTION 7 (FEV_1) OMITTED)



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This translation has been made possible
through a grant from GLAXOSMITHKLINE
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НОЯБРЬ 2001

Пожалуйста, ответьте на вопросы 1 – 6.

Обведите кружком номер ответа, который лучше всего отражает Ваше состояние в течение последней недели.

1. В среднем, как часто за последнюю неделю Вы **просыпались** ночью **из-за астмы**?
   - 0 Никогда
   - 1 Очень редко
   - 2 Редко
   - 3 Несколько раз
   - 4 Много раз
   - 5 Очень много раз
   - 6 Не мог(-ла) спать из-за астмы

2. В среднем, насколько **сильны были симптомы астмы, когда Вы просыпались** утром в течение последней недели?
   - 0 Симптомов не было
   - 1 Очень слабые симптомы
   - 2 Слабые симптомы
   - 3 Умеренные симптомы
   - 4 Довольно сильные симптомы
   - 5 Сильные симптомы
   - 6 Очень сильные симптомы

3. В целом, насколько Вы **были ограничены в своих профессиональных и повседневных занятиях** из-за астмы в течение последней недели?
   - 0 Совсем не ограничен (-а)
   - 1 Чуть-чуть ограничен (-а)
   - 2 Немного ограничен (-а)
   - 3 Умеренно ограничен (-а)
   - 4 Очень ограничен (-а)
   - 5 Чрезвычайно ограничен (-а)
   - 6 Полностью ограничен (-а)

4. В целом, была ли у Вас **одышка** из-за астмы в течение последней недели?
   - 0 Одышки не было
   - 1 Очень небольшая
   - 2 Небольшая
   - 3 Умеренная
   - 4 Довольно сильная
   - 5 Сильная
   - 6 Очень сильная

5.	В целом, какую часть времени в течение последней недели у Вас были **хрипы в груди**?	0 Никогда 1 Очень редко 2 Редко 3 Иногда 4 Значительную часть времени 5 Подавляющую часть времени 6 Все время
6.	В среднем, за последнюю неделю, сколько **доз/впрыскиваний бронходилятатора короткого действия** (например, Беротека/Дитека) Вы делали каждый день? *(Если Вы сомневаетесь в ответе на этот вопрос – пожалуйста, обратитесь за помощью)*	0 Ни одного 1 Обычно - 1 - 2 дозы/впрыскиваний 2 Обычно - 3 - 4 дозы/впрыскивания 3 Обычно - 5 - 8 доз/впрыскиваний 4 Обычно 9 - 12 доз/ впрыскиваний 5 Обычно 13 - 16 доз/ впрыскиваний 6 Обычно - более чем 16 доз/ впрыскиваний