Non-Interventional Study (NIS) Primary Report Synopsis	
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Non-interventional multicenter Study of spirometry Use to diagnose COPD and to Prescribe treatment to COPD patients in the outpatient institutions of the healthcaRe system of the Russian FederaTion

Study dates:	**First Subject In: 24** November 2014 **Last Subject Last Visit:** 31 May 2015

NIS REPORT SYNOPSIS

Study Title: **Non-interventional multicenter Study of spirometry Use to diagnose COPD and to Prescribe treatment to COPD patients in the outpatient institutions of the healthcaRe system of the Russian FederaTion**

Study period	
Date of the first patient in	24 November 2014
Date of the last patient in	31 May 2015
Date of the last patient last visit	31 May 2015
Database lock	02 September 2015

Compound (name, dose, administration route) and concomitant therapy

Not applicable.

Study rationale

Most COPD patients in the Russian Federation visit the primary care physicians for the medical care in outpatient institutions. Doctors of the institutions can refer the patient for spirometry test or to the pulmonologist for consultation (as a rule in such case spirometry is also performed). However, the use of spirometry is a universal routine practice. The spirometry is widely used for primary COPD diagnostics and follow up in some outpatient institutions, in others such test is seldom performed.

New Russian clinical guidelines on treatment of patients with COPD have neither specific recommendations on spirometry performance when examining subjects with COPD risk factors, nor information about how frequent the test must be performed in patients with COPD.

Moreover a significant problem for the Russian Federation is a high prevalence of smokers, provided that it is necessary to note a very low level of COPD diagnostics. The experience of certain institutions and the Day of Spirometry organized by Russian respiratory society show that using spirometry as a method of new COPD cases diagnosis has a great potential. Nevertheless, the results of specific studies that would convince doctors and institution's authority to the necessity of more extensive use of spirometry test are not sufficient.

The second problem that specialists in respiratory medicine face is the fact that no studies of distribution of COPD patients by classes offered by GOLD experts have been conducted in the RF. Results of interviewing and spirometry tests performed in hundreds of healthcare institutions have never been systematized, as a result there are no data about the distribution of patients by obstruction severity,

symptom severity and risk of exacerbation. It is impossible to assess the quality of medical care for COPD patients in the Russian Federation or to plan treatment optimization events without the information.

Therefore, the objectives of the current study were justified by the necessity:

a) to evaluate and justify the value of spirometry as a method of diagnostics for patients with COPD risk factors,

b) to obtain data about distribution of COPD patients by obstruction severity and exacerbation risk degrees using GOLD criteria 2014.

The results obtained in the study were supposed to be used for optimization of diagnostics and treatment of COPD patients in the Russian Federation.

Study Objectives

Primary study objectives

1. To evaluate the diagnostic significance of spirometry as a tool for the primary diagnostics of COPD. To do the, it is supposed to determine the percentage of people with COPD risk factors (long smoking history, age ≥40 years, respiratory symptoms) who have been first-time diagnosed with COPD after spirometry, in relation to the total number of patients who visited the outpatient institutions during the study.

2. To evaluate the distribution of COPD patients who visited the primary care doctors for medical care, by extent of bronchial obstruction (GOLD 1-4), symptom severity and risk of exacerbation (using classification GOLD 2014). To collect and analyze the data about the amount and nature of drug treatment considering the condition severity of patients using GOLD 2014 classification and GOLD 2014 recommendations for the treatment choice.

Secondary objectives

1. To determine the fraction of patients routinely seeking medical attention in the Russian Federation who can be considered in the risk group of COPD development.

2. To evaluate the percentage of COPD patients in routine practice of medical institutions in the Russian Federation among patients who visited outpatient institutions during the study.

3. To evaluate the percentage of doctor's prescriptions for the treatment of COPD patients corresponding to the current international (GOLD 2014) and federal clinical recommendations for diagnostics and treatment of chronic obstructive pulmonary disease.

4. To determine the mean number of puffs of short-acting bronchodilators within 24 hours in COPD patient.

5. To describe social and demographic parameters (age, gender, education, marital status, family income level, invalidity data) of COPD patients who visited physicians of outpatient medical institutions during the study.

6. To evaluate the incidence of concomitant diseases in COPD patient.

7. To evaluate prevalence of smoking, rate of attempts of ceasing smoking, presence of motivation to cease smoking among COPD patients (we estimate how many patients in percent had attempts to quit smoking).

8. To evaluate the disease burden based on the collected data on duration of temporary disability (number of hospitalizations due to COPD exacerbations, calling emergency service due to COPD, requests for outpatient care due to COPD) in the observational study.

Study design

The study was an observational multicenter descriptive study. No hypothesis was checked in the study.

The study was conducted in primary outpatient medical institutions in different cities of the Russian Federation. Primary care doctors who were primary contact for greater part of the population in the Russian Federation including COPD patients were invited as investigators.

The observational descriptive study was conducted within the routine practice of outpatient institutions. Since spirometry was not an integral part of the current universal clinical practice in the Russian Federation, only the sites where spirometry test was routinely used in examination of patients with COPD risk factors and when monitoring condition of COPD patients took part in the study. Therefore the decision about spirometry in every study subject was determined only by the existing treatment approaches.

The study was observational so the investigator enrolled into the study only the subjects with COPD risk factors and COPD patients with already prescribed spirometry test.

The doctor decided to perform spirometry test for the patient regardless the patient's enrollment into the study.

Investigators enrolled patients into the study as they contacted the outpatient institutions. The investigators included patients with COPD risk factors and patients previously diagnosed with COPD into 2 independent groups:

Group 1 – patients with COPD risk factors,
Group 2 – patients previously diagnosed with COPD.

At every site investigators kept records of the number of patients in a provided special form. The investigator recorded in the form:

- a total number of patients who visited the doctor during current working day (without recording personal and medical data)

- a total number of patients with COPD risk factors who visited the doctor during current working day

- a total number of patients with COPD who visited the doctor during current working day including COPD patients who refused to participate in the study.

Group 1. Patients with COPD risk factors

Participation in the study for the group of patients comprised of 2 visits: Visit 1 – "Enrollment/Spirometry and preliminary diagnosis Visit" and Visit 2 "Verification of diagnosis after consultation of the pulmonologist".

"Enrollment/Spirometry and preliminary diagnosis Visit" was performed for 7 days (if spirometry test was not possible to be performed on the day of Study Enrollment Visit). Moreover "Enrollment/Spirometry and preliminary diagnosis Visit" was performed during one day if it was possible to perform the spirometry test and to diagnose on the day or exclusion of COPD diagnosis for patients with COPD risk factors.

Spirometry test was performed during "Enrollment/Spirometry and preliminary diagnosis Visit", preliminary diagnosis was determined, if definitive diagnosis could not be determined once, and, if necessary, the second visit "Verification of diagnosis after consultation of the pulmonologist" was appointed. Analyze of the results of further consultations/tests was carried out during the second visit. Based on the data collected on these two visits the doctor made a definitive diagnosis of COPD or excluded the diagnosis of COPD. It was assumed that there could be not more than two weeks between the first and second visits.

Simultaneously investigators kept daily records of the total number of patients who had an appointment with the doctor. Therefore the investigators could calculate a) percentage of patients with COPD risk factors in relation to the total number of patients seeking medical care and b) the number of newly COPD cases identified based on spirometry in relation to the total number of patients seeking medical care. A special form for keeping records was provided, where a number of patients with COPD risk factors and total number of patients who visited the investigator during the day was recorded.

Enrollment/Spirometry and preliminary diagnosis Visit.

At the visit the patient signed the Patient's Information Sheet and the Informed Consent Form, then the screening patient's number was assigned to the patient.

When the patient was withdrawn from the study his/her screening number was not used repeatedly.

Patients were identified by the screening number, initials and the date of birth.

The screening number contained 6 digits and comprised of 3-digit site number and 3-digit patient's sequence number, for example: if the site number was 020 and the patient's sequence number was 100, then the study screening patient's number was 020100.

All patients who signed the Informed Consent Form with patient's initials, date of birth and his/her screening number were recorded in a special log.

After signing the Patient's Information Sheet and the Informed Consent Form and assigning the screening number the investigator assured that the patient met all the inclusion criteria and had no exclusion criteria.

The patient had spirometry test during this Visit. Based on the obtained results Investigator established or excluded COPD diagnosis in patient with COPD risk factors.

After "Enrollment/Spirometry and preliminary diagnosis Visit" the Investigator recorded all collected data (including assigned therapy in case of confirmation of COPD diagnosis) in the relevant Case Report Form (CRF) pages.

At the visit the following information was collected:

1. Signing Patient's Information Sheet and Informed Consent Form.
2. Demographic data (date of birth, gender).
3. Height and weight.
4. Reason for the patient's visit to outpatient medical institution.
5. Assessment of the status and intensity of smoking: smoking history (pack-years).

6. Respiratory complaints (dyspnea, cough, sputum).
7. Medical history: respiratory diseases identified earlier.
8. Medical history: use of any short-acting bronchodilator (teofillin, salbutamol, fenoterol etc.).
9. Medical history: clinically significant concomitant diseases.
10. Spirometry test and data collection (FEV1 before and after on bronchial spasmolytic inhalation, FEV1/ FVC (forced vital lung capacity) after bronchial spasmolytic inhalation, reversibility per FEV1).
11. Collection of results of additional tests and/or consultation, if they were performed.
12. Determination or exclusion of COPD diagnosis based of tests, including the results of spirometry.
13. To collect information about the assigned therapy of COPD in case of COPD diagnosis.
14. Patient's Questionnaires completion (patient fills).
15. CAT Questionnaire completion (COPD assessment test).
16. CRF completion.
17. The doctor prescribed Visit "Verification of diagnosis after consultation of the pulmonologist" and refered the patient to the requiring tests in case of additional consultation and test.

Visit "Verification of diagnosis after consultation of the pulmonologist".

This visit was performed by the doctor, if on "Enrollment/Spirometry and preliminary diagnosis Visit" only the provisional diagnosis was determined. The doctor assigned consultation of the specialists and various tests, requiring for determination the definite diagnosis.

Collected on this visit data (types of consultations and tests and obtained results of these tests and consultations) were transferred to CRF by the doctor.

Patient's participation in the study was to be completed upon determination or exclusion of the definite COPD diagnosis. Duration of study participation for every patient in the study depended on the terms when the spirometry and additional consultations (if required) could be performed but not exceed 2 weeks.

Group 2 –Patients with previously diagnosed COPD

The enrollment into group 2 was simultaneously and independently on the enrollment to Group 1. Participation in the study for the group of patients consisted of 1 visit: "Enrollment/Spirometry Visit".

"Study Enrollment visit/Spirometry" could be performed during 7 days. Moreover "Spirometry/End of Study Visit" could be performed on the day of enrollment of patients in the study if it was possible to perform spirometry on the day and consultation, if necessary.

At the Study Enrollment visit the patient signed the Patient's Information Sheet and the Informed Consent Form, then the patient's screening number was assigned to the patient.

When the patient was withdrawn from the study his/her screening number was not used repeatedly.

Patients were identified by the screening number, initials and the date of birth.

The screening number contained 6 digits and comprised of 3-digit site number and 3-digit patient's sequence number, for example: if the site number was 020 and the patient's sequence number was 100, then the study screening patient's number was 020100.

All patients who signed the Informed Consent Form with patient's initials, date of birth and his/her screening number were recorded in a special log.

After signing the Patient's Information Sheet and the Informed Consent Form and assigning him/her the screening number the investigator assured that the patient met all the inclusion criteria and no exclusion criteria.

At the visit the following information was collected:

1. Signing Patient's Information Sheet and Informed Consent Form.
2. Demographic data (date of birth, gender).
3. Height and weight.
4. Reason for the patient's visit to outpatient medical institution.
5. Assessment of the status and intensity of smoking: smoking history (pack-years).
6. The date of establishing the COPD diagnosis, date of the first patient's complaints per COPD, number of COPD exacerbations and number of hospitalizations due to COPD, number of calling emergency service due to COPD for the last year (i.e., within the year prior the current visit date).
7. Respiratory symptoms (dyspnea at rest, dyspnea at walking in the quiet rate on a flat surface, dyspnea at walking at a fast rate or at climbing, nocturnal awakening due to dyspnea, constant sputum, weakness, feeling of fullness in the chest).
8. Medical history: clinically significant concomitant diseases.
9. Information about medicines the patient was currently taking per COPD (except for the drugs prescribed within less than 1 month before the current visit): the brand name and INN, dose, frequency, the date of the treatment start, the treatment duration.
10. Mean number of puffs of short-acting bronchodilators within 24 hours for COPD patient with the brand name and INN of the bronchodilator.
11. Number of outpatient visits due to COPD and the number of hospitalizations due to COPD, as well as mean number of days of disability due to COPD for the previous year (i.e., within the year prior the current visit date).
12. CAT Questionnaire completion by patient (COPD assessment test).
13. Saint George Respiratory Questionnaire completion by patient (SGRQ).
14. Patient's Questionnaire (completed by patient).
15. Spirometry test. Spirometry test and obtained results (FEV1 before and after on bronchial spasmolytic inhalation, FEV1/ FVC (forced vital lung capacity) after bronchial spasmolytic inhalation, reversibility per FEV1).
16. CRF completion.

Duration of participation in the study for every patient in the study depended on the terms when the spirometry could be performed but it did not exceed 7 days.

Patient population

Patents with COPD risk factors and patients with previously diagnosed COPD who had been observed in outpatient medical institutions of the Russian federation were enrolled into the study.

General inclusion criteria for patients with COPD risk factors and patients with previously diagnosed COPD

1. Patients who have signed Patient's Information Sheet with Informed Consent Form and approved proceeding the personal data.
2. Patients who had been planned spirometry test before to the inclusion in the study in accordance to the routine clinical practice.

Inclusion criteria for patients with COPD risk factors

Patients with COPD risk factors were to meet all inclusion criteria.

1. Men and women at the age ≥ 40 years at the moment of inclusion to the study.
2. Smoker or former smoker with smoking history of ≥ 10 pack years. Non-smoking patients were included in the study, if they had been undergone by exposure of household and industrial pollutions (living in house with stove heating).
3. Any prolonged (not less than 3 consequent months) respiratory complaints (cough, dyspnea, sputum, feeling of stiffness in the chest).
4. Patients considered by the investigator to be able to complete themselves questionnaires used in the current study.
5. Patients who have never been previously diagnosed chronic obstructive pulmonary disease (COPD).

Inclusion criteria for patients with previously diagnosed COPD

1. Men and women at the age ≥ 18 years with previously diagnosed COPD, regardless on direct reason of seeking for a doctor.
2. Patients considered by the investigator to be able to complete themselves questionnaires used in the current study.

Exclusion criteria for patients with COPD risk factors and patients with previously diagnosed COPD

Patient with COPD risk factors or patient with previously diagnosed COPD could not meet any of the exclusion criteria. If a patient with COPD risk factors or a patient with previously diagnosed COPD met at least one of the exclusion criteria, the patient was not enrolled into the study.

1. Contraindications for performing spirometry tests (severe state of health of patient, acute coronary syndrome, recent chest injury, tracheostomy, etc.) or other reasons that made impossible participation in the study (any acute condition requiring the emergency care).
2. Condition after lungs, bronchi surgeries (lung resection, trachea surgery).
3. Severe diseases complicating clinical assessment of COPD (active forms of pulmonary tuberculosis, congenital abnormalities of the lungs, cystic fibrosis, lung cancer or cancer of upper airway, tracheal stenosis and any other similar conditions).
4. Asthma - only for patients with COPD risk factors.
5. Participation in any interventional clinical trial.

Primary endpoints

The primary endpoint (for the study in patients with COPD risk factors)

The number of COPD cases identified by the spirometry in relation to the total number of patients who visited the outpatient institutions of the Russian Federation during the study.

The primary endpoints (for the study in patients with previously diagnosed COPD)

1. Percentage of prescriptions for patients with COPD that corresponded to the severity of the condition of the patients according to GOLD classification and GOLD recommendations for the treatment choice.

2. Distribution (%) of patients with COPD who contacted the primary care investigators during the study based on bronchial obstruction severity (GOLD 1-4) and classes according to GOLD classification (2014).

Secondary endpoints

The secondary endpoint (for the study in patients with COPD risk factors)

To determine what percentage of patients who contact the medical institutions of Russian Federation daily can be considered at risk of COPD development.

The secondary endpoints (for the study in patients with previously diagnosed COPD)

1. Mean number of exacerbations that required medical care (outpatient administration of systemic corticosteroids and/or antibiotics) for the last year in COPD patients who received monotherapy with inhaled long-acting and super long-acting bronchodilators (tiotropium, glycopyrronium, formoterol, indacaterol) and in patients who were treated with combined drugs containing inhaled corticosteroids and long-acting β2-agonists.

2. Mean number of hospitalizations for the last year in COPD patients who received monotherapy with inhaled long-acting and super long-acting bronchodilators (tiotropium, glycopyrronium, formoterol, indacaterol) and in patients who were treated with combined drugs containing inhaled corticosteroids and long-acting β2 agonists.

3. Use of rescue drugs for symptoms in COPD patients who received monotherapy with inhaled long-acting and super long-acting bronchodilators (tiotropium, glycopyrronium, formoterol, indacaterol) and in patients who were treated with combined drugs containing inhaled corticosteroids and long-acting β2 agonists.

4. Score on Saint George Respiratory Questionnaire at Study Enrollment Visit in COPD patients who received monotherapy with inhaled long-acting and super long-acting bronchodilators (tiotropium, glycopyrronium, formoterol, indacaterol) and in patients who were treated with combined drugs containing inhaled corticosteroids and long-acting β2 agonists.

5. Score on CAT at Study Enrollment Visit in COPD patients who received monotherapy with inhaled long-acting and super long-acting bronchodilators (tiotropium, glycopyrronium, formoterol, indacaterol) and in patients who were treated with combined drugs containing inhaled corticosteroids and long-acting β2 agonists.

6. Mean number of puffs of short-acting bronchodilators for 24 hours in COPD patients who received monotherapy with inhaled long-acting and super long-acting bronchodilators (tiotropium, glycopyrronium, formoterol, indacaterol) and in patients who were treated with combined drugs containing inhaled corticosteroids and long-acting β2 agonists.

7. To evaluate the percentage of COPD patients in the routine practice of the medical institutions.

8. To evaluate the disease burden based on the collected data on the duration of temporary disability (number of hospitalizations due to COPD exacerbations, calls of emergency service due to COPD, seeking outpatient care due to COPD) for the previous year.

Statistics

Data obtained from patient was analyzed by/using methods of descriptive statistics and presented in the form of n (average) ± SD (standard deviation) or N (number of patients) and % to the total number of patients.

Disposition of subjects

10926 patients with COPD risk factors in 33 study sites were assessed concerning participation in the study, 2722 of whom were included in the study. According to the results of the assessment, 602 (22% of patients included in the study) patients were first time diagnosed with COPD by the primary care doctors. Final verification of the diagnosis was performed by pulmonologists who approved diagnosis of COPD in 82% of cases, namely in 495 patients. In total, 367 patients were included in the analysis.

Out of 3515 patients with already diagnosed COPD, who applied/referred to outpatient institutions within the study period, 1505 patients were included. Thus, 1111 patients were included in the analysis.

Demographical data

The age of patients in both study groups was close. The mean age (and SD) in years was 61.32 (8.53) in the group of patient with first time diagnosed COPD and 64.05 (9.10) in the group of patients with already diagnosed COPD.

In both groups the majority of patients were of male sex. The number of mals was 307 (83.7%) in the group of patient with first time diagnosed COPD and 946 (85.2%) in the group of patients with already diagnosed COPD.

Body weight index of patients in both study groups was close. The mean BWI (and SD) was 25.31 kg (4.83 kg) in in the group of patient with first time diagnosed COPD and 26.10 kg (5.271 kg) in the group of patients with already diagnosed COPD.

Results

Smoking

Among patients, who were first time diagnosed with COPD, 75% of men and 63% of women keep smoking. The men, who were diagnosed with COPD during the study, started smoking at the average age of 17.2 years, women at 21.4 years. The average intensity of smoking is 38.6 pack-years.
Only 72% of respondents suppose that there is casual relationship between smoking and the symptoms of the disease, 58% of respondents announced their desire to quit smoking in the future.
Among patients who were previously diagnosed with COPD (on average about 6 years before inclusion in the study) 51% of men and 38% of women keep smoking.

Socio-economic characteristics of patients

Among patients, who were first time diagnosed with COPD, 43% of men and 27% of women are referred to as working age, but in fact 55% of patients keep working.

In the group of patients with previously diagnosed COPD, 27% of men and 19% of women are of working age. In fact, 38% of patients keep working. The average monthly income of patients in this group is 15.5 thousands rubles.

Medical history of COPD

The average period between the first onset of the symptoms and the diagnosis in the group of patients with first-time diagnosed COPD was 8.9 years, and 26.9% of patients had been using short-acting bronchodilators before they were diagnosed with COPD.

The study demonstrated a high prevalence of simple chronic bronchitis in outpatient practice: 2.8 patients with simple chronic bronchitis per 1 COPD patient in the group of patients with COPD risk factor.

Spirometry

A substantial increase in COPD diagnosis can be expected during screening spirometry: 22 newly identified cases of disease per 100 spirometric tests in patients with COPD risk factors.

Among patients who were first time diagnosed with COPD, patients with moderate (65.7%) and severe (18.0%) airflow limitation (average rate of FEV1 61.2% to normal) and marked symptoms – the average score of CAT 17.5 points prevail. 57.5% of newly identified COPD patients have serious comorbid disease. The mean value for FEV1 of patients with previously diagnosed COPD was 49% to normal rate. At the same time in 3.8% of cases mild obstruction was detected (FEV1≥80%), in 43.2% of cases – moderate (FEV1 ≥50% and <80%), in 41.1% of cases – severe (FEV1≥30% and <50%) and in 11.9% of patient very severe (FEV1 <30%) obstruction.

Distribution of patients by GOLD 2014 groups

The study demonstrated that the patients of GOLD A and GOLD C classes were virtually absent at visit in outpatient treatment facilities – these groups have (consequently) 1.4% and 1.8% of patients respectively. Patients who are considered to be in GOLD D (74.3%) and GOLD B (22.4%) groups prevail.

COPD symptoms

The most common COPD symptoms are dyspnea (in 98% of patients) and cough (in 93% of patients). 43% of patients had mMRC dyspnea score of 1, 41% - mMRC score of 2 and 14% of patients had mMRC dyspnea score of 3-4. 76% of patients noted sputum production/ expectoration.

39% of patients noted nocturnal awakening due to COPD symptoms. Patients with nocturnal awakening have a lower quality of life and a high number of exacerbations.

COPD therapy

The results of the study demonstrate that 32% of patients in GOLD B and D groups do not receive drugs to maintain COPD therapy. Among patients who were prescribed drugs for chronic administration, Tiotropium was the most often prescribed (30.8% of the total volume of prescription). Simbicort is on the second place in terms of prescription\according to the total volume of prescription (18.8%). Seretide is prescribed in 15.5% of cases, and relatively new for the Russian market drugs - indacaterol, glycopyrronium are prescribed in 2.2% and 1.2% of cases respectively.

In 40-45% of cases, when physicians chose for treatment ICS/LABA, they prescribed these drugs in combination with LAMA (in group D3 in 63%). ICS/LABA is/was used even in patients with low risk of exacerbations (group B). 34% of patients with COPD combined with asthma did not receive inhaled corticosteroids.

Clinical COPD phenotypes

Among patients included in the study, 58.5% of patients had frequent exacerbations. 37.4% of patients had combination of frequent exacerbations with bronchitis symptoms and in 14% of patients with frequent exacerbations bronchitis symptoms are absent. 12.9% of patients are part of/belongs to/relates to ACOS phenotype. 35.8% of patients had not/did not have more than 1 COPD exacerbation that did not require hospitalization (see table 9 and figure 9). Patients with different phenotypes differ from each other in a number of variables (are fundamentally diverse on a variety of variables), such as FEV1 value, the severity of the symptoms (CAT), the quality of life (SGRQ), the comorbid diseases etc.