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Original Article

# PHYSICIANS' EXPERIENCE AND WILLINGNESS TO PARTICIPATE IN NON-INTERVENTIONAL TRIALS IN BULGARIA

**Emil S. Kostov,**
**Evgeni E. Grigorov[1],**
**Hristina V. Lebanova[2]**

*Medical College,*
*Medical University - Pleven*
*[1]Faculty of Pharmacy,*
*Medical University - Varna*
*[2]Faculty of Pharmacy,*
*Medical University - Pleven*

**Corresponding Author:**
Hristina V. Lebanova
Faculty of Pharmacy,
Medical University - Pleven
1, Kliment Ohridski Str.
Pleven, 5800
Bulgaria
*e-mail: hristina.lebanova@gmail.com*

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## Summary

Non-interventional studies (NIS) are conducted to obtain additional information about a medicinal product prescribed in the usual manner in compliance with the conditions determined in the marketing authorization. They are a valuable source of real-world data for the effectiveness and safety of medicines. This study aims to assess physicians' knowledge of non-interventional studies in Bulgaria and identify the primary factors and barriers hindering the NIS at a national level. An individual anonymous questionnaire with 16 items was distributed among physicians in inpatient and outpatient settings. The results showed that 81.3% (n=147) of the respondents have no experience with non-interventional studies. Physicians' willingness to participate in NIS in the future is high and independent of their previous experience. The main barriers hindering conducting NIS in Bulgaria are related to organization, the conduct and the design of the trials, and, sometimes, the investigators' concerns. There is a need for proper training of the researchers and expanding healthcare resources to grow the NIS sector in Bulgaria in line with the tendencies in Europe.

**Keywords:** **c**linical trial, post-marketing, non-interventional study, pharmaceutical legislation

## Introduction

Non-interventional studies (NIS) are defined in Article 145 of Medicinal Products in Human Medicine Act in Bulgaria as studies „aiming to obtain additional information about the product prescribed in the usual manner in compliance with the conditions determined in the marketing authorization" [1]. A study is defined as non-interventional when it meets the following criteria:

(1) the prescription of a medicine can be considered current practice, and it is within the marketing authorization;
(2) prescribing the medication is independent of the inclusion of the patient in the trial, and it is not pre-determined by a trial protocol;
(3) epidemiological methods are used to analyze the collected data, and no additional procedures are applied to diagnose or monitor patients.

Nowadays, the number of NIS worldwide is exceptionally high and accounts for about ¼ of all studies conducted [2]. Still, in Bulgaria, the non-

interventional studies sector lags far behind the rate of development worldwide. The reasons are rooted both in the specifics of our legislation and its relation to European practices and researchers' familiarity and the interest in conducting this type of research.

NIS characteristics, namely the lower risk of conducting them, compared to interventional clinical trials, explain why they are not under the scope of Directive 2001/20/EC [3]. According to section 1 of chapter 1.7 of EudraLex, edition 9A, Good Clinical Practice (GCP), recommendations do not apply to post-marketing non-interventional studies.

This study aimed to assess physicians' knowledge of non-interventional studies in Bulgaria and identify the primary factors and barriers hindering the NIS at a national level.

## Materials and Methods

Physicians, independent of their previous experience with NIS, were surveyed with a direct individual anonymous questionnaire. The questionnaire was structured on a funnel principle, starting with general questions and moving on to topics related to the aim of the study. The questionnaire can be conditionally divided into two parts, which groups of similar questions:

- The first part included five demographic questions regarding age, sex, specialty, and type of medical practice.
- The second part included 11 questions. They aimed to assess the experience and familiarity of the respondents with interventional and non-interventional trials and examine the opinion of physicians on the factors influencing the conduct of these studies in Bulgaria.

Of the 16 questions, 8 of which were closed, three were open, and four were semi-open. The survey also contained 1 Likert scale.

For the analysis, the data collected from the questionnaires could be divided into three categories:

- demographic data about questions about sex, age, location, years of practice, and specialty;
- experience related to clinical trials, including inquiries related to previous experience with clinical trials and the number of clinical trials;
- benefits and factors pertaining to non-interventional studies, including questions related to the benefits of conducting NIS and the factors accompanying the conduct of trials.

The data obtained from the questionnaire were analyzed with SAS Version 9 [4] using descriptive statistics [5]. Several responses, arithmetic mean, median, standard deviation, minimum and maximum value, are presented [6]. To summarize the quality parameters, the number and percentage of respondents in each category are provided using all non-missing data. Pearson's test was used to check whether the differences between the subgroups were statistically significant [6]. We used a 5% significance level for each comparative analysis.

## Results

A total of 411 respondents completed the questionnaire. Out of these, 156 (38%) were men, while 254 (61.8%) were women. Data on the sex of 1 respondent is missing. A total of 236 respondents filled in their age, and 66.1% had more than 16 years of working experience. The respondents' average age was 47.18 years (median 49 years, range 26-70 years) (Table 1).

Less than half of them - 169 (41.1%) had had previous experience with clinical trials, while 242 (58.9%) had no experience. Based on this parameter, the sample was divided into two groups, and the data is presented concerning the subgroups.

The specialty summary shows that a total of 154 respondents filled in the question regarding their specialty. The specialties are equated to Annexes 2A of the National Health Insurance Fund. Some of the respondents had more than one specialty, and each specialty was counted as a separate category. The summarized statistics showed that half of the respondents who stated their specialties were specialists in the following four areas: pediatrics, internal medicine, pneumology and phthisiology, and cardiology. However, the respondents marked a total of 23 different specialties.

Out of the 411 respondents, 169 (41.1%) had clinical trials experience, with most of them

**Table 1.** Demographic characteristics of respondents

| Category | Total (n=411) |
|---|---|
| **Years of experience** | |
| 5-10 years (n, %) | 73 (17.8%) |
| 11-15 years (n, %) | 52 (12.7%) |
| 16-20 years (n, %) | 91 (22.1%) |
| >20 years (n, %) | 181 (44%) |
| Missing (n, %) | 14 (3.4%) |
| **Place of practice** | |
| City (n, %) | 185 (45%) |
| District capitals (n, %) | 124 (30.2%) |
| Capital (n, %) | 57 (13.9%) |
| Village (n, %) | 34 (8.3%) |
| Missing (n, %) | 11 (2.7%) |
| **Specialty*** | |
| Pediatrics (n, %) | 47 (28.8%) |
| Internal Diseases (n, %) | 18 (11.0%) |
| Pneumology and Phthisiology (n, %) | 18 (11.0%) |
| Cardiology (n, %) | 16 (9.8%) |
| Psychiatry (n, %) | 12 (7.4%) |
| Obstetrics and Gynecology (n, %) | 6 (3.7%) |
| Dermatology (n, %) | 5 (3.1%) |
| Microbiology (n, %) | 5 (3.1%) |
| Neurological diseases (n, %) | 5 (3.1%) |
| Endocrinology and Metabolic Diseases (n, %) | 4 (2.5%) |
| General Practitioner (n, %) | 4 (2.5%) |
| Anesthesiology and Intensive Care (n, %) | 3 (1.8%) |
| Neonatology (n, %) | 3 (1.8%) |
| Rheumatology (n, %) | 3 (1.8%) |
| Ear-nose-throat diseases (n, %) | 2 (1.2%) |
| Clinical Toxicology (n, %) | 2 (1.2%) |
| Diagnostic Imaging (n, %) | 2 (1.2%) |
| Occupational diseases (n, %) | 2 (1.2%) |
| Surgery (n, %) | 2 (1.2%) |
| Pediatric Pneumology and Phthisiology (n, %) | 1 (0.6%) |
| Clinical Laboratory (n, %) | 1 (0.6%) |
| Ophthalmology (n, %) | 1 (0.6%) |
| Emergency Medicine (n, %) | 1 (0.6%) |
| Missing** (n, %) | 257 |

** Physicians with more than one specialty are summarized in different categories, according to their specialties. The percentages are calculated based on the field completion.*

*** Shows the number of respondents for whom the specialty is not stated. The percentage is not presented, as the specialty is summarized according to the information given by respondents.*

**Table 2.** Summary of demographic parameters from experience in interventional and non-interventional clinical trials

| Category | Experience with clinical trials (n, %) | | Experience with Non-Interventional Studies (n, %) | |
|---|---|---|---|---|
| | Yes (n=169, 41.1%) | No (n=242, 58.9%) | Yes (n=81, 19.7%) | No (n=147, 81.3%) |
| **Sex** | | | | |
| Male | 68 (40.2%) | 88 (36.4%) | 32 (39.6%) | 52 (35.4%) |
| Female | 100 (59.2%) | 154 (63.6%) | 48 (59.2%) | 95 (64.6%) |
| Missing | 1 (0.6%) | 0 (0%) | 1 (1.2%) | 0 (0%) |
| Age (Years) | | | | |
| Mean (SD) | 48.69 (9.53) | 46.13 (11.30) | 49.04 (9.96) | 45.49 (10.94) |
| Median | 50 | 46 | 50 | 44 |
| **Experience as a physician (Years)** | | | | |
| 5-10 | 15 (8.9%) | 58 (24.0%) | 7 (8.6%) | 33 (22.4%) |
| 11-15 | 17 (10.0%) | 35 (14.4%) | 10 (12.3%) | 18 (12.2%) |
| 16-20 | 47 (27.8%) | 44 (18.2%) | 23 (28.4%) | 19 (13.0%) |
| >20 | 88 (52.1%) | 93 (38.4%) | 41 (50.7%) | 69 (47.0%) |
| Missing | 2 (1.2%) | 12 (5.0%) | 0 (0%) | 8 (5.4%) |
| **Place of practice** | | | | |
| City | 63 (37.3%) | 122 (50.5%) | 25 (30.8%) | 60 (40.9%) |
| District capitals | 60 (35.4%) | 64 (26.4%) | 37 (45.8%) | 45 (30.6%) |
| Capital city | 42 (24.9%) | 15 (6.2%) | 17 (21.0%) | 15 (10.2%) |
| Village | 2 (1.2%) | 32 (13.2%) | 1 (1.2%) | 19 (12.9%) |
| Missing | 2 (1.2%) | 9 (3.7%) | 1 (1.2%) | 8 (5.4%) |
| **Specialty*** | | | | |
| Pediatrics | 29 (28.4%) | 18 (30.0%) | 14 (20.9%) | 14 (35.8%) |
| Internal Diseases | 16 (15.7%) | 2 (3.3%) | 14 (20.9%) | 1 (2.6%) |
| Pneumology and Phthisiology | 15 (14.7%) | 3 (5.0%) | 14 (20.9%) | 2 (5.1%) |
| Cardiology | 13 (12.7%) | 3 (5.0%) | 9 (13.3%) | 4 (10.2%) |
| Psychiatry | 5 (4.9%) | 7 (11.7%) | 1 (1.5%) | 6 (15.3%) |
| Obstetrics and Gynecology | 1 (1.0%) | 5 (8.3%) | 0 (0%) | 0 (0%) |
| Skin and Venereal Diseases | 3 (2.9%) | 2 (3.3%) | 2 (3.0%) | 0 (0%) |
| Microbiology | 3 (2.9%) | 2 (3.3%) | 2 (3.0%) | 0 (0%) |
| Neurological diseases | 2 (2.0%) | 3 (5.0%) | 1 (1.5%) | 2 (5.1%) |
| Endocrinology and Metabolic Diseases | 2 (2.0%) | 1 (1.7%) | 2 (3.0%) | 1 (2.6%) |
| General Practitioner | 0 (0%) | 4 (6.7%) | 0 (0%) | 3 (7.7%) |
| Anesthesiology and Intensive Care | 3 (2.9%) | 0 (0%) | 2 (3.0%) | 0 (0%) |
| Neonatology | 2 (2.0%) | 1 (1.7%) | 2 (3.0%) | 0 (0%) |
| Rheumatology | 3 (2.9%) | 0 (0%) | 2 (3.0%) | 1 (2.6%) |
| Ear-nose-throat diseases | 1 (1.0%) | 1 (1.7%) | 1 (1.5%) | 0 (0%) |
| Clinical Toxicology | 0 (0%) | 2 (3.3%) | 0 (0%) | 1 (2.6%) |
| Diagnostic Imaging | 0 (0%) | 2 (3.3%) | 0 (0%) | 1 (2.6%) |
| Occupational diseases | 0 (0%) | 2 (3.3%) | 0 (0%) | 0 (0%) |

| Category | Experience with clinical trials (n, %) | | Experience with Non-Interventional Studies (n, %) | |
|---|---|---|---|---|
| | Yes (n=169, 41.1%) | No (n=242, 58.9%) | Yes (n=81, 19.7%) | No (n=147, 81.3%) |
| Surgery | 2 (2.0%) | 0 (0%) | 1 (1.5%) | 0 (0%) |
| Pediatric Pneumology and Phthisiology | 1 (1.0%) | 0 (0%) | 0 (0%) | 1 (2.6%) |
| Clinical Laboratory | 1 (1.0%) | 0 (0%) | 0 (0%) | 1 (2.6%) |
| Ophthalmology | 0 (0%) | 1 (1.7%) | 0 (0%) | 0 (0%) |
| Emergency Medicine | 0 (0%) | 1 (1.7%) | 0 (0%) | 1 (2.6%) |
| Missing** | 75 | 182 | 21 | 109 |

** Doctors with more than one specialty are summarized in different categories, according to their specialties. The percentages are calculated based on the field completion.*

*** Shows the number of respondents for whom the specialty is not filled. The percentage is not presented, as the specialty was summarized according to the specialties mentioned in the questionnaires.*

having participated in 0 - 5 clinical trials (n=119, 29.0%). A group of 31 (7.5%) of the respondents had experience with 6 - 10 clinical trials, 5 (1.2%) of the respondents had had experience with 11 to 20 clinical trials. In comparison, 15 (3.6%) respondents had participated in over 20 clinical trials.

Most physicians considered themselves either not familiar with non-interventional studies (n=147, 35.8%) or rather unfamiliar (n=80, 19.5%). The main sources of information for such trials were everyday medical practice (n=127, 30.9%), publications in the peer-reviewed journals (n=106, 25.8%), medical conferences (n=100, 24.3%), university studies (n=29, 7.1%) and other (7, 1.7%). The proportion of the respondents with experience in NIS was even smaller – only 81 (19.7%) claimed to have participated in a NIS. The average number of NIS they had participated in was 2.58 (range 1-30).

Table 2 summarizes the experience with interventional and non-interventional trials dependent on the respondents' demographic characteristics and medical specialty. Most experienced in both interventional and non-interventional trials were physicians practicing in the following areas – pediatrics, internal diseases, pneumology and phthisiology, cardiology, and psychiatry.

The majority of all respondents (n=248, 60.3%) would prefer to participate in non-interventional studies in the future. Of the remainder, 47 (11.4%) declared they intended not to participate in this type of research. In comparison, 113 (27.5%) were hesitant at the time of the survey (Table 3).

There were some significant differences in their opinions based on clinical trial experience. Among respondents with experience in clinical trials, 79.9% were willing to work on non-interventional studies in the future. Among respondents without expertise in clinical trials, only 46.7% expressed a desire to work on non-interventional studies in the future. In contrast, 16.1% stated that they were unwilling to work on this type of study in the future, and 36.8% could not judge. A similar trend was observed if we consider the respondents' answers according to their experience with non-interventional studies. The relative share of respondents with experience with non-interventional studies, who stated that they would work again on this type of research, was higher (n=71, 87.7%) than the relative share of respondents without experience with non-interventional studies (n=135, 73.8%).

Factors hindering the conduct of non-interventional studies are presented in Table 4. The factors were divided into three groups: group 1 - related to the organization and conducting the trial; group 2 - associated with the design of the non-interventional study; and group 3 - related to the investigators. Among the most important in each group were:

lack of healthcare resources ($p<0.05$) and lack of trained researchers ($p<0.05$);

lack of clinical and scientific rationale of the studies ($p<0.05$), increasing complexity in study design ($p<0.05$) and lack of benefit for the patients ($p<0.05$);

**Table 3.** Willingness to participate in NIS

| | Total n=411 | Experience with clinical trials (n, %) | | Experience with Non-Interventional Studies (n, %) | |
|---|---|---|---|---|---|
| | | Yes n=169 | No n=242 | Yes n=81 | No n=147 |
| **Would you participate in NIS as a researcher in the future?** | | | | | |
| Yes | 248 (60.3%) | 135 (79.9%) | 113 (46.7%) | 71 (87.7%) | 135 (73.8%) |
| No | 47(11.4%) | 8 (4.7%) | 39 (16.1%) | 2 (2.5%) | 13 (7.1%) |
| Cannot answer | 113(27.5%) | 24 (14.2%) | 89 (36.8%) | 6 (7.4%) | 34 (18.6%) |
| Missing | 3 (0.7%) | 2 (1.2%) | 1 (0.4%) | 2 (2.5%) | 1 (0.5%) |
| **Why would you participate in NIS?** | | | | | |
| Missing | 354(86.1%) | 144(85.2%) | 210(86.8%) | 72 (88.9%) | 156 (85.2%) |
| Lack of enough information | 13 (3.2%) | 4 (2.4%) | 9 (3.7%) | 0 (0%) | 4 (2.2%) |
| To gain experience | 9 (2.2%) | 4 (2.4%) | 5 (2.1%) | 2 (2.5%) | 5 (2.7%) |
| They benefit patients and medical knowledge | 7 (1.7%) | 6 (3.6%) | 1 (0.4%) | 3 (3.7%) | 3 (1.6%) |
| It is interesting | 6 (1.5%) | 3 (1.8%) | 3 (1.2%) | 0 (0%) | 2 (1.1%) |
| Source of additional income | 4 (1%) | 4 (2.4%) | 0 (0%) | 2 (2.5%) | 2 (1.1%) |
| Lack of time | 4 (1%) | 1 (0.6%) | 3 (1.2%) | 0 (0%) | 3 (1.6%) |
| Source of experience and knowledge | 2 (0.5%) | 0 (0%) | 2 (0.8%) | 0 (0%) | 1 (0.5%) |
| Depends on the type of study | 2 (0.5%) | 1 (0.6%) | 1 (0.4%) | 1 (1.2%) | 1 (0.5%) |
| Gaining in-depth knowledge on a topic | 2 (0.5%) | 0 (0%) | 2 (0.8%) | 0 (0%) | 1 (0.5%) |
| Lack of interest | 2 (0.5%) | 1 (0.6%) | 1 (0.4%) | 1 (1.2%) | 0 (0%) |
| Additional experience and additional income | 1 (0.2%) | 0 (0%) | 1 (0.4%) | 0 (0%) | 1 (0.5%) |
| Gaining in-depth knowledge, additional experience and knowledge | 1 (0.2%) | 0 (0%) | 1 (0.4%) | 0 (0%) | 0 (0%) |
| End of career | 1 (0.2%) | 0 (0%) | 1 (0.4%) | 0 (0%) | 1 (0.5%) |
| Lack of motivation | 1 (0.2%) | 0 (0%) | 1 (0.4%) | 0 (0%) | 1 (0.5%) |
| Lack of experience | 1 (0.2%) | 0 (0%) | 1 (0.4%) | 0 (0%) | 1 (0.5%) |
| They benefit patients and medical knowledge, additional experience | 1 (0.2%) | 1 (0.6%) | 0 (0%) | 0 (0%) | 1 (0.5%) |

**Table 4.** Factors hindering the conduct of NIS

| Factor | Experience in clinical trials | Total n=411 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Likert scale* | | | | | | p-value** | Subgroups*** | | |
| | | 1 | 2 | 3 | 4 | 5 | Missing | | Not a problem | Neutral | Problem |
| **Related to the organization and conduct of the trials:** | | | | | | | | | | | |
| **Lack of time** | No n=242 | 28 (11.6%) | 33 (13.6%) | 41 (16.9%) | 20 (8.3%) | 9 (3.7%) | 111 (45.9%) | 0.576 | 61 (25.2%) | 41 (16.9%) | 129 (12.0%) |
| | Yes n=169 | 18 (10.7%) | 36 (21.3%) | 38 (22.5%) | 25 (14.8%) | 8 (4.7%) | 44 (26%) | | 54 (32.0%) | 38 (22.5%) | 133 (19.5%) |
| **Lack of healthcare resources** | No n=242 | 26 (10.7%) | 20 (8.3%) | 38 (15.7%) | 35 (14.5%) | 12 (5.0%) | 111 (45.9%) | 0.049 | 46 (19.0%) | 38 (15.7%) | 147 (19.4%) |
| | Yes n=169 | 15 (8.9%) | 16 (9.5%) | 56 (33.1%) | 23 (13.6%) | 15 (8.9%) | 44 (26.0%) | | 31 (18.3%) | 56 (33.1%) | 138 (22.5%) |
| **Lack of medical equipment** | No n=242 | 22 (9.1%) | 22 (9.1%) | 46 (19.0%) | 29 (12.0%) | 11 (4.5%) | 112 (46.3%) | 0.307 | 44 (18.2%) | 46 (19.0%) | 140 (16.5%) |
| | Yes n=169 | 14 (8.3%) | 34 (20.1%) | 41 (24.3%) | 27 (16.0%) | 9 (5.3%) | 44 (26.0%) | | 48 (28.4%) | 41 (24.3%) | 136 (21.3%) |
| **Lack of patients** | No n=242 | 14 (5.8%) | 44 (18.2%) | 43 (17.8%) | 23 (9.5%) | 7 (2.9%) | 111 (45.9%) | 0.151 | 58 (24.0%) | 43 (17.8%) | 130 (12.4%) |
| | Yes n=169 | 25 (14.8%) | 35 (20.7%) | 47 (27.8%) | 14 (8.3%) | 5 (3.0%) | 43 (25.4%) | | 60 (35.5%) | 47 (27.8%) | 119 (11.2%) |
| **Lack of trained researchers** | No n=242 | 5 (2.1%) | 26 (10.7%) | 47 (19.4%) | 42 (17.4%) | 11 (4.5%) | 111 (45.9%) | 0.021 | 31 (12.8%) | 47 (19.4%) | 153 (21.9%) |
| | Yes n=169 | 16 (9.5%) | 29 (17.2%) | 45 (26.6%) | 23 (13.6%) | 13 (7.7%) | 43 (25.4%) | | 45 (26.6%) | 45 (26.6%) | 136 (21.3%) |
| **Related to the design of the non-interventional studies** | | | | | | | | | | | |
| **Lack of clinical and scientific rational of the studies** | No n=242 | 11 (4.5%) | 39 (16.1%) | 54 (22.3%) | 23 (9.5%) | 4 (1.7%) | 111 (45.9%) | 0.003 | 50 (20.7%) | 54 (22.3%) | 127 (11.2%) |
| | Yes n=169 | 27 (16.0%) | 40 (23.7%) | 27 (16.0%) | 24 (14.2%) | 6 (3.6%) | 45 (26.6%) | | 67 (39.6%) | 27 (16%) | 130 (17.8%) |
| **Increasing complexity in study design** | No n=242 | 2 (0.8%) | 29 (12.0%) | 49 (20.2%) | 47 (19.4%) | 4 (1.7%) | 111 (45.9%) | 0.001 | 31 (12.8%) | 49 (20.2%) | 151 (21.1%) |
| | Yes n=169 | 13 (7.7%) | 27 (16.0%) | 58 (34.3%) | 22 (13.0%) | 4 (2.4%) | 45 (26.6%) | | 40 (23.7%) | 58 (34.3%) | 126 (15.4%) |
| **NIS cannot benefit patients** | No n=242 | 9 (3.7%) | 33 (13.6%) | 57 (23.6%) | 27 (11.2%) | 5 (2.1%) | 111 (45.9%) | 0.017 | 42 (17.4%) | 57 (23.6%) | 132 (13.2%) |
| | Yes n=169 | 26 (15.4%) | 29 (17.2%) | 45 (26.6%) | 17 (10.1%) | 6 (3.6%) | 46 (27.2%) | | 55 (32.5%) | 45 (26.6%) | 123 (13.6%) |

| Factor | Experience in clinical trials | Total n=411 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Likert scale* | | | | | | p-value** | Subgroups*** | | |
| | | 1 | 2 | 3 | 4 | 5 | Missing | | Not a problem | Neutral | Problem |
| **Rising cost of research procedures, which is not covered by the sponsor** | No n=242 | 1 (0.4%) | 22 (9.1%) | 54 (22.3%) | 42 (17.4%) | 11 (4.5%) | 112 (46.3%) | 0.094 | 23 (9.5%) | 54 (22.3%) | 53 (21.9%) |
| | Yes n=169 | 9 (5.3%) | 23 (13.6%) | 50 (29.6%) | 32 (18.9%) | 9 (5.3%) | 46 (27.2%) | | 32 (18.9%) | 50 (29.6%) | 41 (24.3%) |
| **Increasing requirements for research documentation** | No n=242 | 1 (0.4%) | 15 (6.2%) | 53 (21.9%) | 44 (18.2%) | 19 (7.9%) | 110 (45.5%) | 0.412 | 16 (6.6%) | 53 (21.9%) | 63 (26.0%) |
| | Yes n=169 | 5 (3.0%) | 17 (10.1%) | 50 (29.6%) | 34 (20.1%) | 17 (10.1%) | 46 (27.2%) | | 22 (13.0%) | 50 (29.6%) | 51 (30.2%) |
| **Related to the investigators:** | | | | | | | | | | | |
| **Disrupting everyday medical practice** | No n=242 | 17 (7.0%) | 42 (17.4%) | 39 (16.1%) | 29 (12.0%) | 4 (1.7%) | 111 (45.9%) | 0.57 | 59 (24.4%) | 39 (16.1%) | 33 (13.6%) |
| | Yes n=169 | 21 (12.4%) | 41 (24.3%) | 39 (23.1%) | 18 (10.7%) | 5 (3.0%) | 45 (26.6%) | | 62 (36.7%) | 39 (23.1%) | 23 (13.6%) |
| **Low budgets for the investigators provided by the sponsor of the NIS** | No n=242 | 3 (1.2%) | 27 (11.2%) | 54 (22.3%) | 38 (15.7%) | 8 (3.3%) | 112 (46.3%) | 0.213 | 30 (12.4%) | 54 (22.3%) | 46 (19.0%) |
| | Yes n=169 | 7 (4.1%) | 16 (9.5%) | 57 (33.7%) | 31 (18.3%) | 12 (7.1%) | 46 (27.2%) | | 23 (13.6%) | 57 (33.7%) | 43 (25.4%) |
| **Negative effect on physician-patient relationship** | No n=242 | 14 (5.8%) | 40 (16.5%) | 44 (18.2%) | 23 (9.5%) | 9 (3.7%) | 112 (46.3%) | 0.003 | 54 (22.3%) | 44 (18.2%) | 32 (13.2%) |
| | Yes n=169 | 38 (22.5%) | 27 (16.0%) | 36 (21.3%) | 18 (10.7%) | 5 (3.0%) | 45 (26.6%) | | 65 (38.5%) | 36 (21.3%) | 23 (13.6%) |
| **Concerns about potential adverse drug reactions** | No n=242 | 2 (0.8%) | 23 (9.5%) | 39 (16.1%) | 49 (20.2%) | 18 (7.4%) | 111 (45.9%) | <0.001 | 25 (10.3%) | 39 (16.1%) | 67 (27.7%) |
| | Yes n=169 | 18 (10.7%) | 27 (16%) | 50 (29.6%) | 25 (14.8%) | 5 (3%) | 44 (26%) | | 45 (26.6%) | 50 (29.6%) | 30 (17.8%) |
| **Insufficient qualification of medical personnel for conducting the studies** | No n=242 | 6 (2.5%) | 16 (6.6%) | 44 (18.2%) | 48 (19.8%) | 19 (7.9%) | 109 (45.0%) | 0.001 | 22 (9.1%) | 44 (18.2%) | 67 (27.7%) |
| | Yes n=169 | 20 (11.8%) | 23 (13.6%) | 47 (27.8%) | 23 (13.6%) | 12 (7.1%) | 44 (26.0%) | | 43 (25.4%) | 47 (27.8%) | 35 (20.7%) |

** Respondents' responses were collected using a Likert scale, where 1 means "No problem" and 5 means "Major problem";*

*** The P-value presented is from a Pearson test. Values below 0.05 indicate that the difference in groups for a given parameter is statistically significant. In contrast, values above 0.05 indicate that the difference is not statistically significant.*

**** The subgroups are defined as follows - (1) Index 1 and index 2 of the Likert scale correspond to „No problem"; (2) Index 3 of the Likert scale corresponds to „Neutral"; (3) Index 4 and index 5 on the Likert scale correspond to „Problem";*

*Note: Percentages are calculated on rows based on respondents with or without experience in clinical trials, respectively.*

negative effect on the physician-patient relationship ($p<0.05$), concerns about potential adverse drug reactions ($p<0.05$), and insufficient qualification of medical personnel for conducting the studies ($p<0.05$).

## Discussion

Non-interventional studies are a valuable source of real-world data for medicine's effectiveness and safety [7,8]. Such studies are helpful not only for medical practitioners and scientific knowledge but also for regulatory authorities and payers [9]. Being low-risk studies, they provide the opportunity to involve a wide array of physicians in various settings (both inpatient and outpatient) with a more significant number of patients. Last but not least, Non-interventional studies can be conducted at a significantly lower cost than interventional studies [10].

The low awareness of medical professionals indirectly involved in conducting clinical trials about NIS suggests the need for additional information campaigns among them. Our results prove that Bulgarian physicians are willing to participate in NIS in the future despite the lack of experience. The practical barriers are mainly related to the design of the NIS and the investigators' perception of their benefit. The main concerns stated were safety, lack of proper training of the researchers, and stringent healthcare resources. Also, there are statistically significant differences in respondents' opinions, based on whether they had or did not have experience conducting NIS compared to other respondents. This difference proves that physicians significantly change their attitude and thoughts about non-interventional trials with acquiring expertise in the field. The established limiting factors differ from those highlighted in the "NIS Development Strategy" published by the Ministry of Health and the regulatory restrictions [11].

## Conclusion

Physicians in Bulgaria are more experienced and knowledgeable about interventional clinical trials than non-interventional studies. The proportion of medical practitioners participating in a NIS is twice as small as those with experience in clinical trials. Nevertheless, the majority of them are willing to participate in a non-interventional study in the future. The main barriers to developing the sector of NIS in Bulgaria are the lack of trained medical professionals and healthcare resources and fear for patients' safety, and possible unwanted effects on the physician-patient relationship.

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