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STUDY OF THE ROLE AND PARTICIPATION OF THE PHARMACIST IN CLINICAL TRIALS OF MEDICINAL PRODUCTS

ABSTRACT

INAUGURAL-DISSERTATION

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The public defense of the dissertation will take place on …… ..2022 by ……. hours in hall 501 of the Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski", Sofia

CONTENTS

ABBREVIATIONS USED

Abbreviations in Cyrillic:

TFEU - Treaty on the Functioning of the EU

LLSAHM - Law on Medicinal Products and Pharmacies in Human Medicine

ZLPHM - Law on Medicinal Products in Human Medicine

ZLAHM - Law on Medicines and Pharmacies in Human Medicine

EMA - European Medicines Agency

AMA - American Medical Association

SG - State Gazette

LZ - medical institution

EEC - European Economic Community

EU - European Union

DCP - Good clinical practice

LP - Medicinal product (s)

DILP - Dossier of investigational medicinal product

DIO - Contract research organization (s)

BDA - Executive Agency for Medicines

Latin abbreviations:

CRA - Clinical Trials Associate

IMP - research medicinal product

ICH - International Conference on Harmonization of Technical Requirements for the Registration of Medicinal Products for Human Use

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyzes

GCP - ICH - Good clinical practice of ICH

FDA - Food and Drug Administration

ERB - Ethical Evaluation Committees

IRB - Institutional Review Board

IEC - Independent Ethics Committee

WHO - World Health Organization

EudraCT - European Union Drug Regulating Authorities Clinical Trials Database

I. INTRODUCTION

The beginning of modern European regulatory practice in the field of medicinal products was set in 1965 with the adoption of Council Directive 65/65 / EEC of 26 January 1965. The Directive lays the foundations for the approximation of laws, regulations and administrative provisions relating to medicinal products. products between EU Member States. A fundamental goal of all rules for the production, distribution and use of medicinal products is the protection of public health by providing quality, safe and effective medicinal products for European citizens. Directive 65/65 / EEC requires that any application for marketing authorization (marketing authorization) of a medicinal product be accompanied by a dossier containing information, documents and evidence of the results of tests and clinical trials performed with the product. Uniform rules are established for the conduct of analytical, pharmacotoxicological and clinical trials of medicinal products and uniform rules are introduced for the compilation of dossiers of medicinal products, as well as for their presentation. EU Member States recognize that the basic principles for conducting clinical trials on humans must be based on the protection of human rights and human dignity in the conduct of medical research, in accordance with the Declaration of Helsinki. The protection of participants in a clinical trial shall be ensured by a risk assessment based on the results of toxicological tests prior to each clinical trial, by controls carried out by ethics committees and the competent authorities of the Member States, and by data protection rules. . In the context of Directive 65/65 / EEC, the requirements for conducting clinical trials in the EU are detailed in Directive 2001/20 / EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the European Union. Member States on the application of good clinical practice in the conduct of clinical trials on medicinal products for human use. The Directive introduces into regulatory practice the principles of Good Manufacturing Practice for Research Medicinal Products and the Principles of Good Clinical Practice, which become mandatory for all Member States. The Guide to Good Clinical Practice is becoming a key document setting out the rules for conducting clinical trials. Good clinical practice is the set of internationally recognized ethical and scientific quality requirements that are met in the planning, conduct, reporting and reporting of clinical trials. Compliance with these requirements ensures public protection and protection of the rights, safety and health of participants in the trial in accordance with the principles set out in the Declaration of Helsinki, as well as the scientific value and reproducibility of clinical trial data. The purpose of the GCP rules is to provide a single standard for the European Community, Japan and the United States in order to facilitate the mutual recognition of clinical trial data by their regulatory authorities. The GCP rules have been developed taking into account current good clinical practices in the European Community, Japan and the United States, as well as those in Australia, Canada, the Nordic countries and the World Health Organization. These rules must be followed when generating data from clinical trials that will be submitted to regulatory authorities. The principles set out in the GCP can also be applied to other clinical trials that could have an impact on human safety and health. Each clinical trial is led by a Principal Investigator. The principal investigator is the physician or dentist designated by the contracting authority, who directs the overall conduct of the clinical trial at the center in accordance with the approved protocol and

the GCP manual and is responsible for the work of the investigators. A researcher is a doctor or dentist appointed by the sponsor and the principal investigator who conducts the clinical trial under the direction of the principal investigator in accordance with the approved protocol and the GCP manual at the clinical trial research center. Good clinical practice also defines specific functions for pharmacists, although not exhaustively, such as:

1. The specialist pharmacist or student of pharmacy explicitly falls within the definition of "Vulnerable groups of patients" - "Persons whose desire to participate in a clinical trial may be influenced by expectations of benefits or their position vis-à-vis senior staff in the hierarchy, related to participation or refusal to participate, for example: medical students, dentistry, pharmacy or nurses, employees in the pharmaceutical industry, serving in the army and persons deprived of their liberty. Other at-risk participants are patients with incurable diseases, the elderly, the unemployed or beggars, patients in emergencies, ethnic minority groups, the homeless, vagrants, minors and those who are unable to consent. "

2. Responsibilities of pharmacists with respect to the "investigational medicinal product": The investigator is responsible for the reporting of the investigational medicinal product at the site of the clinical trial. The researcher may delegate some or all of his / her reporting responsibilities to the pharmacist or other appropriate person under the direction of the researcher, where permissible or required. The researcher and / or pharmacist or other person designated by the researcher shall keep the records of the medicinal products received at the venue, an inventory of the products at the center, the quantities used by each participant and returned to the sponsor.These documents contain dates, quantities, batches and numbers, expiration date (where possible) and unique code numbers that indicate the medicinal products and participants. Researchers shall keep records indicating that participants have received the appropriate doses specified in the plan and confirmation and accountability of all medicinal products received from the sponsor. " 3. Involvement of pharmacists in research teams: If the clinical trial is conducted by a team, the principal investigator is responsible for the team. The research team may include - doctors, dentists, pharmacists, biostatistics, nurses, laboratory assistants, PhD students, specialists and others. at the discretion of the principal investigator and in accordance with the clinical trial protocol. Ten years of experience in the application of Directive 2001/20 / EC have been reported twice in 5-year periods, with both positive and negative sides and disadvantages being identified by Member States. Based on long-term analyzes and discussions with stakeholders, a decision was made at EU level to draw up new rules for conducting clinical trials and, as a final result, Regulation (EU) № 536/2014 of the European Parliament was published on 16 April 2014. Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20 / EC. The Regulation introduced a new conceptual system for "Clinical study", "Clinical trial", "Low-intervention clinical trial", "Non-interventional study", Tested medicinal product, etc. The authorization procedures, the importance of the Committees on Ethics, Monitoring, Control, etc. have completely changed. The regulation has radically changed perceptions of clinical trials of medicinal products (PM) and the functions of medical professionals. The Regulation recognizes the claimed protection of human dignity and the right to the integrity of the individual as recognized in the Charter of Fundamental Rights of

the European Union ("the Charter"). In particular, the Charter requires that any intervention in the field of biology and medicine cannot be carried out without the free and informed consent of the person concerned. Directive 2001/20 / EC contains an extensive set of rules for the protection of participants. These rules are preserved in the new Regulation. The regulation outlines clear rules for cooperation with the WHO, the International Conference on Harmonization (ICH), the World Medical Association, the Council of the Organization for Economic Co-operation and Development (OECD). The Regulation is in full compliance with Directive 95/46 / EC and Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of individuals with regard to the processing of personal data by the institutions, bodies, offices and agencies. Union agencies and on the free movement of such data by the Member States under the supervision of their competent authorities and builds on the legal norms contained in the Treaty on the Functioning of the EU (TFEU).

In the present dissertation we will study scientific, regulatory and scientific-practical rules and norms determining the place, role, participation and functions of masters of pharmacy in clinical trials of medicinal products in humans. We will consider the place of the pharmacist in compliance with scientific quality requirements in the planning, conduct, reporting and reporting of clinical trials, production of research medicinal products, in accordance with good manufacturing and good laboratory practice, ethical norms and standards, activities of Ethics Committees , monitoring, preparation of the Researcher's Brochure, control, sanctions, etc.

II. GOALS AND TASKS

II.1. Goals

1.1. To analyze and identify the scientific, regulatory, scientific-applied and legal opportunities for pharmacists to participate in clinical trials, research and non-interventional studies of drugs, their functions and responsibilities, rights and obligations, and opportunities for professional realization.

1.2. To determine the actual participation of pharmacists in Bulgaria in clinical trials for the period 2016 - 2019, incl. II.

2. Tasks

2.1. To analyze the current regulatory framework for conducting clinical trials of medicinal products in Bulgaria, in the context of Bulgaria's membership in the EU.

2.2. To identify possible places for professional realization of pharmacists in the various stages of clinical trials, in accordance with current applicable law.

2.3. To examine with objective tools the readiness of hospital pharmacists to participate in clinical trials and non-interventional studies of medicinal products, in accordance with the latest regulatory changes in Ordinance № 28 of December 9, 2008 (amended and supplemented SG No. 81 of October 20, 2015).

2.4. To study the compliance of Principal Investigators in clinical trials to hire and work with hospital pharmacists in accordance with the requirements of the GCP and regulatory changes.

2.5. To study and evaluate the readiness of hospital pharmacists to participate in clinical trials and non-interventional studies of medicinal products among clinical trial associates / specialists (clinical monitors).

III. MATERIALS AND METHODS

The main methods used for the preparation of this dissertation are documentary analysis, content analysis and survey method.

1. We conducted an analysis of the content of the legislation at European and national level in order to outline the current regulatory framework for conducting clinical trials of medicinal products in Bulgaria, in the context of Bulgaria's EU membership, and which allows masters of pharmacy to participate. in clinical trials.

2. We conducted "content analyzes" of the Good Clinical Practice Guide to determine the possible functions of pharmacists in clinical trials.

3. Questionnaire method.

We conducted three (3) prospective, longitudinal, multicenter surveys in Bulgaria.

QUESTIONNAIRE № 1: Analysis of the readiness of hospital pharmacists to participate in clinical trials and non-interventional studies of medicinal products.

We have developed a questionnaire containing 10 closed-ended questions. Data collection was performed using the "direct individual survey" method.

The target group is 98 masters of pharmacy working as hospital pharmacists throughout the country.

Study period - 2017 – 2019

Data were processed using descriptive statistical methods with the software product SPSS version 19.

QUESTIONNAIRE № 2: Measurement of compliance of Principal Investigators in clinical trials to hire and work with hospital pharmacists in accordance with the requirements of the GCP and regulations.

We have developed a questionnaire containing 10 closed-ended questions. Data collection was performed using the "direct individual survey" method.

The target group is 42 doctors who participated in clinical trials of medicinal products as principal investigators in various centers in the country.

Study period - 2017 - 2019

Data were processed using descriptive statistical methods with the software product SPSS version 19.

QUESTIONNAIRE № 3: Study to assess the readiness of hospital pharmacists to participate in clinical trials and non-interventional studies of medicinal products among clinical trial associates / specialists (clinical monitors).

We have developed a questionnaire containing 10 closed-ended questions.

Data collection was performed using the "direct individual survey" method.

The target group is 48 collaborators / clinical trial specialists who have participated in clinical trials of medicinal products as monitors, across the country.

Study period - 2017 - 2019

Data were processed using descriptive statistical methods with the software product SPSS version 19.

IV. RESULTS FROM OWN RESEARCH AND ANALYSIS

IV.1. RESULTS BY TASK 2.1. - Analysis of the current regulatory framework for conducting clinical trials of medicinal products in Bulgaria, in the context of Bulgaria's membership in the EU.

Regulation (EU) № 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use and repealing Directive 2001/20 / EC was published on 16 April 2014. The final provisions provide for the Regulation to enter into force on 26 May 2016. A transitional period of three years is foreseen, during which the tests for which an application for authorization was submitted before the entry into force of the Regulation will continue to be regulated. of Directive 2001/20 / EC and the two regulatory systems will overlap. The new legal framework represents a significant innovation in the procedures for authorizing and conducting clinical trials across the EU. A new set of harmonized rules is being established, which all Member States must apply to all clinical trials conducted throughout the European Union. The regulation provides new possibilities for processing the documentation of clinical trials in all subsequent stages of the process. A single authorization is introduced to be valid for all Member States of the Community. A single electronic portal is being set up, through which all data relating to each clinical trial conducted throughout the European Union will pass. The need to revise and improve the regulatory framework for clinical trials has been substantiated and endorsed in the light of the problems identified during the operation of Directive 2001/20 / EC. Achieving a broad public and political consensus led to the amendment and repeal of the directive and the adoption of the new general regulation. The reasons for the creation of the new regulation can be considered in various aspects. One of the main reasons for this radical legal change is the difficulties experienced in conducting clinical trials of varying degrees of application of Directive 2001/20 / EC by national competent authorities. Careful consideration of the process of implementing Directive 2001/20 / EC in different countries shows high levels of bureaucracy, which greatly influences the planning and implementation of clinical trials in different countries. Administrative problems are often related to the implementation of the administrative requirements of the directive, and examples of unjustified requirements can be given. These problems were also expressed in the need for multiple applications involving more than one Member State. Another important change is the limitation of the long and uncertain time intervals required for the authorization of a clinical trial in the various regulatory bodies in the countries of the European Union. The shortcomings and uncertainties provided by the directive in the fast-growing clinical trial sector have led to debate and discussion on how to change this.

As a result of these discussions, it was decided by all Member States to create a common European regulation to be implemented by the entire European Union, thus making the European Union a more competitive environment for conducting clinical trials. Through the implementation of a regulation in this area, an application is made for the provision of equal conditions and prevention of administrative burdens. The implementation of Regulation (EU) № 536/2014 necessitates national reorganization combined with processes improving coordination and cooperation between the national competent authorities of the Member

States and the ethics committees. National approaches and reforms mainly cover administrative organization and coordination, with an emphasis on the work of ethics committees. It is envisaged that a reduced number of ethics committees will be involved in the approval of clinical trials of medicinal products in the Member States. This measure introduces a liberal approach to the evaluation of applications for clinical trials and will reduce the administrative burden of conducting them. The regulation is too long and detailed, it contains 99 articles, which are divided into 19 chapters, and 7 annexes are part of it. Because it is a regulation, not a directive, it is immediately applicable and binding in all Member States, without the need to be transposed into the various legislations of the Member States. "A regulation is a legislative act of the European Union that is immediately enforceable, as a rule, in all Member States at the same time. Regulations differ in principle from directives, which are not directly applicable but must first be transposed into the national law of the Member States. Regulations may be adopted by different legislative procedures depending on their subject matter. " The creation of regulations is particularly important for the synchronization of European legislation. The main objective of the regulations is to achieve a homogeneous right throughout the European Union. They are binding in their entirety in all Member States. Homogeneous legislation throughout the European Union provides new opportunities for the development of various fields, and is also of great importance in the field of medicine. The harmonization of legislation, in particular on clinical trials, provides preconditions for a new stage in their development and implementation throughout the Union. A uniform legislative framework would allow for better planning and management of each project. The new Regulation (EU) № 536/2014 on clinical trials on medicinal products is part of the European regulatory framework through which the European Commission gives a strong impetus to research and industrial progress. This is new legislation that fills a number of regulatory gaps in clinical trials by creating a single framework for authorizing clinical trials by all Member States concerned with a single evaluation of results. Each clinical trial shall be subject to prior assessment of compliance with scientific and ethical standards and shall be authorized in accordance with the provisions of Regulation (EU) (536/2014. The assessment of compliance with ethical standards shall be carried out by the Ethics Committee in accordance with the law of the Member State concerned. Member States shall ensure that the timing and procedures for evaluation by the Ethics Committee are consistent with the timing and procedures set out in A thorough review of the definitions and objectives of the new document allows to define and monitor the following - there is a clear guarantee that authorization procedures will be efficient and fast - Figures 4 and 5, Table 6. Also, simplification of specific obligations of sponsors . On the other hand, the public interest is protected by ensuring public access to information about clinical trials - their conduct and results. Direct cooperation between Member States is being established and to this end the European Medicines Agency (EMA) will set up and maintain an electronic portal and database for clinical trials at EU level. The new legislative document addresses various features and details of conducting a clinical trial. An important emphasis is on the rules for the labeling of investigational medicinal products as well as auxiliary medicinal products. Regulation (EU) № 536/2014 on clinical trials of medicinal products for human use includes clear safety reporting rules (adverse reactions and unexpected serious adverse reactions) and strict protection of certain categories of persons, including compensation for harm. Regulation

(EU) № 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use was introduced in accordance with the principles set out in the Helsinki Declaration on Clinical Trials.

IV.2. RESULTS BY TASK 2.2. To identify possible places for participation and professional realization of pharmacists in the various stages of clinical trials, in accordance with current applicable law. Each clinical trial is led by a Principal Investigator. The principal investigator shall be the physician or dentist designated by the Contracting Authority, who shall direct the overall conduct of the clinical trial, in accordance with the approved protocol and the GCP manual, and shall be responsible for the work of the investigators.

A researcher is a doctor or dentist appointed by the sponsor and the principal investigator who conducts the clinical trial under the direction of the principal investigator in accordance with the approved protocol and the GCP manual at the clinical trial research center.

Art. Article 63 (1) of Regulation (EU) № 536/2014 provides that investigational medicinal products shall be manufactured using manufacturing practices that guarantee the quality of those medicinal products in order to ensure the safety of participants and the reliability and sustainability of clinical data, derived from the clinical trial ("good clinical practice").

Good clinical practice also defines specific functions for pharmacists, although not exhaustively, such as:

1. The specialist pharmacist or student of pharmacy explicitly falls within the definition of "Vulnerable groups of patients" - "Persons whose desire to participate in a clinical trial may be influenced by expectations of benefits or their position vis-à-vis senior staff in the hierarchy, related to participation or refusal to participate, for example: medical students, dentistry, pharmacy or nurses, employees in the pharmaceutical industry, serving in the army and persons deprived of their liberty. Other at-risk participants are patients with incurable diseases, the elderly, the unemployed or beggars, patients in emergencies, ethnic minority groups, the homeless, vagrants, minors and those who are unable to consent. "

2. Responsibilities of pharmacists with respect to the "investigational medicinal product": The investigator is responsible for the reporting of the investigational medicinal product at the site of the clinical trial. The researcher may delegate some or all of his / her reporting responsibilities to the pharmacist or other appropriate person under the direction of the researcher, where permissible or required.

The researcher and / or pharmacist or other person designated by the researcher shall keep the documents for the medicinal products received at the venue, an inventory of the products in the center, the quantities used by each participant and returned to the sponsor or in an additional place. These documents contain dates, quantities, batches and numbers, expiration date (where possible) and unique code numbers that indicate the medicinal products and participants. Researchers keep documents stating that they are participants received the

appropriate doses specified in the plan and confirmation and reporting of all medicinal products received by the sponsor. "

The last decade has seen a significant increase in the number of clinical trials worldwide, and this opens up a number of new opportunities for those wishing to work in the research and science industry. The design, coordination and analysis of a clinical trial requires a multidisciplinary team consisting mainly of principal and sub-researchers, clinical research coordinators, pharmacists and clinical trial specialists (CRAs).

The pharmacist involved in the overall process of a clinical trial plays a fundamental role in the way clinical trials are conducted, contributing in various forms to the trial process. The pharmacist can use his experience and cooperate directly in various pharmaceutical aspects such as determination of drug composition and monitoring of indications, dosage, application, contraindications, side effects and interactions of investigational medicinal products. In addition, pharmacists can help ensure the safety of participants and their rights, which are mainly protected by ethics committees and the various country-specific regulatory bodies.

For each of these functions, the pharmacist must be familiar with the clinical trial protocol, the informed consent form, the researcher's brochure, and the standard operating procedures of the research center, which include regulatory, ethical, and legal requirements.

The role of pharmacists is to ensure that the dispensing and receipt of the medicine is recorded in the trial documentation or in the interactive voice response system.

The pharmacist is also primarily responsible for dispensing drugs, as are other researchers. In clinical trials, it is very common for patients to make mistakes with their prescribed medications, and in many cases the pharmacist is the first to detect and report and document this.

3. Quality system of medicinal products. The quality system of the medicinal products, which is required by the manufacturer, according to art. 5 of Commission Delegated Regulation (EU) № 2017/1569 and which is properly designed, established and verified by the manufacturer must be described in written procedures, in accordance with the applicable law for investigational medicinal products described in EudraLex, Volume 4, Part I, Chapter 1.

The production of investigational medicinal products is more complex than authorized medicinal products due to the lack of fixed practices, the existence of various designs and hypotheses for the conduct of clinical trials and the subsequent design of packaging. The processes of randomization and coding contribute to increasing complexity with further increasing the risk of cross-contamination of the product and mixing of products. In addition, information on the potential and toxicity of the product may be incomplete and there may be no full process validation. It is even more possible to use authorized products that have been repackaged or modified in any way. These challenges require the availability of staff with excellent knowledge and training in the application of good manufacturing practice for investigational medicinal products. The pharmacist is a highly qualified specialist who can play a key role in the creation and control of these processes. The increased complexity of

production operations requires the use of a highly efficient quality system to be implemented and managed by the pharmacist.

4. Product specifications and manufacturing instructions may be changed during development, but control and follow-up of changes must be properly documented and maintained. Deviations from pre-defined specifications and instructions must be recorded and investigated, with appropriate corrective and preventive measures. Procedures must be flexible in order to be able to adapt to the changes that occur with increasing knowledge of the processes and must be appropriate to the product development phase.

Well-qualified and trained pharmacists can play an active role in implementing and controlling change.

There may be an additional risk to patients in the manufacture of medicinal products for clinical trials compared to those treated with authorized medicinal products.

The role of the pharmacist as a specialist familiar with the application of good manufacturing practice in the manufacture and import of investigational medicinal products aims to ensure that participants are not exposed to undue risk and the results of clinical trials will not be compromised by inadequate quality. safety or efficacy resulting from unsatisfactory production or import conditions.

Pharmaceutical staff may cooperate in order to ensure the continuity of batch quality with the same investigational medicinal product used in the same or different clinical trials, and that changes during the development of the investigational medicinal product will be adequate. documented and substantiated.

5. The product specification file must be kept up to date with the progress of product development, providing an appropriate traceability to previous versions. The file must include or refer to at least the following documents:

5.1. Specifications and analytical methods for starting materials, packaging materials, intermediates, bulk products and finished products;

5.2. Production methods;

5.3. Testing and methods during the production process;

5.4. Approved copy of the label;

5.5. Appropriate authorizations for clinical trials and their modifications, clinical trial protocol and randomization codes, as appropriate;

5.6. Appropriate technical agreements with contracting authorities and contractors, as appropriate;

5.7. Stability Plan and reports;

5.8. Details of plans and measures for reference and retention samples;

5.9. Storage and transport conditions;

5.10. Information on the supply chain, including the places of manufacture, packaging, labeling and testing of investigative medicinal products, if possible in the form of a comprehensive diagram. The pharmacist, a member of a team for the creation and review of a product specification plays an important role in the creation and review of this document. Pharmacists have extensive scientific knowledge and qualifications that allow free handling of the necessary principles and terminology in order to create and develop the document - product specification.

6. The selection, qualification, approval and maintenance of suppliers of starting materials, including their purchase and acceptance, must be documented as part of the quality system of medicinal products in order to ensure the integrity of the supply chain and to prevent the supply of counterfeit products. All personnel involved in the manufacture, import, storage and handling of investigational medicinal products must be properly trained in relation to the requirements specific to these types of products. The pharmacist is a suitable participant in the control system because he has the necessary qualifications in order to track specific markers of various processes.

7. The level of supervision must be commensurate with the risks posed by the individual materials, taking into account their source, the manufacturing process, the complexity of the supply chain and the end use of the material in the investigational medicinal products. The supporting evidence for each supplier's approval and approval of the materials must be properly documented and maintained. Pharmacists can play an active role in tracking risks and identifying and documenting problems. While documented problems can be used for risk assessment and the implementation of new procedures in order to increase quality as a result of supervision.

8. Staff. The requirements for staff are set out in Article 6 of the Commission Delegated Regulation (EU) № 2017/1569. Where applicable, EudraLex, Volume 4, Part I, Chapter 2 should also be taken into account. The specified requirements are namely:

8.1 At each manufacturing site, the manufacturer must have a sufficient number of competent personnel with the necessary qualifications to be able to ensure that the quality of the investigational medicinal products is required for the use for which they are intended.

8.2 The duties of the management and supervisory staff, including the qualified persons responsible for the implementation and application of good manufacturing practice, shall be defined in their job descriptions. Hierarchical relationships are defined in an organization chart. The organization chart and job descriptions shall be approved in accordance with the manufacturer's internal procedures.

8.3 Such staff shall be given sufficient authority to perform their duties properly.

8.4 Staff shall be provided with initial and follow-up training, covering in particular the following areas:
(a) theory and practical application of the concept of quality in the manufacture of medicinal products;
b) good manufacturing practice. The manufacturer checks the effectiveness of the training.

8.5 The manufacturer shall develop hygiene programs, including procedures relating to the health, hygiene practices and clothing of staff. The programs are adapted to the performed production operations. The manufacturer guarantees compliance with the programs.

All personnel involved in the manufacture, import, storage and handling of investigational medicinal products must be properly trained in relation to the requirements specific to these types of products. Even when the number of staff involved in the manufacture or import of investigational medicinal products is small, individual persons responsible for the production and quality control must be designated for each batch.

Through his high knowledge of the details of the various regulatory provisions and requirements, the pharmacist can cooperate in the initial and subsequent training of staff, as well as identify gaps in training. The organization of subsequent refresher training in order to comply with the established high standards in the manufacture of medicinal products.

9. Qualified person. The responsibilities of the qualified person are set out in Article 62 of Regulation (EU) № 536/2015 and further clarified in Article 12 of the Commission Delegated Regulation (EU) № 2017/1569. According to Directive 2001/83 / EC:

A qualified person holds a diploma, certificate or other evidence of formal qualifications obtained after completing a university course of study or a course recognized as equivalent by the Member State concerned for at least 4 years of theoretical and practical training in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology. However, the minimum duration of a university course may be three and a half years if followed by a year-long course of theoretical and practical training, including a 6-month course in pharmacy in a public pharmacy, certified by an examination at university level. In the case of two university courses or the coexistence of two courses recognized by the State as equivalent in a Member State, and if one lasts four years and the other three years, the three-year course culminating in a diploma, certificate or other official certificate a qualification obtained after completing a university course or a recognized equivalent shall be considered eligible for duration under the second subparagraph in so far as diplomas, certificates or other evidence of formal qualifications obtained on completion of both courses are recognized as equivalent by the State concerned.
The course includes theoretical and practical training based on at least the following basic subjects at a minimum: experimental physics; general and inorganic chemistry; organic chemistry; Analytical Chemistry; pharmaceutical chemistry, including analysis of medicinal

products; general and applied biochemistry (medical); physiology; microbiology pharmacology; pharmaceutical technology; toxicology; pharmacognosy (study of the composition and effects of natural active ingredients of plant and animal origin).

Training in these subjects should be balanced so as to enable the person concerned to fulfill the obligations set out in Article 51. As some of the diplomas, certificates or other evidence of formal qualifications referred to in the first subparagraph do not meet the criteria laid down with this paragraph, the competent authorities of the Member State shall certify that the person concerned holds a certificate of the necessary knowledge of the subjects covered above.

The qualified person shall be required to have at least two years' practical experience in one or more establishments authorized for the manufacture of medicinal products, to have participated in the qualitative analysis of medicinal products, in the quantitative analysis of active substances and in the testing and testing of medicinal products. medical products.

The qualified person authorizing the use of the finished batch of investigational medicinal products for clinical trials must ensure that there are systems in place that meet the requirements of good manufacturing practice and have excellent knowledge of the development of medicinal products, clinical trial processes and the supply chain for the relevant lot. The pharmacist meets the criteria for education provided to a qualified person in accordance with the envisaged regulatory framework. Pharmacists therefore have a key role to play in fulfilling the above responsibilities.

10. Documentation. The documentation must be generated and controlled in accordance with the principles described in detail in EudraLex, Volume 4, Part I, Chapter 4. The retention period of the instructions and documents required to demonstrate compliance with Good Manufacturing Practice should be determined accordingly. of the type of document, subject to the requirements of Article 8 of the Commission Delegated Regulation (EU) № 2017/1569. The documentation also includes the product specification file.

10.1. The documents included in the Product Specification Dossier shall be kept for a period of at least 5 years. The manufacturer introduces and maintains a documentation system in which, depending on the activities performed, the following information is recorded: specifications; production formulas; production and packaging instructions; procedures and protocols, incl. procedures for general production operations and conditions; records relating in particular to the various production operations carried out and records relating to the lots; technical agreements; certificates of analysis;

10.2. The documentation system guarantees the quality and completeness of the data. The documents are clear and error-free and are kept up to date.

10.3. The manufacturer shall keep the product specification file and batch documentation for at least five years after completion or termination of the last clinical trial in which the batch was used.

10.4. When using electronic, photographic or other data-processing systems, the manufacturer shall first validate the systems to ensure that the data will be stored properly during the storage period referred to in paragraph 3. The data stored by such systems must be easily retrieved. in readable format.

10.5. Electronically stored data is protected against unauthorized access, loss or damage to data by methods such as duplication or backup and transfer to another storage system. Audit trails are maintained, ie. records of all relevant changes and deletions in this data.

10.6. Upon request, the documentation shall be provided to the competent authorities.
The documentation must be generated and controlled in accordance with the principles set out above. Pharmacists are the only medical professionals who have the competencies above - to participate in all stages of documenting the processes, as well as in the control of various types of documentation.

11. The sponsor has specific responsibilities for keeping the basic clinical trial dossier and is obliged to keep this documentation for at least 25 years after the end of the trial. The clinical trial master file shall be archived in such a way as to ensure that it is easily accessible upon request by the competent authorities. If the sponsor and the manufacturer are different persons, the sponsor must agree with the manufacturer to fulfill the sponsor's requirement to keep the basic clinical trial dossier.
The agreement on the storage of such documents and the type of documents to be retained must be specified in an agreement between the sponsor and the manufacturer. The pharmacist may participate in the archiving process by observing the basic requirements for archiving in order to meet the requirements set out in the regulatory framework.
12. Participation of pharmacists in research teams. The research team may include doctors, dentists, pharmacists, biostatistics, nurses, laboratory assistants, doctoral students, specialists and others. at the discretion of the principal investigator and in accordance with the clinical trial protocol.

13. Coordinating Commission. A commission, which may be appointed by the contracting authority, to coordinate the conduct of multicenter clinical trials. Because the Contracting Authority must implement a quality management system at all stages of the testing process. The contracting authority must focus on the test activities that are essential to ensure the protection of people and the reliability of the test results.
The pharmacist can play an active role in quality management, including the design of effective clinical trial protocols and tools and procedures for data collection and processing, and the collection of information that is essential for decision-making.

The pharmacist may be part of a coordinating committee that monitors the quality of the overall process when conducting multicenter clinical trials.

14. Coordinating researcher. Researcher appointed to coordinate researchers from the various centers involved in the multicenter trial.
A pharmacist may be appointed as a coordinating researcher by performing activities related to the management of the activities related to the investigational medicinal product. The main activity is to coordinate the activities related to the delivery of the investigational product; providing training to pharmacists at the research center; developed study-specific documents, including guidelines for pharmacy pharmacists; communication with stakeholders, including distributors and third parties; observed treatment appointments; and quality assurance monitoring to ensure compliance with institutional and international regulations on the supply and storage of the investigational medicinal product.

15. Contract Research Organization (DIO). A natural or legal person or scientific organization that has entered into a contract with the contracting authority to perform one or more of the test functions and obligations of the contracting authority.

As an alternative to the specific work as a pharmacist in a research project, to have the role of assistant / coordinator in order to help the researcher comply with the requirements of the research project, aiming to obtain reliable test results and ensure the well-being of participants, participants in the trial, and the documentation is reliable and complete in order to accurately assess the safety and effectiveness of the test therapy. The accuracy of the data entry is verified by a clinical trial monitor / specialist, who is also responsible for assessing whether the clinical trial was conducted in accordance with the GCP / ICH and applicable laws. All clinical trials require continuous data and safety monitoring, which is sent to the Data Management Committee for each sponsor. Through follow-up visits, a clinical trial monitor / specialist can act as a liaison between the sponsor and the research center.

16. Direct access. Authorization to examine, analyze, verify and reproduce all records and reports relevant to the evaluation of a post-authorization clinical trial. Each party (eg local or foreign regulatory authorities, contracting authority monitors and verifiers) with direct access shall take all necessary precautions in accordance with applicable regulatory requirements to maintain the confidentiality of participants' identities and information held by the contracting authority. The pharmacist may be part of audit and / or inspection committees in order to monitor and establish control over the application of regulatory requirements and compliance with the prescribed clinical protocol.

17. Documentation. All records in any form (including, but not limited to, written, electronic, magnetic, optical, electroencephalographic, radiographic, electrocardiogram, chromatogram) describing or recording the method, conduct and / or test result, factors affecting the test and the action taken.

The pharmacist has a direct and essential role in documenting the main processes in the conduct of the clinical trial, both the specific processes in the release of the medicinal product and in the production and all research activities.

18. Independent witness. A person who: does not participate and has no interest in the clinical trial; cannot be influenced by test participants; attend the signing of the informed consent if the participant or his / her legal representative cannot read, and read the informed consent form and any other written information provided to the participants. The pharmacist may act as an independent witness if there is no direct or indirect interest in the clinical trial. In this case, it can help to read and acquaint the patient / participant with the necessary information.

19. Inspection. Official inspection by the control authorities of documents, conditions, archives and all other sources of data which they consider relevant to the clinical trial and which may be kept at the place of the clinical trial, the contracting authority's / DIO's office or other places, which these control bodies consider appropriate. The pharmacist may be part of audit and / or inspection committees in order to monitor and establish control over the application of regulatory requirements and compliance with the prescribed clinical protocol.

20. Institution (medical). Medical establishments where clinical trials are conducted. The pharmacist may be a representative of a medical institution, in making a decision to participate and concluding a contract with the Assignor, in order to provide a pharmaceutical service necessary for the fulfillment of the requirements for the granting of medicinal products.

21. Interim clinical trial report. Report on the provisional results of the study and their evaluation based on analyzes performed during the clinical trial. The pharmacist may be involved in the preparation of partial reports and their analysis of the interim results of clinical trials.

22. Tested medicinal product. A investigational medicinal product is a dosage form of an active substance or placebo that is being tested or used as a comparison in a clinical trial, including products for which a marketing authorization has been granted but is used for an unauthorized indication or for additional information on the authorized form , or are completed (dosage form or packaged) in a different way from the permitted form.

The pharmacist has an active role in the administration and dispensing of medicinal products in clinical trials.

At the same time, the pharmacist may provide additional drug randomization to patients if delegated to this activity, as well as cooperate with the research team at all stages of prescribing the medicinal product and the possible concomitant risks of taking the investigational medicinal product and possible drug interactions and adverse events.

23. Researcher. A researcher is a doctor or dentist appointed by the sponsor and the principal investigator who conducts the clinical trial under the direction of the principal investigator in accordance with the approved protocol and the DCI manual of the clinical trial research center. If the clinical trial is conducted by a team, the researcher is the team leader and is called the principal investigator. The pharmacist can be part of the research team, playing a significant role in conducting the clinical trial.

24. Researcher's brochure. Document containing all clinical and non-clinical data on investigational medicinal product (s) relevant to the use of investigational medicinal products on humans. The pharmacist may be involved in the preparation and updating of the Researcher's Brochure document, in particular in the part concerning pharmacological and / or pharmacodynamic / pharmacokinetic data.

25. Monitoring. Action to monitor the development of the clinical trial and ensure that it is conducted, recorded and reported in accordance with the protocol, SOP, DCP and applicable regulatory requirements. The pharmacist may participate in the active monitoring / verification of data obtained and documented by the research teams, aiming to document the observed adverse events, as well as all activities accompanying the conduct of the clinical trial.

26. Monitoring report. Written report from the monitoring person to the contracting entity after each site visit and / or any test-related communication under the contracting authority's SOP. The pharmacist can prepare or verify monitoring reports on the monitoring of data collected by the research team. Quality Assurance. All planned and systematic actions that are established to ensure that the data are received, documented (recorded) and reported and that the test is conducted in accordance with the GCP and applicable regulatory requirements.

27. The pharmacist may be involved in the development of systems and protocols to ensure the correct and reliable documentation of the data obtained.

28. Quality control. Working techniques and actions taken within the quality assurance system to verify that the quality requirements of the test activities are met. The pharmacist may perform quality control functions in order to ensure compliance with the quality requirements in conducting clinical trial activities.

29. Regulatory bodies. National competent authorities for quality control, efficacy and safety of medicinal products, as well as bodies that evaluate the submitted clinical documentation and conduct inspections. The pharmacist may be part of teams assessing quality control, efficacy and safety of investigational medicinal products.

30. The pharmacist, as part of the research team, may report serious adverse events as required by the regulations and the test report. At the same time, the pharmacist can participate in the evaluation of the data obtained on adverse drug events.

IV.3. RESULTS BY TASK 2.3. To examine with objective tools the readiness of hospital pharmacists to participate in clinical trials and non-interventional studies of medicinal products, in accordance with the latest regulatory changes in Ordinance № 28 of December 9, 2008, as amended. and ext. DV. no. 81 of 20 October 2015

In this section we will present the results of the Survey № 1: Analysis of the readiness of hospital pharmacists to participate in clinical trials and non-interventional studies of medicinal products.

The study included 98 masters of pharmacy working as hospital pharmacists in hospitals across the country.

Study period - 2017 - 2019

The distribution by gender is even, with the largest share of respondents in the age range 41-50.

In order to monitor whether the interviewed master pharmacists continue their training and conduct additional specialization courses.

Less than half of the respondents have acquired an additional clinical and / or non-clinical specialty. Those who have indicated an additional specialty have specialized in three main scientific fields - "Clinical Pharmacy", "Organization and Economics of Pharmacy" and "Hospital Pharmacy".

The majority of the surveyed hospital pharmacists do not have an additional specialization in Hospital Pharmacy, due to the fact that by mid-2016 such a specialty has not been approved. In 2016, the Ministry of Health approved a curriculum for specialization in "Hospital Pharmacy". The specialization program is in line with the general framework for the specialty of the European Association of Hospital Pharmacy. The purpose of this specialization is to train specialists working in the health system who perform specific activities and to provide highly specialized services related to the selection, preparation, storage, preparation and distribution of medicines and medical devices in hospitals. The work experience of the interviewees is in the range between 1 and 30 years, only three hospital pharmacists indicate that they have more than 30 years of experience in the field of hospital pharmacy. The main groups of respondents state that they have more than 5 years of experience in the field of hospital pharmacy. These results show that people working in the field have enough experience, which gives the opportunity to advise medical professionals and patients on the safe, effective and efficient use of drugs in order to achieve better results in drug therapy of patients.

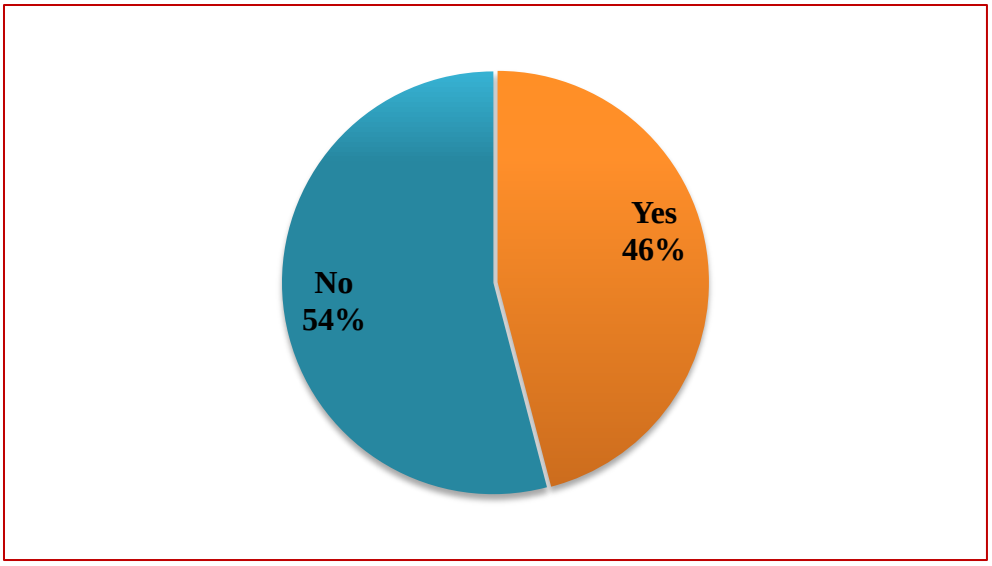

Figure 1. Question "Have you successfully completed good clinical practice training?"

Considering the obtained results, it is observed that the predominant number of respondents do not have successfully completed training in good clinical practice. This trend is easily predictable due to the fact that at the time of the survey, very few hospital pharmacists were included in the research teams.

At the time of the survey, 65% of hospital pharmacists surveyed had not participated in clinical trials. These results show that the introduction of the new regulation is likely to lead to an increase in their number. This, in turn, provides an opportunity to improve the quality of clinical trials in Bulgaria, due to the participation of specialists who will strictly comply with the requirements for storage and handling of research medicinal products.

The majority of respondents have not participated in clinical trials to date and have not conducted Good Clinical Practice training. After analyzing the data obtained, only 17 of the surveyed hospital pharmacists confirmed that they were familiar with the nature of non-interventional studies of medicinal products. The majority of respondents state that they are not familiar or are not fully acquainted, they need additional information. This correlates with the fact that most of them have not completed a course in good clinical practice. Further efforts are needed on further training in this area. Each member of the research team should be trained in GCP rules and then be eligible to participate in a test.

More than half of the respondents stated that they did not know the nature and differences between interventional and non-interventional clinical trials.

The results are shown, which show that only 23% of the surveyed hospital pharmacists confirm that they are well acquainted with the duties of the hospital pharmacist as part of the clinical trial team. Hospital pharmacists need to receive additional training on the nature of clinical trials. The majority of the surveyed master pharmacists in hospital pharmacies declare their desire to participate in additional training to acquire knowledge of good clinical practice

and regulations regarding the pharmacist's participation in clinical trials. Most of the respondents need additional training on the nature of the amendments to Ordinance № 28 of December 9, 2008, as amended. and ext. DV. No. 81 of October 20, 2015, effective as of January 1, 2017 for clinical trials. It is also observed that the majority of pharmacists surveyed indicate that the medical institutions have not taken sufficient action to bring their organization to work in line with the adopted changes.

IV.4. RESULTS BY TASK 2.4. Let's study the compliance of the Chief Researchers in Clinical Trials to hire and work with hospital pharmacists in accordance with the requirements of the GCP and regulatory changes.

We have developed a questionnaire containing 10 closed-ended questions. Data collection was performed using the "direct individual survey" method. The target group is 42 doctors who participated in clinical trials of medicinal products as principal investigators in various centers in the country.

Study period - 2017 - 2019

Data were processed using descriptive statistical methods with the software product SPSS version 19

The gender distribution of the respondents shows that the predominant principal researchers surveyed are men. The main age group of the respondents is over 40 years old. The main researchers surveyed indicated their acquired specialty. From the presented results it can be concluded that specialists were interviewed - chief researchers from different fields of medicine.

Respondents state that they have more than 10 years of work experience. This shows that most of the surveyed doctors have many years of experience in the field of medicine. This gives them the opportunity to know in detail the system of healthcare, monitoring and communication with patients.

The surveyed principal investigators state that they have more than 10 years of experience as medical specialists, as well as participation in a large number of clinical trials as principal investigators.

More than half of the respondents confirmed that they had experience with more than 50 patients who participated in clinical trials with medicinal products in the last year alone. This enabled the surveyed researchers to gain experience in the field of clinical trials with medicinal products, as well as communication and monitoring of participants. They may provide a reasoned position on the clinical part of the clinical trials. The majority of respondents confirm that they are familiar with the differences between interventional and non-interventional studies, which confirms that specialists have experience in the field and creates preconditions for future participation in a clinical trial.

The presented data show that most of the main researchers are aware of the differences between the differences between interventional (clinical trials) and non-interventional studies of medicinal products.

Over 60% of the respondents say that they have a problem with the process of conducting clinical trials. This speaks to a misunderstanding of part of the process and difficulty for principal investigators to carry out their work on these projects, which should necessitate changes aimed at further training these researchers. The majority of principal investigators indicate that they have difficulty in the overall process of storing investigational medicinal products, as part of clinical trials or non-interventional studies.

More than half of the respondents indicated that they are not or are not fully aware of the changes in Ordinance № 28 of December 9, 2008, as amended. and ext. DV. No. 81 of October 20, 2015 /, regulating the mandatory participation of hospital pharmacists, as part of the research team of each clinical trial. Respondents indicate that they expect the inclusion of a pharmacist in the research team to improve the organization and process of storage and release of investigational medicinal products.

This would improve the storage conditions of the research product under appropriate conditions, tracking the availability of the investigational medicinal product, receiving and dispensing the investigational product, monitoring the overall condition of patients and identifying, reporting probable drug interactions, and in some specific and specific cases - The pharmacist is blinded and aware of the medicinal product of each patient, unlike some of the research team (including the principal investigator) who are blinded and do not know which product the patient is on.

The main source of information on the changes in the legislation related to the nature of clinical trials are the contracted research organizations, a smaller part of the respondents in this study indicated that they were informed about the changes in the regulations for clinical trials of drugs by the administration of the medical institution.

It is observed that the majority of the surveyed researchers point out that the medical establishments have not taken sufficient actions to bring their organization to work in accordance with the adopted changes.

The majority of respondents indicated that they had received information about the changes from contracted research organizations. They also point out reservations about the implementation of the mandatory participation of Master Pharmacists as part of their research teams.

IV.5. RESULTS BY TASK 2.5. Study to assess the readiness of hospital pharmacists to participate in clinical trials and non-interventional studies of medicinal products among clinical trial associates / specialists (clinical monitors).

We have developed a questionnaire containing 10 closed-ended questions.

Data collection was performed using the "direct individual survey" method. T

he target group is 48 collaborators / clinical trial specialists who have participated in clinical trials of medicinal products as monitors, across the country.

Study period - 2017 - 2019

Data were processed using descriptive statistical methods with the software product SPSS version 19.

From the processed results it is observed that both sexes are equally represented in the survey. The main age group of the respondents is between 25 and 40 years old. The surveyed clinical trial specialists indicated that they have a master's degree.

Among the clinical trial specialists surveyed, 62% indicated that they have a medical specialty. In many clinical trial companies, the medical specialty is the criteria for hiring.

Among the respondents, the majority state that they have between 6 and 10 years of work experience as a clinical trial specialist.

It can be concluded from the data obtained that the specialists involved know the nature of the clinical trials. The majority of respondents answered that they were aware of the differences between interventional trials and non-interventional studies of medicinal products. Clinical trial specialists receive annual additional training in good clinical practice and the regulatory framework at national and European level.

Clinical trial specialists have an average of more than 10 medical establishments and indicate a high level of knowledge of the nature of clinical trials, as well as the differences between interventional clinical trials and non-interventional trials.

Respondents categorically state that a large part of the medical establishments with which they work in their daily practice, the hospital pharmacy is not responsible for the storage and release of the tested medicinal products.

From the data collected, it is clear that at the time of the survey on the storage and release of investigational medicinal products in the research centers with which clinical trial specialists work, the principal investigators or sub-investigators included in the research team are responsible. This puts at risk the overall process of dispensing and storing medicinal products used in clinical trials. The management of this specific process is necessary to be performed by specialists who perform specific activities and provide highly specialized services related to the selection, preparation, storage, preparation and distribution of medicines and medical devices in medical institutions for hospital care.

Clinical trial specialists point out that they have seen some problems with the overall process of storing and dispensing investigational medicinal products for clinical trials.

The majority of the respondents state that they are not fully informed about the changes of October 21, 2015 in Ordinance 28 on the structure, order and organization of the work of pharmacies and the nomenclature of medicinal products).

These results show that regulators, as well as relevant associations, need to conduct additional and more comprehensive information campaigns in order for the newly introduced regulations to reach specialists in the relevant field more efficiently.

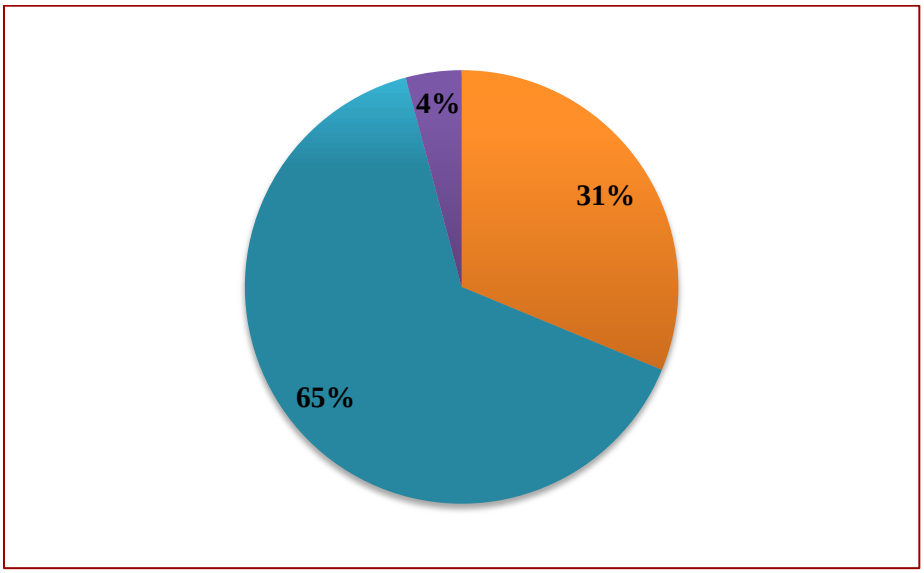

Figure 2. Question 8: "Do you think that the inclusion of a pharmacist in the research team will improve the organization and storage and relaxation process?"

The majority of respondents accept the legislative changes made to include a pharmacist as a member of research teams, needed and reasonable, but consider that this has its shortcomings.

Much of the respondents indicate that they are not fully informed about the regulatory changes made, but also assess the current organization of storage and relaxation of the examined medicinal products as unsatisfactory.

V. Main conclusions from dissertation work

In connection with the studies carried out on the role and participation of the pharmacist in clinical trials of medicinal products, the following main conclusions can be made:

1. The review of literary sources shows that both in Bulgaria and globally, the role and participation of pharmacist in clinical trials of medicinal products are insufficiently examined, described and analyzed.

2. Scientific, regulatory and scientific and practical rules and norms determining the place, role, participation and functions of pharmaceuticals can be identified as fundamental to conducting and providing the quality of clinical trials of medicinal products in humans.

3. The main role of the pharmacist can be defined and must be focused in compliance with the scientific quality requirements for planning, conducting, reporting and reporting clinical trials, the production of research medicinal products, in line with good manufacturing and good laboratory practice, Ethical norms and standards, the activities of the Ethics committees, monitoring, preparation of the researcher's brochure, control, sanctions.

4. Pharmacists are recognized as the only medical professionals who have the necessary knowledge and competences to ensure the storage and relaxation of tested medicinal products may participate at all process documentation stages as in their monitoring and control.

5. The role of the pharmacist in conducting clinical trials is not specifically defined by the rules for good clinical practice, therefore needs to be supplemented but does not limit their participation in clinical trials. It is unsatisfactory to implement changes in legislation as well as the readiness of hospital pharmacists and members of research teams to include and assign specific activities to pharmacists.

6. Promised and converted surveys and field studies that are specific for dissertation workshops show that pharmacists are not ready for active and responsible involvement in clinical trials need specific training and acquisition of additional skills and competences .

VI. Contributions

VI.1 Scientifically-Theoretical

1. For the first time, a comprehensive and comprehensive regulatory, scientific and practical analysis of the role and participation of the pharmacist in clinical trials of medicinal products in Bulgaria.

2. Basic guidelines and vision for development of the profession of pharmacist and the need to acquire specific skills and competences to participate and an active role in clinical trials are formulated.

VI.2 Scientific and methodical

1. Methodological instruments - questionnaires that can be used in medical and social nesting and targeted studies of progress and development of pharmacists in clinical trials of medicinal products in the future. VI.3 Scientific-Applied 1. The opportunities, advantages, disadvantages and "narrow" places in the realization of pharmacists in the conduct of clinical trials of medicinal products in Bulgaria are presented.

2. The research carried out shall make the formulation of specific recommendations for the development of students for educational and qualification degree in the professional field of Pharmacy and can help specialize and develop new areas of realization of master pharmacists.

VII. Scientific publications related to dissertation work

1**. ATANASOV V**, Hristov E, GETOV I, Violeta Getova V, Parvova I. In-Depth Analysis of the Role and Involvement of Pharmacists In Clinical Studies, Clinical Trials and Non-Interventional Studies of Medicinal Products. ARCH BALK MED UNION. (**2021**) 56 (Supplement 1): S68-69. Scopus

2. **V. ATANASOV**, I. GETOV, SURVEY OF THE KNOWLEDGE AND ATTITUPTS OF MEDICAL TRIALS. Pharmacia, Vol. 63, no. 2/2016, Scopus

3. S. STOEV, H. LEBANOVA, E. NASEVA, **V. ATANASOV**, I. GETOV, AD-HOK COMPARATE ANALYSIS OF RECOMBINT MEDICINES FOR ASSISTED REPRODUCTION TECHNIQUES, BULGARIA 6TH CONGRESS OF PHAMMACY IN Macedonia, Madeconian Pharmaceutical Bulletin, 62 (Suppl) 73-74 **(2016)**, ISSN 1409-8695, UDC: 615.065 (497.2)

4. SVETOSLAV STOEV, **VLADIMIR ATANASOV** AND ILKO GETOV, THE ROLE OF PATIENTS COMPLIANCE - AN example with Willingness to participate in clinical trials, CBU International Conference on Innovations in Science and Education, Prague, March 23 - 25, 2016, Vol.4 (2016) 767-772, Web of Science

5. **Vladimir Atanasov**, Emil Kostov, Hristina Lebanova, Violeta Ghettova, Maria Popova, Ilko Ghettov, essence and peculiarities of non-interventional studies of medicinal products, science pharmacology 2016 1 (7): 19-24.

6. **ATANASOV**, S. STOEV, I. GETOV, REVIEK AND COMMENT ON DESIGN FOR EFFICACY OF INVESS OF PARMACY WITH INTERNATIONARY DISEASE, SANDANSKI Bulgaria, **2016**