MEDICAL UNIVERSITY OF SOFIA

FACULTY OF PUBLIC HEALTH

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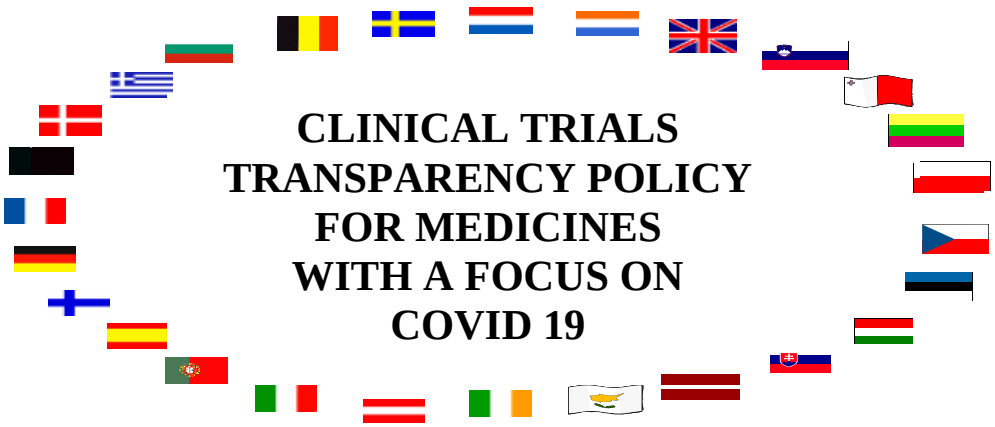

DISSERTATION ABSTRACT FOR AWARDING OF EDUCATIONAL AND SCIENTIFIC DEGREE "DOCTOR"

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"Social Medicine and Organization of Health Care and Pharmacy

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The dissertation contains **148** pages, with **5** tables, **30** figures and
The bibliographic reference includes 119 titles, of which **17** are in Cyrillic and **102** are in Latin.

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The public defence will take place on April 15, 2024. 11:00 a.m., room 7. Defence materials are available at the secretariat of the Dean's Office of the Faculty of Public Health S, Sofia Medical - University, "Tsaritsa Yoanna - ISUL" UMBAL, 8 "Byalo More" Street, Sofia and on the Internet the page of Sofia University.

The materials for the defence are available in the Science Department of the Faculty of Public Health "Prof. Dr. Tzekomir Vodenicharov DMSc ", University Hospital "Tsaritsa Yoanna – ISUL" EAD, ul. Byalo More 8, Sofia and on the website of MU – Sofia.
The numbering of the tables and figures does not correspond to the same in the dissertation.

Abbreviations in English	
ADR	Adverse Drug Reaction
BDA	Bulgarian Drug Agency
CAT	Committee for Advanced Therapies
CEC	Central Ethics Commission
CHMP	Committee for Medicinal Products for Human Use
EECs	Eastern European Countries
ECCI	Ethical Commission for Clinical Trials
EC	European Community
COMP	Committee for Orphan Medicinal Products
CRO	Contract research organization
CTA	Clinical Trial Application
CT	Clinical Trials
CTD	Clinical Trial Directive
CTIS	Clinical Trials Information System
EEC	Eastern European Countries
CTMS	Clinical Trial Management System
EMA	European Medicines Agency
EudraCT	Eudra Cliniacal Trial
EVCTM	EudraVigilance Clinical Trial Module
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
GCP	Good Clinical Practice _
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices
ICH	International Conference of Harmonisation
IECs	Institutional Ethics Committees
ICMRA	International Coalition of Medicines Regulatory Authorities.
ICSR	Individual Case Safety Reports
LEC	Local Ethic Committee
NIH	National Institutes of Health
NCAs	National Competent Authorities (NCAs)
PDCO	Pediatric Committee

PIP	Pediatric Investigation Plan
PRAC	Pharmacovigilance Risk Assessment Committee
PvH	Pharmacovigilance
R&D	Research and Development
RWE	Real-World Evidence
ZLPHM	Law for the medicinal products in the humane medicine in Bulgaria
USA	United States of America

1 Figures

2 Tables

3 Introduction

Clinical trials are systematic studies of medicines in humans that aim to study the efficacy and safety of a drug. For a medicinal product to be placed on the market, it must be accompanied by documents showing the results of the tests it has undergone.

The American Registry (www.clinicaltrials.gov) summarises the clinical trials by country worldwide since 1997, and the European Registry started the same activity in 2004. Registries are extremely important for clinical trials as they contain very significant scientific and professional information. WHO has unified a platform for all leading registries in the world. (International Trials Registry Platform) In 2023 the WHO platform includes 20 global registries, where sponsors and stakeholders could search for objective information about a given clinical trial.

Publication of a clinical trial summary is the second main requirement by the EU based on the Clinical Trials Transparency Guide as it can also provide objective information that guides to seek more in-depth information in the relevant area.

Summary results for all clinical trials must be published in the registries where they were originally registered within 12 months of the completion of the clinical trial, by Regulation (EC) 536/2014.

Regulation (EC) 536/2014 of the European Union, which entered into force in 2014, required sponsors to publish the results of certain clinical trials within 12 months and they will now be part of the CTIS system from 01 of February.2023.

Despite all clinical trials being registered in the EU, around a third to a quarter of certain clinical trials are missing results.

Providing pooled results from older clinical trials is equally important, but will require a different approach. Many of the medicinal products in use today were developed in the 1990s or earlier, so the results of older clinical trials are very relevant to current medical practice.

Publication of results in the EU after completion of the trial

All information relevant to the interpretation of clinical study results should be proactively disclosed and made available to the scientific community.

The publication of clinical trial reports contains the information researchers need to fully understand behaviour and outcomes.

The advantages of the area are more than the challenges, and this is also the reason for the large number of clinical trials conducted in recent years in the indicated countries (Bulgaria, Romania, Poland, Hungary and Slovakia) together with the other EU countries and additional parameters had been studied.

One of the main problems was-to achieve a sufficient volume of test results. It was necessary to conduct well-organized and multi-centre trials quickly, even in the context of COVID-19, for which quite specific rules were introduced in the EU, to facilitate clinical trials and not be stopped, additional rules were introduced to ensure continuity in pandemic conditions, remote visits, delivery of research products, via courier services to patients and several other online facilities.

The data from the analysis indicate that the Republic of Bulgaria is among the first 15 countries in the EU for CT and among the leading 7 countries in the EU in the last three years for COVID-19 CT, as indicated in the dissertation work.

According to the total number of CTs, the majority of them are concentrated in Hungary, Poland, the Czech Republic and Bulgaria, which ranks these countries among the leaders of Eastern European countries in the EU, and 26.3% of all CTs for the last 10 years are in CEE.

The conclusions, recommendations and contributions of this dissertation confirm the next step, which will be a more in-depth analysis of the individual characteristics and the introduction of the CTIS system and the impact on sponsors, regulators and ethics commissions, as in the transition period until 01 of February .2025. , as well as in general.

4 Relevance of the problem of data transparency in clinical trials, conclusions from the literature review as a basis for a scientific hypothesis

Transparency in clinical trials has its regulatory framework, which started to operate with the introduction of Regulation (EC) 536/2014, but whether the regulatory rules will lead to process improvement can only be commented on if we have an analysis based on objective data.

The new moments with the introduction of CTIS and how it will affect the system after the launch and 01 of February 2023, as well as the dynamics in the EE-EU countries, have not been analyzed, as the analyses and publications are quite scarce.

CTs for the last three years are numerous, but no global scientific data can be found regarding their dynamics or number, only regarding specific diseases or prevention have been published.

Based on that the development of that study fell into the period of COVID-19, the focus was on the publicity of this data, given the importance of the problem we were witnessing (2020 - 2023).

In the scientific literature, a limited number of scientific data can be found to analyse the regulatory environment from the CE-EU before and after the entry of Regulation (EC) 536/2014.

Another important aspect besides the regulatory framework is whether available public databases, such as CT registries and others, provide sufficient information through which parameters and details for these studies can be analysed.

5 AIMS, OBJECTIVES AND METHODOLOGY

5.1 Aim of the study

The dissertation aims to analyse the regulatory framework of CTs in the EU, respectively in the Republic of Bulgaria, as well as the system of transparency and accountability of data in the completed clinical trials in the EU, which supports the scientific approach in drug development.

5.2 Tasks on dissertation work

1. To analyse the regulatory framework for the initiation, termination and reporting of clinical trials data, by Regulation (EC) 536/2014;
2. To compare and analyse parameters for completed clinical trials from EU countries, as well as from EU and US public CT registries;
3. To compare and analyse completed and ongoing studies in Eastern European countries in the EU, as well as from all EU countries according to certain indicators;
4. To compare and analyse publicly available data on completed and ongoing clinical trials for COVID-19 in EU countries.

5.3 Methodology - the methods used are:

- **Historical method**

In reviewing the literature and historical chronology of the regulatory frameworks for clinical trials, connectivity and upgrading, to prepare a review and analysis of the regulatory requirements on the territory of the EU and in the Republic of Bulgaria, for the launch, completion and reporting of data in clinical trials.

- **Documentary method**

Research documents on the regulation of clinical trials of the modern legislative framework, 2000 - 2020. to follow Directive 2001/20/EU and implementation of Regulation (EC) 536/2014.

Documents regarding the introduction of a regulatory framework for clinical trials in the Republic of Bulgaria from 1995 to 2023.

Study of documents, directives, regulations, guides and articles, and public reports related to the history, development and implementation of changes in the CT regulatory framework, as well as information on drug safety in the EU countries studied

Internet references and content review of US and EU official websites and registries identified in the study.

- **Empirical method**

Extraction of data from various sources according to the specified tasks, using data from clinical trial registries, reporting documents from the Bulgarian Drug Agency Agency (BDA), European Medicines Agency (EMA), European Commission (EC) and World Health Organization (WHO).

- **Comparative analysis**

Comparison of data from the two registries in EU countries: completed studies in the three phases in adult patients, phased studies, pediatric studies, and studies with published data and without published data. The data covers both sexes.

Comparison, to analyze the selected indicators, to reveal connections and dependencies between the EU countries with certain parameters for each country separately regarding the advantages and challenges before them.

- **Tabular-graphic method**

Graphs and tables have been created for information on studies in EU countries and from the registries indicated in the methodology.

- **A method for information systematising**

Comparison of results according to the purpose of the study and preparation of an analysis to prove the main hypothesis and tasks.

5.4 For the study, the following data, materials and samples are set:

1. Example of clinical trial registries from:

• **The American register and the European register** for completed clinical trials with published results in the Republic of Bulgaria, Hungary, Romania, Slovakia, and Poland from 01.01.2011 till 01.01.2023;

• **The European Register for Clinical Trials** for completed and ongoing clinical trials in the Republic of Bulgaria, Romania, Hungary, Slovakia and Poland from 01.01.2011 till 01.01.2023;

- **The European Clinical Trials Register for** completed and ongoing clinical trials for all EU countries from
  - 01.01.2012 till 30.09.2022
  - 2004 till 30.09.2023 concluded on data reporting.

- **About the European register for COVID-19 clinical trials for** 3 years for completed and ongoing clinical trials for the period 01.12.2019-30.09.2023. on data accountability

6 Results and Discussion

6.1 Regulatory framework and impact of Directive 2001/20/EC in the EU

Directive 2001/20/EC of 4 April 2004 was the critical legislative document governing clinical research in the Union, leading to revisions and modifications to the national laws, regulations and administrative provisions of the EU Member States. The application of GCP ICH E 6 in the EU-EEC started before the accession in 2004 of the first EU-EEC. The Directive had to be introduced into Bulgarian legislation by the end of 2007 after the country had access to the EU.

The implementation of the Clinical Trials Directive 2001/20/ EC (CTD) has significantly increased clinical trial data safety, ethical aspects, quality and reliability in the EU. On the other hand, the CTD has limited the EU's competitiveness as a location for clinical trials and drug development, mainly due to the increasing administrative burden and rising costs of clinical trials in the EU.

6.2 Registered clinical trials worldwide 2000-2023.

Clinical trials are a key driver of medical innovation and progress. Medical researchers undertake to provide volunteers in trials to study whether certain medicines, medical devices and treatments are safe and effective for use. Clinical trials typically seek to determine the effectiveness of a medicine, medical device, or treatment, and compare the outcomes of a group of patients to a control group that receives another drug or a placebo.

The medical research and development process is complex, time-consuming and resource-intensive. Each year, pharmaceutical companies, universities and other research groups conduct about 20,000 clinical trials involving more than two million patients worldwide, at an estimated cost of more than US$60 billion.

According to the data of the largest global registry of the USA, by 2021 clinical trials exist, with nearly one-sixth of these data available to interested parties Fig. 6, with a total of 393,263 registered in the world, of which 127,009 (32%) are in the USA.

The American Register

Until 2021 a total of 393,436 trials are registered in the American Clinical Trials Registry. Until 29 August 22023, these tests have reached 464,218.

Despite the large number of studies that have been registered since 2000, only about 1/7 (13%) of these study data are publicly available.

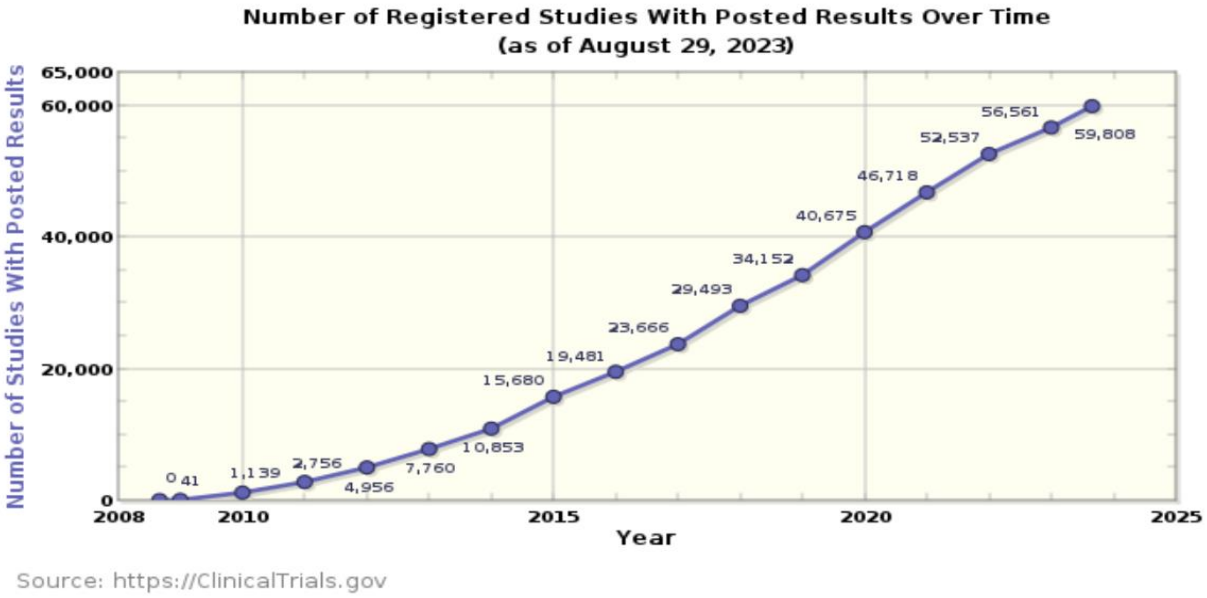

Figure 1 Number of registered CTs with published results 2008-2021.

Figure 1 shows that in 2023 this result is retained as out of a total of 437,527 and two (14%) 59,808 have published results, which is a confirmation that there was no imperative normative basis to oblige the sponsor to publish its clinical trial data.

Current penalties include a maximum of $10,000 for the first 30 days of delay and up to a maximum of $10,000 per day for each further delay. In April 2021 FDA issued its first notice of noncompliance to Acceleron Pharma for not submitting clinical trial results to ClinicalTrials.gov. According to an analysis in 2020, less than half of all clinical trials have published results within a year of a study's completion. Government and academic sponsors had the lowest compliance rates, with only 33.8% of studies fully compliant within 12 months of being published.

The European Register is the basis for the transparency of data from clinical trials/studies can be traced in the EU register, where 41619 summary results based on registered studies have been published in the EudraCT database. This has been mandatory for sponsors since July 2014, even though the register dates back to 2003.

In the EU, as of 30.09.2023. total of 45,688 clinical trials that were completed, 18,492 (40%) were with public information, despite this being a legal requirement in the EU since 2014, which is a significantly better result than the US registry and is clearly due to the requirements in Regulation (EC) 536/2014.

6.3 Analysis of implementation of the CTIS system in the member states of the European Union

The countries that are members of the European Union, including those from Eastern Europe, have had a serious development push in the healthcare sector in the last decade. Some of them as the first 10 countries that joined in 2004 have a longer history in the Union. Other, although relatively new members, such as Bulgaria, Romania (2007) and Croatia (2012) show flexibility, adaptability and proactivity in their policies, which significantly improved the health sector in their country, as well as several health indicators.

The last decade has been characterised by several key moments that have shaped the countries' health policy. These are the recovery from the financial crisis of 2009, the passage through the difficult period of adaptation, the political and financial crisis and the new EU countries, whose 2020-2023 ended with the global COVID-19 pandemic having a severe impact on clinical trials. The introduction of many new rules in this direction in order not to block clinical trial projects has given a new impetus to decentralized combined with hybrid clinical trials.

The global crisis of the COVID-19 pandemic presented the world with another problem in the field of clinical trials and guidelines were introduced with a view not to blocking studies during the pandemic, with the main motto being not to endanger the patient and his safety. The problem of the pandemic caused serious difficulty for the health systems of the countries, which proved how unprepared they were in such an emergency, with extremely new rules being introduced at the EU level as well. R. Bulgaria also managed to do very well and BDA introduced rules to make it easier for sponsors and patients in our country to conduct CTs.

Conducting a clinical trial is a long and complex process, requiring permission from the regulator and the ethics committee, conducting and collecting an extraordinary set of data collected over a long period. The data that is collected and statistically processed is one of the most important parts of the clinical trial itself. For this reason, special attention is paid to the security of storage of test results and documentation. According to Regulation No. 536/2014 of the European Parliament and the Council on clinical trials of medicinal products for human use and repealing

Directive 2001/20/EC, the sponsor and the investigator shall archive the contents of the clinical trial master file for at least 25 years after the end of the clinical trial.

Because of the sensitivity of clinical trial information and the importance of keeping it intact and archived until the necessary time when it needs to be processed to authorize the substance. Documents have also been introduced in the EU to protect personal data, which includes the protection of personal data of patients from clinical trials and this is strictly controlled.

From May 1, 2004 to January 30, 2023. according to Directive 2001/20/EC EudraCT is the European Clinical Trials Database of the European Union Regulatory Authorities, before CTIS was introduced, it was the database of all interventional clinical trials of medicinal products submitted to the National Competent Authorities (NCAs) of the European Union (EU), the European Economic Area (EEA), as well as for all trials conducted outside the EEA that are part of a Pediatric Investigation Plan (PIP) and/or are conducted under Article 45 or 46 of Regulation (EC) No. 1901/2006.

From January 31, 2023, all initial applications for clinical trials in the European Union (EU)/European Economic Area (EEA) are submitted through the Clinical Trials Information System.

The EudraCT database is now limited to making changes to EU /EEA Clinical Trial Applications for which the initial submission was made before 31 January 2023. This transition period will last until 21 January 2025, when all CTs in the EU should be transferred to CTIS.

In the case of a multi-country trial, sponsors must ensure the harmonisation of their clinical trial under the Directive through EudraCT before transferring their trial to CTIS, for which a CTIS Clinical Trial Transition Guide has been introduced. The clinical trial application recommends a contact person to whom patients can turn at any time with questions.

6.4 Historical overview of authorisation of clinical trials in the Republic of Bulgaria

Bulgaria is the country that had the longest and most complicated process for approval of a clinical trial until the launch of the CTIS system. Currently, the approval process first goes through the regulatory agency BDA and second to the ECCT (Ethic Committee for Clinical Trials), preparing a single opinion that is uploaded to the CTIS system, through which the sponsor is notified.

Until 2018 in the Republic of Bulgaria a Central Ethic Commission (CEC), subordinated to the Council of Ministers had issued opinions on ethical issues. At the last level was the Central Ethical Commission on Professional Ethics, which monitored the work of the other two bodies and could refer to problems related to the two bodies. A Central Cehic Commission could rule on disputes, but this Commission does not exist, since Regulation (EC) 536/2014 does not provide a regulatory framework for such a structure in the EU.

6.5 Regulatory environment of clinical trials in Bulgaria for the period 1995-2022.

BDA carries out the regulatory and control activities on the clinical trials (CTs) conducted in the country, which includes evaluation of the documentation for issuing approval for conducting clinical trials with medicinal products, as well as subsequent control over the progress of the studies.

The first law in Bulgaria regulating clinical trials was the Law on Medicines and Pharmacies in Human Medicine (LMPHM) from 1995. The adoption of CTD 2001/20/ EC led to significant revisions to clinical trials in 2007.

After the entry into force of the Law on Medicines and Pharmacies in Human Medicine in 1995, the number of clinical trials in Bulgaria, according to the annual reports of the BDA, increased from 88 in 1999 to 175 in 2006, which represents an increase of 52%. In the following years, the number of clinical trials grew steadily.

Despite the COVID-19 pandemic, 200 new clinical trials were initiated in Bulgaria in 2020 and 2021. The above data show the interest in researching new molecules and the evolution of clinical trials in Bulgaria since 1995, after the introduction of the first legal requirements. Bulgaria's accession to the EU in 2007, led to a significant increase of clinical trials, where the average annual number of clinical trials is 215 in the last decade. **(Figure 2)**

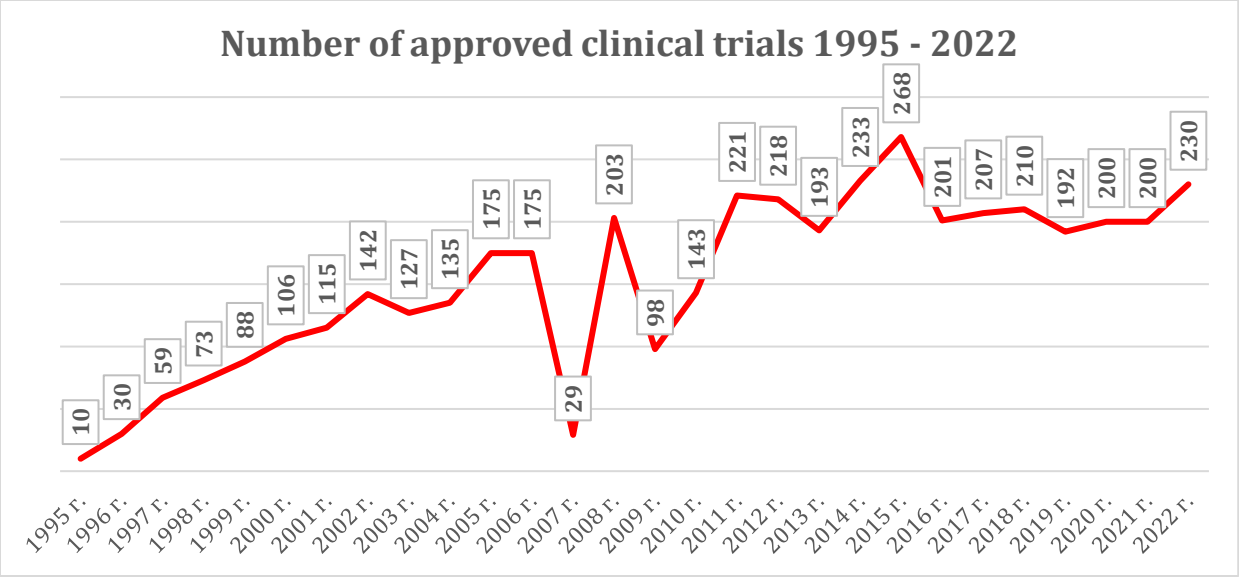

Figure 2 Clinical studies in the Republic of Bulgaria

By 2020, the total number of CTs launched and conducted in Bulgaria according to the clinicaltrials.gov system is 2064, of which (64%)1328 have a "completed" status, which proves a serious experience for Bulgarian clinical trial researchers.

In 2022 new clinical trials 230 started and 956 applications for approval of significant amendments were submitted in the Republic of Bulgaria. For the last 10 years, the Republic of Bulgaria has had an average of 215 new studies annually, which shows that our country is very reliable for such medicines studies. **(Figure2)**

6.5.1 Regulatory framework of CTs in the Republic of Bulgaria - national normative documents.

The country's CT regulatory framework is aligned with the EU requirements and is subject to strict monitoring and control. For this purpose, ordinances and regulations have been created at the national level to shape the framework and approve the necessary documents for CT. Ordinance No. 31 of 12.08.2007 on determining the rules for Good Clinical Practice (E6), defines the rules and regulates the control of their implementation. The Ordinance also defines the requirements for the content and form of the documentation that is submitted for the start of a clinical trial and non-international study as well, as upon change and termination of a clinical trial and non-international study. This Ordinance includes the documentation requirements of CTs.

6.5.2 Follow-up of safety in clinical trials in the Republic of Bulgaria

BDA monitors the safety of medicinal products subject to clinical trials by evaluating the received safety reports of the clinical trial. Monitoring of clinical trials

also includes review of various notification documents, final reports and other documents.

6.6 Advantages and challenges of conducting clinical trials in the Republic of Bulgaria

After the entry into force of Directive 2001/20/EC in 2007, which ensures the safety of patients in clinical trials, and after all regulatory requirements at the European level have been recognized at the national level, Bulgaria is rapidly gaining popularity in the CT market and has become a preferred partner in large multicenter studies. As a result of the reforms made in the legislation and the regulated regimes and procedures, the number of clinical trials in the country is growing gradually. The European Regulation (EC). 536/2014 on clinical trials of medicinal products for human use is the Medicinal Products in Human Medicine Act of 2018.

The aim is to harmonize the Bulgarian legislation on clinical trials with the relevant European regulations, as well as to improve the situation regarding the administrative procedures for conducting clinical trials. The harmonization of Bulgarian legislation with European Regulation (EC) 536/2014, issued by the European Parliament on April 16, 2014. for clinical trials of medicinal products for human use, as well as the repeal of Directive 2001/20/EC, is mandatory under European Union law. Regulation (EC) 536/2014 enters into force on May 28, 2016, which practically makes it part of the Bulgarian legislation, given that Bulgaria is part of the European Union. Amendments to the Law on Medicinal Products in Human Medicine (LMPHM) completely changed the existing structure of ethics committees and the approval process for CTs.

A stable regulatory environment for the development of the clinical trials sector is ensured by the country's membership in the EU and the harmonisation of national legislation with European law. This is a major advantage for the country to attract sponsors and this is evident in the number of CT trials that have been started since 2007 **(Figure 2)**

Bulgaria has a high potential for conducting CTs due to the availability of competent and highly qualified medical personnel, as well as the rapid and efficient recruitment of participants for CTs, as well as the affordable costs for the sponsors. In recent years, the pharmaceutical industry has changed some of its strategies and directions related to clinical trials. Preventive medicine that is aimed at individuals, more specialised treatment, and personalised medicine, are major factors for big pharma companies, to go to focused CTs.

Bulgaria has a strong advantage due to its geographical and demographic profile. On a national level and as a result of state reforms and additional funding from the EU,

the industry in the country is developing at a rapid pace. There has been rapid growth in the number of clinical trials and increased capacity in drug discovery and development.

However, the country's shortcomings are not unique and are aimed at an outdated or available technological base in the medical sites for conducting modern tests.

Political problems are not the only threat to the clinical trials sector in the Republic of Bulgaria. International competition shifts the focus to other EEC-EU countries, such as Poland, the Czech Republic and Hungary, which in terms of the number of clinical trials surpass the Republic of Bulgaria.

The CT sector is extremely dynamic, and high-tech and requires a large resource of fixed assets, personnel and improvements. The Republic of Bulgaria actively participates in this market, so it must be ready for constant changes and regulatory updates with a single goal, increasing the number of CTs and the better positioning of the country in the sector, and hence patient access to new therapies.

Most clinical trials are multi-centre, in which one or several countries may participate and are strategically preferred because of patient recruitment and meeting deadlines. The communication between the CRO companies and the sponsors is at the necessary professional level, and on the other hand, the medical professionals have gained experience in the field of CT and are well qualified, with great interest and desire to participate in clinical trials from a financial point of view and due to working with high-level class scientific teams.

Regulatory principles and norms for conducting CTs through compliance with Good Clinical Practice standards, national legislation, the specific requirements of the designated country/site and compliance with local practice for conducting CTs.

The number of CTs in the Republic of Bulgaria has been gradually increasing over the last decade. What the Eastern European countries (EEC) in the EU offer is a new opportunity with a good location, highly qualified medical staff, a wide palette of patients, and good organization and management of the processes for approving a given CI. All these prerequisites undoubtedly provide the key to the success of these EU countries in the field of CT.

There are several advantages to the country for conducting CTs:

- The centralised structure of the health care system;
- A centralised system of CT approval by the BDA and an Ethics Commission
- Sufficient numbers of new, naive patients who participate for the first time in CT;
- Easy access to large patient groups, through patient organizations, etc .;
- Rapid recruitment of patients, over 380 medical facilities in the country;
- High efficiency for conducting CT;
- Qualified and trained personnel in CRO.
- High quality of data collected by CRO.

The weaknesses facing the Republic of Bulgaria in the field of CT, which negatively affect the sector and can lead to the reduction and withdrawal of large pharmaceutical companies can be summarized as follows:

- Medical facilities where there are:
  - Insufficient available technological base in the medical centres and medical facilities for hospital care to conduct modern tests;
  - Inefficient management of the centres, which can be public or private medical facilities can lead to complications in the procedures, given that the local ethics commissions are eliminated and the "contact person" is introduced.

Regardless of the shortcomings and problems facing the healthcare system of the Republic of Bulgaria, it remains the preferred choice among the other Eastern European countries in the EU in the sector for the implementation of CT.

6.7 Analysing data on completed clinical trials in the Republic of Bulgaria, Romania, Poland, Hungary and Slovakia from EU and US public CT registries

According to the American Registry, the Republic of Bulgaria, a country famous for its developing healthcare sector, actively participates in total (n = 862) clinical trials. Hungary contributed significantly with (n =1392) clinical trials. for the appointed period. **(Table1)**

Indicator	CT in Romania	CT in Slovakia _	CT in Republic of Bulgaria	CT Poland	CT in Hungary
CT with unpublished data for Phase I-III	164 (23%)	121 (24%)	265 (31%)	609 (30%)	378 (27%)
CT with published data for Phase I-III	549 (77%)	377 (76%)	597 (69%)	1430 (70%)	1014 (73%)
Total completed CTs	713	498	862	2039	1392

Table 1 Data from the American (US) CT Registry from 01.01.2012 - 01.01.2023.

Meanwhile, according to the American (US) Clinical Trials Registry, Poland, with a robust healthcare infrastructure, has (n =2039) clinical trials conducted within its borders. In Romania, (n =713) clinical trials were performed, and Slovakia, characterized in this area, hosted (n =498) clinical trials also for the same period.

Comparing the ratios of clinical trials with results to those without published results provides valuable insight into the nature of research in these countries. Hungary stands out with a relatively high ratio of (73%) published data versus (27%) not yet

published, indicating a proactive approach to ensuring that trials produce meaningful results. Poland, although leading in the total number of clinical trials (n =2039%), has a slightly lower rate of reporting (70%), suggesting a need for a greater focus on the disclosure of final results.

In the reporting of the tests in these countries, Bulgaria shows the lowest result 69%, Romania it is (77%) and Slovakia (76%), and the different trials may have started at different times hence their reporting may be at different times and that the reporting period has not yet ended. (**Table 1**) (**Figure3**)

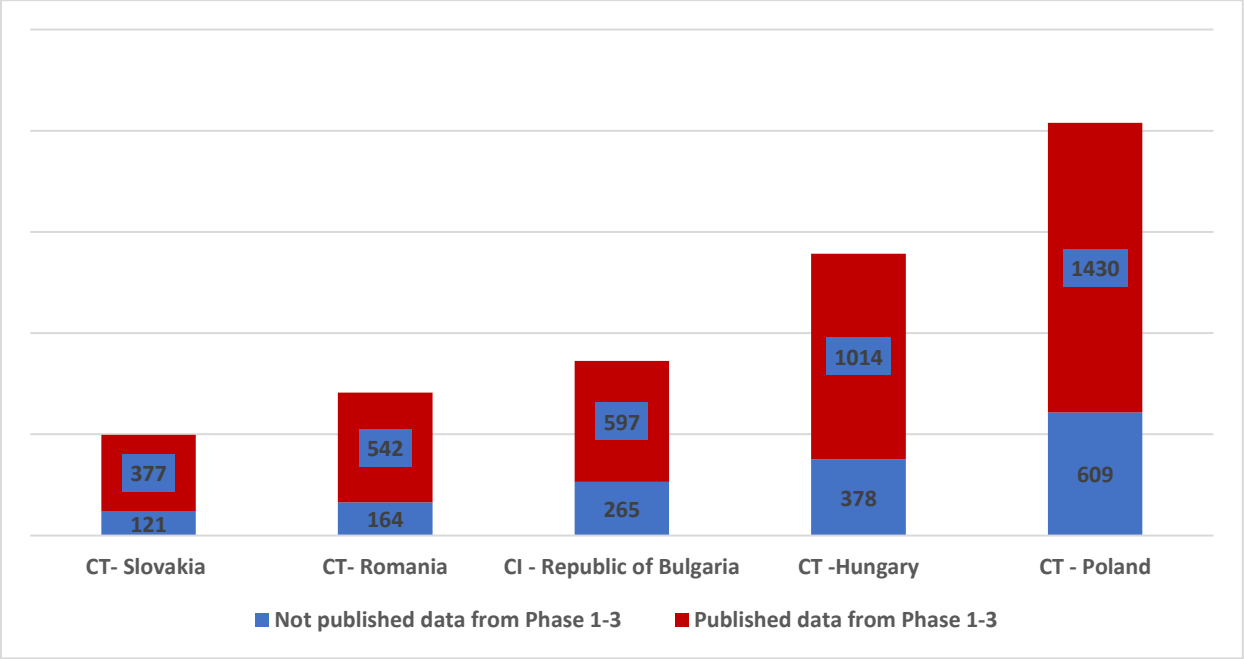

Figure 3 Data from the American (US) CI Registry from 01.01.2012-01.01.2023.

In the EMA database for the same period (01.01.2012-01.01.2023) for the Republic of Bulgaria, there are (n =1381) registered completed clinical trials, out of them 1084 (78%) have published results, and 297 (22%) have no results. In contrast, the FDA database shows 862 completed trials, with 597 (69%) having results and 265 (31%) without results.

This shows that the EMA database offers more accurate results regarding clinical trial results for the surveyed period in the 5 countries studied. (**Table 2)**

Indicator	CT in Romania	CT in Slovakia _	CT. in R. Bulgaria	CT Poland	CT in Hungary
CT with % unpublished data for Phase I-III	164 (31%)	196 (20%)	297 (22%)	663 (26%)	543 (22%)
CT with % published data for Phase I-III	369 (69%)	759 (80%)	1084 (78%)	1879 (74%)	1948 (78%)
Completed clinical trials	533	955	1381	2542	2491

Table 2 Data from the European Register of CTs from 01.01.2012-01.01.2023.

The EU CT database includes 2491 completed clinical trials for Hungary, with 1948 (78%) trials with published results and 543 (22%) without results. On the other hand, the US - ---FDA database for Hungary listed 1392 completed studies (46%), a smaller number entered the FDA database, with reported data close to those in the EU (73%) with results and 378 (27 %) without results. The EMA database again presents a more comprehensive picture of clinical trial data for the presented period in Hungary. **(Table 1)(Table 2)**

In Poland, the European Registry database includes 2542 completed clinical trials, 1879 (74%) of which have results and 663 (26%) without results. The FDA database, by comparison, documents 2039 completed trials, again documenting 20% fewer completed CTs, with 1430 (70%) having results and 609 (30%) without results, and here again the reported data are close to those of the EU. Data from the European CT Registry reflect a higher level regarding the results of clinical trials in Poland for the appointed period.

EC database shows that Romania (n =533) completed clinical trials, with (n =369) (69%) trials having published results (n =164) (31%) without results. The US-FDA database reports Romania with 25% (n =180) more trials than the EU completed trials, 549 (77%) with results and 164 (23%) without results.

EC database of CT s lists for Slovakia (n =955) completed clinical trials, in which (n =759) (80%) had published results and 196 (20%) had no results. The FDA database includes significantly fewer trials (35%) than the EU for Slovakia (n =498) completed trials, (n =377) (76%) with results and 121 (24%) without results. (**Figure** 4**)**

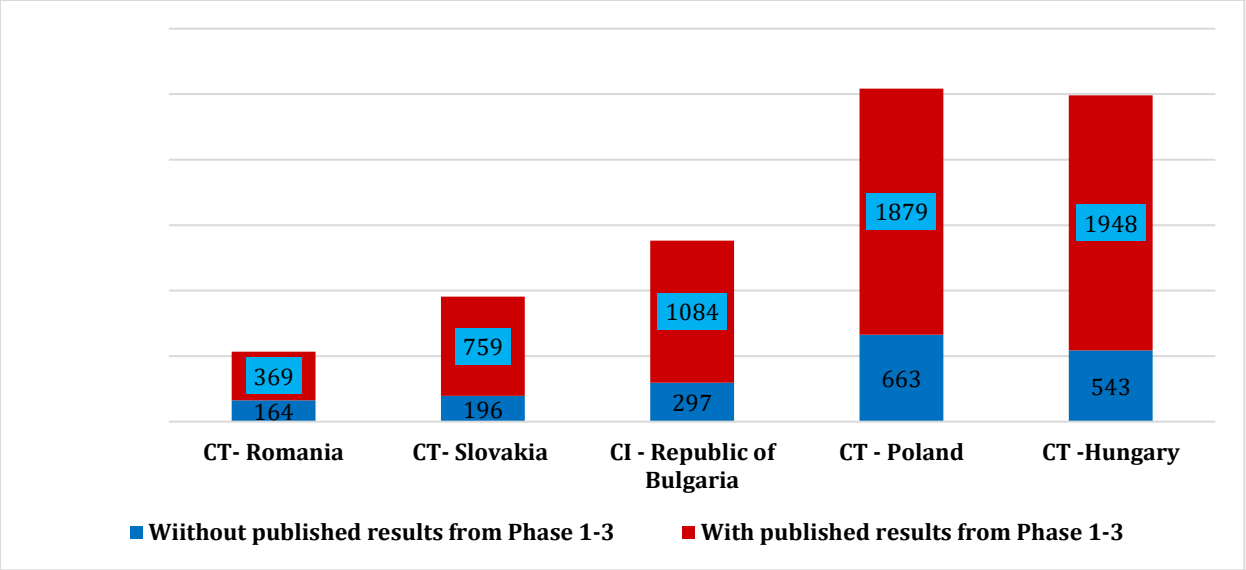

Figure 4 Data from the European Register of CT s from 01.01.2012-01.01.2022.

The EU database again provides a more detailed overview of clinical trial data in Slovakia and Bulgaria, whereas for Romania the US-FDA Clinical trials register is more detailed.

In summary, while both databases provide valuable information, the EMA database stands out for its extensive transparency, offering a more comprehensive and detailed view of the clinical trials conducted in these countries, especially Bulgaria, Hungary and Poland.

Clinical trial data in the five countries indicated a different number for the specified period (01.01.2012-01.01.2022) with the European Medicines Registry, confirming that not all are entered into the FDA registry. The two databases are quite dynamic, and regardless of whether the same period was studied, the data varies, which confirms that the sponsors are constantly entering data and that the best option for the sponsor is to investigate both registries in parallel.

When comparing clinical trial data from the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) databases for Bulgaria, Hungary, Poland, Romania and Slovakia, it is clear that the EMA database provides more detailed information and visibility regarding clinical trials conducted in these countries.

7 Analysis of the results of the survey conducted in EU countries

7.1 Comparison of data from clinical trials in selected EU countries of Eastern Europe

The PRAC reports in detailed annual reports the pharmacovigilance (PhV) activities undertaken at the national level, which are reported by the national competent authorities of all Member States. To make a quantitative analysis of the state of these activities in Bulgaria, Greece Romania, Slovakia and Poland, with the data taken from the EMA annual report for the period 2015 - 2018. (**Table 3)**

All five countries are undertaking activities in the field of (PhV) for the reporting period, which are aimed at training health professionals and patients; programs to incentivize ADR reporting; development of methods and channels for reporting, tracking and presentation of ADRs, which can be reported on the submitted Risk Management Plans to EMA. Their systematic reporting can be seen from the EMA reports and it can be traced that for the specified period they are between the total number submitted for 4 years 2015 - 2018, from 491 Slovakia, Romania 1607, and the most are in Poland 3534, but this can also be attributed to the different number of applications for marketing authorisations that are submitted in the different countries. **(Table 3)**

Europe is making extraordinary efforts and investments in developing better and more reliable systems for reporting adverse drug reactions during clinical trials. Pharmacovigilance during clinical trials is an extremely important factor for both the patient and the medical team, as well as for the Sponsor and the country where the study is conducted.

A strong regulatory framework in the EU is the basis for good accountability and transparency in the process. All three countries, Bulgaria, Hungary and Romania, strictly follow the procedures and regulations for PvH in the Union. Each of them has developed laws, regulations and programs to monitor the reporting and description of drug reactions both during clinical trials and for products from the free market.

With changes to the European system in 2016 and 2017, the number of applications submitted to EudraVigilance increased. Member States increasingly understand the need for an adequate safety system and process during clinical trials to be publicly available.

Year	**Bulgaria (BG)**	**Hungary**	**Romania (RO)**	**Slovakia (UK)**	**Poland (PL)**
2015	448	400	419	135	1012
2016	427	450	371	150	903
2017	395	550	548	111	825
2018	291	400	269	95	794
Total number of Risk Assessment Plans (RMPs) submitted	1561	1800	1607	491	3534

Table 3 Total number of submitted risk assessment plans for CT (Risk management plans, RMPs) (2015-2018)

The most important thing in the clinical trial is patient safety. A strict ADR reporting framework and a strong focus on pharmacovigilance in recent years are paying off and increasing safety for patients during CT. All five countries have a long way to go in terms of improving national PhV systems, and this is reflected in the presented results in**.**

8 Analysis of clinical trials over 10 years in the EU

8.1 Regulatory analysis of clinical trials conducted in CEE-EU (comparison between Bulgaria, Romania, Poland, Hungary and Slovakia)

The five countries in this part of the analysis (Bulgaria, Romania, Poland, Hungary and Slovakia) are members of the EU and as such have common legislation on clinical trials. The CTD is an important legal act governing the conduct of clinical trials in the EU, is Directive 2001/20/EC, ICH which harmonized the rules for trials in the EU member states and facilitated the development of medicines.

CTD requirements have been introduced into the national legislation of all EU-EEC, even if implementation is not always as intended. The following requirements

were introduced under Directive 2001/20/EC before Regulation (EC) 536/2014 entered into the surveyed countries :

- Regulatory deadlines (the official evaluation schedule in Hungary was 75 days without the option to stop the clock, 60 days for Bulgaria)
- Document requirements in the local language (application forms, informed consent, labels, patient materials). Different settings of documents to competent authorities and ethics commissions (about 10-15 documents in Slovakia compared to significantly more in Bulgaria 44)
- Some countries, such as Romania, suffered from severe delays in regulatory assessment (301 days on average in 2019 vs. 60 days by law)

The Clinical Trials Regulation will standardize the submission, assessment, timing and oversight of clinical trials across the EU. Sponsors can register for a clinical trial in up to 30 EU/EEA countries through a single application, which includes submission to competent national authorities, ethics committees and public clinical trial registration.

8.2 Phase analysis of completed and ongoing clinical trials in the five EU countries

In this study, we compared the prevalence of completed clinical trials and those still ongoing in the five EU-EEC studies, including Bulgaria, Hungary, Poland, Romania and Slovakia, according to certain indicators.

Over the entire period (**1 January 2012 to 30 September 2022),** clinical trial data for the five EC-EEC were retrieved from the EU Clinical Trials Register. Various indicators were reported and analysed. The data was analysed based on several metrics: total number of completed and ongoing clinical trials,-study phase distribution, number of pediatric studies and prevalence of rare disease studies, were compared between countries in the selected region.

This shows that the number of completed and ongoing trials does not correspond to the population of the country it indicates that many other factors are taken into account. (**Figure 5)**

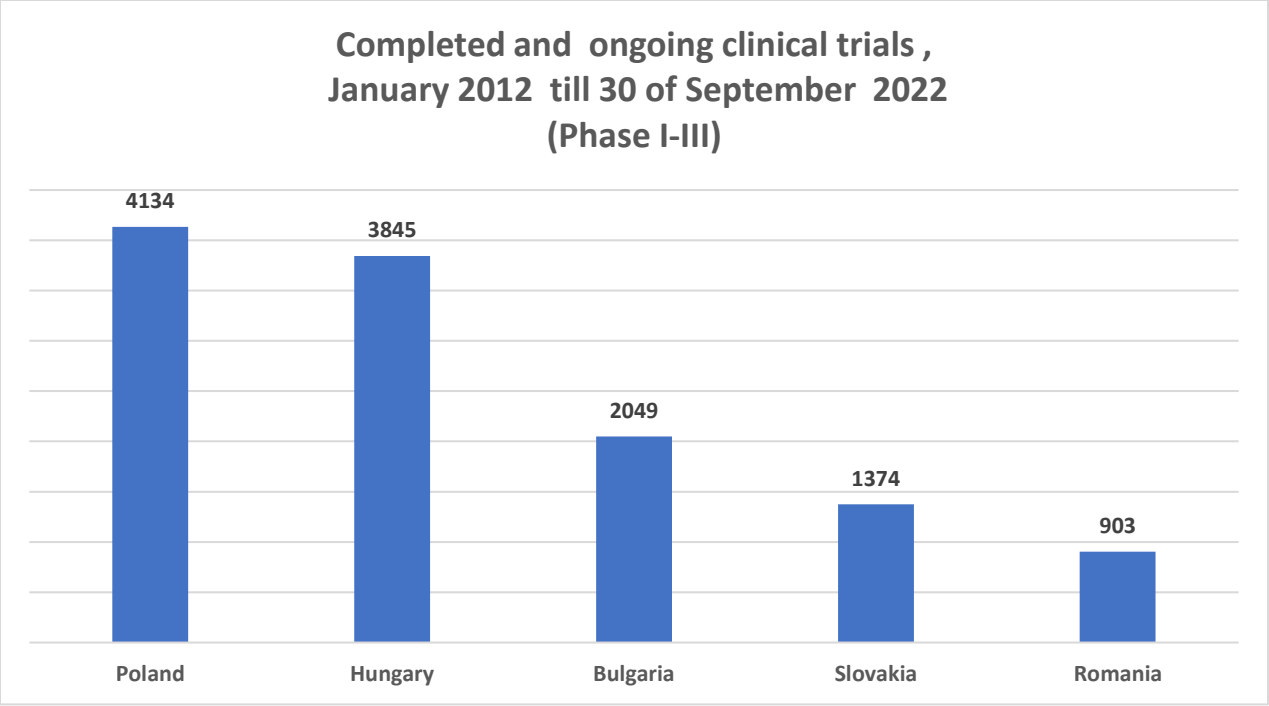

Figure 5 Total number of completed and ongoing clinical trials as of 01.01. 2012 until 30.09. 2022 (Phases I-III)

The total number of completed clinical trials is analysed and the top three countries in terms of prevalence are Poland, Hungary and Bulgaria, with Hungary having the highest number of completed trials (n =2404) and Poland having only 0.2% less (n = 2399). The results for Romania (n =514) and Slovakia (n =932) are in favour of Bulgaria, which has 62% and 30% more completed (n =1337) and ongoing clinical trials (n =712), respectively, despite the larger population in Romania (19.3 million inhabitants).

To analyse which part of the studies prevail according to the data from the EU Clinical Trials Register, they are divided into clinical trials that have been completed and those that are still ongoing. It can be seen that more than 50% of the studies have already been completed, but a large part is still ongoing. (**Figure 6)**

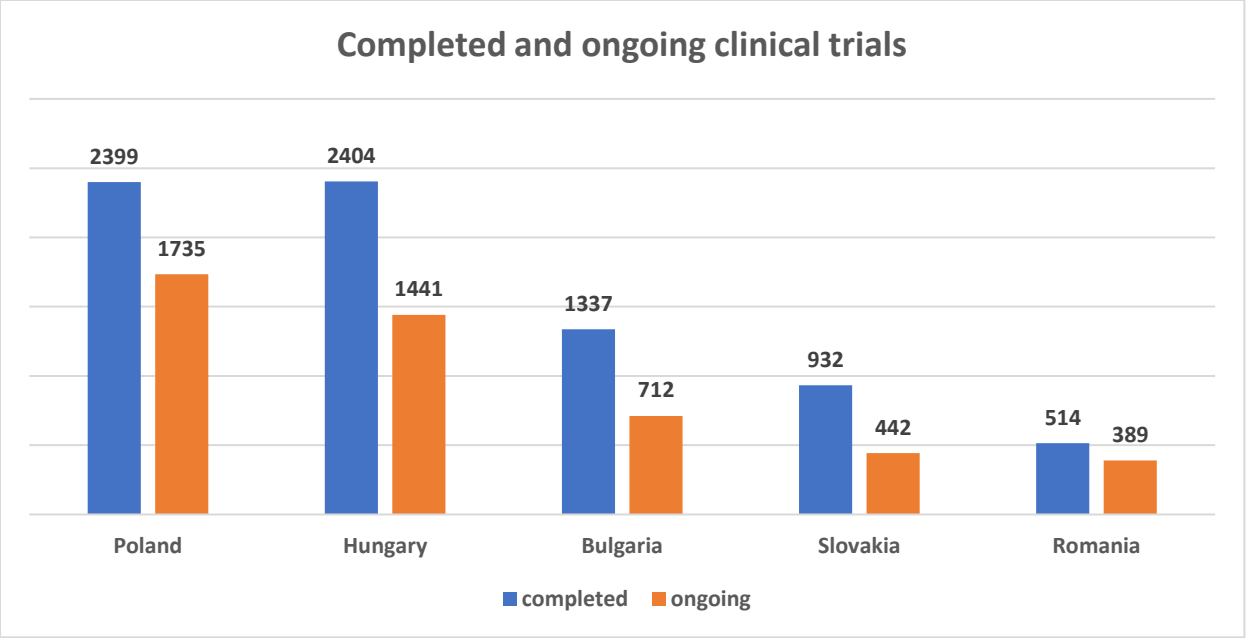

Figure 6 Number of completed CTs and CTs that continue to be held in CEE-EU (01.01.2012 - 30.09.2022). (Phases I - III)

To provide a more accurate picture of the distribution of clinical trials in the analysed countries, the number of completed and ongoing trials per 100,000 inhabitants was calculated (based on EUROSTAT data) and the results were summarized. Hungary (n =39) leads and Bulgaria (n =29) comes second of these five countries, ahead of Slovakia (n =25), Poland (n =11) and Romania (n =5).

Based on these parameters, the majority of sponsored clinical trials are concentrated in Hungary and Bulgaria, even though Romania and Poland are countries with larger populations. (**Figure 7)**

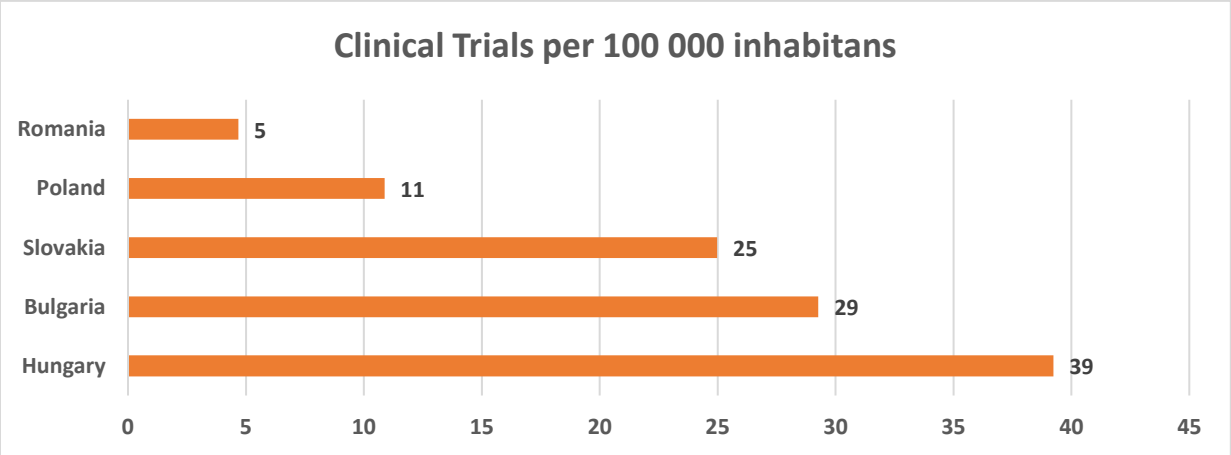

Figure 7 Number of CTs completed and ongoing CTs per 100,000 inhabitants for the period 01.01.2012 - 30.09.2022. (Phases I-III)

The next indicator that covers the five analysed countries is Phases I, II and III of completed and ongoing clinical trials in the five selected EU-EECs analysing which phases are most preferred by sponsors in these Eastern European countries.

Phase III trials in all five EU-EEC are followed by Phase II and Phase I, and this distribution is consistent across all five countries. The share of phase III trials allocated by country sponsors ranges from 62.1% (Poland) to 73.6% (Slovakia), with Bulgaria (67.6%) in third place among the five EC-EEC countries.

Since these clinical trials are used as evidence in the drug authorization files, this shows that the pharmaceutical industry has great confidence in the quality of the data that these countries generate, because as was clear from the literature review, this Phase is primarily evidence-based, in terms of safety and efficacy, and this is where the largest number of patients is required, with patient recruitment being the sponsor's greatest challenge. (**Figure 8)**

Phase II trials ranged from 24.7% (Slovakia) to 33.3% (Poland), and the prevalence of phase I trials ranged from 1.7% (Slovakia) to 4.3% (Poland).

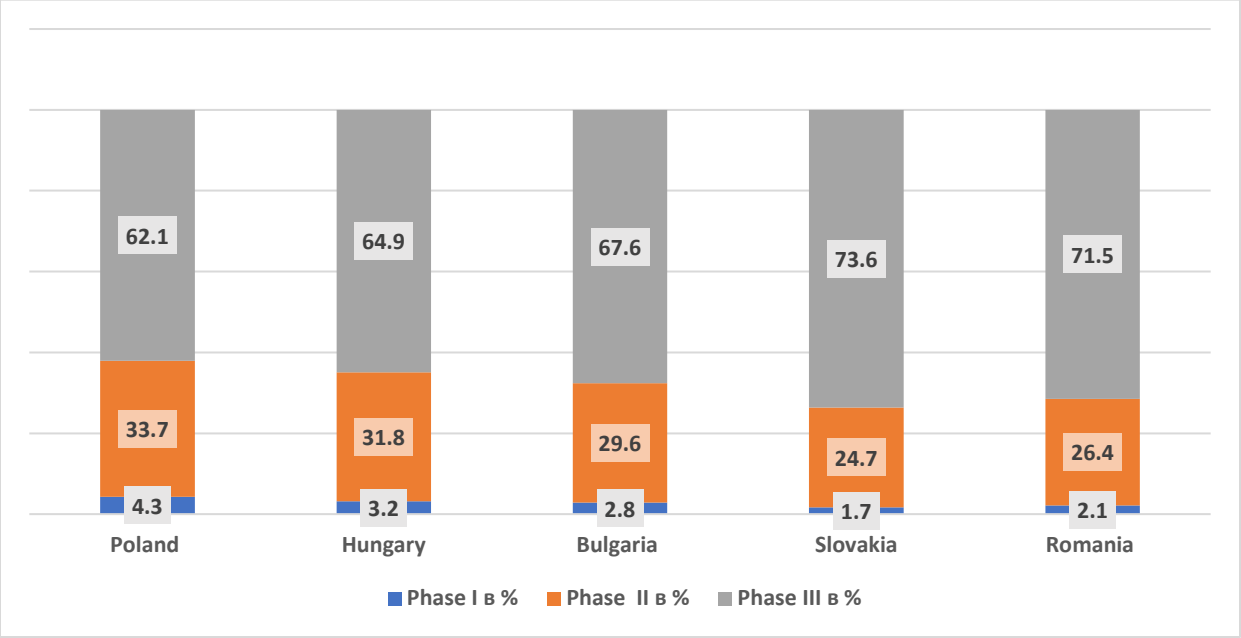

Figure 8 CT Distribution by Phases for the period 01.01 2012 - 30.09.2022 (Phases I-III)

The small number of phase I studies may be attributed to the fact that these studies included a small number of patients and were performed in a few specialised centres and the Eastern European region of the EU to ensure proper study monitoring. Multiregional, multicenter phase I trials are quite rare, although they have become more popular in recent years with the increasing use of complex clinical trials with

multiple arms. Similar to the other countries studied, the picture of clinical trials in the Republic of Bulgaria is diverse based on available data for approximately eleven years.

8.3 Analysis of completed and ongoing clinical studies with indications of rare disease and children in five CEE-EU

Patient recruitment with rare diseases is considered one of the key challenges in the clinical trials industry worldwide. Conducting trials in pediatric patients also presents a challenge, as children are considered vulnerable research that should only proceed if the trial involves no more than minimal risk and there is a perspective of direct clinical benefit to the participant. Therefore, these types of trials were also the subject of this study to determine the experience available in these countries, if any, in the selected EEC-EU. (**Figure 9)**

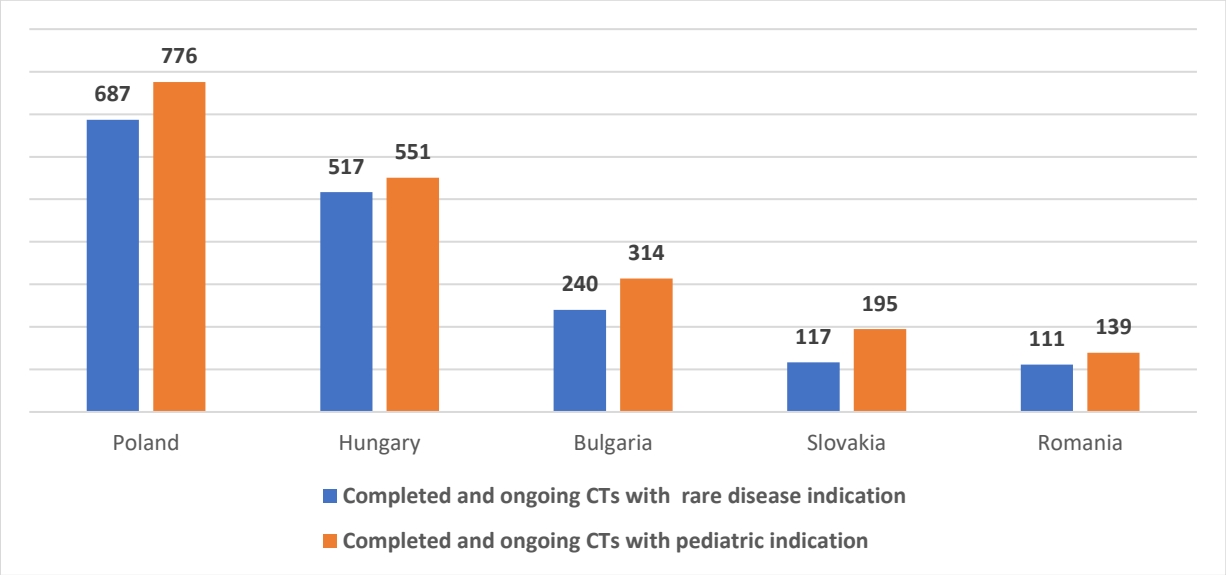

Figure 9 Distribution of completed and ongoing CTs (Phases I-III) for indications of rare diseases and CTs in children in EU countries from 01.01.2012 - 30.09.2022.

Figure 9 shows the number of completed and ongoing pediatric studies and clinical trials in rare disease indications over the 11 years considered in the five EU-EEC countries studied. There is a significant difference between the number of completed and ongoing clinical trials in the five countries analysed.

The most pediatric studies were in Poland (n =776) and Hungary (n =551), with 29% fewer than in Poland. The Republic of Bulgaria represents a smaller number of them (n =314), while the other studied countries, Slovakia (n =195) and Romania (n =139), represent respectively 38% and 56% less number of conducted pediatric drinking sessions. Poland, with the largest population, allows most such trials, apparently also because of a greater opportunity regarding a wider option for different childhood diseases.

Taking into account differences in the population size of the surveyed countries, the percentage of completed and ongoing pediatric clinical trials in the studied countries per 100,000 people ranged from 5.62 in Hungary to 0.72 in Romania. The Republic of Bulgaria is in second place (4.49), and third ranks- Slovakia (3.55). **(Table 4)**

The wide range of morbidity in this age group, qualified specialists and limited access to the most advanced innovative medicinal products for many disabilities and life-threatening conditions in children of different ages lead to a large number of clinical trials in pediatric studies in this region.

The analysis of the total number of clinical trials with indications for rare diseases conducted during the same 11-year period in the five countries showed that in terms of the total number of conducted trials, the Republic of Bulgaria is in third place (n =240), although there are significantly smaller population than Poland (n =687) and Hungary (n =517).

For the nearly 11-year study period, rare disease indications accounted for 16.6% in Poland and 13.4% in Hungary of all ongoing and completed clinical trials. The remaining countries, Romania 12.2% (n =111), Bulgaria 11.7% (n =240) and Slovakia 8.5% (n =117) also had similar data for rare diseases.

Pathology is also important in a given country, but also here the willingness of the patients themselves to participate in trials. The restrictions in the Republic of Bulgaria for new therapies can also be listed as a leading factor in this direction.

When data are presented per 100,000 inhabitants, Hungary (n =5.28) and Bulgaria (n =3.43) show the best results, followed by Slovakia (n =2.13), Poland (n =1.81) and Romania (n =0.58). (**Table 4;Figure 10)**

Indicator	Bulgaria	Slovakia	Poland	Hungary	Romania
CTs in rare Diseases	**3.43**	**2.13**	**1.81**	**5.28**	**0.58**
Pediatric CTs	**4.49**	**3.55**	**2.04**	**5.62**	**0.72**

Table 4 Frequency per 100,000 people of completed and ongoing CTs (Phases I - III) in EU-EEC countries from 01.01 2012 - 30.09. 2022.

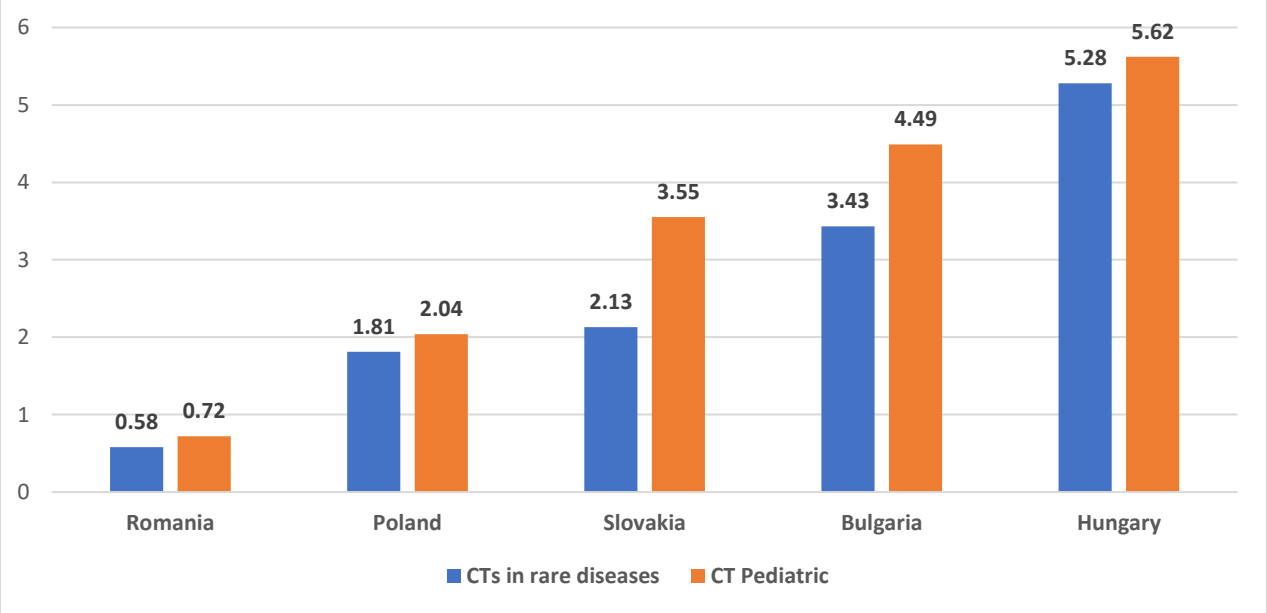

Figure 10 Frequency per 100,000 people of completed and ongoing **CT**s (Phases I - III) in EEC- EU countries from 01.01.20 23 - 30 .09. 2022

8.4 Completed and ongoing clinical trials in all EU member states from 01.01. 2012 til 30.09. 2022 as a benchmark for the five studied CEE- EC

In the 1990s, political changes encouraged the international integration of clinical research in the EU, and today numerous trials have attracted partners from across the continent. Many publications highlight the history and current status of international clinical trial collaboration in Central and Eastern Europe, which began in the late 1990s and the beginning of the previous decade

To analyse the clinical trials in the five CEE-EU countries studied and establish a baseline for them, was decided to compare the five selected CEE-EU countries with the rest of the EU member states. Data was extracted for all EU Member States for completed and ongoing clinical trials as of 1st January 2012 until September 30, 2022. The provided total number of trials and number of trials per 100,000 inhabitants were calculated using EUROSTAT data for each country.

Within the same period, 19030 were the clinical trials in all Eastern European EU countries (Poland, Czech Republic, Bulgaria, Slovakia, Romania, Lithuania, Latvia, Estonia, Croatia), which represents 26.3% of all completed and ongoing clinical trials in the EU. The most clinical trials were conducted in Poland (21%), Hungary (20%), the Czech Republic (18%) and Bulgaria (10%) among the ten CEE-EU countries. **(Figure 11)**

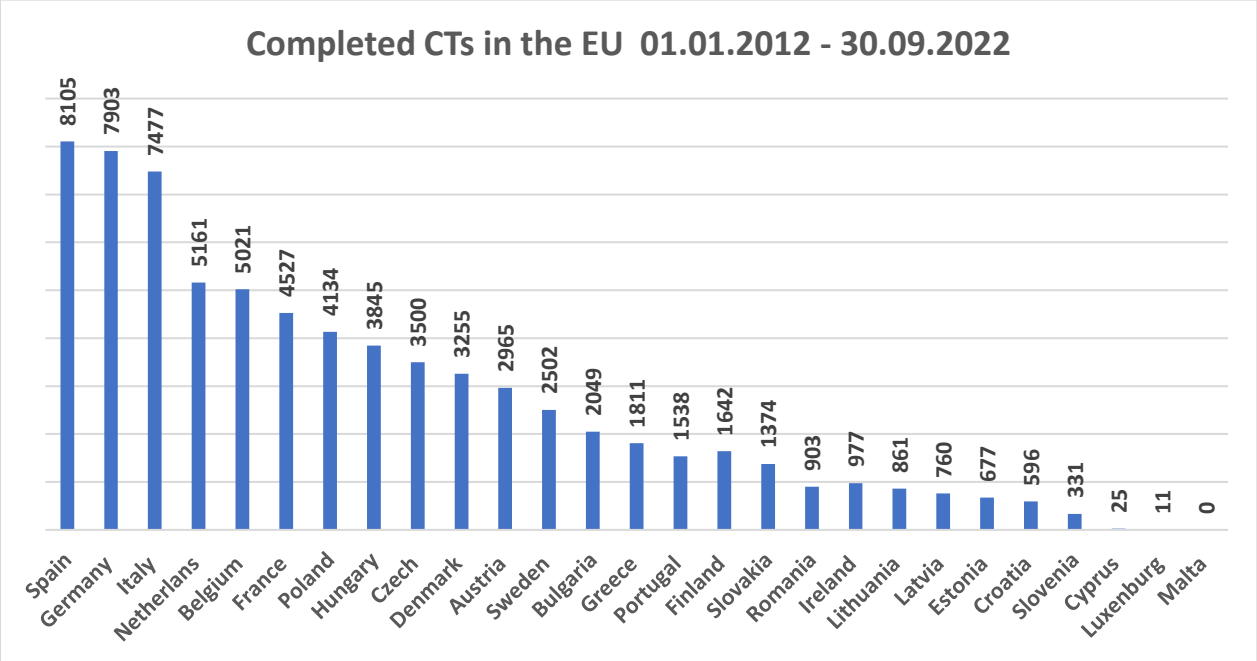

Figure 11 Total number of completed and ongoing CTs in the EU as of 01.01.2012. until (30.09.2022)

Over the past ten years, the completion of clinical trials in the EEA-EU countries has improved dramatically compared to the situation in 2010, when the percentage of clinical trials conducted in this region was only 12-13% of all clinical trials in the EU.

According to studies (2010 and 2014), Central and Eastern Europe has increased its market share of biopharmaceutical-sponsored clinical trial sites to 12.5-13.6%, with a relatively stable market growth of 12.2%, maintaining its position as a top destination among emerging markets.

The older EU member states, namely Spain (n =8105; 11%), Germany (n =7903; 10.9%) and Italy (n =7477; 10.3%), represent the largest number of ongoing and completed clinical trials in all EU Member States (n =72215). This is because most of the innovative industries and clinical research traditions are still located in these countries. From 1 January 2012 to 30 September 2022, a total of 72215 ongoing and completed clinical trials were conducted in all EU Member States**.**

From 2007 to 2011 Dombernowsky et al. reported a significant decrease (-3.9%) in the number of clinical trial applications (CTAs) in several western EU countries. Hartman observed declines in several countries, such as the Netherlands, Germany, France and the United Kingdom (1.9%, 2.3%, 3.0% and 5.3% annual average respectively). This trend may be due to a variety of variables, including the CTD of the EU, local and national policy decisions, and a potential global shift in clinical trial activity.

Since 2014, the number of CTAs in the old EU member states has increased significantly by 10%, but this can be linked to the global increase in clinical trials in the world and the search for new therapies for new unmet health problems. Regardless of the growth of CT in Eastern Europe, some authors report saturation and decline trends in the second decade of the 21st century, as this is clearly due to the rather bureaucratic approaches in the EU after the introduction of the Directive 2001/20 D. Considering the number of completed and ongoing clinical trials per 100,000 inhabitants (based on EUROSTAT data) in each EU member state presents interesting findings.(**Figure 12**)

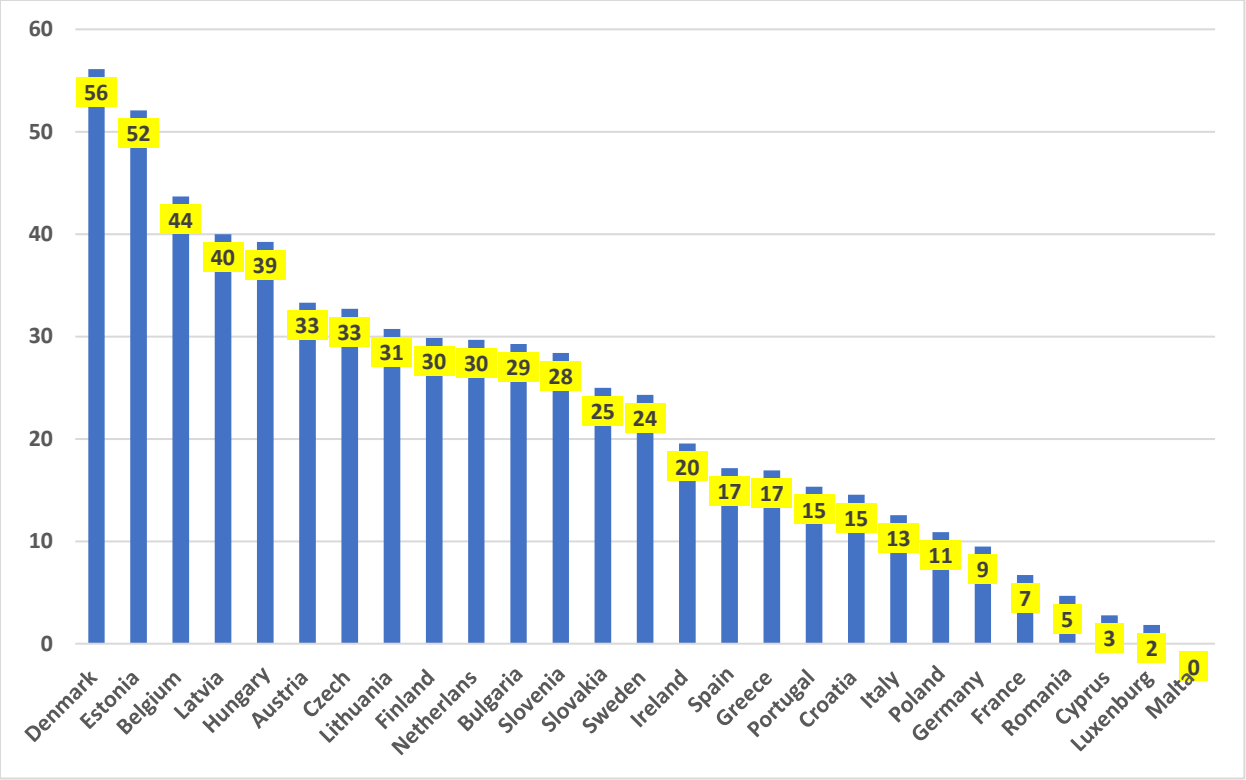

Figure 12 Completed and ongoing CTs (Phases I - III) per 100,000 inhabitants in all EU member states.

Most of the CEE-EU, including Hungary, the Czech Republic, Lithuania and Bulgaria, fall between n=29 and n =33 trials per 100,000 inhabitants. These countries rank among the top eleven in the EU with the highest number of clinical trials conducted over the roughly 11-year period analysed Bulgaria ranks eleventh with (n =29) trials per 100,000 inhabitants, ahead of countries with much larger populations such as Spain (n =17), Germany (n =9), France (n =7) and Poland (n =11). According to the results, Denmark ranks first (n =56) for the tested period 100,000 inhabitants, followed by Belgium (n =44), Austria (n =33), Finland (n =30) and the Netherlands (n =30). (**Figure 12**)

Despite the larger increase in the clinical trials EU-EEC over the last decade, there is a positive trend in the clinical research landscape in Western Europe, where 74% (n =53185) of all completed and ongoing clinical trials in the EU were undertaken in the old EU MS throughout the studied period.

8.5 Data transparency in clinical trials in the EU

To check what is the general picture of the data that is published in the EU Clinical Trials Register, the studies from 01.01.2004-30.9.2023 were tracked, removing completed trials and reporting those with published results. (**Figure 13;Figure 14**)

The highest result shows Iceland at 74%, while the lowest result ~~is~~ in Cyprus and Norway at 25-36%. Bulgaria is among the first 10 countries with 63%, with the EU countries having much better results than the old EU member countries. From the results, it is clear that in Spain and France, which lead in clinical trials, the reporting is below 50%.

This can be justified by the fact that in the countries of Eastern Europe, CTs are mainly sponsored by the pharmaceutical industry, while in the old EU member states there are many academic clinical trials and by several data, their reporting has been the weakest and that reflects on those countries. The average reporting rate in the EU is 53%. Several reports indicate that mainly university CTs do not announce clinical trial results. It tracked what the percentage of accountability was and how many studies were with and without publicly available results.

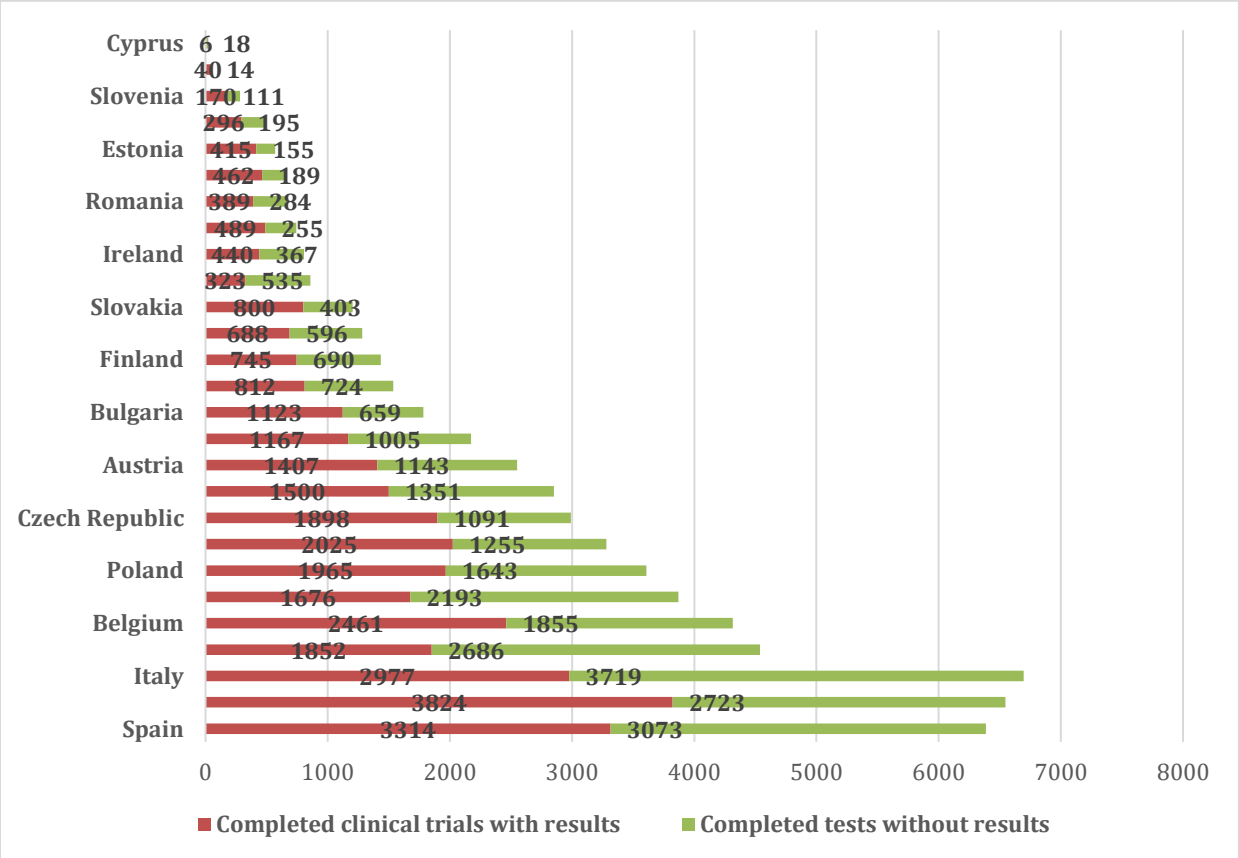

Figure 13 Completed CTs in the EU with published results (Phases I - III) EU member states. (01.01.2004 - 21.9.2023)

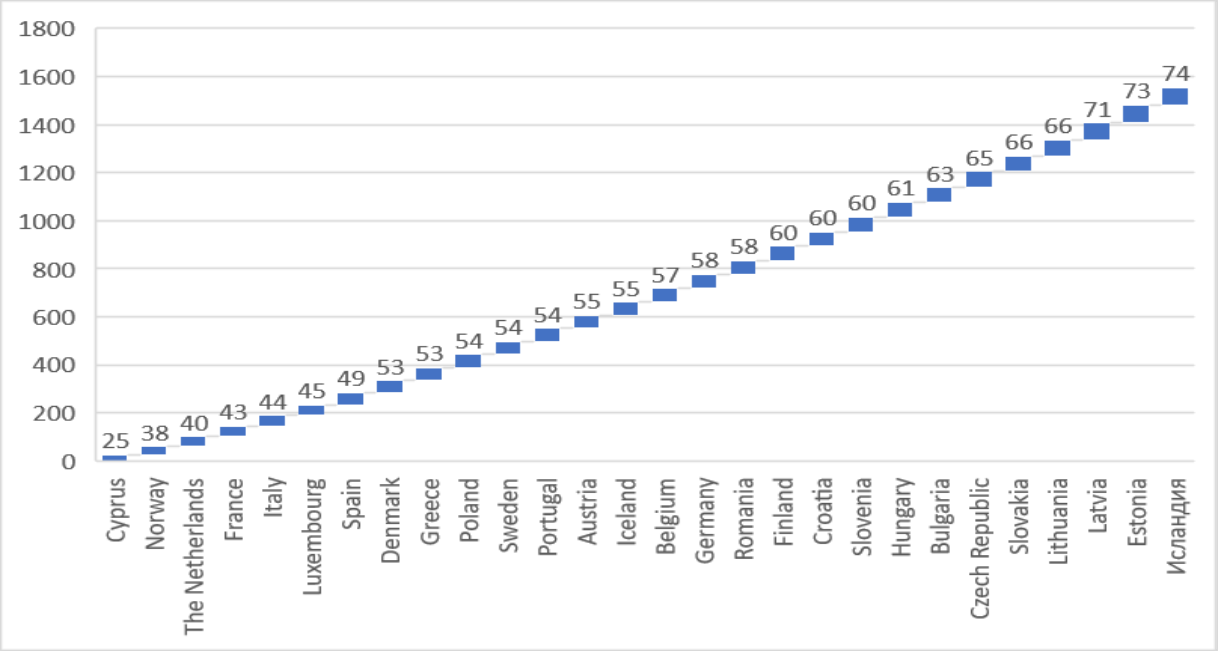

Figure 14 Completed clinical trials in the EU with published results in percentage terms (Phases I - III) EU member states. (01.01.2004 - 30.9.2023)

8.6 Advantages and challenges of conducting clinical trials in the EU-EEC

The EU regulatory environment for conducting clinical trials to protect research subjects without affecting drug development is gradually evolving with all current EU and worldwide ICH standards in this area. The introduction of the new EU Regulation (EC) 536/2014 with a centralised single submission and approval is expected to create a better environment for clinical trials in the EU, improve opportunities and increase interest in conducting clinical trials in the EU.

Indications are that the most registered studies are in oncology, traumatology, cardiology, allergology and neurology. However, within all therapeutic categories, oncology indications predominate in the EEC-EU and represent a significant proportion of all ongoing trials in these countries.

Based on the study, the investigators in the listed five countries had conducted trials in different phases, where phase III prevalence is 73.6%. It is suggested that the large patient population in the five studied countries in the EEC-EU is one of the reasons for conducting such trials in these countries.

Rare disease indications are also an opportunity for clinical trials in this region, providing ideal options for sponsors to easily recruit patients.

Pediatric trials accounted for up to 18.8% of all completed and ongoing trials in the five EU-EEC countries surveyed, indicating that there is sufficient experience with this vulnerable patient group in these countries.

Therefore, the EU-EEC is a region where the inclusion of a patient with a rare disease or the conduct of pediatric trials can provide additional benefit to the sponsor. Bulgaria should be considered a desirable location for trials in this key area, as there is still a large number of unmet medical needs and patients have limited access to many new therapies.

Conducting clinical trials in Eastern European countries also offers leading researchers the opportunity to network with the global medical community and publish their results. It also promotes the exchange of scientific knowledge on healthcare standards in the EEC.

The high performance of the centres in these countries is accompanied by compliance with regulatory requirements and data quality standards comparable to those in the western regions of the EU. Experienced professionals in this EU region have a strong scientific interest and are highly motivated to conduct clinical trials. These specialists work in large teams to publish new data on unmet and underserved medical needs. Clinical trials could also be used as a basis for further scientific development at an academic level.

in the CEE-EU, such as university hospitals teaching clinics and postgraduate medical colleges. In Eastern European Union countries, teaching hospitals and university clinics employ many medical practitioners compared to their Western counterparts. According to EUROSTAT data, Bulgaria has 427 (per 100,000 inhabitants) directly practicing medical doctors, while Germany has 458, Spain 447, and Hungary 314.

Any Regulatory Drug Agency in the EU can inspect all clinical trials taking place in the country. For the Regulatory Agency, the purpose of the inspection is to gather evidence, assess the quality of a particular activity and determine whether or not it meets existing regulatory requirements. Central and Eastern Europe (CEE) is one of the regions with the lowest percentage of inspections requiring formal or voluntary action, and sites in CEE are accompanied by regulatory compliance and data quality standards that are no lower than those in the West regions. The percentage of inspections for which no follow-up was indicated was 36.9% for Western Europe, 55.7% for CEE, and 44.3% for sites in the United States.

Based on the study and published analysis in the EU, the benefit and reason for conducting clinical trials in this EU region can be listed as follows:

Reliability and predictability of regulatory deadlines, based on European Commission requirements;

- Big population patients;
- Different access to innovative medicines;
- A large number of medical staff on the head of the population;
- Experienced medical willing staff for conducting clinical trials;
- Experienced CRO staff;
- High potential for recruitment of staff (proven from numerous CTs);
- Distribution by all clinical predominance phases on phase III.
- Competitive price on the patient;
- Short per cent on dropped outpatients.
- Inspections on clinical trials with no lower results from the Western countries;
- Experience in paediatric clinical trials.

There are a lot of opportunities for pharmaceutical companies Yes undertake clinical trials with different demographical characteristics on patients and indications for rare diseases in different phases. For such pharmaceutical companies, there are numerous advantages and benefits, including experienced staff on the object, Member State of the EU with harmonised provisions of the EU for conducting high-quality clinical trials and last place, cost-effective price.

The scientific publications regarding the advantages of clinical trials in EEC are limited and future sponsors of clinical trials could benefit from the data collected therein.

The significant urban population provides faster recording and easier tracking of the patients. These populations often consider clinical trials as reliable opportunities for healthcare for access to innovative therapies and careful monitoring in specialised healthcare establishments which leads to high levels of detention on patients. Except this, the quality of the data is comparable to any other country from the EU and is of good value. Therefore the Eastern European countries in the EU are practical and easy option for conducting global and European clinical trials.

The present study showed that there is a high number of studies which are related to a large number of prepared and well-equipped teams for doing clinical tests in Bulgaria. They are included in the Register for Clinical Tests in Bulgaria, published on the site of BDA before the CTIS starts.

Qualified researchers are willing to conduct clinical trials for different reasons like reputation, professional growth and financial incentives. This part of the survey

shows, that the benefits from the conduct of clinical tests in the countries from CEE - EU and especially in the Republic of Bulgaria are obvious, with advantages, presented and discussed in the survey.

9 Analysis of COVID-19 for clinical trials in EU countries

The European Union maintains a database of clinical trials that are conducted on the territory of the member states, including information on COVID-19 trials.

Bulgaria is in eighty-seventh place in the world in terms of the number of infected people per one million inhabitants (over 187 thousand) and in second place in the world (after Peru) in terms of the number of deaths per one million inhabitants (over five thousand) (data from June 2022). As of May 2023, it is in 59th place with a significant total number of infected patients. As of October 2023, total cases (1.321117) and active cases (5154), are the basis for conducting a significant number of studies on COVID-19 in our country for the last three years.

9.1 General information for COVID-19

COVID-19 is a disease caused by SARS-CoV-2, which appeared at the end of 2019 and spread very quickly throughout the world. In the first two years of the COVID-19 pandemic, more than 450 million cases were reported worldwide, more than 100 million in the EU alone. SARS-CoV-2 is mainly spread, through respiratory droplets, including aerosols, from an infected person who sneezes, coughs, talks, sings or breathes near other people. The drops can be inhaled or deposited in the nose and mouth or the eyes.

9.1.1 EMA's role in the safety of vaccines against COVID-19

The European Medicines Agency (EMA) has published updates on the safety of COVID-19 vaccines authorized in the EU. The EMA released a monthly update on each authorised vaccine against COVID-19. The safety updates summarized data that became available after the vaccine was licensed. They also indicated whether the safety information required further clinical study. During the COVID-19 pandemic, EMA sought to accelerate the development of effective medicines and vaccines against COVID-19.

During the public health emergency, EMA has ensured that the safety assessment and monitoring of medicines against COVID-19 is a priority so that patients in Europe have access to high-quality, safe and effective medicines. EMA worked closely with its partners in the European Medicines Regulatory Network and the European

Commission to take swift and coordinated regulatory action in all EU Member States. EMA remained fully committed to supporting the EU's response to the threat of COVID-19 and ensuring that new or adapted vaccines and therapeutics can be made available as needed. EMA supported a general statement on the prioritization of clinical trials for COVID-19 published by the International Coalition of Medicines Regulatory Authorities (ICMRA).

Drug regulatory authorities from around the world jointly developed this statement to accelerate global collaboration and facilitate the development and evaluation of therapies, diagnostics and vaccines against COVID-19. ICMRA has published a document on some of the practices being implemented by international regulatory bodies during the COVID-19 pandemic to enable remote oversight of Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) activities. The purpose of this document is to provide transparency to stakeholders regarding the approaches taken so far during the pandemic.

Drug regulatory authorities have also encouraged trial research teams to make results available, both to clinical trial participants and the public, so that the global research community can benefit from this information to avoid unnecessary costs in case of failure. clinical trials and the duplication of similar research projects.

Global regulatory authorities have emphasized a commitment to collaborate, expedite and share the assessment of all clinical trial results on COVID-19 submitted to them. They also committed to providing clear and transparent benefit-risk analyses to support the approval of effective and safe drugs, biologics and vaccines against COVID-19. The development of a common statement on clinical trials, following a series of meetings and discussions among ICMRA members, on the criteria for prioritizing planned trials, aims to ensure rapid evaluation and approval of therapies and vaccines against COVID-19. Progress was monitored and discussed with all ICMRA members and reported on continuously and this was and continues to be done on the EMA website.

Clinical trials are subject to strict regulations and procedures designed to ensure the safety of their participants. The basis of the EMA recommendations was to reduce the risk of exposure of clinical trial participants (patients, investigators and monitors) to viral infection while at the same time ensuring the quality of study data.

Except for the most essential patient and monitoring visits, all other visits were converted to telephone or video visits. It was even necessary to temporarily stop some studies and include new centres and delay the recruitment of new patients. As a last resort, centres have had to be closed entirely, transferring patients from one centre to another, to meet patient safety and continuity of care requirements.

The Medicines Executive Agency (EMA) followed the EMA's recommendations by taking an even more conservative approach, recommending that sponsors not start any new clinical trials that have been approved at all, and stop recruiting new patients from already started trials.

In addition to promoting remote patient follow-up where possible, as well as remote monitoring, BDA is committed to prioritising any protocol changes aimed at maintaining patient safety and continuity of care during the pandemic.

Clinical trials are conducted by regulatory regulations and ethical standards and guidelines that guide them and protect the rights and safety of participants. These regulations vary by country and region, but typically include safety protocols, procedures for regulatory approval of trials, and established ethics committees that monitor compliance with the rules and principles of Good Clinical Practice.

Before clinical trials can begin, they must go through a rigorous approval process from regulatory authorities and ethics committees. This includes presenting detailed information about the trial protocol, objectives, methods, expected outcomes and potential risks, informed consent, investigator brochure, etc.

Regulators and ethics committees review and evaluate this information to ensure that the clinical trial meets the necessary safety standards and ethical requirements. All of these elements were present in COVID-19 as well.

Throughout the clinical trial process, continuous monitoring and data reporting are performed. Qualified monitors monitor the implementation of the protocol, monitor the safety of the participants and check the documentation. If adverse events or violations are detected, they are reported and require immediate safety measures.

9.1.2 Analysis of Clinical Trials during COVID-19

In connection with all these encouraging measures, an analysis of completed and ongoing clinical trials was carried out, so that we could convincingly confirm whether the set initiatives of the International Coalition of Medicines Regulatory Authorities (ICMRA) and respectively the EMA have yielded results.

For this purpose, we tracked the total number of clinical trials in all EU countries in the period 01.12.2019-30.09.2023, e (n= 28450), whreras the Republic of Bulgaria in 13th place among all EU countries in terms of the total number of studies for the indicated period, which again confirms the good regulatory environment, experienced teams and successful recruitment of patients. Leading countries with the largest share of all CTs in the EU for the specified period are Italy (n=3718), Spain (n=2995), and Germany (n=3410). Poland (n =1829) is even ahead of France (n=1773), undoubtedly accounting for the high population size, in addition to all the other clinical trial data available in these countries, for successful implementation of similar projects and - quick recruitment of patients**.(Figure 15)**

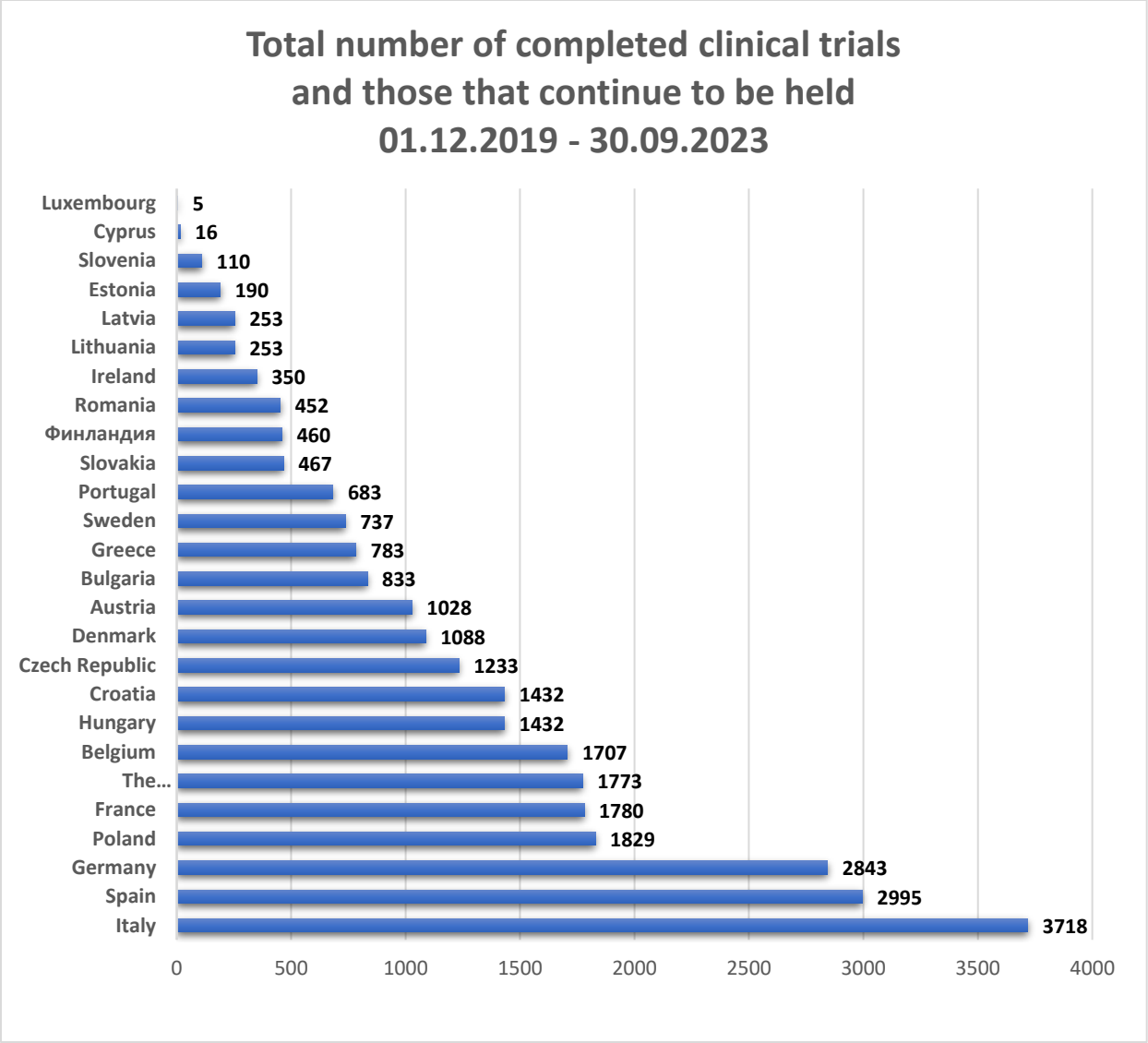

Figure 15 Total number of completed CTs and CTs that continue to be held 01.12.2019 - 30.0 9.2023. in the EU.

Of the total number of clinical trials that have ended and those that are still ongoing for the period 01.12.2019 - 30.09.2023 (Phases I - III) for COVID-19 is (n =260), as Leading countries in the field of COVID-19 clinical trials are Spain (n= 29), Germany (n=36), France (n=17), Italy (n=28), while for the countries Croatia, Slovenia, Estonia, Cyprus, Luxembourg and Malta there is no data that they are conducted similar trials for COVID-19.

The conduct of similar clinical trials in the Republic of Bulgaria is proof that there are trained teams that work according to all modern standards of the GCP, as well as the high incidence of COVID-19 for the period under study.

These data are extremely positive, as the Republic of Bulgaria ranks seventh in terms of COVID-19 clinical trials in the EU or among the top 10 countries for the period under study and among the first half of the EU countries in terms of the total number of conducted trials.

Leaders again in the number of CTs that have been completed and reported in Germany (n =22), Spain (n =18), and Italy (n =16), and in these countries data transparency already reaches 100%. The average rate of data publication in these trials in the EU, albeit for such a short period, is 64% for all EU countries, and here we cannot yet report whether the one-year period has already expired for those that have ended, but this percentage is quite high, considering the short time**. (Figure 16;Figure** 17**)**

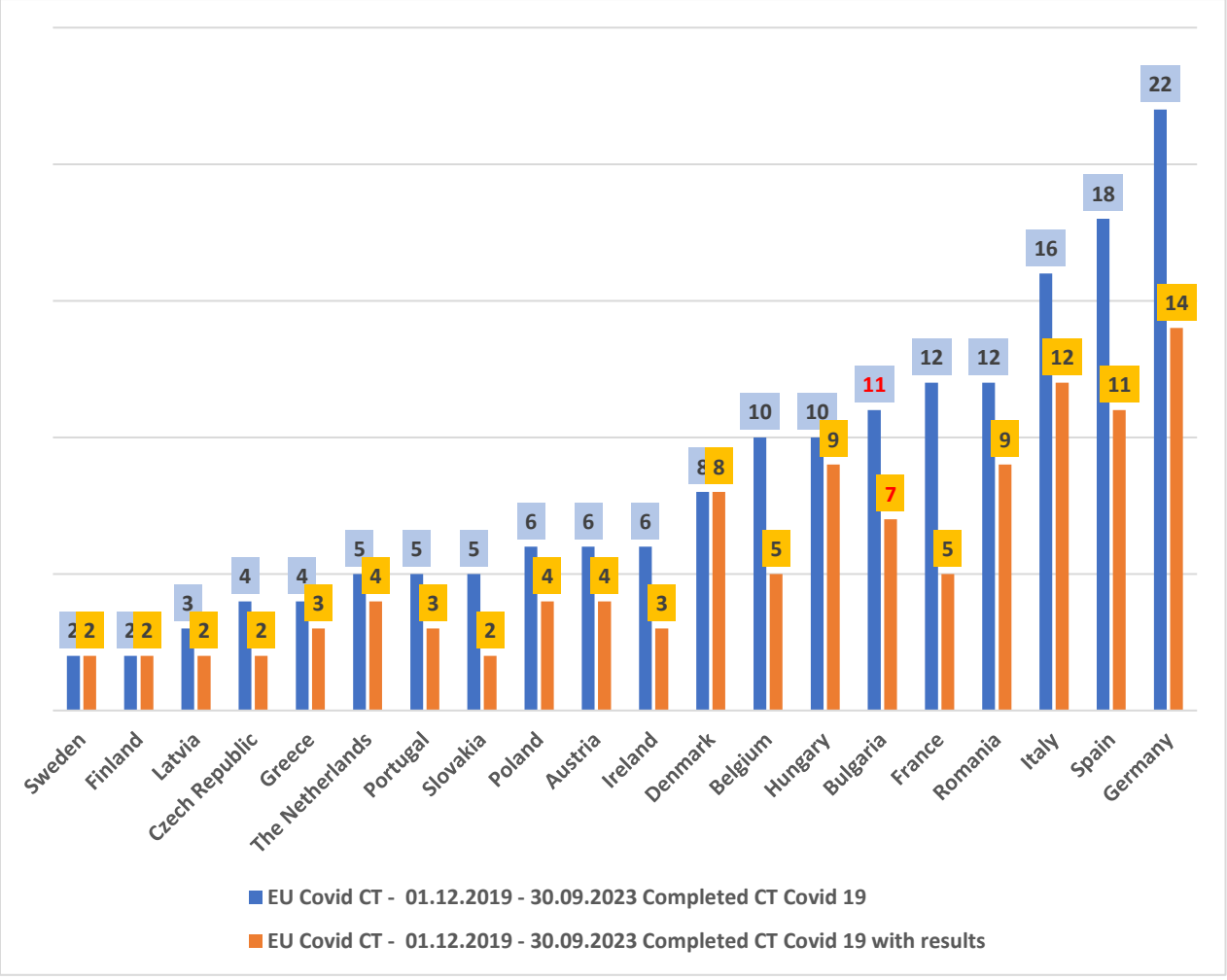

Figure 16 Number of completed CTs for COVID-19 and CTs with published results (Phases I - III) from 01.12.2019 - 30.09.2023

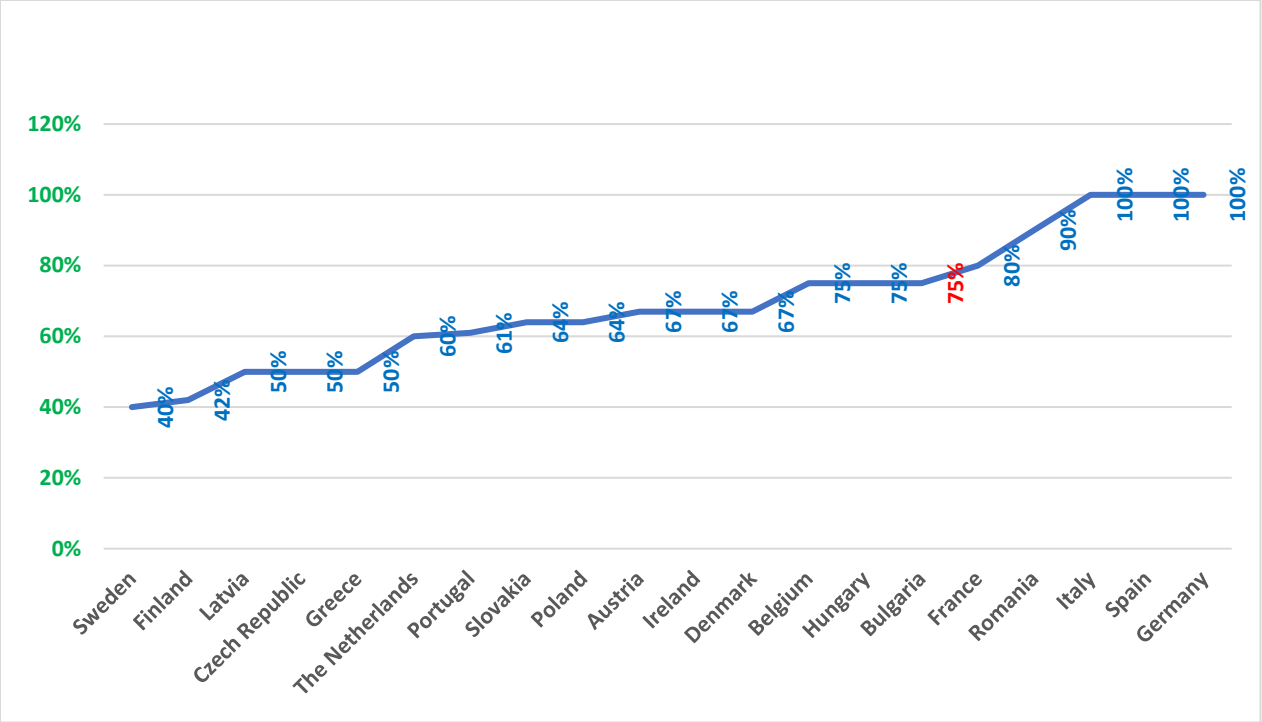

Figure 17 Number of completed CTs for COVID-19 with published results expressed in percentage ratio (Phases I - III)

Clinical trials are having a big impact on the fight against COVID-19. They enabled the timely evaluation of the effectiveness and safety of new drugs, vaccines and diagnostic methods, which data, at the beginning of the pandemic, were scarce, uncertain and inconclusive, which in turn led to much disagreement between individual regulatory agencies about effectiveness and safety of vaccines, and hence further uncertainty, among the medical community and the population.

The results of such trials have the potential to change and improve medical practice by providing healthcare personnel and the public with comprehensive information about the most effective and safe approaches to the prevention, treatment and control of COVID-19, rather than relying on medical reports and myths that also existed in our country, for which scientific evidence was not provided.

10 Final words

Conducting clinical trials requires a huge investment of resources, finances, and trained teams that work in an ever-changing environment.

These include the participation of patients, scientific teams, clinics and health organizations, which must provide the necessary resources, personnel and infrastructure to conduct the trials.

The detailed presentation of the regulatory framework for clinical trials and drug safety of EU countries, as well as their comparison by key parameters such as the number of clinical trials and various parameters lead to the highlighting of key points that we could classify as conclusions:

A relationship is being established between the regulatory authorities and ethics committees in the EU countries included in the CTIS regarding the relief of the burden, and the deadlines in the CT approval process, which is expected to affect the number of trials in the EU and respectively in the country and hence access to new medicines ;

The weight of the legislative framework of the healthcare system affects not only the number of clinical trials but also the attractiveness of the individual country to the big pharmaceutical companies.

All five countries, Bulgaria, Poland, Hungary, Romania and Slovenia, have a well-organized process for drug safety and adverse drug reaction reporting. They strictly follow pharmacovigilance procedures and regulations, and have a strict regulatory framework to monitor the reporting and description of drug reactions both during clinical trials and for products from the open market.

Detailed information on the clinical trials sector and pharmacovigilance in the EU countries Bulgaria, Poland, Hungary, Slovenia and Romania is of utmost importance for patient safety and the five countries follow rules and report their RMPs annually.

Over the past decade, Eastern European countries in the EU have seen a 25% increase in clinical trials. They managed to attract the pharmaceutical industry**.** All five CEE-EU countries show outstanding results in the clinical trials sector.

The countries of Central and Eastern Europe in the EU (CEE - EU) manage to prove their strengths and establish their place among the other member states.

The result confirmed that the long-term membership of the Republic of Bulgaria in the European Union is already a reliable factor for approving clinical trials in the country and it is in the first half of the CEE - EU countries.

Clinical trials for COVID-19 contributed significant results and achievements in a tense, epidemiological environment, which had many uncertainties regarding the development of the disease, therapies and immunizations the Republic of Bulgaria is among the top 10 countries for conducting CT COVID-19 for the research three-year period, which orders R. Bulgaria in a worthy place.

Clinical trials for COVID-19 are essential to addressing this global pandemic because they are the only evidence-based source. They provide a scientific basis for the effectiveness and safety of new medicinal products, which is essential and this information, not media, and this information should be followed by health professionals.

The simplified procedures for CT from 2023, together with the highly qualified medical staff and the obvious availability of sufficient patient groups, motivate and increase the interest of pharmaceutical companies to invest in the region and prefer it to several other Western European countries.

The guarantee of success is membership in the European Union, as the region of Eastern European countries with the EU have far better positions in the health sector than the rest of the non-members.

The advantages of the region are more than the challenges, this is the reason for the large number of clinical trials conducted in recent years in the Eastern European countries in the EU studied, along with the additional parameters analysed.

In conclusion, it should not be overlooked that the 21st century is the century of technology, artificial intelligence, and decentralized clinical trials, as a new approach, and that research should be seen as a solution to the problems and challenges facing society, and not as an obstacle and even less as a source of new inequalities.

11 Conclusions

The benefits of data transparency in clinical trials

The need for increased data sharing will improve industry collaboration and public access to clinical trial information. The discovery of new trends, insights and hypotheses has the potential to support future research and faster drug approvals, which is in the interest of patients, clinicians, researchers and the industry as a whole.

1. From 01.02.2022 CEE-EU have a uniform regulatory framework for the launch of CTs, for drug safety and their reporting. The large number of documents required for regulatory approval in the various CEE-EU has been overcome with the new EU CTIS system. This will be another serious advantage for these EU countries.

2. When comparing the two CT registries in the US and the EU regarding CIs with published results, the data strongly favours the EU.

3. The analysis performed in this study showed that the number of completed and ongoing trials does not depend only on the size of the country's population, but many other factors are involved. Through all the investigated parameters in this study of five Eastern EU countries, including Bulgaria, Hungary, Poland, Romania and Slovakia, the advantages of conducting research in this part of the EU have been analyzed.

4. The results show that the Republic. Bulgaria actively participates in clinical trials in the EU, ranking in the first half among all EU/EEA member states, taking into account the total number of CTs for the study period.

5. Based on the country's population (100,000 inhabitants) R. Bulgaria (n =29) has similar results to the Netherlands (n =30) and Slovakia (n =28) and is ahead of many large Western EU countries such as Spain (n =17), Germany (n =9) France (n = 7). This shows that the procedure at CT Republic Bulgaria has improved significantly due to many positive aspects.

6. The study showed that of all CTs included in the analysis in total, the prevalence of phase III studies in the five countries studied ranged from 62.1% to 73.6%, with Poland leading in these countries, apparently due to a large patient population in several diseases where many therapeutic approaches are scarce and still unresolved.

7. In the five examined countries in the EU - EU according to indicators, CTs for rare diseases are from 8.5% to 16.6% and it is clear that they are the subject of such studies, which is very key for discovering therapies.

8. CTs in pediatric trials are from 15.3% - 18.8% among the five countries studied (Bulgaria, Hungary, Poland, Romania and Slovakia), which makes the countries of Eastern Europe in the EU extremely reliable for conducting such scientific research, considering that when allowing for use, demonstration of pediatric use is required unless the MAH deviates and reserves this type of CT for a later stage.

9. Ongoing and completed clinical trials (n =19030) conducted in all ten CEE-EU (from 1 January 2012 to 30 September 2022) showed a remarkable increase over the last decade, accounting for a large proportion (26.3%) of all ongoing and completed trials in the EU (n =72215), showing an almost two-fold increase over the last 10 years.

10. After the detailed analysis of the CT and pharmacovigilance sector in (Bulgaria, Hungary, Poland, Romania and Slovakia) positive aspects are outlined.

11. Some of the countries in the EU-EEC, such as Hungary and Poland, have an advantage in the number of clinical trials, but in other indicators, such as per 100,000 people, Bulgaria ranks second after the five countries studied

12. Highest CT score with published data since the registry was introduced in 2004. shows Iceland 74%, with the lowest result ~~in~~ Cyprus and Norway 25-36%. Bulgaria is among the first 10 countries with 63% of published results, and the countries of the IE-EU have much better results than the old member countries.

13. In the entire EU for the period studied, COVID-19 from a total of (n = 260) CTs completed for a nearly three-year period from 01.12.2019 to 30.09.2023. (n =111) 64% have already published results, which is a very positive aspect of scientific development.

14. The main factors that improve the entire CT system in the IE-EU countries include the improved EU regulatory environment, well-trained medical staff, rapid recruitment, lower fees and obtaining high-quality data from sponsors. All these results prove that in the CEE-EU there is a good environment for attracting sponsors of clinical trials and conducting them, and the results themselves prove a two-fold increase in the last 10 years, with more than ¼ of the studies being carried out in the countries of the IE- EU.

The conclusions drawn establish positive and negative regularities between the health system and the compared parameters of the five EU countries. A unique interrelationship is established between factors that have not previously been analyzed in such a direction in the scientific literature of the Republic of Bulgaria.

12 Recommendations

The analysis can be used as a basis for future developments and for establishing new interrelationships between the individual factors characterising the clinical trials and drug safety sector.

To the Ministry of Health:

A more detailed study of the characteristics of individual European countries and their impact on clinical trials, especially after the introduction of the new CTIS system, is recommended, to track a number of parameters and whether they create an easier regulatory environment for both applicants and regulators and ethics committees.

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To the European Medicines Agency (EMA) and the Medicines Executive Agency (EMA):

As a consequence of the introduction of the CTIS system, the competent authorities related to medicines in the EU (the EMA and in the individual EU countries) should monitor whether the EU countries respect the deadlines for starting CTs and publish their data after completion and whether the new system alleviates the regulatory framework for CTs against Directive 2001/20/EU, as a basis for rapid entry of new medicines.

To non-governmental organizations from the health sector:

The positive and negative trends in the country and the EU regarding CT after the introduction of CTIS should be the subject of further studies in this area. Consideration of this interrelationship in future analyses of the topic by various interested scientific communities is recommended.

13 CONTRIBUTIONS

13.1 Scientifically theoretical contributions

1. For the first time, a comprehensive analysis of the regulatory framework of clinical trials in the Republic of Bulgaria from their introduction for the period 1995 - 2023 is made, indicating the strengths as well as several administrative burdens in the field of interventional trials before the introduction of the CTIS system in the EU.

2. Several regularities have been deduced, which led to the global change of the European requirements for clinical trials in the EU countries, as well as several positive results for the conduct of clinical trials in the Eastern European region of the EU, and the publication of these data could help to attract such projects in the region from the IE-EU.

3. For first time the challenges of Regulation (EC) 536/2014have been analysed and the start of the CTIS system within 6 months of its implementation has been discussed for the first time.

4. Different periods in EU countries have been analyzed regarding the transparency of data in CT, using published data on COVID-19 as an example and focus, which proves that R. Bulgaria has a favourable environment for these CTs and ranks 7th in the EU.

5. The two CT Registries in the EU and the US have been compared, and the results are in favour of the European Registry, which can reliably serve all interested parties to access objective information and data, which will save a lot of resources and funds and shed light on future studies.

6. Several advantages of conducting CT tests have been analysed in the countries of Eastern Europe from the EU, which also concern several advantages for the Republic of Bulgaria and hence the attraction of sponsors and access to new therapies for patients.

13.2 Contributions of an applied nature

1. The changes in European medicinal legislation since 2000 have been thoroughly analysed, including challenges with the introduction of Regulation (EC) 536/2014.

2. Several analyses have been made in the field of clinical trials, which prove the development of CTs in the countries of Eastern Europe in the EU and their increase of 26.3% in the EU for the last 10 years and the reliability for sponsors to conduct future studies in this region.

3. Guidelines for transparency of CT data and where interested parties can access this information are outlined. Transparency of data from a CT is important as it aims to improve the allocation of public health resources and limit failures in medical research, as well as avoid unnecessary repetition of similar research in humans and accelerate medical progress to discover new treatments and successful therapies.

4. CTs for COVID-19 have been tracked and an analysis of trial accountability has been made, which shows that 66% of the data from these trials are publicly available in the EU and can be used by interested parties, including medical professionals.

5. This scientific study shows that all clinical trials have initiation information and are registered in the EU, and also indicates how much is accessible and publicly available. The transparency of these clinical data improves decision-making by healthcare professionals and patients, as well as patient safety by ensuring that all adverse reactions during CT are reported.

14 LIST OF PUBLICATIONS

1. Milkov, **D., Dimitrov** & D., Kurtelova, N. (2021) Transparency of the data from the clinical trials in the EU. *Healthy politics and management, 21 (4)*, 16-21.

2. **Dimitrov, D.,** Milkov, D., Jafer, N., & Benisheva, T. (2022) Transparency on the data at clinical trials in countries from Eastern Europe, Bulgaria, Hungary and Romania. " Human, society, medicine ". Collection reports MBAL" Dr. At . Dafovski" AD - Kardzhali, April 27, 2022, 118-123

3. Benisheva, T., Milkov, D. Kopanarov, V., Ivanov, I **., Dimitrov, D** ., Todorova, V., Dzhafer, N., Chavkova, I., Todorova, L. & Gebert, L. (2023) Conducting clinical trials in five Eastern European countries (EU - EECs) with a focus on Bulgaria. *Biotechnology & Biotechnological Equipment,* Volume 37, 2023, Issue 1, 1-11 2226741, https://doi.org/10.1080/13102818.2023.2226741

4. T. Benisheva - Dimitrova, Nigyar Jaffer, Dimitar Milkov, **Dimitar Dimitrov ,** Veselina Slavkova . Bulgaria among top 10 EU countries in clinical studies with COVID-19; 6th National conference " Public health and challenges in front of the health department system";6th National conference - " Public Health: Challenges in front of the health department system ", MU- Pleven 26-27 May 2023. Proceedings report.

Participation in scientific forums and conferences

1. **D. Dimitrov**, Clinical Trials and Transparency. Foundation Skills in Drug Regulatory Affairs, Training Course organized by Bulgarian Association for Drug Information (BADI), Sofia, Bulgaria, 1 3 th of May 202 2. Presentation

2. **Dimitrov, D.**, Milkov, D. Jafer, N., & Benisheva, T. (2022) Transparency on the data at clinical trials in countries from Eastern Europe, Bulgaria, Hungary and Romania. Report for the online conference " Human, society, medicine " MBAL" Dr At. Dafovski" AD - Kardzhali, April 27, 2022.

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