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Research paper

Number of clinical trials of new therapeutic agents in the European Union countries of Central and Eastern Europe, 2000–2019

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ABSTRACT

Introduction: The clinical research market of the European Union (EU) countries of Central and Eastern Europe has been experiencing a dynamic growth of clinical trials in the last 10 years. Oncology and cardiology are the areas where the most clinical trials are conducted.

Aim: This study aims to analyze the clinical research market including countries, medical fields and trial phases in the EU countries of Central and Eastern Europe. The comparative analysis of countries is divided into 5-year periods.

Material and methods: Clinical research market analysis was carried out in 11 EU countries of Central and Eastern Europe: Bulgaria, Croatia, Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, and Slovenia. In searching for the number of clinical trials, the ClinicalTrials.gov database was used.

Results and discussion: From 2000 to 2019, 6497 clinical trials were conducted in the EU countries of Central and Eastern Europe. There were 1840 clinical trials registered in Poland, 1188 in Czechia, and 1005 in Hungary. The most clinical trials were registered in the field of oncology (22%), followed by cardiology (16%) and neurology (12%). Phase III trials representing as much as 60% (n = 2854) of all conducted medical experiments. The highest increase in the number of clinical trials in the last two 5-year periods (2010–2014 and 2015–2019) was recorded in Estonia, at 471%.

Conclusions: There has been a significant increase in the number of clinical phase III trials in the EU countries of Central and Eastern Europe, mainly in Poland, Czechia, and Hungary.

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1. INTRODUCTION

Cardiovascular diseases and cancer are responsible for 5.8 million deaths in Europe every year.[1,2] Due to the development of diagnostic methods, better prophylaxis, and new effective therapies over the last few decades, it has become possible to prolong patients' lives by as much as several years. An inseparable element of this success is the testing of new drugs in clinical trials. The transformation in Central and Eastern European (CEE) countries after the collapse of socialism, political stabilization, healthcare reform, and the introduction of European Union (EU) directives on clinical trials has contributed to a significant increase in the number of clinical trials in this region. That is, Central and Eastern Europe is a developing market in terms of clinical trials.

The region has over 101 million inhabitants in the EU countries. The many potential patients, lower procedural costs than Western Europe, and political stability are excellent incentives for sponsors to conduct clinical trials in this region.[3] There has been a noticeable increase in the number of registered clinical trials in Central and Eastern Europe since 2010.

2. AIM

This study aims to analyze the clinical research market in the EU countries of Central and Eastern Europe.

3. MATERIAL AND METHODS

In searching for the number of clinical trials in particular CEE countries, the ClinicalTrials.gov database was used. ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world, provided by the United States National Library of Medicine. Clinical research market analysis was carried out in 11 CEE countries belonging to the EU: Bulgaria, Croatia, Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, and Slovenia. The number of clinical trials conducted annually from January 1, 2000, to December 12, 2019 was determined in particular fields of medicine: oncology, neurology, cardiology, pulmonology, rheumatology, pediatrics, and others. The results for the number of clinical trials are presented on the map of the CEE countries.

3.1. Limitations of study

The Clinicaltrials.gov database may not contain all studies from 2000–2019 in the CEE region. Part of the research, especially from the beginning of the 2000s, was not registered or was registered with a delay.

3.2. Statistics

The mean, median, standard deviation, obliqueness, kurtosis, and range have been calculated for use as descriptive statistics. In the forecast of the number of clinical trials, a simple linear regression was carried out for the data, and the parameters of the linear model and R^2 values were estimated. The forecast was based on the R^2 value.

Table 1. Clinical trials in CEE countries without divided into fields of medicine.

General (without division into medical fields)	Bulgaria	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania	Poland	Romania	Slovakia	Slovenia
01.01.2000–31.12.2004	2	5	7	1	9	0	1	10	3	5	3
01.01.2005–31.12.2009	14	12	30	8	19	1	4	48	15	13	9
01.01.2010–31.12.2014	80	41	197	28	185	39	46	284	108	68	37
01.01.2015–31.12.2019	425	211	954	160	792	158	197	1498	406	266	161
Total	521	269	1188	197	1005	198	248	1840	532	352	210

Table 2. Descriptive statistics for the clinical trials in Central and Eastern Europe divided into 5 years of analysis without a division into the fields of medicine.

CEE countries	Mean	Median	Standard deviation	Skewness	Kurtosis	Range
Bulgaria	130.25	47.00	199.470	1.831	3.360	423
Croatia	67.25	26.50	97.092	1.852	3.447	206
Czechia	297.00	113.50	446.108	1.796	3.213	947
Estonia	49.25	18.00	74.714	1.864	3.504	159
Hungary	251.25	102.00	369.425	1.733	2.943	783
Latvia	49.50	20.00	74.577	1.673	2.679	158
Lithuania	62.00	25.00	92.315	1.724	2.903	196
Poland	460.00	166.00	702.534	1.830	3.354	1488
Romania	133.00	61.50	187.952	1.656	2.619	403
Slovakia	88.00	40.50	121.926	1.706	2.837	261
Slovenia	52.50	23.00	73.835	1.772	3.125	158

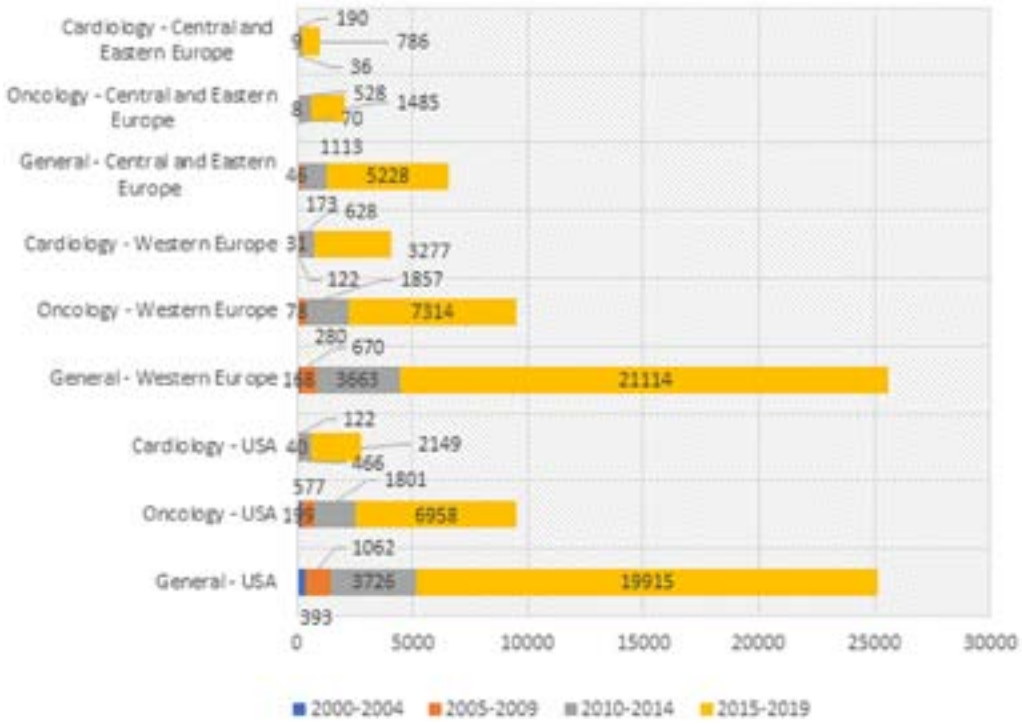

Figure 1. Number of clinical trials in Central and Eastern Europe, Western Europe and the United States divided into 5-years period.

4. RESULTS

From 2000 to 2019, 6497 clinical trials were conducted in the CEE countries belonging to the EU. Various aspects of the research (n = 6470) carried out from 2000 to 2019 in the previously mentioned countries were analyzed, without any division into medical fields. There were 1840 clinical trials registered in Poland, 1188 in the Czechia, and 1005 in Hungary (Table 1). A descriptive analysis of the number of clinical trials has been conducted (Table 2) that considers the rapid increase in the number of trials in the last 5 years. Biases and kurtosis have been calculated, which indicate that the number of clinical trials from 2000 to 2014 remained mostly stable, with a rapid increase in the last 5 years. The data were compared with the number of clinical trials in Western Europe, the United States, and the world. As we can see (Figure 1), 262% more clinical trials were conducted in Western Europe than in Central and Eastern Europe from 2015 to 2019.

The largest percentage of the clinical trials market among CEE countries from 2000 to 2019 was in Poland (28%), followed by the Czechia (18%) and Hungary (15%). In the remaining countries (Bulgaria, Romania, Slovakia, Slovenia, Croatia, Estonia, Lithuania, Latvia), 39% of all clinical trials in Central and Eastern Europe were conducted. In Poland, we can notice a significant (from 624 to 2894 trials) increase in the number of medical centers participating in clinical trials compared to the last two 5-year periods (Appendix 1). In CEE region the vast majority of research has focused on drug technology (n = 6427), rather than medical device (n = 43).

The highest increase in the number of clinical trials in the last two 5-year periods (2010–2014 and 2015–2019) was recorded in Estonia, at 471% (from 28 to 160 trials conducted within 5 years). Bulgaria was second, with 431% (from 80 to 425 trials conducted within 5 years). Poland was third, with 427% (from 284 to 1498 trials conducted within 5 years). During the last 5 years (2015–2019), 5228 clinical trials were conducted in the CEE countries of the EU, 370% more than in the period from 2010 to 2015, when 1113 trials were conducted (Figure 2).

Analyzing the number of clinical trials conducted from 2000 to 2019 in the countries belonging to the EU in the Central and Eastern Europe region, it is clear that most clinical

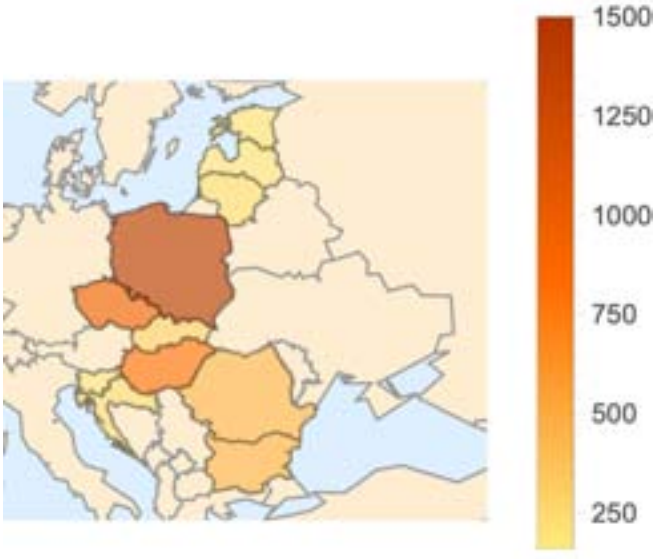

Figure 2. Clinical trials in Central and East Europe without divison into medical fields, 2015–2019.

trials were registered in the field of oncology (22%), followed by cardiology (16%) and neurology (12%). Among clinical trials in oncology conducted in Central and Eastern Europe between 2000 and 2019, the largest number of trials was registered in Poland (n = 678), followed by the Czechia (n = 411), and Hungary (n = 352). In comparing the two 5-year periods (2010–2014 and 2015–2019), it is possible to notice a dynamic increase in the number of trials in oncology (by 181.2%, from 528 to 1485 trials). In cardiology, 1024 clinical trials were analyzed, with 303 being conducted in Poland, 224 in the Czechia, and 143 in Hungary. Comparing the two 5-year periods (2010–2014 and 2015–2019), an increase in the number of clinical trials by 307.2% was noted (from 5193 to 5786 trials). The number of clinical trials in oncology in Central and Eastern Europe amounted to 22.4% of the number of trials conducted in the same period in Western Europe and 21.2% of the number conducted in the United States. In terms of cardiology, the number of CEE trials was 25.2% that of Western Europe and 35.2% that of the United States.

An analysis of the numbers of trials in particular phases (I–IV) from 2000 to 2019 was carried out. Phase III trials dominate in CEE countries, and in the last 5 years, a significant increase in such was observed, with phase III trials representing as much as 60% (n = 2854) of all conducted medical experiments. Phase I trials constituted only 4.6% (n = 201) of experiments. Analyzing the number of clinical trials per 500 000 inhabitants for individual CEE countries from 2015 to 2019, it was shown revealed most trials were conducted in Estonia (n = 61.53), followed by the Czechia (n = 44.78), and Latvia (n = 41.14). The largest numbers of oncology trials were conducted in the Czechia (n = 13.94), Hungary (n = 13.94), and Lithuania (n = 8.06). In the field of cardiology, the most trials were conducted in the Czechia (n = 8.35), Slovenia (n = 8.00), and Latvia (n = 7.81).

The number of drugs approved by the FDA for cancer and cardiovascular diseases from 2000 to 2019 was analyzed. The results indicate that the large number of clinical trials is reflected in the number of approved drugs. In oncology, an average of 16 drugs per year have been approved since 2010, and in the field of cardiology, an average of 4 drugs per year have been approved. The final stage of the analysis included the forecast for increased clinical trials during the next 5-year period (2020–2024). The forecast indicates a further increase in the number of clinical trials. Without a division into therapeutic areas in the 5-year forecast (2020–2024), the highest increases were recorded in Poland (n = 1635, R^2 = 0.746), Czechia (n = 1049, R^2 = 0.758), and Hungary (n = 880, R^2 = 0.772).

5. DISCUSSION

In the first decade of the 21st century, the clinical trials market had only just begun to develop in the CEE countries due to difficulties involved in introducing appropriate regulations for clinical trials and the low interest of pharmaceutical companies.

The development of the clinical research market in the fields of oncology and cardiology in the Czechia, Poland, and Hungary may be explained by changes in legislation and pro-European policy. The first step was joining the EU and obtaining European funds, which contributed to dynamic growth. The publication by the European Parliament and the Council of a series of 'clinical trials' directives, i.e., Directive 2001/20/EC, the first EU directive harmonizing standards of good clinical practice in EU countries, was especially important.[4] The new EU members were obliged to implement the principles of the directive into national legislation. Directive 2005/28/EC established detailed guidelines for good clinical practice in the conducting of clinical trials of medicinal products for human use and the requirements for the authorization of the production and importation of such products.[5] Directive 2009/120/EC amended Directive 2001/83/EC of the European Parliament and Council on the Community Code relating to medicinal products for human use for advanced therapy.[6] The last initiative is Regulation (EU) No. 536/2014 of the European Parliament and Council, published on April 16, 2014, regarding clinical trials of medicinal products for human use and repealing Directive 2001/20/EC.[7,8] Indeed, implementing EU directives is one of the essential factors in developing clinical trials in this region.

The health policy in the countries of Central and Eastern Europe during the transformation period was aimed at rebuilding social health insurance. There has been a change in the financing sources of health services from the budget model (general taxes) to the social insurance model (employee contributions). Communist health systems were centrally planned and administered, funded mainly by general government revenues, and delivered by state employees working in government-owned facilities.[9,10] Health reform in the countries of Central and Eastern Europe has included a reduction in the size of the hospital sector, decentralization, the expansion of private providers, a change in the methods of payment accepted by providers, and efforts to improve public health.[11–13] The implementation of health insurance was generally more successful in central Europe than in the countries of the former Soviet Union. This may have been due to significant differences in tax revenues, upon which the health system was based.[14] The expansion of clinical trials and the interest level of pharmaceutical sponsors in a given country may become measures of the evolution of healthcare. As Rechel and McKee noted in their review of the literature of health reform in Central and Eastern Europe over the past two decades, as in the rest of the world, many decisions were made based on politics rather than evidence.[15]

Cancer and cardiovascular diseases are the leading causes of death among the European population. The dynamic growth of research in oncology and also cardiology is significant for patients seeking new therapeutic options. Regarding oncology, from 2010 to 2020, the Food and Drug Administration (FDA) has approved an average of around 16 drugs each year. The possibility of developing targeted anticancer therapies has never been greater than now. In recent years,

there has been an explosion in biomedical research data and a better understanding of the molecular basis of cancer, enabling rational choices among potential treatment goals. Oncology has now become one of the most active areas of clinical research development.[16] Access to new therapeutic options in various fields of medicine is notable.[17]

Central and Eastern Europe has made an economic leap in the clinical trials market over the last ten years, becoming a key player on the international arena, and countries such as Poland, Hungary, and the Czechia are challenging Western European countries in terms of the number of clinical trials conducted.

6. CONCLUSIONS

There has been a significant increase in the number of clinical phase III trials in the EU countries of Central and Eastern Europe, mainly in Poland, Czechia, and Hungary. Half of the clinical trials are conducted in the fields of oncology (22%), cardiology (16%), and neurology (12%), which directly affects the number of registered drugs. In oncology, an average of 16 drugs per year are registered, and in cardiology, an average of 4 drugs per year are registered.

Conflict of interest
None declared.

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Ethics
The authors did not need the opinion of a bioethics committee to use publicly available data from the ClinicalTrials.gov database.

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