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Country Attractiveness for Conducting Clinical Trials – A Literature Review

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ABSTRACT

Purpose: Clinical trials are a big business worldwide, bringing benefits to patients and the healthcare systems of the countries that attract them. However, despite the extremely high scientific interest in clinical research in the medical literature, there is very little economic literature on clinical research and, in particular, on the factors that influence a country's attractiveness for clinical research. The purpose of this paper is to provide a review of this literature and the main approaches and findings used.

Approach: For this paper, the WoS CC database was first searched and papers on clinical trials published in 2015 or later were analyzed, with a focus on papers from the research area of business economics and public administration. Subsequently, an overview of the most important published papers on the study of the attractiveness of countries is then provided, and the methodological principles and results of the analyzed papers are explained.

Findings: A review of the literature shows that there are few studies investigating the attractiveness of countries for clinical research. Furthermore, the published papers are often small and examine individual cases or small samples of countries. However, the most important factors identified are the speed, reliability and efficiency of the hospital system and

the predictability of regulations. The cost of research in each country, although not unimportant, is secondary to the key factors highlighted.

Practical Implications: Clinical trials are of great importance for human health. However, they are also important for economic reasons but are underrepresented in the scientific literature dealing with them. This paper provides researchers with a framework for future scientific research. However, as it focuses on the study of the attractiveness of clinical trials, it is also useful for regulators and policy makers to gain a better understanding of this field.

Originality/Value: This paper offers an overview of an important but neglected scientific field and, by systematizing and interpreting the research and its results, enables further development and facilitates future research.

Keywords: clinical trials, country attractiveness, factors, costs, regulation

Privlačnost držav za izvajanje kliničnih raziskav – pregled literature

POVZETEK

Namen: klinične raziskave so velik posel po vsem svetu, saj prinašajo koristi pacientom in zdravstvenim sistemom držav, ki jih pritegnejo. Kljub izjemno velikemu znanstvenemu interesu za klinične raziskave v medicinski literaturi pa je ekonomske literature o kliničnih raziskavah, zlasti o dejavnikih, ki vplivajo na privlačnost države za klinične raziskave, zelo malo. Namen tega članka je podati pregled te literature ter glavnih pristopov in ugotovitev.

Pristop: najprej je bila preiskana baza podatkov WoS CC, analizirani pa so bili članki o kliničnih raziskavah, objavljeni leta 2015 ali pozneje, s poudarkom na delih iz raziskovalnih področij poslovne ekonomije in javne uprave. Nato je podan pregled najpomembnejših objavljenih člankov o preučevanju privlačnosti držav, pojasnjena pa so tudi metodološka izhodišča in rezultati analiziranih del.

Ugotovitve: pregled literature kaže, da je malo študij, ki bi preučevale privlačnost držav za klinične raziskave. Poleg tega objavljeni članki pogosto niso obsežni in obravnavajo posamezne primere ali majhne vzorce držav. Kljub temu so kot najpomembnejši dejavniki prepoznani hitrost, zanesljivost in učinkovitost bolnišničnega sistema ter predvidljivost predpisov. Stroški raziskav v posamezni državi – čeprav niso nepomembni – imajo sekundarno vlogo v primerjavi s poudarjenimi ključnimi dejavniki.

Praktične implikacije: klinične raziskave so zelo pomembne za zdravje ljudi. Pomembne so tudi z ekonomskega vidika, vendar so v znanstveni literaturi, ki jih proučuje, podzastopana. Ta članek raziskovalcem nudi okvir za nadaljnje znanstveno raziskovanje. Ker se osredotoča na preučevanje privlačnosti kliničnih raziskav, je koristen tudi za regulatorje in oblikovalce politik pri boljšem razumevanju tega področja.

Izvirnost/vrednost: članek ponuja pregled pomembnega, vendar zapostavljenega znanstvenega področja ter z njegovo sistematizacijo in interpretacijo raziskav ter rezultatov omogoča nadaljnji razvoj in olajša prihodnje raziskave.

Ključne besede: klinične raziskave, privlačnost držav, dejavniki, stroški, regulativa

JEL: I11, I18, M10

1 Introduction

Clinical trials are scientific research trials conducted to assess and demonstrate the safety and efficacy of a new drug, treatment option or a medical device, or to demonstrate their efficacy for an indication previously not approved for. Kramer and Schulman (2012) define clinical trials as *a means of gathering information about medical products or services*. Alvarenga and Martins (2010) mention the biblical story of the king Nebuchadnezzar's order for keeping a strict diet of meat and wine as the first document controlled clinical trial – where the prophet Daniel established the control arm by adhering to a diet of only pulse and water, and eventually showing that him and his friends became prettier and better-fed than the others.

Clinical trials are conducted in four phases, different in their aims and the study sample involved - the number of patients that the drug is investigated on. Phase I and II clinical trials enroll a smaller number of patients, and their aim is to provide initial safety data and to determine the target dose ensuring therapeutic effect. Phase IV trials aren't mandatory and aren't always conducted for every drug. Apart from further demonstrating safety and efficacy, phase III trials demonstrate equivalence or superiority of the investigational medicinal product (IMP) compared to other previously available treatment options. Those trials are conducted on a larger number of patients which make a statistically significant sample – depending on the study design, this can range from several hundred to more than 20.000 patients. After the successful completion of a phase III trial, the clinical trial sponsor can request marketing authorization for the IMP from regulatory agencies.

According to a report by Fortune Business Insides, the global clinical trials market is estimated to be worth USD 60.94 billion in 2024. According to the same source, phase III trials account for 46.8% of this amount, which is close to the usual estimate of nearly 50% of total clinical trial spending. Not only because of the big share of phase III trials in the market size, but also due to the fact that phase III clinical trials require the inclusion of the highest number of patients among all the mandatory phases of clinical trials and are most often conducted in multiple countries, phase III clinical trials are of primary interest for this paper.

Clinical trials are therefore a highly valuable and multi-beneficial activity worldwide, not only for patients, but also for healthcare systems and the scientific community. They give patients access to experimental, often more effective therapies that would otherwise not be available, improving health outcomes and quality of care. In addition, participation in industry-funded clinical trials can lead to significant cost reductions in conventional therapies, a phenomenon known as "cost avoidance" – i.e. the avoidance of costs for regular drugs and diagnostics that would otherwise be necessary.

Clinical trials also bring significant economic benefits to healthcare organizations. For example, according to research (Walter et al., 2020), for every euro invested in industry-supported trials in Austria, an economic multiplier of 1.95

was generated and new full-time jobs were created. In addition to these effects, participation in clinical trials promotes the professional development of medical staff, improves the scientific monitoring of clinical practice and establishes high research and ethical rules, which ultimately increases the quality of healthcare and the efficiency of the healthcare system. Some further specificity of the clinical trials industry is provided by work (Amato et al., 2017) which shows that global investments in biomedical research and development increased by 18.4% between 2007 and 2012, while during the same period the investment levels in North America and Europe remained the same or decreased. They also state that the number of human trials worldwide rose from 12,018 to 234,321 between 2004 and 2016, and that the share of clinical trials in the European Union decreased by 15% from 2009 to 2015, i.e. that the EU is lagging. Given this, the clinical trials industry is a global industry that brings a range of advantages and economic benefits to the countries where these trials are conducted. Since the economic literature on clinical trials is very scarce, there is a need for further research. The economic and regulatory benefits and challenges of clinical research for public health systems should not be overlooked. This paper therefore provides an overview of the scientific literature on this topic, which does not originate from the field of health, but from the fields of economics and business.

2 Overview of the Economic Importance of Clinical Trials

Clinical research and investment in the development of new medicines in general are not only of enormous value to human health but also generate significant costs for the companies that carry them out, while at the same time bringing considerable economic benefits to patients, hospitals and public health systems. Varmaghani et al. (2020) emphasize the economic importance of developing new pharmaceutical products: the development process from molecule creation to market approval takes 10 to 15 or more years, the approval rate for drugs entering the clinical trial phase is less than 12% and conducting phase I–IV clinical trials accounts for 75% of total development costs. The total cost of clinical trials for new drugs up to their market launch is estimated at USD 266 to 802 million. Furthermore, they find that between 2006 and 2010, the Turkish state was able to save almost USD 311,096,130 through medicines that were provided free of charge to patients as part of clinical trials and that would otherwise have been paid for by the national healthcare system. D'Ambrosio et al. (2020) present the results of their study on the treatment of oncology patients over a period of four weeks, in which 126 patients were treated free of charge as part of 34 clinical trials. The cost of standard therapy for these patients in clinical practice would have amounted to €517,658 over this period, which corresponds to a saving of €5,487 per patient over four weeks. Walter et al. (2020) state that 116.22 million euros invested in industry-funded clinical trials in Austria in 2018 generated an added value of 144.2 million euros, and that treatments worth 100 million euros were funded by clinical trials in Austria each year. This study shows that industry-funded clinical trials not only contribute to the advancement of

healthcare, medical care and science, but also have a positive effect on the economy as a whole. Kaló et al. (2014) outline the impact of clinical trials on the Hungarian economy, citing a direct effect of 0.163 contribution to Hungarian GDP and an additional indirect contribution of 0.033% of GDP due to savings in the healthcare system resulting from not having to pay for treatments that would otherwise be covered.

Table 1 shows the number of phase III clinical trials conducted in selected countries in the five-year period from 2015 to 2019. The data source used was the Citeline Trialtrove business intelligence system due to its more complete data than the US FDA's ClinicalTrials.gov database (Stergiopoulos et al, 2019), and a filter was applied to show only the number of clinical trials funded or commissioned by the pharmaceutical industry – in other words, all trials whose sponsor or funder was a government agency, academic organization or similar entity were excluded. The reason for not including non-industry sponsors is that they do not make their decisions on the choice of country in which to conduct a trial based on commercial or economic considerations. Instead, their decisions are based on other factors, such as existing collaborations with academic institutions in other countries, countries that are members of the academic consortium conducting the study, etc.

Table 1: Number of phase III clinical trials, commissioned by the pharmaceutical industry (2015–2019)

Country	Number of trials	Average no. of patients per site per month	Country population (millions)	No. of clinical trials per million inhabitants
United States	2525	5.72	339.9	7.43
Germany	1440	4.64	83.2	17.29
Spain	1339	0.34	47.6	28.18
Canada	1324	4.84	38.7	34.14
United Kingdom	1304	4.84	67.7	19.25
Italy	1221	0.45	58.9	20.74
France	1198	0.57	64.7	18.50
Poland	1170	0.53	41.0	28.52
Belgium	933	0.56	11.8	79.84
Russia	914	0.37	144.4	6.33
Australia	910	0.38	26.4	34.42
Hungary	871	0.39	10.1	85.76

Czech Republic	825	0.36	10.5	78.61
Netherlands	748	0.59	17.6	42.46
South Korea	741	0.26	51.8	14.31
Israel	664	0.25	9.8	72.37
Austria	574	0.51	8.9	64.07
Taiwan, China	572	0.35	23.9	23.91
Ukraine	538	0.37	36.7	14.64
Bulgaria	535	0.35	6.7	80.00
Romania	512	0.32	19.9	25.74
Turkey	512	0.27	85.8	5.97
Sweden	504	0.42	10.6	47.49
Denmark	492	0.50	5.9	83.24
Switzerland	397	0.38	8.8	45.13
China	387	0.21	1425.7	0.27
Greece	378	0.26	10.3	36.55
Portugal	367	0.23	10.2	35.81
Slovakia	317	0.37	5.7	54.70
Finland	315	18.63	5.54	56.80
Serbia	315	0.30	7.1	44.06
Ireland	284	0.24	5.1	56.16
Lithuania	242	0.42	2.7	89.02
Norway	233	0.30	5.5	42.56
Croatia	218	0.34	4.00	54.38
Latvia	212	0.49	1.8	115.83
Estonia	209	0.52	1.3	158.00
India	208	0.39	1428.6	0.15
Slovenia	89	0.33	2.1	41.99

Source: authors' calculation by using Trialtrove business intelligence system, owned by Citeline, Worldometer and estimate based on the 2022 revision of UN data.

The middle column shows the coefficient representing each country's efficiency in participating in clinical trials based on the average number of patients enrolled per trial site (i.e. a single hospital or outpatient clinic under the supervision of a principal investigator) per month.

The speed of implementation and completion of a clinical trial depends primarily on how quickly suitable patients are enrolled at the participating trial sites in the countries involved in the study. Intuitively, one might conclude that countries with large populations contribute the most to the number of patients enrolled in clinical trials and, consequently, the most clinical trials are conducted in those countries. However, the column "Number of clinical trials per million inhabitants" in Table 1 reveals a discrepancy between countries: certain countries with larger populations and higher average number of patients per trial site per month have a lower number of clinical trials per million inhabitants than other countries with smaller populations and the same patient enrollment factor (for example, Germany, with a population of 83.2 millions and a patient enrollment factor of 4.64, has fewer clinical trials per million inhabitants (17.29) than Italy, with a population of 58.8 million and a patient enrollment factor of 0.45, and 20.74 trials per million inhabitants). In addition, there are countries with approximately the same population in which the number of clinical trials per million inhabitants differs considerably. An example of this is Denmark and Finland: Denmark, with a population of 5.9 million and a patient recruitment factor of only 0.5, has 83.24 clinical trials per million inhabitants, while Finland, with a population of 5.5 million and a very high patient recruitment factor of 18.63, has only 56.8 clinical trials per million inhabitants.

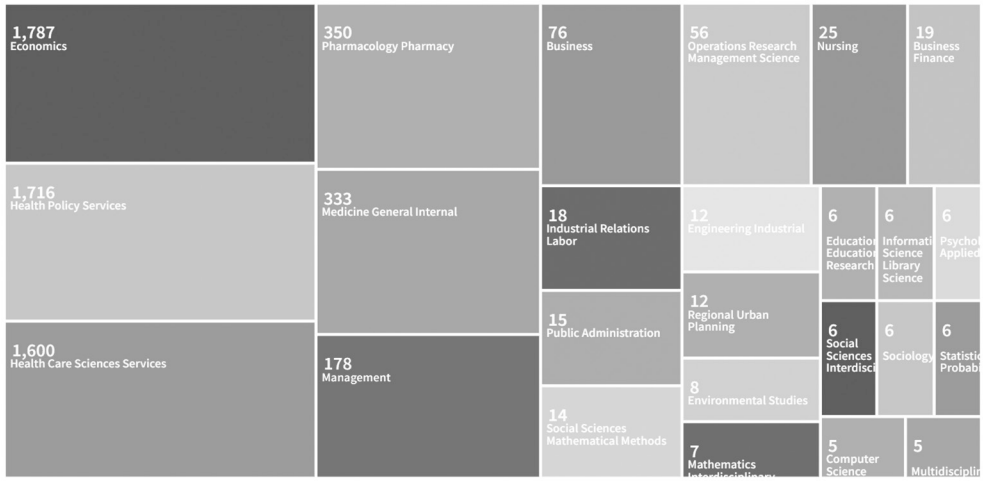
3 Literature Review

Due to its great economic importance – both in terms of market size and the large number of jobs in the industry – the clinical trials industry is an interesting and promising research topic, yet still relatively under-researched from an economic perspective. The following two figures show the number of scientific papers published since 2015 on Web of Science whose topic is clinical trials.

Figure 1: The number of papers on the topic of clinical trials in Web of Science 2015–2025.

Source: Web of Science

Figure 2: The number of papers on the topic of clinical trials in the research areas of business economics and public administration Web of Science 2015–2025.

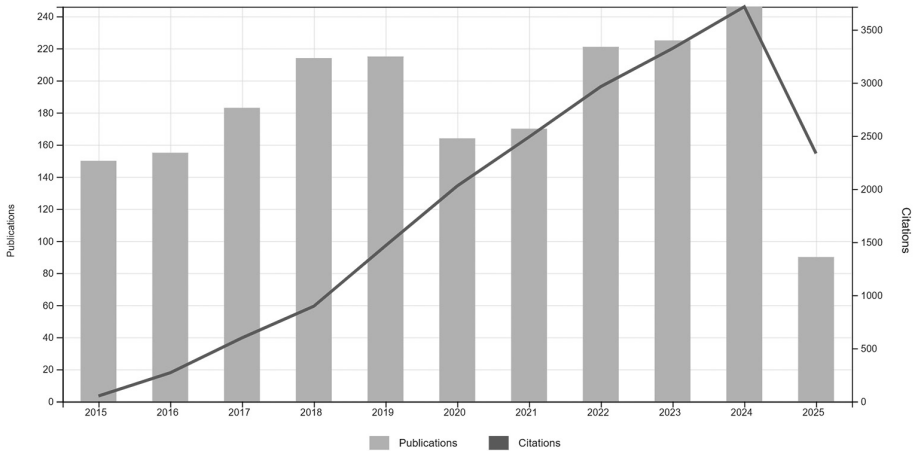


Source: Web of Science

Figure 1 shows the tree-map of published papers in the last ten years in the Web of Science Core Collection (WoS CC) in all subject areas on the specified topic. Although the total number of published papers is enormous and more than half a million (582,495), it is understandable that these are mainly on medical topics. However, when the search is narrowed down to the research areas of business economics and public administration (Figure 2), the total number of all types of research papers is only 2033, of which only 15 are in

the area of public administration. This shows that clinical trials are severely neglected in public administration and even in economics, which is difficult to understand given the importance of this sector in these areas. Even though the number of published papers is very modest, the number of citations of these papers is increasing rapidly (Figure 3), which shows the importance of the topic. The analysis of keywords for clinical trial in business economics and public administration carried out with VOSviever shows (Figure 4) that country attractiveness, decision factors, etc. are underrepresented even in this research area.

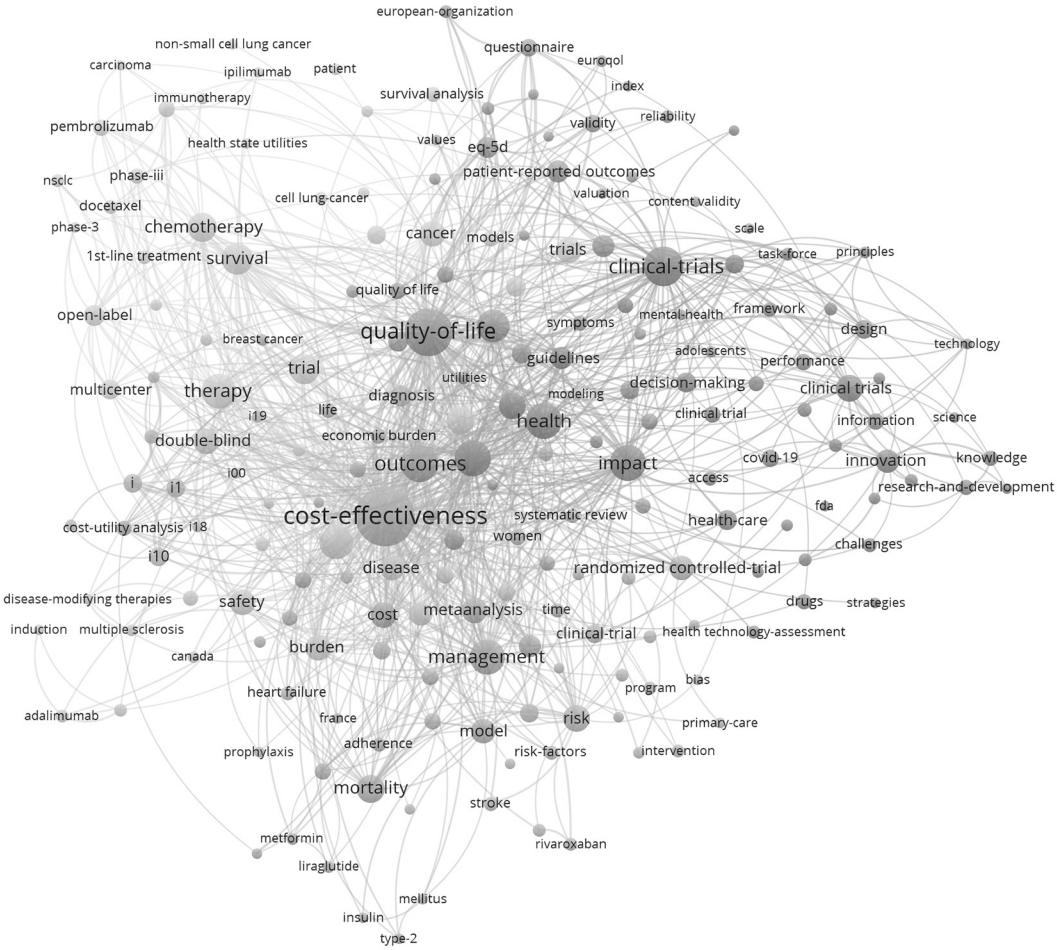
Figure 3: Papers on the topic of clinical trials in the area of business economics and public administration – times cited and publications over time.



Source: Web of Science

Due to the importance of the topic, the following part of the paper provides an overview of the relevant literature, which is limited to the very small number of studies that analyze the attractiveness of countries for clinical research. The overview is neither limited to specific databases nor to the publication period analyzed above, and is divided into several research clusters based on the focus of the individual contributions.

Figure 4: Keyword analysis of papers on the topic of clinical trials in the research areas of business economics and public administration Web of Science 2015–2025.



Source: created by the authors based on the data from the WoS CC database and using VOSviever.

3.1 Attractiveness of Host Countries

According to Lee (2016), the concept of country attractiveness is used to measure the characteristics of a particular country in relation to its markets. He explains that the concept of country attractiveness can be defined as the relative importance of individual advantages and the perceived ability of the country to provide these individual advantages. Lee notes that empirical research indicates that a country's attractiveness is simultaneously influenced by several factors, including tangible factors such as market size, market growth potential, level of economic development (or per capita income), and market openness in the context of the political and institutional environment.

The same author points out that a country's attractiveness for foreign investment can be positively influenced by improving socio-political stability to reduce the risk of foreign investment, improving the level of human development (e.g., providing services that affect the quality of life, a well-educated workforce, socio-cultural conditions such as education, healthcare, culture, etc.), managing the overall investment climate, and reducing the perception of bribery and corruption by business entities.

Avetisyan (2020) lists market capacity, population size, degree of economic openness, inflation, taxes, exchange rate stability, etc. as factors for attracting foreign direct investment, on which most authors agree. He notes that institutional instability has a negative impact on foreign investment. He argues that the experience of several countries has shown that the effective functioning of political and economic regulatory institutions has a greater impact than a number of macroeconomic indicators. As negative factors identified in numerous studies, he cites non-transparent regulatory policies, the dominance of state ownership and the lack of an investor protection system, a weak rule of law and violations of economic freedoms. According to Avetisyan, when analyzing these factors, it was found that the political stability factor is statistically more significant than the inflation rate.

The few papers that have explored the factors that contribute to the attractiveness of countries for conducting clinical trials generally support the proposition that investments flow to countries with greater socio-political stability, transparency, education levels and quality, etc. Murthy et al. (2015) conducted an analysis of data from the online clinical trials registry ClinicalTrials.gov and classified trials as conducted in either low-income or high-income countries based on the location of the countries in which they were conducted. In their research, they find that clinical trials (i.e. industry-funded trials, excluding academic and other clinical trials funded by other sources such as public funding, etc.) are traditionally conducted in high-income countries (wealthy countries), as this is where the infrastructure for conducting such trials is developed and where most pharmaceutical companies are based.

However, Murthy and colleagues point out that this trend has changed in recent decades and that clinical trials are increasingly being conducted outside wealthy countries, resulting in the number of countries where clinical trials are conducted doubling between 1995 and 2005. By analyzing data available on the US FDA's online registry (ClinicalTrials.gov), they found that more than a quarter of clinical trials are conducted in non-wealthy countries, while most are conducted in both wealthy and non-wealthy countries. Glass et al. (2016) note that clinical trials are cheaper to conduct in countries such as India and South America compared to North America and Western Europe, and that patient recruitment is also faster and cheaper there. The same authors believe that the search for so-called treatment-naïve patients, i.e. patients who have not previously received treatment for their diseases, is a motivation for conducting clinical trials in non-wealthy countries. Due to poorer healthcare provision compared to wealthy countries, these countries may have larger pools

of untreated patients who are more suitable for participation in clinical trials, and both patients and physicians are more motivated to participate as participation in a clinical trial offers free healthcare and access to the latest therapeutic options. Murthy et al. (2015) find that among non-wealthy geographic regions, the largest proportion of clinical trials are found in non-Western Europe and Asia. They further note that investigative centers in these countries enroll more subjects than trials conducted only in wealthy countries, indicating that non-wealthy countries contribute significantly to the speed and objectives of trials. Although they also cite the lower costs in these countries as a likely factor, they support the thesis that the motivation for including non-wealthy countries in clinical trials and their attractiveness lies in the ease of recruitment of treatment-naïve patients with chronic diseases. Even if other studies indicate that the costs of trials do not play a (major) role in decision-making, the speed of conducting and completing clinical trials is certainly a key factor. The reason for this is the patent protection of the investigational product, which expires 20 years after the patent application and includes the period in which the clinical trials are conducted. Faster recruitment of patients to achieve the required statistical sample therefore contributes directly to a faster completion of the study and the start of commercial use of the investigational product. Glickman et al. (2009) highlight that the pharmaceutical industry benefits from the cost reductions due to globalization by conducting some activities in countries with relative advantages where there is a large population for clinical trials and sales in addition to cheaper labor, mentioning in particular South America and India.

Moscicka et al. (2013) present the specific characteristics of Central and Eastern European countries in their paper and highlight the reasons for the growing demand for these countries: centralized healthcare systems with a small number of specialized centers serving a large number of patients; well-trained physicians and nurses; both public and private healthcare facilities have access to treatment-naive patients (unlike in Western European countries where this is becoming increasingly difficult); existing systems of vertical patient referral in these countries, resulting in minimal competition for patients between medical centers; and the availability of lifelong medical records for patients, allowing for low rates of failed screenings and early withdrawal of patients from studies. They also point out that the migration rate in this region is much lower compared to Western Europe, which allows for better long-term follow-up of participants. Other factors that contribute to the attractiveness of the region include good technical equipment with modern diagnostic devices and the medical, pharmaceutical or scientific education of clinical trials staff. Croatia and Serbia are cited as examples of countries where approval to start a clinical trial takes longer than in other countries, namely five to six months. They conclude that the quality of clinical trial conduct in Central and Eastern European countries does not lag behind the quality in Western European countries.

3.2 Factors Influencing the Decision on the Choice of Country

Silva et al. (2016) state that when selecting a country, trial sponsors should consider: the country's capacity to provide clinical evidence, investigator qualifications, number of patients with access to advanced medical care, communication capacity in terms of access to computers and the internet, intellectual property protection and market orientation. They also emphasize that the complex relationships between pharmaceutical companies and public institutions, as well as companies' attitudes toward the rules on compensation and payments in a given country, the degree of involvement of investigators in setting these rules, and general data on the country's market and healthcare system (population, gross domestic product per capita, healthcare expenditure per capita) may influence the decision on the location of a clinical trial. Silva et al. (2016) also note in their review that when selecting countries, their ethnic groups, epidemiological status of the disease, medical practice and geographical proximity must be considered and emphasize that not taking into account differences between countries may result in the need for a larger sample size and longer research duration.

Ippoliti (2013) conducted an econometric analysis of the economic efficiency of clinical trial assessment procedures in 29 European countries and their competitiveness in the human trials market, using panel data from 2004 to 2007. Based on this research, he finds that a country's population is statistically significant for competitiveness. He concludes that this suggests that trials are conducted more frequently where there are more potential patients in need of treatment. The same applies to the number of doctors: a higher number of doctors in a particular country has a positive effect on the decision of pharmaceutical companies to include that country. He also emphasizes that there is a positive correlation between the efficiency of the approval system for studies and investment in pharmaceuticals.

Gerhring et al. (2013) conducted an anonymous online survey on attitudes towards clinical trials in Europe (SAT-EU), in which the factors influencing the selection of trial sites in Europe were assessed. They highlight the negative impact of administrative burden on the competitiveness of clinical trials. They emphasize the critical importance of the speed with which feasibility data is collected and the speed with which a clinical trial is initiated. They believe that the track record of trial sites and the ability to quickly and effectively access all relevant information for sponsors and clinical trial organizers is of great importance. An eye-opening study based on an analysis of specific clinical trial sites (Dilts and Sandler, 2006) has identified an unusually high number of steps involved in the decision to initiate a clinical trial. A large proportion of these steps were found to be non-value adding and had no impact on the safety of the trial or the drug. The authors suggest that, following the example of other industries, removing such administrative hurdles could significantly speed up the process and improve patient care without compromising the integrity of the trial or patient safety.

Górecka and Szałucka (2013) highlight the existence of several market selection models in the literature and state that international market selection is usually considered as a sequential process where less attractive markets are gradually eliminated at each stage, eventually leading to the selection of a potential target market. They note that a systematic approach to international market selection is crucial, as this decision-making requires processing a large amount of information from many different and complex markets. The criteria for evaluating countries must be defined before the screening phase, as they ultimately have a direct impact on the screening results. They also emphasize that a number of criteria is proposed in the literature that can be used and measured, but there is no consensus on them and their selection depends on which criteria each author believes are most appropriate for a particular situation. These criteria are directly related to the objectives of a company's international expansion and vary depending on the type of market entry and what the company specifically wants to achieve in the target market.

Górecka and Szałucka (2013) further emphasize that while there are numerous indicators in the literature to measure the criteria for selecting foreign markets, there is no consensus on a standardized variable that would make this process less subjective. They also emphasize the lack of agreement on the relative weight or importance of individual criteria – some studies suggest assigning equal weight to all criteria, while others suggest that certain criteria may be more important than others. They note that the literature on international marketing identifies two main approaches for determining target markets during the initial selection of countries: grouping and ranking. The grouping method categorizes countries into groups based on the similarity of their commercial, economic, political and cultural dimensions, which helps to identify possible synergies between these markets. This approach assumes that companies prefer to enter countries from the same group (cluster) in which they already operate successfully. The ranking method ranks countries according to their attractiveness for market entry and evaluates them based on one or more criteria. This approach provides decision-makers with an aggregated measure of market attractiveness. The authors emphasize that although both methods are recognized as important tools for analyzing a large number of countries with heterogeneous markets, they should only be used in the preliminary phase of market assessment.

Bordet et al. (2015) analyzed the state of the clinical trials market in France and drew conclusions on the areas that need to be improved in order to increase the country's competitiveness. They conclude that France's productivity is perceived negatively in the eyes of the clinical trials industry compared to other countries. Negative factors cited include high costs, slow patient recruitment and a high proportion of trial sites closing without a single patient being enrolled. After the lengthy and costly approval process to start a clinical trial and the logistical challenge of starting the trial at each individual site, the closure of a trial site without patient recruitment is a worst case scenario for any trial sponsor. In their paper, Bordet and colleagues analyzed the findings of the French Strategic Council for the Health Industries (Conseil Stratégique

des Industries de Santé – CSIS), which established a public-private partnership to improve participation in clinical trials and proposed measures to reduce the time needed to sign contracts, enroll 80% or more of the planned number of patients in at least 80% of sites, and close fewer than 15% of sites without enrolled patients. They conclude that the results of the studies on the effectiveness of these measures show that it is possible to increase the country's attractiveness for industry-sponsored clinical trials.

Alemayehu et al. (2018) conducted a study by reviewing literature indexed in PubMed, Embase, CINAHL and Web of Science as well as the WHO Global Health Library, searching for keywords such as barriers, challenges, clinical trials and developing countries. The focus of their research is on the barriers to conducting clinical trials in developing countries. The most common barriers cited were lack of financial and human resources, barriers in ethical and regulatory approval systems, an underdeveloped research environment, operational barriers and competition from potential clinical trial investigators, e.g. lack of time and other priorities due to their other assignments. Based on a systematic review of the literature and internal communications from the European Clinical Research Infrastructure Network (ECRIN) related to the ECRIN-IA project from 2013 to 2017, Djurisic et al. (2017) cite insufficient knowledge of clinical trials and trial methodology, excessive monitoring, restrictive data protection laws and lack of transparency, complex regulatory requirements and inadequate infrastructure as barriers. They also mention lack of funding as a barrier, but this refers to academic and public clinical trials, not industry-funded ones, which are not the subject of this paper. Carvalho et al. (2021) present their view on the state of the clinical trials industry in Portugal. They highlight clinical trial organizational units as key to the success of clinical trials, as they believe they enable adequate feasibility studies, recruitment and retention of participants. As key factors for the success of clinical trials and also as competitive factors for strengthening clinical trials in Portugal, they mention the motivation and awareness of the trial teams, combined with a high level of reliability and good relationships between healthcare professionals and trial participants.

Based on eleven semi-structured interviews with employees of multinational pharmaceutical companies in Denmark who are involved in decisions on the awarding of clinical trials, Dombernowsky et al. (2017) describe the decision-making process for country selection. The headquarters of the trial sponsors – pharmaceutical companies – make the decision in collaboration with Contract Research Organizations (CROs – companies that organize and supervise the conduct of clinical trials for the sponsor) and their subsidiaries in individual countries. For fully outsourced trials, the decisions are made by the CROs, while in other cases the sponsor's head office makes the decisions. The sponsor's subsidiaries provide the head office with data on their country, the feasibility of a specific trial, the availability of human, organizational and technical resources, the track record and the availability of so-called key opinion leaders. For this study, the decision-makers on country allocation were interviewed. The results show that all respondents consider timely patient

recruitment to be one of the most important factors by which headquarters evaluate the performance of their subsidiaries, followed by the quality of the data obtained. It has been shown that smaller countries must continually demonstrate their success in patient recruitment to be included in new clinical trials, as smaller countries are not automatically selected by sponsors. In contrast, larger countries are often included in clinical trials regardless of their previous success in patient recruitment, due to other factors such as the potential for post-approval drug sales. An example of this is the United States, which, according to data from another study cited by Dombernowsky et al.(2017), recruited only two-thirds as many patients compared to other countries, but still participated in a very large number of clinical trials. The number of patients enrolled per month and per trial center is considered a measurable indicator of a country's success. Another factor is the speed with which a trial can be operationally initiated – in other words, a shorter time to obtain approval and sign contracts with individual healthcare facilities means a faster start to patient recruitment and more time for recruitment. The same study has shown that a lack or absence of investigator experience in conducting clinical trials does not necessarily mean that such sites will be rejected for participation. The reason for this is that the trial sponsor can compensate for this lack by providing more resources for training and monitoring the conduct of the trial.

Benisheva et al. (2023) conducted a study by reviewing legal documents, EU regulations and directives, and publications and reports on local and EU requirements for conducting clinical trials and analyzing statistical data from the EU Clinical Trials Register for Bulgaria, Hungary, Poland, Romania, and Slovakia on the total number of clinical trials conducted in these countries, Romania and Slovakia on the total number of completed and ongoing phase I-III interventional clinical trials, the prevalence of trials in rare disease diagnoses, the distribution of completed trials by phase and the number of completed and ongoing trials in the European Economic Area countries and all EU Member States from 2012 to 2022. Based on their research findings, they conclude that the number of clinical trials in a particular country does not correspond to the country's population size, but that other factors play a role in the choice of country, such as the reliability and predictability of regulatory timelines, a large number of medical personnel per capita, experienced medical personnel willing to conduct clinical trials, experienced CRO personnel, large potential for patient recruitment, competitive costs per patient, low patient dropout rates and satisfactory results in regulatory inspections.

Jeong et al. (2017) compared elements from nine representative countries with the US and used multiple linear regression to analyze factors associated with the distribution of trial sites. Through their research on characteristics and related factors in the context of globalization of clinical trials, they present a predictive model for the distribution of clinical trials that includes the following indices: EFI (Economic Freedom Index), HEC (Health Expenditure per Capita), HCI (Human Capital Index) and IPRI (Intellectual Property Rights Index). They find that the distribution of clinical trials can be satisfactorily ex-

plained by factors related to healthcare system infrastructure (HEC), a free market and low bureaucracy (EFI), access to higher education (HCI) and intellectual property rights (IPRI). They also point out that the literature mentions that the cost of clinical trials per country also has an influence, which may partially explain the determination of trial locations, but this data was not included in their research, and further studies are needed to explain other factors that influence the allocation of clinical trials by country.

3.3 The Influence of Costs

In relation to the cost of clinical trials by country and its influence on the selection of countries to conduct trials, research findings show contradictory results. Jeong et al. (2017) find that cost reduction is one of the main reasons why sponsors choose developing countries to conduct trials in countries such as China, India and South America. Gehring et al. (2015) found in their analysis that a favorable pool of suitable patients, speed of approval and online availability of trial site information are much more important than costs and government subsidies. Dombernowsky et al. (2017) also conclude that the costs of allocating clinical trials by country is less important. They refer to a 2009 report in which a survey of 362 clinical trial stakeholders found that 80% of respondents would prefer to meet patient recruitment targets 10% faster than reduce costs by 20%. A study conducted by Goehring et al. (2013) also found that the costs of conducting clinical trials was significantly less important compared to factors such as an appropriate patient pool, speed of the approval process and the existence of disease management networks.

Dombernowsky et al. (2019) also note that cost is less important than other factors in the selection of trial sites, but that it can still play an important role in the selection of countries. However, they note that the research findings suggest that cost is more important when the sponsor's headquarters evaluates the efficiency of CROs – i.e. external partners – than when it evaluates the performance of its own subsidiaries. Although research findings are not consistent regarding the importance of the cost level in a given country for enrollment in clinical trials, the inclusion of less wealthy countries can most likely be explained by their comparative advantages over wealthy countries, leading to faster recruitment of the required number of patients, as also stated by Bordet et al. (2015). On the same topic, Gehring et al. (2013) state that the impact of direct costs is limited and that indirect or hidden costs, such as the loss of time due to slow bureaucracy, slow patient recruitment or poor overall efficiency of trial sites, have a significant negative impact.

Although there is evidence that cost is not the decisive factor when selecting a country to conduct clinical trials, the costs of the entire process are very high and by no means negligible. Kramer and Schulman (2012) point out that regardless of the factors driving up the cost of developing new medicines, the impact of rising costs is clear: Higher research costs result in fewer new medical products coming to market, less knowledge about the products that do come to market, and less research on public health issues.

3.4 The Influence of Regulations

Gerhring et al. (2013) point out that the negative impact of a suboptimal regulatory environment does not necessarily have a negative impact on investigator selection – provided the investigator is known and visible, has proven competencies, information about their research center is easily accessible and they are able to enroll the required patients in the trial. Efficiency in terms of speed of patient recruitment takes precedence over the weight of negative factors in the regulatory and institutional environment.

Bansal (2012) highlights the following difficulties in conducting clinical trials globally from a US regulatory perspective: properly obtained and truly informed consent from subjects, differences in medical practice and standard of care, acceptance of data from other countries due to (non)compliance with US Food and Drug Administration (FDA) regulations, and ethnic factors due to different genetic profiles.

Pharmaceutical companies apply for patent protection for a newly discovered drug with the relevant regulatory authorities before starting clinical trials. In the USA (FDA, n.d.) and in the EU (Garattini and Finazzi 2022), the duration of drug patent protection is 20 years. The possibility of obtaining a patent for their discovery triggered a hunger for innovation in the pharmaceutical industry (Nedelcheva, 2019). The goal of clinical trial sponsors is to complete all three phases of clinical trials as quickly as possible in order to be able to start marketing the drug and exploiting it commercially. This means that the longer clinical trials take to complete, the shorter the period for exclusive commercial use. Once patent protection expires, generic manufacturers are free to start producing the drug without paying royalties. Investigating the causes of these discrepancies is the basic idea of this research: to identify the factors that make some countries more attractive than others for conducting clinical trials. In the context of speed of approval, Silva et al. (2016) cite the example of China, which has succeeded in reducing the time required for the approval of clinical trials by centralizing the regulatory authority and reducing conflicting regulations between the central and local levels of government.

In another paper, Gehring et al. (2015), based on data from the same SAT-EU study using Italy as an example, also point out that the regulatory environment influences sponsors' decisions on where to conduct their trials. Their research identified three areas that are critical to a country's competitiveness: the availability of information needed for clinical trials, the predictability and speed of clinical trial approvals by ethics committees and regulatory authorities, and the availability of necessary equipment. The issue of equipment availability highlighted in this paper is a somewhat surprising factor, as in multinational clinical trials sponsors generally assume that they will need to provide at least some (if not most) of the equipment for the trial sites. At first glance, this appears to be merely a logistical challenge, but it can also be interpreted as a lack of capacity to conduct clinical trials and is indeed an unfavorable factor in this context – even if its importance is questionable and unproven. In relation to the predictability and speed of the clinical trial approval process, the

authors note that the approval process and subsequent contracting with trial sites is so lengthy and demanding that by the time a clinical trial is launched in Italy, international clinical trials may have already reached their statistical sample and completed patient recruitment. As a conclusion and recommendations to improve Italy's competitiveness, as possible improvement models they mention the harmonization of national approval systems (at the level of ethics committees and the healthcare institutions themselves), including the improvement of procedures for contracting with healthcare institutions to bring them in line with the clinical trial approval process, and increasing the visibility of centers of excellence, i.e. making information about trial sites available on the Internet.

3.5 Further Observations on the Criteria for Clinical Trials

Strüver and Ibeneme (2021) examined the status of clinical trials in Nigeria and South Africa based on data from the ClinicalTrials.gov registry, the Pan African Clinical Trials Registry, the National Health Research Database from South Africa and the Nigeria Clinical Trials Registry and analyzed the data using descriptive statistics and trend analysis. They conclude that clinical trial sponsors do not appear to prioritize diseases that are prevalent in a particular country, such as plague in Nigeria, for which there is a large pool of patients. They conclude that sponsors do not select countries according to local health needs, but according to their own business priorities. They also highlight that sponsors appear to have a greater interest in non-communicable diseases, which can be considered international diseases. By analyzing a random sample of 5% of clinical trials registered in the WHO International Clinical Trials Registry Platform as interventional trials in the active patient recruitment phase, Viergever et al. (2013) came to the similar conclusions – they state that their research indicates that the correlation between disease incidence and the global distribution of clinical trials is low, and that clinical trials are much more common in higher income countries than in lower income countries.

4 Results and Discussion

Locating clinical research in a particular country, region or hospital has almost no negative consequences, while the positive effects are numerous and easy to understand. The economic impact of clinical trials on national healthcare systems is multifaceted:

- Patients receive free access to the most innovative therapies
- Treatment in clinical trials is free for both patients and the healthcare system
- Physician-investigators involved in clinical trials receive an additional source of income
- Some of the money goes directly to national healthcare systems in the form of a direct contribution to clinical trial budgets

– Part of the money flows indirectly into the national budget and the public healthcare system in the form of taxes, contributions and other fees

Based on an overview of the clinical trials market, it is clear that the success of countries in attracting this form of foreign investment varies widely. This paper analyzes some of the key studies that attempt to highlight the reasons why some countries are more successful than others in attracting clinical research, i.e. the factors that influence the decision of companies to conduct clinical research.

This research shows that the attractiveness of a country for conducting clinical trials is based on its ability to offer important economic, legal and infrastructural advantages that encourage investment in clinical research. The most important factors that make it attractive include political stability, a well-developed and accessible healthcare and research infrastructure, a high level of education, especially of medical personnel, and a transparent administrative system with a low level of corruption. All of this creates a favorable environment for pharmaceutical companies looking for efficient and reliable conditions for conducting clinical trials.

We found it particularly interesting that, according to some studies, Central and Eastern European countries have become competitive destinations over the last decade. Their attractiveness is enhanced by the existence of centralized healthcare systems with several large clinical centers, which enables the rapid recruitment of large numbers of patients. In addition, the availability of so-called "treatment-naïve" patients, i.e. patients who have not yet been treated for certain diseases, makes these countries suitable for testing the efficacy of new therapies. High-quality and experienced medical staff, modern diagnostic equipment and a stable population with low out-migration also increase the opportunities for long-term follow-up of test subjects, which is crucial for the success of many clinical studies. As the public healthcare systems of the most successful CEE countries are similar to those of other countries in this region, it is possible that other countries will become more receptive to such studies in the future.

In developing countries, especially in Asia and South America, more and more clinical trials are being conducted. The main reasons for this are the large number of patients available and the significantly lower costs compared to developed countries, which makes this region attractive to pharmaceutical companies seeking efficiency and cost rationalization as part of their global research strategies.

Previous studies have shown that pharmaceutical companies use a number of quantitative and qualitative criteria when selecting a country to conduct clinical trials. One of the most important is the size of the population, as a larger number of potential subjects increases the likelihood of successful and rapid recruitment. Similarly, a larger number of available physicians has a positive impact on the trial sponsor's decision, as this is an indication of the healthcare system's ability to support complex research activities.

One of the most important criteria is the speed of patient recruitment, as time is a limited resource in the context of the duration of patent protection. In addition, the efficiency of study initiation, i.e. the speed with which regulatory approvals are obtained and contracts are signed with research sites is often a decisive factor in the choice of a target country. Research sponsors value countries and sites that are known for fast and reliable procedures, and the existence of "key opinion leaders" – experts with international reputation who can contribute to the credibility and visibility of the study and, eventually, the drug once it is placed on the market – carries additional weight in the decision-making process.

Other important factors are the availability of digital infrastructures, the level of protection of intellectual property, the transparency of the regulatory system and the quality and reliability of the data collected. All of these elements combine to form the perception of the country as a professional and predictable destination for investment in clinical trials.

Interestingly, and somewhat counter-intuitively, a growing body of research suggests that cost alone is not the deciding factor in country choice. The overall cost of clinical trials is extremely high, but research shows that factors that directly impact the speed and success of trials (such as the ability to recruit patients quickly, the efficiency of regulatory procedures and the high quality of data collected) are increasingly being prioritized.

Although cost per patient may play a role, especially when assessing the efficiency of external partners such as CROs, it has less weight in the context of internal decisions by pharmaceutical companies on the allocation of trials to their own subsidiaries. Considering that the total cost of developing a new drug can be as high as USD 800 million, the priority is usually on speeding-up the process rather than maximizing savings. This confirms that, although costs are not negligible, strategic and operational factors carry greater weight in decision-making in the long term. This is particularly evident from the fact that when pharmaceutical companies enter Phase III of clinical research, patent protection already begins, so the speed and reliability of the trial process are of crucial importance. In this context, indirect costs – such as delays in study approval, slow administrative procedures or poor organizational infrastructure – can have a much more negative impact on the success of a trial than direct financial costs alone. For trial sponsors, time becomes a key currency, as a longer trial duration shortens the time available for exclusive commercialization of the drug before patent protection expires.

The country's regulatory framework is one of the key elements in the decision-making process for conducting clinical trials. Although an unfavorable regulatory environment does not automatically disqualify a country – especially if there are experienced and visible researchers – the speed and predictability of regulatory procedures still have a major impact on the attractiveness of the country. Studies show that lengthy approval processes and complex administrative requirements can significantly slow the start of patient recruitment, reducing the overall effectiveness of trials and increasing time to market.

In addition to the speed of approval, the availability of information about research sites and the existence of clear guidelines and procedures also play an important role. A lack of equipment or resources at the trial site can further delay the start of a trial, while the predictability of the approval process reduces risk and increases sponsor confidence. Even if regulation itself is not the only decisive factor, it largely shapes the perception of the country as a reliable and efficient partner in the global clinical research chain.

5 Conclusions

This research shows that the most important factors in attracting clinical trials in a country are economic, legal and infrastructural advantages that enable research to be carried out quickly, efficiently and reliably. These include, above all, political stability, a well-developed and accessible healthcare and research infrastructure, a high level of training for medical staff and a transparent and effective regulatory system with a low level of corruption. In this context, time becomes the key factor: the speed of patient recruitment and study approval plays a decisive role, while direct costs are less important than operational efficiency and data quality.

Central and Eastern European countries have proven to be particularly competitive due to their centralized healthcare systems, large numbers of patients, including those not previously treated, and highly qualified medical staff. Although more and more trials are also being moved to Asian and South American countries due to lower costs, the location decision is increasingly based on the country's overall ability to support the rapid and reliable conduct of trials. The key message is that the quality of organization, speed of administration and predictability of regulations are often more important than price alone – as delays and bureaucratic obstacles can cause more harm than high financial costs.

Given that clinical trials are a big business, and that countries have or should have an interest in attracting them for a number of reasons, this research is particularly useful for authorities and regulators. But it is also important for decision makers at the hospital and clinical system level to focus on the attraction factors for clinical trials.

It should be noted that not only is there little economic literature on clinical trials, but most of the work referred to in this review is non-empirical, such as commentaries, review articles or studies that are not comprehensive and are based on individual cases or on small samples of countries. Therefore, the factors influencing clinical trial decisions still need to be investigated and analyzed.

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