REPORT
INDUSTRY CLINICAL TRIALS IN POLAND

Possibilities to increase number and scope of trials in Poland

2021

INFARMA POLCRO

REPORT: Industry Clinical Trials in Poland
Possibilities to increase number and scope of trials in Poland

Commissioned by:
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Foreword

When Directive 2001/20 / EC in Poland was implemented in 2004 paper CRFs and clinical trials were being performed at doctor's offices by the primary investigator, who was the main and only member of the research team. From this perspective, changes that have taken place on our market between 2004 and 2021 can be considered revolutionary. In addition, from January 31 2022, the long-awaited Regulation (EU) No. 536/2014 of the European Parliament and of the Council of April 16, 2014 on clinical trials of medicinal products for human use and the repeal of Directive 2001/20 / EC, will come into effect. We also hope that the legislative process on the Clinical Trials Act will be completed by this time. Both regulations and the changes introduced by them will increase Poland's competitiveness as a place to conduct clinical trials by implementing transparent legal regulations enabling the use of European standards and introducing additional facilities and mechanisms encouraging the conducting of clinical trials.

We continue to await entry of both regulations into force, however in the meantime, the COVID-19 pandemic has changed our environment. As the result, the clinical trial development process has never been as fast or under such close public scrutiny as it is now. COVID-19 has become a major challenge for healthcare systems, research communities, and the pharmaceutical / biotechnology industry. Therefore in 2020, the regulatory environment changed to adapt to the new reality.

Due to the pandemic and the related limitations, novel global solutions for conducting clinical trials have been introduced on a much larger scale. Changes in the management and monitoring of clinical trials have shown that thanks to these technologies, some data can be collected without the need for patients visit sites or frequent monitoring visits. The shift of clinical-trial activities closer to patients has been enabled by evolving technologies and services. Tools such as electronic consent, telehealthcare, remote patient monitoring, and electronic clinical-reported outcome (ePROs) allow investigators to maintain contact trial participants without in-person visits. Unfortunately, not all solutions can be applied in Poland, thus not all clinical trials using new solutions and technologies go to Poland.

Along with growing interest in the possibility of implementing decentralized clinical trials in Poland, certain aspects of medical practice require legislative adaptation. It is necessary to change the regulations to reduce restrictions on home care and to increase the responsibility and independence of medical personnel performing some of the medical procedures at patient homes (nurses, pharmacists), including the right to perform injections. At the same time, the current regulations make it practically impossible to monitor medical records outside sites, apart from the possibility of limited data verification in accordance with EMA Guidelines for conducting clinical trials during the COVID-19 pandemic. Furthermore, there are no regulations specifying the rules for the use of electronic medical records for the purposes of clinical trials, including remote monitoring and access to electronic source documents. In other countries such solutions exist, allowing for effective supervision of patient safety in clinical trials.
We started preparations for the report entitled "Industry Clinical trials in Poland – possibilities to increase number and scope of trials in Poland" in 2020. This report is a joint project of INFARMA and POLCRO. For the first time, the report not only describes the trends observed in recent years in Poland, but also compares them to global trends. This allowed analysis on which areas of clinical trials in Poland are developing fast, and which require additional investment, introduction of new processes, or regulation. As was highlighted in the report, innovative industry-led clinical trials conducted in Poland in 2020 granted access to more than 25,000 Polish patients to novel and cutting edge experimental therapies. Further development in this area is still possible if the regulations in Poland keep pace with global changes in clinical trials. Therefore, both INFARMA and POLCRO observe global trends to implement them locally or inform the competent authorities about the need to adjust our regulations. It is time for Polish patients and investigators to have access to real-time innovation through timely adaptation of regulations and introducing additional facilities and mechanisms, as well as effective cooperation within the international environment of clinical research.

Agnieszka Skoczylas
President of POLCRO

Innovation and R&D are crucial to economic growth, fostering innovation, creating more healthcare resilience, and improving global competitiveness. Over the past few decades, we have witnessed huge progress in the treatment of both common and rare diseases owing to, i.e., the development of effective, safe and innovative drugs, while the research-based pharmaceutical industry has entered a new era of development. Today, pharmaceutical companies are researching more than 7,000 molecules that offer a promise of better and longer lives for patients, and breakthrough cell and gene therapies are becoming more accessible. In 2020, the EMA approved 55 new active substances, mainly in infectious diseases, immunology and hematology, representing an increase of 80% compared to 2019. Additionally, the COVID-19 pandemic has further emphasized the importance of **research efforts in the area of identifying and developing new drugs and vaccines** for COVID-19. The development of COVID-19 therapeutics, diagnostics and prophylaxis has activated various types of partnerships with public health authorities and has demanded a concerted effort on the part of regulators, sponsors, research companies and researchers alike. As a result, vaccines were developed, manufactured, and delivered to the market within just 12 months.

Clinical trials are necessary for developing new medicines and vaccines, and serve to test their efficacy and safety. They are **crucial to the patients** who participate in them as they offer a chance to receive a new treatment that has the potential to improve their quality of life, help them manage their disease, and in some cases to prolong or to save their lives. Clinical trials contribute to the development of knowledge of the use of innovative medicines and treatments, build scientific output of researchers and research centers and influence economic growth and a country's international standing. Therefore, a proper clinical trials strategy can help achieve greater economic development, create more added value, foster innovation and R&D, as well as support a healthier and health-resilient society.

INFARMA is one of the initiators of periodic reports on clinical trials, the aim of which is to analyze the status of clinical trials in Poland, their effects on patients, the market and various stakeholders, as well as the prospects for further development. A report entitled "Clinical trials in Poland" (2005) indicated that Poland has the potential to develop a clinical trials market due to its large patient population, well-educated medical staff and relatively low costs. However, the changes in the European clinical trials market following the Regulation on clinical trials of medicinal products (536/2014) required Poland to take decisive adaptation measures. As the current **Report "Clinical Trials in Poland – Possibilities to increase the number and scope of trials in Poland"** indicates, the recommendations of the previous report regarding the adaptation measures are still valid and ongoing. Furthermore, it also provides an in-depth analysis of the clinical trials market in Poland against the benchmark of other markets and global trends.

This report was prepared at a crucial time, before the entry into force of the Clinical Trials Act, one of the objectives of which, in addition to the introduction of Regulation 536/2014, is to increase the attractiveness of conducting clinical trials in Poland. As the results of the report show, **the socio-economic benefits of clinical trials** in Poland are the result of a sustained trend of growth in the number of clinical trials, owing to which the economic value of trials exceeded USD 1.4 billion in 2020 (15% of total R&D investment in Poland). Approximately 9,000 jobs have been created and more than 25,000 patients have gained access to novel and cutting-edge therapies, ranking Poland high in terms of patient access to experimental therapies. The above is particularly important in a context where many modern therapies which are standard in the EU, are not available to patients in Poland or are available to a very limited group of patients, and participation in a clinical trial is an available therapeutic option (out of 152 drugs registered by the European Medicines Agency in 2016-2019, only 42 were available in Poland prior to the pandemic). The disproportion between clinical trial market share and pharmaceutical market share is also visible in this context. In addition, the report highlights scenarios for the development of the clinical trials market in Poland and presents examples of practices from other countries which can be used to maintain **Poland's 11th place in the global clinical trial market.**

So how can the attractiveness of Poland as a destination for conducting clinical trials be increased? The most **important challenge for the clinical trials market in Poland** will be to seize the opportunities arising from new European regulations and to implement solutions for innovative and more complex clinical trials using new technologies, together with research promotion and enhancing international scientific cooperation. Clinical trials are increasingly incorporating novel and innovative clinical trial designs throughout all phases of drug development with the aim of accelerating patient access to new medicines and improving the efficiency and the success rate of clinical trials. The chance of success of the dynamic development of clinical trials depends on the complexity and amiability of regulations in the country where they are conducted. Therefore, a government strategy with regard to clinical trials and the cooperation of many stakeholders, both government agencies, representatives of the medical community, centers conducting clinical trials, patient representatives and representatives of sponsors and CROs, is essential. It can be expected that – while recognizing the importance of clinical trials – government agencies will undertake initiatives to increase investment commitment of innovative pharmaceutical companies and Poland will be able not only to maintain, but also to improve its position among clinical trials market leaders.

Bogna Cichowska-Duma
Director General of INFARMA

Executive summary

Since the mid 1990s Poland, together with the rest of CEE, has grown into a powerhouse of innovative biopharmaceutical industry clinical trials (iBPCTs): in 2019 it ranked 11th globally in terms of iBPCT market share, and during the 2014-2019 period posted 5th largest iBPCT market share gain globally, behind China, Spain, South Korea and Taiwan (details on ranking methodology are provided in this report). The socioeconomic impact of this market share is very significant: in 2019 the economic value of iBPCTs represented more than USD 1.3 billion (15% of total R&D investment in Poland), some nine thousand jobs in Poland were related to iBPCT, and more than 25,000 Polish patients gained access to cutting edge experimental therapies in 2019 alone. In 2019, Poland ranked 12th globally in terms of population-adjusted accessibility to experimental therapies, and ranked 7th in terms of industry-country reputation index (details on ranking methodology are provided in this report). The reasons which propelled CEE, and Poland specifically, to this global rock-star status are many, but primarily centered around higher site productivity vs. established markets, lower costs driven by a combination of lower labor costs, compounded by productivity-based cost per-patient gains, lower trial set-up costs vs. established markets, higher productivity of sites and a solid quality reputation. The factors that were enablers of the iBPCT growth in Poland were: a centralized healthcare system, motivated investigators capable of recruiting and retaining patients in the studies, and comparatively low costs.

However, this report also identified several areas where Poland has underperformed vs. its global peers:

- One of the largest imbalances (7th globally) between the pharmaceutical market share and the share of clinical trials (with an almost a 4x research bias),
- Medical thought leadership: Poland ranked only 26th in terms of medical research prominence index (net medical research citations), behind much smaller countries e.g., Austria and Greece,
- Poor international medical research collaboration,
- Absence of national-level clinical trial (CT) infrastructure supported by technology (e.g., EHR data mining),
- Inadequate professionalization of majority of CT sites,
- iBPCTs have not been one of the priority focus areas of the government so far (and they should!).

This report identified the following scenarios of iBPCT markets trends in Poland:

- Growth: market share growth of 3.5% p.a. during 2021-2030 to achieve (in 2030) iBPCT levels per capita comparable to Spain (which we view as a suitable benchmark)

however, there is a reasonable probability of an alternative scenario:

- Correction: a market share decline (approx. 25% between 2021-2030) driven by one of the largest imbalances (7th globally) between pharmaceutical market share and share of clinical trials (with an almost a 4x research bias)

The delta between the Growth and the Correction scenarios would be USD 6.3 billion during the 2021-2030 period, with an annual impact of USD 1.3 billion in 2030.

It is the delta which is the opportunity prize to go after by adopting bold, growth-focused measures (examples of which are described in this Report). Given the very significant socio-economic impact of industry clinical trials (CTs) in Poland, the identification and adoption of effective measures in support of the Growth scenario (e.g. building CT Infrastructure supported by technology, promotional activities (both international and national), growing international medical research collaborations, financial incentives for sponsors of iBPCTs and Contract Research Organizations, or CROs) should become one of the government's priority focus areas.

Introduction

This report is a sequel to two previous reports on the importance of industry clinical trials in Poland (1) (2). While the previous reports focused primarily on highlighting societal benefits in terms of savings to the national healthcare fund, the primary source of information on clinical trial trends in Poland was based on the number and type of clinical trials in Poland reported by the Competent Authority in Poland and based on the data published by the European Medicines Agency (EMA) as part of the Marketing Authorization approvals. (3) This report builds on the previous reports' findings and provides additional benchmarks vs. key CT markets and well as other markets relevant to Poland. Several important methodological changes have been made in the report. This report provides additional granularity which helps identify areas of strength of Polish CT markets as well as opportunities: Poland is benchmarked on other markets on a time axis across a range of parameters including but limited to:

- Global CT market share based not only on number of clinical trials (frequency of use) but equally importantly on the number of clinical trial sites in those studies (depth of use),
- Market share of Poland in industry and non-industry (academic) clinical trials,
- Poland CT market penetration (average population-adjusted number of sites/study),
- Percentage of industry global CTs in Poland (trending and by phase),
- Percentage of global industry CTs by therapeutic indication in Poland,
- Patient accessibility to clinical trials in Poland,
- Representation by Phase,
- Representation by therapeutic indication,
- Use of Polish CT market by CT sponsors,
- Assessment of country reputation,
- Quality: US FDA findings trending vs. other markets,
- Pharma sales trending (pharma sales market share vs. CT market share),
- Ranking of Poland across a range of these parameters (and changes over the years).

In addition, this report also benchmarks Poland on other important parameters which influence sponsors' willingness to allocate new clinical trials: time (e.g., duration of clinical trial start-up), cost, productivity (number of patients/site relative to other sites in the same study) and quality. This report also provides answers to the following questions:

- **Is Poland gaining or losing market share of global industry clinical trials?**
- **Is Poland adequately represented in development of new products across all phases and all indications?**
- **What are the financial and socio-economic impacts of the measured market share changes?**

This report benchmarks the clinical trial market in Poland with other global markets and provides examples of best practices from countries around the world and thus aims to offer an objective external perspective. The aim is to juxtapose such external benchmarking perspectives of this report and cross-check some of the concepts against realities among the key stakeholders of clinical trials in Poland (e.g., pharmaceutical sponsors of clinical trials in Poland, CROs, clinical investigators and SMOs, patient organizations, and government institutions, including but not limited to the Medical Research Agency (Agencja Badań Medycznych, ABM), the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych, URPL), the National Health Fund (Narodowy Fundusz Zdrowia; NFZ), the Ministry of Health, and the Ministry of Development, Labor and Technology).

GLOBAL CLINICAL TRIAL MARKET ASSESSMENT

CHAPTER 1

Chapter 1. Global clinical trial market assessment and benchmarking of Poland

by Vladimir Misik

1.1 Global clinical trials

Driving factors for globalization of clinical trials

During the past 20 years or more than 20 years, biopharma has increasingly moved parts of their development programs outside of the traditional markets North America and Western Europe, driven primarily by their efforts to boost productivity of pharma development in search of ways to shorten clinical trial duration and reduce cost per clinical trial patient. The EMA listed several operational and technical considerations that led to the conducting of clinical trials in a widening range of countries (4):

- Availability of patients willing to participate in clinical trials and with the relevant disease profile,
- Availability of qualified investigators willing and available to conduct the trials,
- Preparation for marketing authorization application in those countries,
- Willingness of patients to participate in trials due to trial facilitating access to higher standard of care or medications not otherwise available to them,
- Search for lower costs,
- More rapid approval of trials,
- Small number of relevant patients in traditional developed markets,
- Availability of treatment-naïve patients,
- Difficulty of recruiting patients due to differences in standard of care across developed countries.

The globalization of clinical trials started with the adoption of ICH GCP in 1997 (5) and resulted in a geographic shift away from the traditional clinical trials markets of North America and Western Europe, during which can be documented by the following facts:

- *while in 1995, 94% of global clinical trials have been conducted in North America and Western Europe, by 2005, this percentage was less than 80% (6),*
- *in 2005, 80% of clinical trial patients recruited in pivotal trials came from North America and EU, by 2008, this percentage was only 66% (4),*
- *during the 15 months prior to December 2009, North America and Western Europe lost 4.3% of their clinical trial sites to the rest-of-the-world (RoW) (7), and this trend continued past 2010 (8).*

Investigator-initiated or academic clinical trials (IITs)

Investigator-initiated clinical trials are an important complement to iBPCTs. Unlike iBPCTs which are conducted with a specific intent to develop a new drug, the typical purpose of IITs is the advancement and optimization of already existing therapies and/or development of new treatment options which may not be commercially interesting. (9)

Investigator-initiated academic clinical research—conceived and developed by physician– scientists—has contributed substantially to the development of modern therapies, played a critical role in discovering targeted therapies, and driven innovation in design and execution of company-sponsored pivotal trials. (10)

IITs also foster international medical collaboration and help advance medicine. IITs are thus a sign of a healthy and well-functioning healthcare system. (9) (11)

Benefits of conducting clinical trials

Clinical trials respond to human, social and financial goals as they relate to the development of new drugs, devices and vaccines. They are the nexus between science and practice and reveal crucial information about the products they test. In the long term, they will result in the ability to cure or cope with disease, improve quality of life, and prevent decline or disability. In the immediate term, they are important to our understanding of disease, generate knowledge that is used in many different ways in both industry and patient care settings and offer patients and clinicians rare opportunities for novel and advanced treatment options (12). Often patients are further incentivized to participate in order to gain access to highly qualified clinicians and facilities that may otherwise be unavailable.

Research and development (“R&D”) clinical trials pass through three stages before a drug is approved and sold for consumption.

Phase 1:
the experimental drug or therapy is given to either a small number of healthy human subjects or, depending on the type of molecule, on patients (less than 100), to evaluate the safety, determine a safe dosage range and identify any side effects.

Phase 2:
the treatment is given to a larger group of patients (100 – 500) to evaluate its effectiveness and further evaluate its safety.

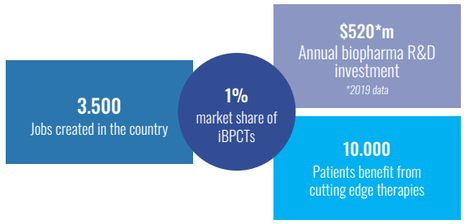
Phase 3:
the largest stage in which the treatment is administered to large groups of patients (1,000 – 5,000) to determine effectiveness, further monitoring of side effects and compare with placebo and/or other available treatment options.

Once completed, data from successful clinical trials define safe and effective use of the drug, device or vaccine and help to obtain a marketing authorization.

Phase 4:
studies and registries are conducted after commercial launch of a product to further monitor safety and efficacy profile in real world settings and often in comparison with other available treatment options.

Clinical trials attract the world’s leading clinicians and create employment opportunities for thousands of highly qualified personnel. Finally, they generate important revenues for organizations and for the economy, a consideration which is intimately tied to the well-being of society. (12)

Socio-economic value of iBPCTs



Infographics 1: Socioeconomic value of 1% global market share of iBPCTs. See Annex 1 for methodology and data sources.

Patients

Patients and their families are perhaps the greatest beneficiaries of participation in clinical trials. Regardless of the standard of healthcare in the country, clinical trials offer access to cutting-edge medical technology and innovative therapies to a select group of participants. Furthermore, as these studies are closely monitored to ensure safety, patients have greater access to highly qualified physicians providing confidence in the care they receive. In addition to personal care, many subjects are also motivated to participate in clinical trials as a means to contribute to the development of science and medicinal breakthroughs for future generations.

Healthcare institutions

Participation in clinical trials not only enhances the quality of medical staff participating in them, but is also known to attract leading clinicians, resulting in better clinical outcomes for the organization. It can also reinforce the development of centers of excellence – through a cyclical combination of trials, outcomes, critical mass, patient choice, leading clinicians, grants, prestigious reputations, access to technology and equipment as part of the research, academic mission and the bench-to-bedside paradigm. (12)

Clinicians

Participation in clinical trials allow clinicians to gain knowledge and first-hand experience with innovative drugs and potential side effects – resulting in invaluable confidence and competence when prescribing these medicines to future patients. Studies have confirmed a positive correlation between physicians participating in clinical trials and their subsequent prescription of the new, first-in-class drugs. (13) Furthermore, participation in trials brings personal benefit to doctors as they have increased exposure to sought after cutting-edge research and technology as well as fostering positive international collaboration among clinical investigators. In a recent survey of investigators, over 50% listed advancement in scientific knowledge and the opportunity for scientific publication as personal incentives for participation. (14)

Economy

Carrying out clinical trials involves large numbers of personnel-creating jobs and tremendous skills development as mentioned above. Furthermore, there is a marked increase in cash inflow for the public health system through fees and taxes paid by clinical trial sponsors, trial regulatory fees and ethical committee fees. (1) In Canada, an estimated USD 300 million in potential clinical trial revenues were attracted through new clinical trial contracts in 2007-2008. (12) According to a PricewaterhouseCoopers report on Poland, there was an estimated PLN 240 million (ca. USD 40+ million) savings for the National Health Fund in 2009 and USD 80 million in 2014 for oncology studies alone, as patients received treatments that were co-financed by clinical trials sponsors. (1) (2) And, as described in the Socio-economic impact of Industry CTs chapter of this Report , the cumulative economic value of iBPCTs in Poland during 2014-2020 period was almost USD 8 billion. One should also keep in mind the number of additional service providers involved, including laboratories, courier services and translation services among others that benefit from the conduct of clinical trials.

Government

The government holds significant influence, whether directly or indirectly, over the level of participation of the country in clinical trials, and hence the degree to which the above benefits are realized. The stringency of legislation (e.g. requirement of inclusion of patients in clinical development of compound submission for marketing authorization), timelines for approvals, clinical trial study material importation complexities, etc., are all factors that play into whether the country is considered for participation in a clinical trial. However, the government also stands to benefit from clinical trials. Regulatory agencies and ethics committees must be staffed and well-trained in order to ensure confidence in the population to participate in clinical trials, thus creating more jobs and provide greater diversification. Furthermore, through the development of these oversight agencies, the government has first-hand knowledge of the efficacy and safety of innovative medicines even before they arrive on the market, having a direct impact on the safety and health of the population and potentially reducing an increased burden on the domestic healthcare system.

Global competition for clinical trials

During the past three decades, the pharmaceutical industry enjoyed periods of significant growth in the developed markets with sales growth outperforming GDP growth and there was little motivation to look elsewhere, with the majority of clinical development for new products conducted in North America and Western Europe (15). The reliance on these traditional pharmaceutical markets for both development and consumption has been diminishing during the past two decades.

During the past three decades, the pharmaceutical industry enjoyed periods of significant growth in the developed markets with sales growth outperforming GDP growth and there was little motivation to look elsewhere, with the majority of clinical development for new products conducted in North America and Western Europe (15). The reliance on these traditional pharmaceutical markets for both development and consumption has been diminishing during the past two decades.

Presently, the situation is very different. The biotech and pharmaceutical industry (“biopharma”) has increasingly moved parts of its development programs outside of the traditional markets of North America and Western Europe, driven primarily by efforts to boost productivity through shortening the duration of clinical trials and reducing cost per patient (4) (16) (15). One of the leading causes of a missed clinical trial completion date is patient recruitment, taking up to 30 percent of the clinical trial timeline (17). When considering that a typical patent life of an innovative compound/device is 20 years and on average it takes 10-15 years for a drug to be brought to market, any delays in the development process can have monumental consequences in terms of lost revenue, and hence lost potential research and development spend for future studies. There are numerous country- and site-specific factors at play that can impact the speed of recruitment including regulatory requirements and contracting negotiations.

However, each site equally faces the challenges of recruiting as many patients as possible that meet the complex inclusion/exclusion criteria set for enrollment. It therefore stands to reason that the larger the eligible patient population a nation has, the greater the pool of applicable subjects for patient enrollment. Competition for a finite pool of eligible patients as well as interested and willing investigators who have time to conduct high-quality research have proved to be challenges for countries such as the United States that have hosted clinical trials for decades and have saturated their markets to such a degree that meeting enrollment targets can be challenging.

Over the past two decades, a majority of the traditional markets, while increasing the number of clinical trials in absolute numbers, have been slowly losing market share to emerging regions. In light of the increasing migration of clinical trials internationally and the clear health and other societal benefits clinical trials bring, many countries have attempted to bolster their attractiveness through various measures and policies, some of which are highlighted in this report.

Answers to the following questions will be assessed:

- Why are North America and countries in Europe eager to retain clinical trials despite their relatively saturated clinical trial markets?
- How are smaller pharma markets and emerging markets able to stand out among the traditional large pharma markets?
- What steps are these countries taking to ensure returning clinical trials revenues and associated benefits?

1.2 Clinical trials market in Poland - Global benchmarking

This chapter describes the CT market in Poland across a range of parameters and benchmarks Poland against other key global markets.

Poland market share and global trending

During the past 25 years, Poland established itself as one of global iBPCT's powerhouses: in 2019, Poland was ranked 11th globally in terms of iBPCT market share (Figure 1), and during 2014-2019 period, achieved 5th largest iBPCT market share gain globally, behind China, Spain, South Korea and Taiwan (Figure 2). Also, in relative terms, the Polish iBPCT market grew to 8th globally, almost 10% in relative terms during 2014-2019, while the market share of North America, most of EU countries (except Spain) as well as majority of the CEE countries declined over the same period (Figure 3).

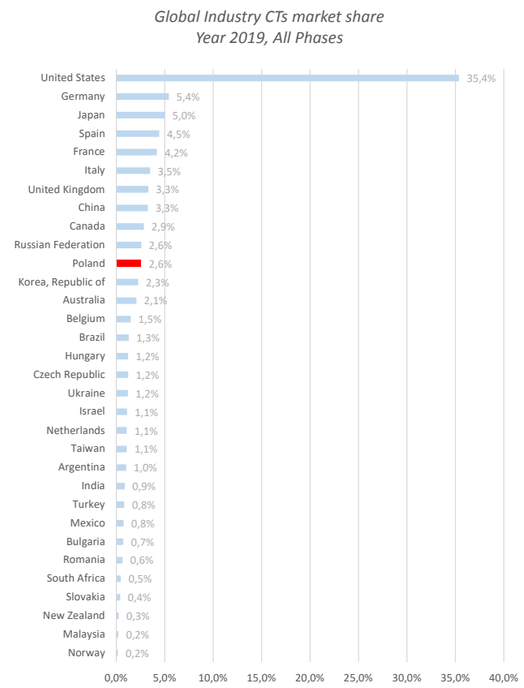


Figure 1. Industry sponsored Ct market share 2019; all phases. Mkt share in countries calculated as % of all global active CT sites in country.

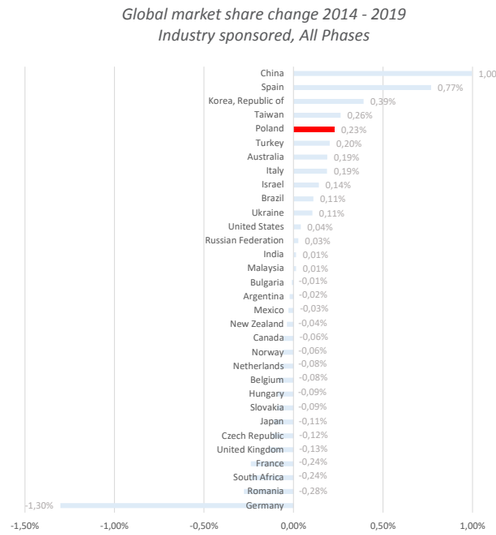


Figure 2. CT market share trending 2014-2019. calculated as = Mkt share 2019 - Mkt share 2014. Industry sponsored CTs all phase = Mkt share based on % of active CT sites.

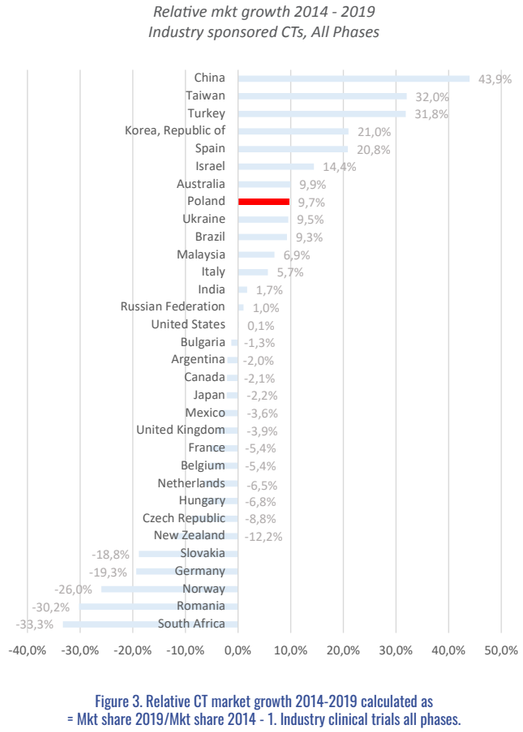


Figure 3. Relative CT market growth 2014-2019 calculated as = Mkt share 2019/Mkt share 2014 - 1. Industry clinical trials all phases.

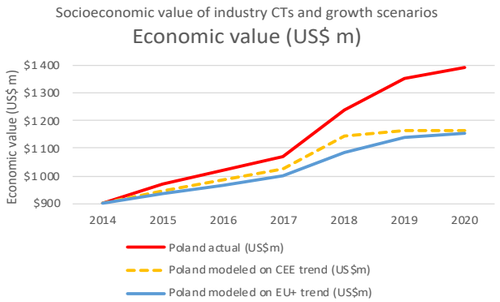
Socio-economic impact of Industry CTs

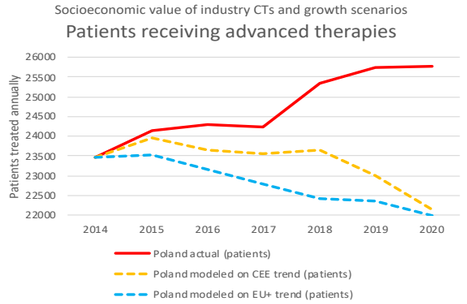
As was highlighted in the Executive Summary, in 2020, the economic value of iBPCT surpassed USD 1.4 billion (15% of total R&D investment in Poland), created approximately nine thousand jobs in Poland related to iBPCT, and granted access to more than 25,000 Polish patients to novel and cutting edge experimental therapies in that year alone.

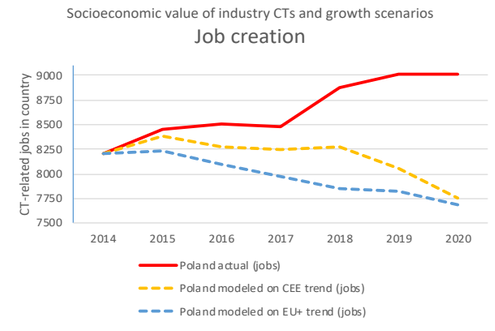
The significance of these figures is best illustrated by evaluating alternative growth scenarios, as shown in Figure 4. Actual iBPCT market growth in Poland during 2014-2020 for the economic value, job creation and the estimated number of patients receiving advanced experimental therapies, is denoted by a solid red line (see Methods in Annex 1). The alternative growth scenarios are calculated by applying the annual growth rates of EU+ countries (blue dotted line) and CEE countries (yellow dotted line) respectively to the 2014 iBPCT market figures for Poland.

The embedded table shows quantification of the cumulative 2014-2020 economic value, job creation and the estimated number of patients receiving advanced experimental therapies and the delta between Actual and the Alternative growth scenarios. The results are striking: if Poland's iBPCT market followed the growth trajectory of the CEE group of countries it would have lost more than USD 600 million in economic value derived from iBPCTs during 2014-2020, almost 1,300 iBPCT-related jobs would have been lost/would not have been created, and some 9,500 fewer patients in Poland would have received advanced experimental therapies. Similarly, if Poland's iBPCT market followed the growth trajectory of the EU+ group of countries it would have lost more than USD 700 million in economic value derived from iBPCTs during 2014-2020, more than 1,300 iBPCT-related jobs would have been lost/would not have been created, and some 13,000 fewer patients in Poland would have received advanced experimental therapies.

As discussed in the following chapters of this report (see Assessment of Growth Potential of Clinical Trial Market in Poland), assuming that iBPCT market growth will always continue would be a risky assumption: without a robust series of governmental and academic interventions the iBPCT market, growth in Poland with all associated socio-economic benefits could easily turn into a steady and painful decline as the lessons from the neighboring countries demonstrate.







Economic value	2014	2020	Sum 2014-2020	Delta vs actual
Poland actual (US$m)	$900	$1 395	$7 945	-
Poland modeled on CEE trend (US$m)	$900	$1 162	$7 333	-$611
Poland modeled on EU+ trend (US$m)	$900	$1 155	$7 177	-$767
Job creation				
Poland actual (jobs)	8211	9017	806	-
Poland modeled on CEE trend (jobs)	8211	7755	-456	-1262
Poland modeled on EU+ trend (jobs)	8211	7694	-517	-1323
Patients				
Poland actual (patients)	23460	25763	172952	-
Poland modeled on CEE trend (patients)	23460	22158	163450	-9502
Poland modeled on EU+ trend (patients)	23460	21982	159688	-13264

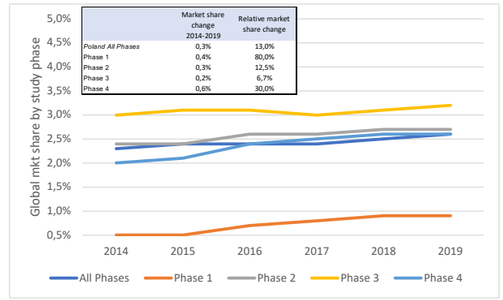
Figure 4. Socio-economic impact of Industry CTs. The economic value (USD), job creation and number of patients receiving advanced experimental therapies was estimated from iBPCT market share (see Methods in Annex 1). Scenarios are calculated applying the annual growth rates of EU+ countriesand CEE countries respectively to the 2014 revenues in Poland. EMBEDDED TABLE: Quantification of the cumulative economic value, job creation, and number of patients receiving advanced experimental therapies in Poland and delta vs. growth scenarios shown in the graphs.

Poland market share by Phase

This chapter analyzes Poland's iBPCTs market by study phase. As seen from Table 1, although across all phases Poland's share of active iBPCTs in 2019 was around 11%, in terms of the largest Phase 3 segment, Poland participated in 34% of all globally active Phase 3 iBPCTs. Phase 2 and Phase 3 studies represented more than 80% of all active iBPCTs studies and more than 90% of all active iBPCTs sites in Poland. Phase 4 represented only approx. 3% all iBPCTs sites and studies in Poland. The fastest growing segment during 2015-2019 was Phase 1, followed by Phase 4 and Phase 2 (Figure 5).

2019 Data	Active Studies	% Studies in Poland	Share of global studies in each phase	Active sites	% Sites in Poland	Share of Global CT sites in each phase
Poland All Phases	**1749**	**100,0%**	**10,9%**	**11173**	**100,0%**	**2,6%**
Phase 1	49	2,8%	1,6%	166	1,5%	0,9%
Phase 2	429	24,5%	11,6%	2247	20,1%	2,7%
Phase 3	1031	58,9%	34,0%	7828	70,1%	3,2%
Phase 4	59	3,4%	10,9%	361	3,2%	2,6%
Poland Phase N/D	181	10,3%		571	5,1%	

Table 1. Poland's Industry CT market by Phase. Number and % of studies and sites in 2019 in Poland. Share of global studies shows % of all registered industry CTs in each Phase in which Poland participates. (e.g., Poland participates in 34% of all Ph 3 studies while it only carries 3.2% of all Phase 3 sites)



	Market share change 2014-2019	Relative market share change
Poland All Phases	0,3%	13,0%
Phase 1	0,4%	80,0%
Phase 2	0,3%	12,5%
Phase 3	0,2%	6,7%
Phase 4	0,6%	30,0%

Figure 5. Global market share of Poland by study phase 2014-2019, Industry sponsored CTs

These data demonstrate that the Polish iBPCT market is maturing from historical reliance on Phase 3 studies to being represented strongly among the Phase 2 sites (with 2.7% of global share) combined with a rapid Phase 1 growth (albeit from low historical levels). At the same time, it is worth mentioning that Poland's share of global Phase 1 studies still remains low in relative terms compared to other developed markets, e.g. in Germany 8%, UK 11%, Spain 10% of all active studies in 2019 are in Phase 1, compared to less than 3% in Poland as shown in Table 1.

Poland's market share by Disease area and by Diseases and Conditions

In this chapter, we analyzed Poland's iBPCTs market by Disease area (higher-level MeSH term – e.g. diseases of Digestive system) and also by Diseases and Conditions (lower level MeSH term – e.g. Ulcerative colitis). As seen from Figure 6, neoplasms (oncology) have been the leading disease area in Poland as well as globally. In terms of growth, the fastest growing disease areas in Poland during the 2014-2019 period were digestive system diseases (66% growth), skin & connective tissue diseases (48% growth), and neoplasms (46% growth) while globally the major growth areas were hemic and lymphatic diseases (mostly haemato-oncology and lymphomas) and neoplasms (oncology) followed by nervous system diseases. It appears therefore that while Poland has been overrepresented in digestive system diseases (primarily Crohn's and Ulcerative colitis) it has been underrepresented in iBPCTs for hemic and lymphatic diseases and nervous system diseases (Figure 7 and Table 2).

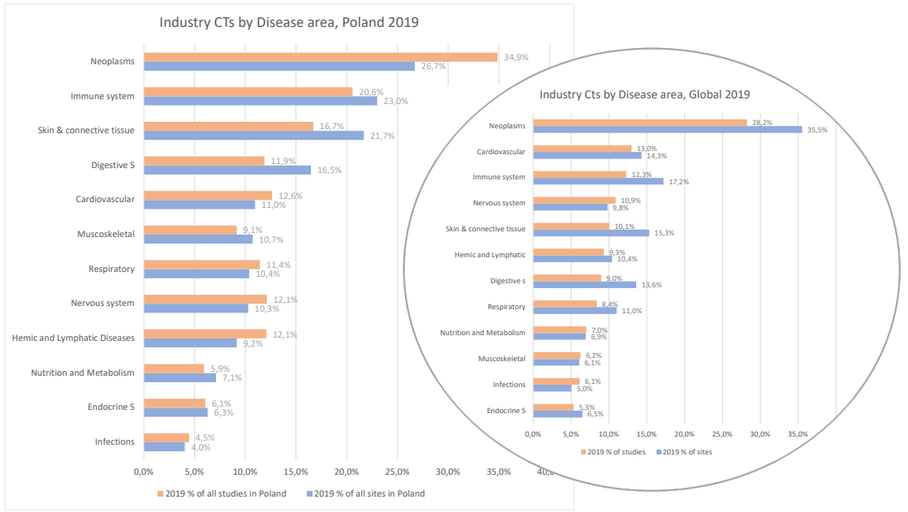


Figure 6. Industry CTs in Poland by Disease Area (MeSH terms) in 2019. Figure Insert: Global figures. A single study may be attributed to more than one DA, thus, while the % of DA is accurate the sum of all DAs % would appear artificially as more than 100%. Largest DA representing more than 80% of global industry CTs shown.

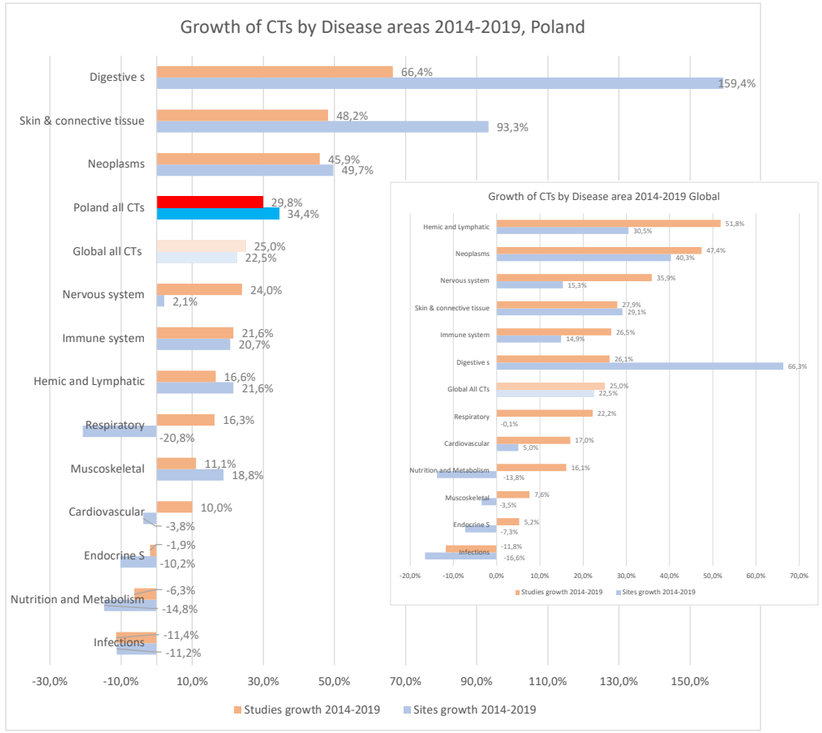


Figure 7. Growth 2014-2019 of Industry CTs and CT sites in Poland by Disease Area (MeSH terms).
Figure Insert: Global figures. For benchmarking purposes CT growth figures 2014-2019 across all CTs in Poland and globally is shown.

Disease Area (MeSH terms)	2019 % of studies in country*	2019 % of sites in country*	Poland share of sites in DA 2019	Studies growth 2014-2019	Sites growth 2014-2019
Poland Neoplasms	34,9%	26,7%	1,9%	45,9%	49,7%
Total Neoplasms	28,2%	35,5%		47,4%	40,3%
Poland Hemic and Lymphatic	12,1%	9,2%	2,3%	16,6%	21,6%
Total Hemic and Lymphatic	9,3%	10,4%		51,8%	30,5%
Poland Immune system	20,6%	23,0%	3,4%	21,6%	20,7%
Total Immune system	12,3%	17,2%		26,5%	14,9%
Poland Cardiovascular	12,6%	11,0%	2,0%	10,0%	-3,8%
Total Cardiovascular	13,0%	14,3%		17,0%	5,0%
Poland Nervous system	12,1%	10,3%	2,7%	24,0%	2,1%
Total Nervous system	10,9%	9,8%		35,9%	15,3%
Poland Respiratory	11,4%	10,4%	2,4%	16,3%	-20,8%
Total Respiratory	8,4%	11,0%		22,2%	-0,1%
Poland Skin & connective tissue	16,7%	21,7%	3,6%	48,2%	93,3%
Total Skin & connective tissue	10,1%	15,3%		27,9%	29,1%
Poland Infections	4,5%	4,0%	2,1%	-11,4%	-11,2%
Total Infections	6,1%	5,0%		-11,8%	-16,6%
Poland Nutrition and Metabolism	5,9%	7,1%	2,6%	-6,3%	-14,8%
Total Nutrition and Metabolism	7,0%	6,9%		16,1%	-13,8%
Poland Digestive system	11,9%	16,5%	3,1%	66,4%	159,4%
Total Digestive system	9,0%	13,6%		26,1%	66,3%
Poland Endocrine system	6,1%	6,3%	2,5%	-1,9%	-10,2%
Total Endocrine system	5,3%	6,5%		5,2%	-7,3%
Poland Muscoskeletal	9,1%	10,7%	4,5%	11,1%	18,8%
Total Muscoskeletal	6,2%	6,1%		7,6%	-3,5%
Poland All			**2,6%**	**29,8%**	**34,4%**
Total All				**25,0%**	**22,5%**

*NB: A single study may be attributed to more than one DA – thus while the % of DA in country is accurate the sum of all DAs % would appear artificially as > 100%

Table 2. Overview of Largest Disease Areas (DAs) Globally and in Poland: 2019 representation of DAs,
Poland's market share by DA, and trial and site growth 2014 - 2019. Largest DA represent more than 80% of global industry CTs shown.
For easy visual benchmarking, Data in each column are color-coded, darker tones representing larger numbers in each column.

When analyzing the largest Diseases and Conditions (MeSH term) (Figure 8 shows top 30 diseases and conditions in Poland and globally (blue insert); darker shaded bars denote oncology CTs) it is clear that **oncology and hemato-oncology CTs are underrepresented in Poland relative to the global picture**: while the majority of the top 30 global diseases and conditions in which industry CTs are conducted classify as oncology, in Poland it is the minority. This trend also holds across a larger sample: while in Poland a minority of the top 50 diseases and conditions for which CTs are conducted classify as oncology (48% of trials and 34% of sites), globally a majority of the top 50 diseases and conditions for which CTs are conducted are oncology: 58% of trials and 52% of sites (data not shown).

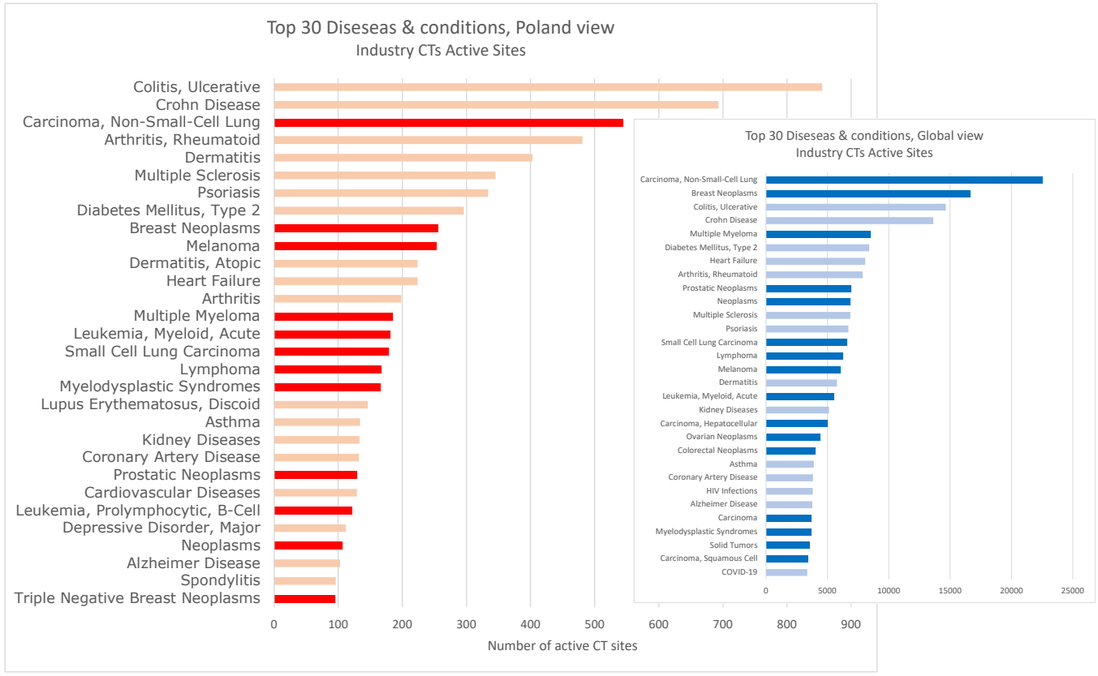


Figure 8. Top 30 diseases and conditions (based on active sites in 2020): Poland view (red bars), insert: Global view (blue bars).
Darker shaded bars denote oncology Disease area. industry CTs. all study Phases, 2020 data.

Utilization of Poland by industry sponsors of CTs

As Table 3 shows, the largest industry sponsors globally (ranked by the number of CTs across all phases) are also the largest sponsors in Poland. This group of sponsors accounts for 45% of all active industry CT sites globally and 51% of active sites in Poland.

Rank Poland (studies)	Parent Sponsor	Mkt share Poland (studies)	Mkt share Poland (sites)	Rank global (studies)	Parent Sponsor	Mkt share Global (studies)	Mkt share Global (sites)
1	Hoffmann-La Roche	7,6%	8,9%	1	AstraZeneca	2,4%	5,8%
2	AstraZeneca	5,8%	7,0%	2	Novartis	2,3%	5,3%
3	Bristol-Myers Squibb	4,7%	4,2%	3	Hoffmann-La Roche	2,2%	6,9%
4	Merck Sharp & Dohme	4,6%	4,3%	4	Pfizer	2,0%	4,4%
5	Novartis	4,5%	3,6%	5	Johnson & Johnson	1,9%	4,1%
6	Johnson & Johnson	4,3%	4,9%	6	Bristol-Myers Squibb	1,6%	4,0%
7	Pfizer	3,7%	7,4%	7	Eli Lilly and Company	1,4%	3,9%
8	Eli Lilly and Company	3,1%	4,9%	8	Merck Sharp & Dohme	1,4%	3,4%
9	AbbVie	3,1%	3,2%	9	AbbVie	1,4%	4,8%
10	Bayer	2,6%	2,6%	10	Bayer	1,3%	2,6%
	Top 10 Subtotal	44,0%	50,9%			17,9%	45,0%

Table 3. Top 10 Industry sponsors of CTs in Poland and Globally (ranked by number of CTs all phases).
Top 10 group share of the total number of CTs and CT sites in Poland and Globally shown.

However, as data in Figure 9 show, there are significant differences in terms of utilization of Poland among the top 30 sponsors, with all but one of the top 30 sponsors in Poland allocating higher share of their global portfolio to Poland than the industry average (breadth of allocation). At the same time Figure 9 insert and Figure 10 demonstrate significant variation in terms of involvement of sites in Poland (depth of allocation).

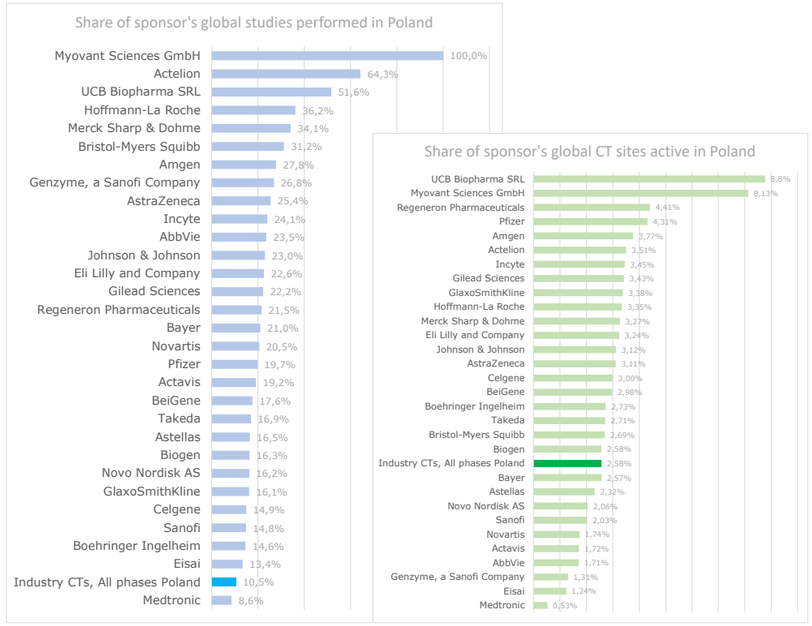


Figure 9. Sponsor-level utilization of CT market in Poland (based on studies active in 2020): Share of sponsor's global studies performed in Poland (blue bars). Insert: Share of sponsor's global CT sites active in Poland (green bars). Darker shaded bars represents Poland's share of global industry CTs across All Phases, 2020 data.

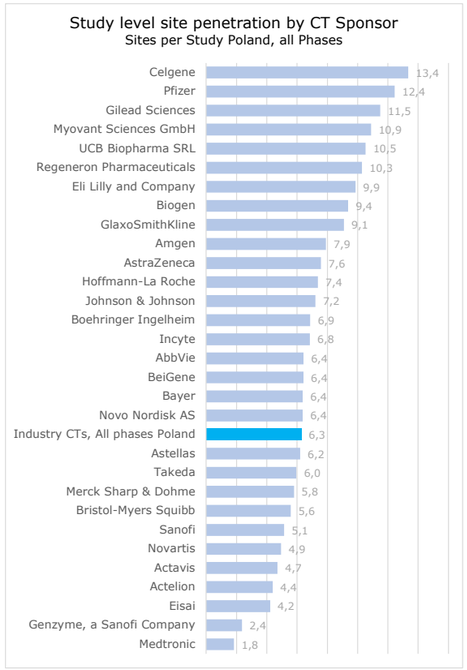


Figure 10. Study level site utilization by CT Sponsor: average number of Sites per Study by sponsors in Poland, all Phases

Patient accessibility to industry clinical trials

Patient accessibility to clinical trials has been calculated as described in the Methodology, data sources, and model assumptions chapter of this Report: accessibility to CTs is defined as the number of Phase 2 and Phase 3 BPCT sites per 1 million population and expressed relative to the US levels.

As shown in Figure 11, **Poland, with 67% accessibility relative to the US levels, ranks prominantly among countries with high level of patient accessibility to CTs (ranks 12th globally and 8th in Europe, ahead of Germany, France, Italy and the UK).**

Given that patients are the principal beneficiaries of novel treatment modalities this is a very strong message worthy to be publicised. Likewise, the results counter concerns that patients in Poland may carry undue burden of pharmaceutical development, since countries such as Belgium, Israel, US, Canada and Spain have higher accessibility levels. When setting realistic growth expectations for the Polish Industry, CT market accessibility levels of more than 80% the US levels should be targeted (this could be achieved partially by growing number of active sites in industry CTs by more than 25% vs the current levels).[1]

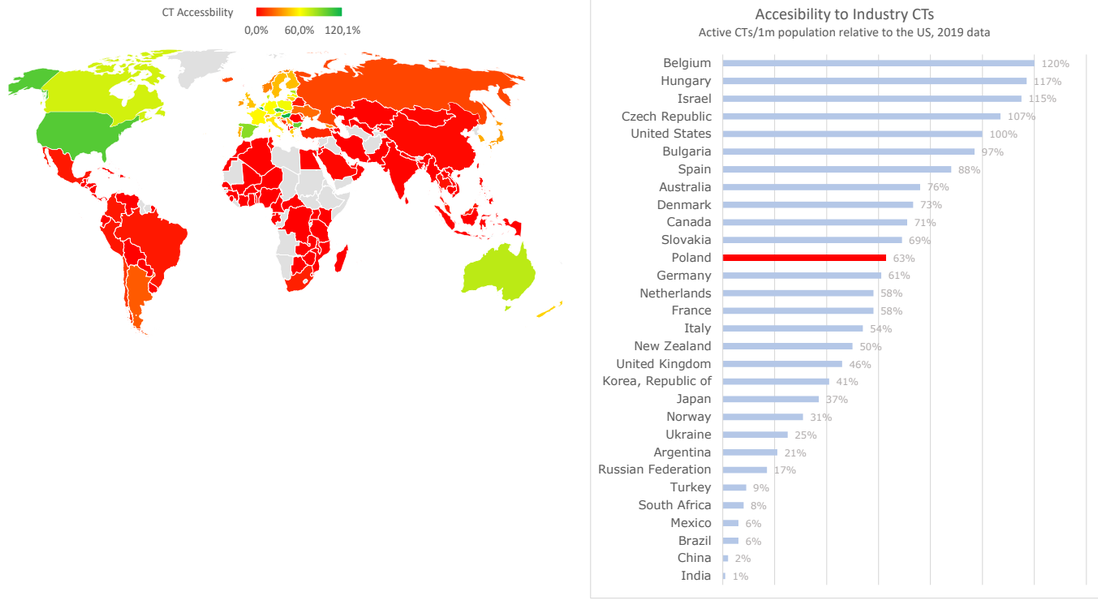


Figure 11. Accessibility to clinical industry clinical trials. calculated as number of clinical trial sites per 1m population relative to the US levels (US = 100%). Insert: Accessibility levels for selected countries.

Quality: Site inspection findings

A 2014 Euroscientist editorial concluded the CEE (including Poland) is a clinical trials Eldorado based on quality not cost (18). Data in this chapter demonstrate that while quality (approximated by severity of US FDA site inspection findings) of Poland and CEE sites in general has been solid, it was not substantially better vs several other global markets and the apparent regional competitive advantage determined during 2008-2014 period has diminished during 2014-2020 period (Table 4).

During the 2014-2020 period, Poland has been the third most inspected country outside of the US, but ranked only 22th based on overall quality of inspection outcomes (measured in terms of severity of inspection findings: higher percentage of inspections with no objectionable conditions or practices found during the inspection (classified as No Action Indicated), were used as a surrogate to better quality and, conversely, higher percentage of inspections where objectionable conditions or practices were found (classified as Voluntary Action Indicated, or Official Action Indicated), used a surrogate to deficient quality) (Figure 12). While data demonstrate that Poland in this quality parameter is not underperforming vs. many large global competitors, **these data also do not provide evidence to the claim that exceptional quality is one of the main drivers of iBPCTs to Poland and to CEE in general.**

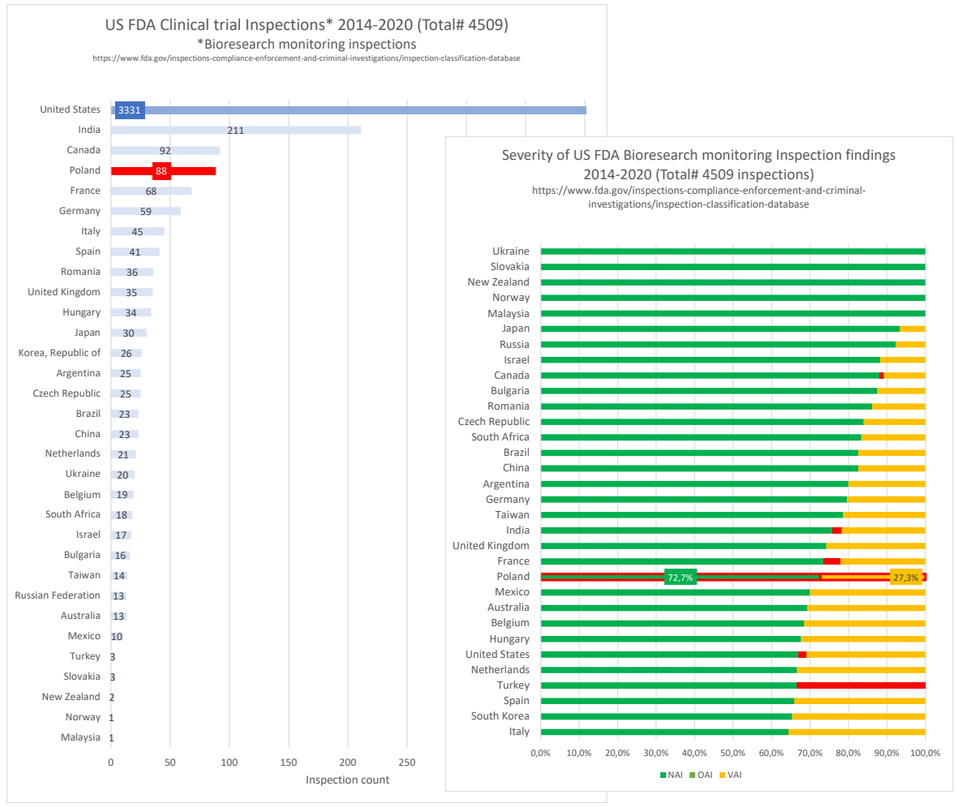


Figure 12. US FDA Bioresearch monitoring inspections 2014-2020 US FDA. total of 4509 inspections conducted globally during the period.
Insert: severity of inspection findings. NAI = no action indicated, VAI = Voluntary action indicated, OAI = Official action indicated.
Source: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database

[1] There are some obvious limitations to this approach: e.g., in rare disease indications or oncology indications where the number of available sites in the country is limited.

US FDA Bioresearch Monitoring Inspections

	Finding severity 2008-2013			2008-2013 # Inspections	Finding severity 2014-2020			2014-2020 # Inspections
	NAI	OAI	VAI		NAI	OAI	VAI	
North America	**50,9%**	**6,8%**	**42,3%**	**2253**	**67,6%**	**2,0%**	**30,4%**	**3423**
United States	50,8%	6,9%	42,3%	2215	67,1%	2,0%	31,0%	3331
Canada	55,3%	2,6%	42,1%	38	88,0%	1,1%	10,9%	92
Australia/New Zaeland	**62,5%**	**0,0%**	**37,5%**	**8**	**73,3%**	**0,0%**	**26,7%**	**15**
Australia	57,1%	0,0%	42,9%	7	69,2%	0,0%	30,8%	13
New Zealand	100,0%	0,0%	0,0%	1	100,0%	0,0%	0,0%	2
Asia	**53,9%**	**2,0%**	**44,1%**	**102**	**76,7%**	**1,6%**	**21,7%**	**318**
Japan	57,1%	0,0%	42,9%	7	93,3%	0,0%	6,7%	30
China	50,0%	11,1%	38,9%	18	82,6%	0,0%	17,4%	23
India	63,2%	0,0%	36,8%	38	75,8%	2,4%	21,8%	211
South Korea	60,0%	0,0%	40,0%	15	65,4%	0,0%	34,6%	26
Taiwan	75,0%	0,0%	25,0%	4	78,6%	0,0%	21,4%	14
Malaysia	0,0%	0,0%	100,0%	5	100,0%	0,0%	0,0%	1
Western Europe	**49,5%**	**0,9%**	**49,5%**	**214**	**71,2%**	**0,9%**	**27,9%**	**337**
Germany	51,8%	0,0%	48,2%	56	79,7%	0,0%	20,3%	59
United Kingdom	33,3%	3,3%	63,3%	30	74,3%	0,0%	25,7%	35
Spain	73,3%	6,7%	20,0%	15	65,9%	0,0%	34,1%	41
Italy	59,1%	0,0%	40,9%	22	64,4%	0,0%	35,6%	45
France	50,0%	0,0%	50,0%	38	73,5%	4,4%	22,1%	68
Belgium	66,7%	0,0%	33,3%	6	68,4%	0,0%	31,6%	19
Netherlands	44,4%	0,0%	55,6%	9	66,7%	0,0%	33,3%	21
Norway	66,7%	0,0%	33,3%	6	100,0%	0,0%	0,0%	1
Eastern Europe	**64,0%**	**0,5%**	**35,5%**	**203**	**79,3%**	**0,0%**	**20,7%**	**280**
Poland	69,1%	0,0%	30,9%	55	72,7%	0,0%	27,3%	88
Bulgaria	28,6%	0,0%	71,4%	7	87,5%	0,0%	12,5%	16
Czech Republic	61,1%	0,0%	38,9%	18	84,0%	0,0%	16,0%	25
Hungary	60,0%	0,0%	40,0%	10	67,6%	0,0%	32,4%	34
Romania	66,7%	0,0%	33,3%	12	86,1%	0,0%	13,9%	36
Slovakia	33,3%	0,0%	66,7%	3	100,0%	0,0%	0,0%	3
Russia	74,5%	0,0%	25,5%	55	92,3%	0,0%	7,7%	13
Ukraine	60,0%	0,0%	40,0%	20	100,0%	0,0%	0,0%	20
Latin America	**69,6%**	**0,0%**	**30,4%**	**56**	**79,8%**	**0,0%**	**20,2%**	**89**
Brazil	59,1%	0,0%	40,9%	22	82,6%	0,0%	17,4%	23
Argentina	87,5%	0,0%	12,5%	16	80,0%	0,0%	20,0%	25
Mexico	42,9%	0,0%	57,1%	7	70,0%	0,0%	30,0%	10
MEA	**57,1%**	**0,0%**	**42,9%**	**35**	**84,8%**	**2,2%**	**13,0%**	**46**
Israel	100,0%	0,0%	0,0%	5	88,2%	0,0%	11,8%	17
Turkey	0,0%	0,0%	100,0%	1	66,7%	33,3%	0,0%	3
South Africa	52,4%	0,0%	47,6%	21	83,3%	0,0%	16,7%	18
Grand Total	**52,3%**	**5,5%**	**42,2%**	**2871**	**69,7%**	**1,7%**	**28,6%**	**4509**

Table 4. US FDA Bioresearch monitoring inspections 2008-2020 US FDA and severity of findings (as % of total inspections in country).
Total of 7380 inspections conducted. Severity of inspection findings: NAI = no action indicated,
VAI = Voluntary action indicated, OAI = Official action indicated.
Source: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database

Site productivity

Site productivity (i.e., the number of patients per site) is a key parameter driving cost per patient at the study level. Site productivity therefore should be used when comparing true country level clinical trial cost.

Productivity data is not readily available information as the number of patients recruited in each country and the corresponding number of sites is not always reported by sponsors of clinical trials in the clinical trial registries. For this report we have utilized information published by the EMA (3). The EMA report includes pivotal studies (including number of sites and patients per study) used in support of MAAs submitted to the EMA during Jan 2005 - Dec 2012[2]. Aggregate country-level productivity data calculated from data in this report are shown in Table 5.

[2] Only studies identified by the applicant as pivotal at the time of MAA were included, majority of them Phase 3, while supportive trials (Phase 1, most of Phase 2, and some Phase 3 not identified by applicants pivotal) were not included in the EMA analysis. Likewise, clinical trial data from products which did not make it to the market were not included. The year under which EMA reported the trial data is the year when the product has been first submitted for marketing authorization, while the underlying data refer to pivotal trials submitted in support of this MAA with most of these trials ongoing several years prior to the year of MAA submission.

Country/region	2006-08 No. CTs	No. of Sites	% sites	No. Patients	Site productivity (% of avg)	2009-11 No. CTs	No. of Sites	% sites	No. Patients	Site productivity (% of avg)
Western Europe	**1433**	**7957**	**28%**	**102484**	**95%**	**1408**	**9673**	**27%**	**115207**	**101%**
France	156	1238		14612	88%	155	1305		9750	63%
Germany	196	1841		22660	91%	189	2358		31240	112%
Italy	139	835		9514	84%	120	993		10582	90%
Spain	141	812		9870	90%	139	1068		8803	70%
UK	139	795		8673	81%	147	985		7869	68%
Eastern Europe	**538**	**2580**	**9%**	**48611**	**140%**	**581**	**3616**	**10%**	**48662**	**114%**
Bulgaria	31	152		1904	93%	42	277		3841	118%
Czech Republic	71	338		6176	135%	86	844		10766	108%
Hungary	76	333		5672	126%	77	485		7139	125%
Poland	116	876		19746	167%	128	948		14094	126%
Romania	47	261		3940	112%	64	326		3848	100%
Slovakia	34	119		1558	97%	46	223		2485	95%
CIS	**135**	**1041**	**4%**	**16337**	**116%**	**189**	**1690**	**5%**	**22824**	**115%**
Russia	92	781		13087	124%	116	1139		14495	108%
Ukraine	34	240		3093	96%	62	511		7542	125%
North America	**509**	**12500**	**44%**	**130364**	**77%**	**495**	**14265**	**40%**	**138281**	**82%**
Canada	189	1151		14604	94%	207	1673		21470	109%
USA	320	11349		115760	76%	288	12592		116811	79%
Africa	**74**	**477**	**2%**	**13681**	**213%**	**99**	**428**	**1%**	**8232**	**163%**
Israel	**58**	**343**	**1%**	**6040**	**131%**	**70**	**370**	**1%**	**4494**	**103%**
Japan	**7**	**119**	**0%**	**1705**	**106%**	**22**	**441**	**1%**	**2548**	**49%**
Asia	**270**	**1076**	**4%**	**26047**	**179%**	**400**	**2208**	**6%**	**37714**	**145%**
China	12	135		3580	197%	27	273		4473	139%
India	39	285		6053	157%	108	761		10654	119%
Korea, South	40	169		2276	100%	60	393		3845	83%
Australia/NZ	**125**	**624**	**2%**	**5774**	**69%**	**123**	**757**	**2%**	**6570**	**74%**
Australia	96	539		4921	68%	100	684		5912	73%
New Zealand	29	85		853	74%	23	73		658	76%
MENA	**42**	**132**	**0%**	**1672**	**94%**	**67**	**258**	**1%**	**2870**	**94%**
Egypt	2	3		130	321%	7	24		353	125%
Turkey	28	98		926	70%	44	196		1569	68%
Central/South America	**337**	**1745**	**6%**	**33069**	**141%**	**405**	**2297**	**6%**	**37242**	**138%**
Argentina	79	619		9942	119%	90	716		9824	116%
Brazil	66	425		10612	185%	74	598		7916	112%
Total	**3542**	**28637**		**386228**		**3878**	**36049**		**424871**	

Table 5. Aggregate country-level productivity data were calculated from (3)

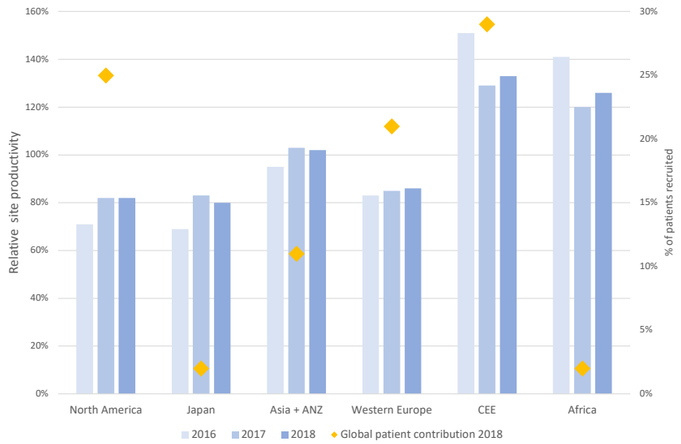


Figure 13. Site productivity index - Regional view (bar charts). Relative patient contribution across the project sample also shown (yellow diamonds). Source: LongTaal CT Performance Analytics - Productivity Comparative view (www.longtaal.com); Blinded de-identified data from an unbiased large CRO; Included: more than 200 largest global projects (all therapy areas) active in 2016, 2017 and 2018.

Such site productivity assessment is rather crude as it does not adequately reflect project- level performance and data may be biased by significant overperformance of a country in one of the studies with high global average site patient recruitment. In order to evaluate site productivity across multiple projects a meta-analysis has to be performed across multiple projects to arrive at a site productivity index, which allows a meaningful comparison of site productivity across multiple countries and multiple studies.[3]

Results of such meta-analysis are shown in Figures 13 and 14, demonstrating above average productivity of sites in CEE in general (Fig. 13) and in Poland specifically (Fig. 14).

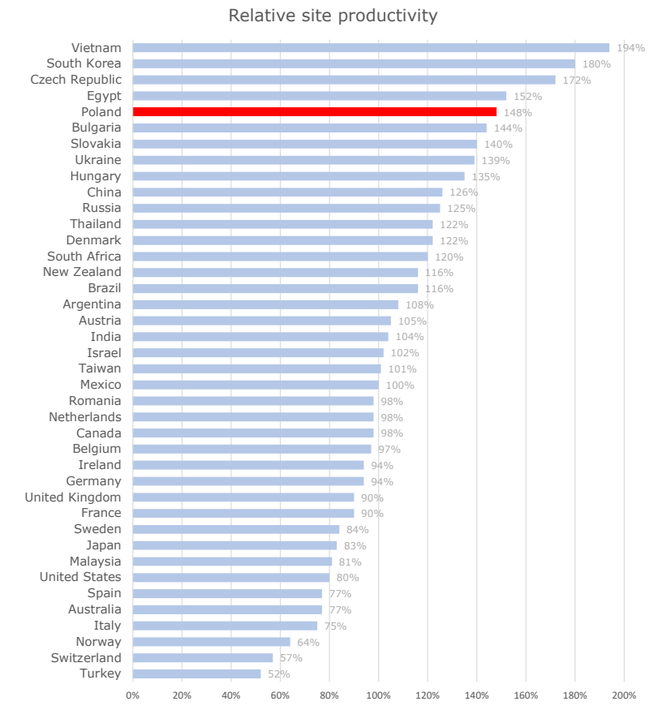


Figure 14. Site productivity index - Country view. Source: LongTaal CT Performance Analytics - Productivity Comparative view (www.longtaal.com); Courtesy of the top 10 CROs; Projects included: more than 200 largest global projects (all therapy areas) active in 2016, 2017 and 2018.

These data demonstrate that Poland, together with several other countries in CEE outperformed site productivity in established CT markets in North America and Western Europe. However, several other emerging markets also offer a very competitive site productivity.

Site productivity, alongside of with study start-up timelines, are some of the key performance indicators which we recommend to follow as markers of competitiveness of Poland vs its peers. Significant and consistent decline across one or both of these parameters may have a lasting adverse reputational impact for a country, resulting in erosion of confidence of sponsors and ultimately loss of CT market share with the resulting negative socio-economic impact for the country.

[3] Site productivity index is determined not as an absolute number of patients recruited by site but as a multiple of the average number of patients recruited per site in a study: i.e., if the average number of patients per site in e.g., lymphoma study was 1.5, a site which recruited 3 patients would have a relative productivity index of 2 (or 200%) in that study. Meta-analysis across multiple studies allows calculating an aggregate productivity index and thus compare productivity of sites across countries. Thus, an aggregate site productivity index of 1.5 (or 150%) at a country level, calculated across a sample of projects, implies that across the sample of studies sites, that country has a 50% higher productivity than study average. Using such methodology one can compare productivity of sites across multiple countries.

Start-up timelines

Competitiveness of a country for inclusion into a new clinical trial is heavily influenced by the country's sites proven ability to be ready quickly to start enrolling patients – the so-called study start-up duration. For the vast majority of sponsors of clinical trials and CROs, the study start-up duration based on previous experience often determines which countries get included in a study. A history of chronic lengthy start-up processes may disqualify a country even if it has a good patient recruitment potential.

It is important to keep that in mind, since as demonstrated in the previous section, while productivity of CT sites in Poland is generally quite competitive, the same does not apply to study start-up. As data in Figures 15 and 16 demonstrate, **Poland historically ranked among countries with slowest study start-up**: Figure 15 shows data measured in terms of duration (days) between identification of study sites and their initiation collected during the 2014-2015 period. Data from 2016-2017 (Fig. 16) also demonstrate that Poland remained among the 'slow' countries using a different start-up timelines methodology (average time (in days) until the first subject to be enrolled within the country from the date of the first site initiated within the study).

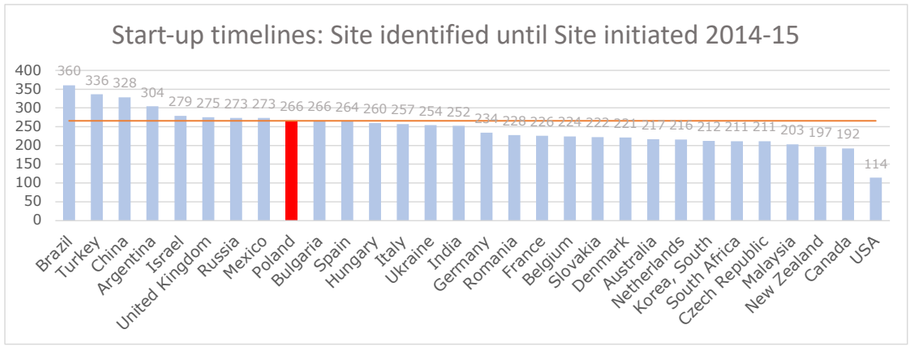


Figure 15. Study start-up Period 2014-2015: Mean time (in days) between the time site was identified and site was initiated.
Source: LongTaal CT Performance Analytics - Start-up Timelines Comparative view (www.longtaal.com);
Blinded data by unbiased top 10 CRO. Countries with more than 50 cycle times included.

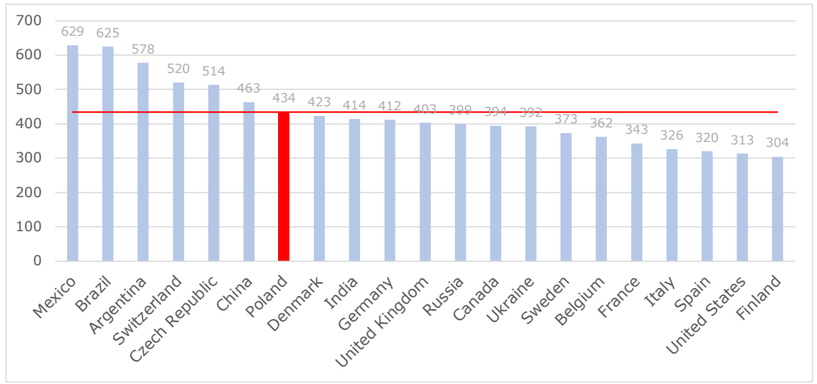


Figure 16. Study start-up 2016-2017 data: Average time (in days) until the first subject was enrolled within the country from the date of the first site initiated within the study.
Source: IMS Enrollment Analytics Data from close of recruitment, Adapted from (19)

However, it appears that Poland might have turned a corner on this start-up weakness as evidenced by the data in Figure 17. An INFARMA member company published data indicating that start-up timelines (Median number of weeks from Protocol Approval to Site Activation) in 2019 was on par with the global median and in 2020 improved to 32% faster than the global median.

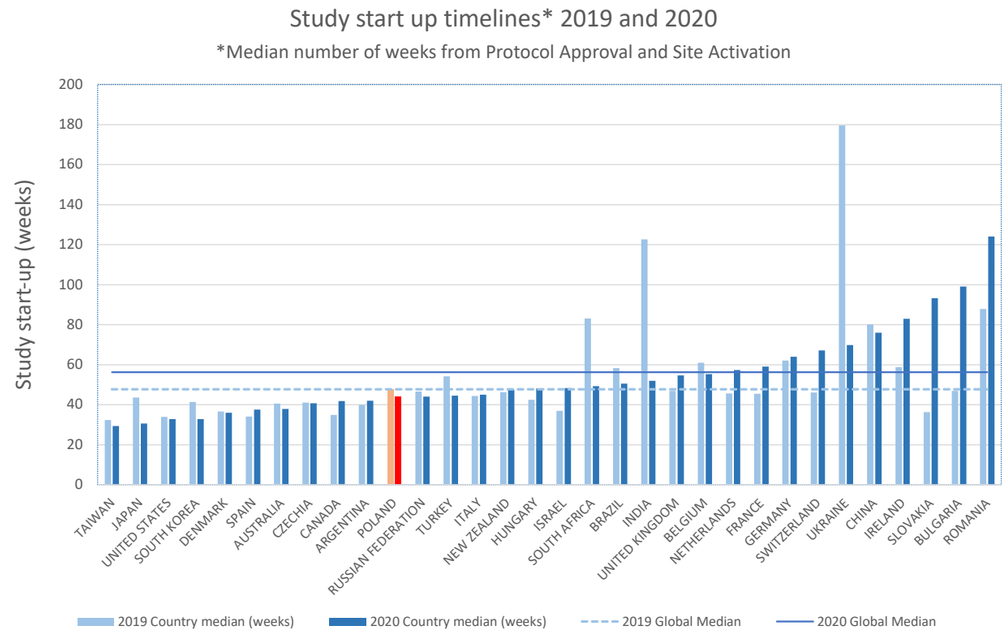


Figure 17. Study start-up timelines 2019 and 2020 measured as Median number of weeks from Protocol Approval to Site Activation. Blinded data by unbiased large pharma company.

Additional evidence of improvement is based on the reduction of Poland's study planning timelines (measured as time from the final protocol to the first site activated in the country) by a POLCRO member company. The planning timelines have been reduced by two weeks between 2017-18 and 2019-20 to 22 weeks (Figure 18) and Poland's planning timelines were better than then the global median. Another POLCRO member utilizes the current study planning timelines (defined as time in weeks from Final Protocol and/or model ICF received to site initiation): 17 weeks for simple sites, 28 weeks for medium complexity sites and 36 weeks for high-complexity sites.

In the chapter of this report on *Start-up process: strengths, limitations and recommendations*, changes which occurred post-2018 and which could have resulted in the observed start-up improvement in Poland are discussed.

Based on a recent micro survey within selected POLCRO and INFARMA member companies, there is still a large variation of start-up experience in Poland, with the average number of days from the time of submission to regulatory authorities until the first patient was enrolled ranging from 96 days to 251 days (average timelines from all submissions by each company in Poland during 2019-2020 period).

Given the importance of the study start-up cycle times as inclusion criteria for a country in global trials and the historically poor reputation of Poland in this area, more evidence needs to be collected from POLCRO and INFARMA member companies over the next several years to determine whether Poland has indeed achieved significant and sustained start-up improvements and strengthened its global competitiveness in this area.

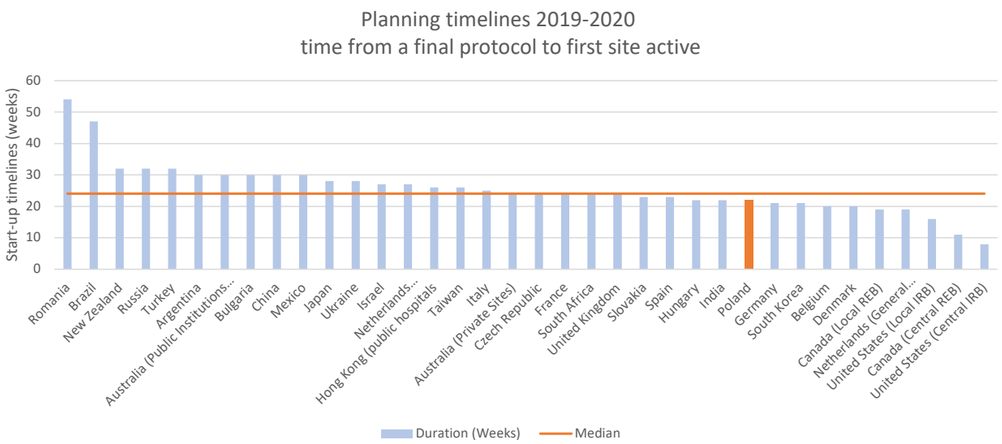


Figure 18. Study planning timelines 2019-2020 from an unbiased mid-sized CRO: time from a final protocol to first site activated

Clinical trial cost

There are various methodologies to assess clinical cost. We recommend that the headline figure to look at should be cost per patient, since it comprises not only the investigator and hospital fees and patient reimbursement expenses, but also laboratory and pharmacy costs, fees of monitoring staff, regulatory and EC fees, courier and IP shipment expenses, as well as import and export fees. For most large sponsors of clinical trials this is one of the key benchmarking figures.

Figure 19 demonstrates that **Poland performs well in terms of this metric**. Going forward it should be one of the key benchmarking metrics to watch – the key success indicator next to the actual costs listed above is site productivity as there is a large portion of study costs unrelated to number of patients: e.g. regulatory and EC fees, start-up component of the investigator and hospital fees, and many other fees and expenses that are only partially linked to the number of recruited patients, e.g. monitoring expenses.[4]

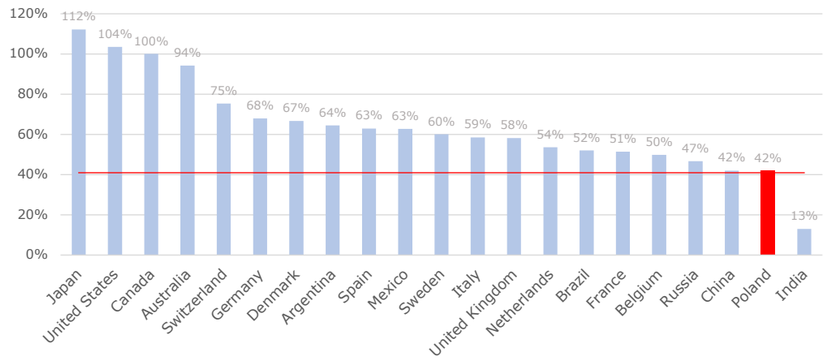


Figure 19. Average cost per patient across all phases and therapeutic areas provided by third Party, non-biased large pharma data company (2016-17), Costs are indexed to the US. Source (19)

[4] Example: if a country has the overall study costs 20% below study average and site productivity of 120%, the resulting cost per patient in such country may be up to 40% lower than average.

Data adapted from (20) shown in Figure 20 also demonstrate the cost advantage of Poland – unlike the data shown in Figure 19 these data show the overall study cost in a country relative to the US.

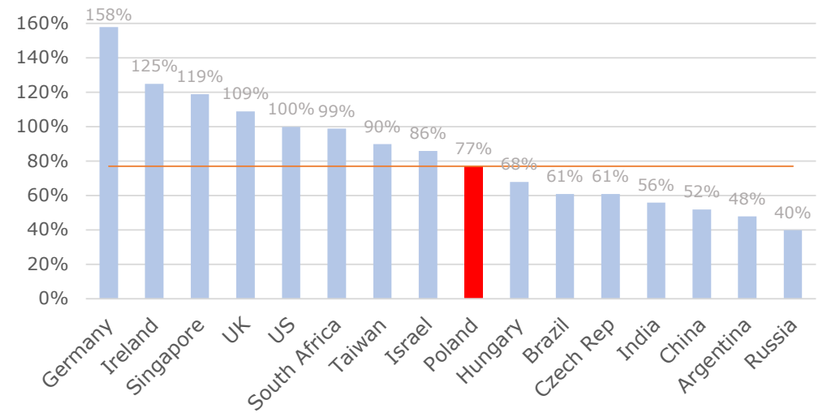


Figure 20. Comparative cost of conducting CTs (manpower, rental, IT & operational costs) relative to the US.
Source: (20) Quoted as: Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)

Comparison of clinical trial daily monitoring labor costs also **confirms cost advantage of Poland vs. majority of the large markets**, while labor costs in emerging markets are still significantly lower (Figure 21).

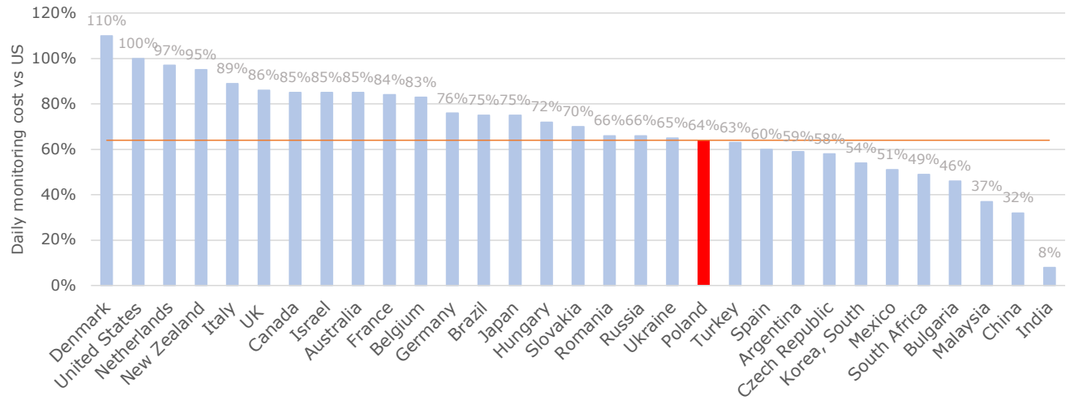


Figure 21. Daily monitoring costs relative to the US. Source: LongTaal CT Performance Analytics - Labor monitoring costs comparative view (www.longtaal.com);
Blinded data by unbiased top 10 CROs. Largest regional CT markets; Data from 2017

Participation in development vs. participation in consumption of pharmaceuticals

Clinical trials reputation index

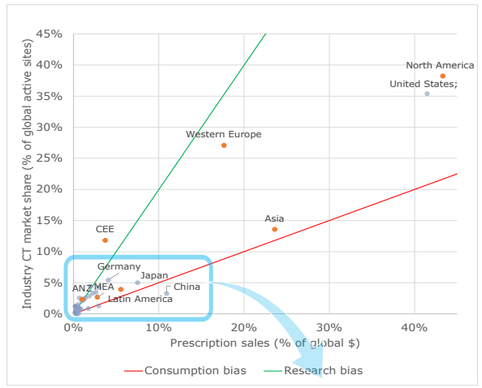
Based on meta-analysis of allocation patterns of industry CTs across geographies, a country's market share of global prescription sales is generally a strong predictor for market share of industry CTs (% of global sites in country) (21).

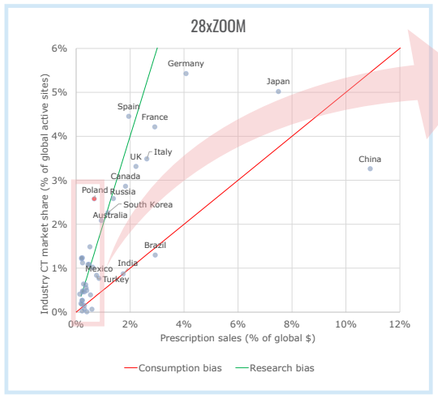
This finding is not surprising since it is well known that exposure of the key opinion leaders (KOLs) and other future prescribers to the products during early phase (Phase 2 and 3) clinical trials is of critical importance for the commercial success of a product when launched (22) (23).[5] Optimal Return on Investment (ORI) thus dictates allocating highest share of global iBPCT budgets for recruitment of patients in future high-prescribers' markets first.

As shown in Figure 22, for the vast majority of large pharmaceutical markets, this allocation pattern of clinical trials is visible with their iBPCTs market share (% of global sites) generally resembling the Prescription sales market share. By "resemblance" we mean that for the majority of countries iBPCT market share is somewhere between greater than 1/2 of the Prescription sales market share and less than two times the Prescription sales market share.

This can be described as:
iBPCTs market share = Prescription sales market share x R, where R ∈ (0.5; 2)
The green line in Figure 20 delineates R = 2 and the red line R = 0.5.

Among the large pharmaceutical markets only China falls well outside the red line indicating a strong consumption bias: although, with its fast-growing CT market China is now closing this gap and rapidly raising to prominence in the global iBPCT arena.





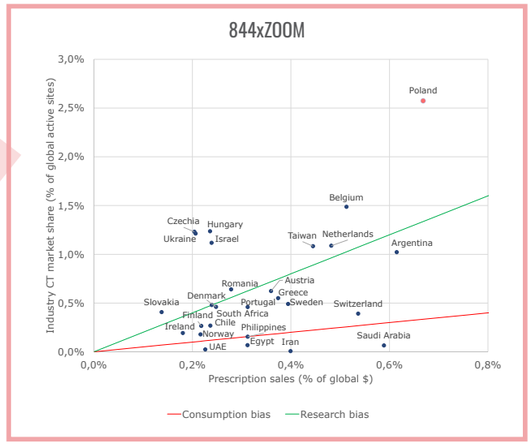


Figure 22. Relationship between share of prescription sales and industry CT market share. Regional view (Top panel) and expanded country-level views (Lower panel: 28x zoom and 844x zoom). Based on 2019 data.

A majority of the smaller pharmaceutical markets also fall within the segment between the green line (research bias, R=2) and the red line (consumption bias, R = 0.5). Closer examination of the countries positioned well-above the green line reveals only a handful of countries such as Belgium, the Czech Republic, Hungary, Israel, Ukraine and also Poland, with a strong research bias i.e., disproportionally high allocation of iBPCTs relative to their pharma market importance.

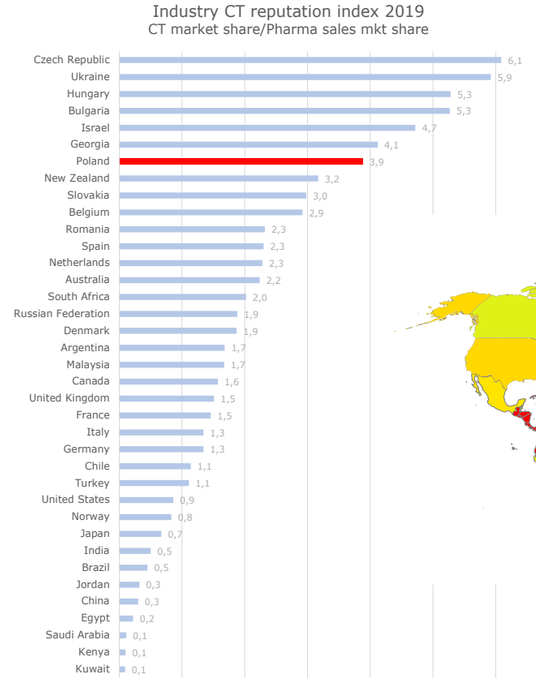
On the other extreme (well below the red line) are markets with a consumption bias i.e., disproportionally low allocation of iBPCTs relative to their pharma market importance: next to China, a majority of countries in MENA belong to this group.

This is certainly not a random pattern since the position of the vast majority of countries in this diagram does not change, or changes only slightly, over a period of several years (data not shown). Therefore, it must be a result of systematic inclusion of certain countries perceived across multiple sponsors as offering exceptional value in one or more areas, including, but not limited to, predictable timelines and speed of study start-up, access to multiple sites per country, professional CT support of sites, motivated investigators with sizeable patient pool with high patient retention, and uncomplicated CT logistics (24). On the flip side are countries which are not perceived as offering such exceptional value among industry sponsors of CTs.

We therefore introduced a quantifiable measure of county's reputation among sponsors of industry CTs, a so-called iBPCT Reputation Index:

$$R = \frac{\text{Industry CT market share (\% of global iBPCT sites)}}{\text{Share of prescription sales (\% of global sales)}}$$

Figure 23 shows the iBPCT Reputation Index by countries around the globe, with Poland, along with Israel and several CEE markets ranking among countries enjoying the highest reputation among sponsors of CTs.



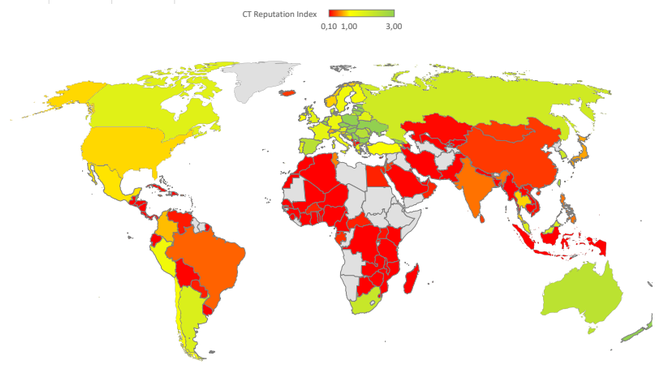


Figure 23. Industry CT reputation index = Industry CT market share/Pharma sales market share. 2019 data. Insert: CT Reputation index for selected countries.

[5] The importance of early exposure of KOLs and other future prescribers to the products during early phase (Phase 2 and 3) for a commercial success of a product when launched has been demonstrated in several studies (13) (64) (65). A study by Corrigan and colleagues in a study conducted in the U.S. demonstrated that physicians who had been investigators in a clinical study were more likely to prescribe the study drug than were matched control (non- investigator) physicians over the 18 months following the product's launch. The study found that for all therapeutic indications, investigator-physicians made the study drug available to patients sooner after product launch and more frequently than did control physicians (13). In another study Lubloy also demonstrated that at prescriber level, doctors' participation in clinical trials increase the likelihood of early adoption (64). Similarly, a study by Moynihan at al. has shown a general mistrust of physicians towards information from promotional material of pharma companies' in stark contrast to substantial trust in colleagues' personal experiences and opinions, when interpreting clinical trial data, or their own experience. (65)

Can Poland and CEE continue to defy gravity?

To fully appreciate the unique position of Poland and CEE we have plotted the iBPCT market share of Poland (red line) and CEE (blue line) relative to the share of pharmaceutical sales (Figure 24). The data demonstrate that while during period 2010 and 2015, the share of Poland's as well as CEE's global prescription sales has shrunk, the iBPCT market share continued to grow over the same period (indicating growing reputation among sponsors of CTs). Since 2015, we see a slow but steady growth of pharmaceutical share of CEE with a committal decrease of global share of iBPCTs, suggesting perhaps a beginning of a correction for CEE, with declining Reputation index during 2015-2019 for the CEE.

At the same time Poland defied this regional trend and managed to grow its share of iBPCTs (and maintain/grow) iBPCT reputation over the same period. The one billion (USD) question is: can Poland retain and even grow its current high reputation or will it start correcting over time: i.e., share of iBPCTs coming closer towards its pharmaceutical share? The difference between these two scenarios at 2019 levels would be approximately USD 1 billion (difference between estimated actual iBPCT revenues and hypothetical revenues based on iBPCT market share equal to the share of pharmaceutical sales).

This report provides some guidance and examples of best practices to follow for Poland to prevent risk of erosion of the current high iBPCT reputation.

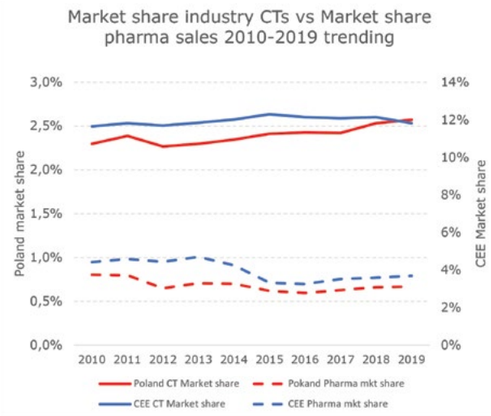


Figure 24. Comparison of Industry CT market share and Pharmaceutical sales market share trending 2010-2019 in CEE (Blue lines) and Poland (Red lines).

Thus, as stated in the title of this chapter, Poland has been boxing above its weight class in the clinical trial market, benefiting (together with the rest of CEE) from proximity of these markets to large European pharma markets, centralized healthcare systems offering easy access to large patient populations, and motivated investigators - coupled with the following factors which emerged in 1990s:

- growing competition of sponsors of CTs for clinical trial sites in these markets
- declining site productivity in traditional markets
- high per patient cost in traditional markets
- and the resulting increasing time and cost to develop new drugs

Meanwhile, the global playing field has changed as a number of business-hungry pharmerging countries are rapidly gaining market share (notably China, South Korea, Turkey, Malaysia) and also traditional pharma markets have been adopting measures to prevent further erosion of their market share (12) (25) (26) (27).

In order for Poland to continue to receive such relative high allocation of global clinical trials and enjoy corresponding financial and societal benefits it must provide:

- **continuous effort to consistently outperform global competitors across multiple relevant parameters including, but not limited to, predictable timelines and speed of study start-up,**
- **access to multiple sites per country,**
- **professional CT support of sites,**
- **motivated investigators with sizeable patient pool with high recruitment and patient retention,**
- **uncomplicated CT logistics, low per-patient cost, trusted data quality.**

Losing competitive advantage, across one or more of these parameters would almost inevitably lead to loss of Poland's iBPCT market share, which has already impacted most other CEE markets. If Poland is set to achieve its full potential it will not be sufficient to just retain status quo, but will have to introduce additional attractors to sponsors of clinical trials, detailed in the Recommendation chapter of this report.

Non-industry/Academic CTs

Data in Table 6 demonstrate that Poland and CEE are lagging behind most other developed countries and regions in terms of participation in non-industry/academic clinical trials with only 22% of trials active in 2019 being academic (vs global more than 80%) and only approx. 2% of CT sites in Poland were academic, vs global average of 44%.

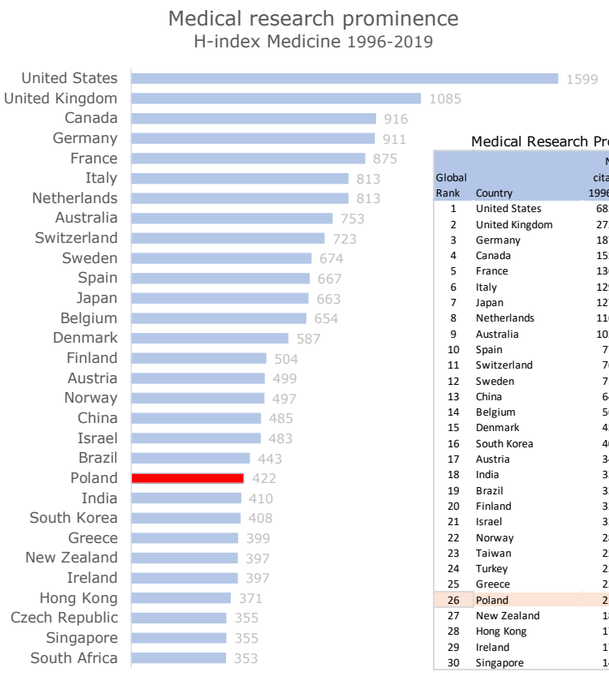
However, as further discussed in the chapter on non-commercial clinical trials in the Stakeholders' perspectives of this report, a substantial number of domestic academic CTs appear to only be registered in Poland via the Polish regulatory agency (URPL) and not reported via EUDRACT or clinicaltrials.gov registries. A likely explanation for this reporting gap is that a majority of the academic CTs registered by the URPL are domestic academic clinical trials suggesting that Poland is lagging behind other developed markets in terms participation in international collaborative networks. These data suggest that while Poland is a power-house in terms of industry research this does not translate to robust collaborative international academic research. **Increasing Poland's participation in collaborative international academic research should be one of the focus areas.** Chapter on *Non-commercial clinical trials in Poland* in the Stakeholders perspectives section provides additional insights on this topic.

Non-industry CTs	Non-industry active Studies	Non-industry CTs as % of all trials in country	Non-industry active Sites	Non-industry sites as % of all CT sites in country	Non-industry CT sites global mkt share
North America	31176	76,9%	222307	57,2%	64,1%
United States	27750	75,6%	212303	58,0%	61,2%
Canada	4098	61,1%	10004	44,6%	2,9%
Australia/New Zaeland	682	25,8%	3235	24,1%	0,9%
Australia	656	26,0%	2897	24,3%	0,8%
New Zealand	142	24,4%	338	22,8%	0,1%
Asia	12185	71,8%	22662	27,7%	6,5%
Japan	311	16,7%	1237	5,4%	0,4%
China	6409	78,1%	11817	45,5%	3,4%
India	494	54,0%	1061	21,9%	0,3%
Korea, Republic of	1720	49,7%	3636	27,1%	1,0%
Taiwan	1162	51,6%	1420	23,2%	0,4%
Malaysia	189	40,1%	292	23,6%	0,1%
EU+ (EU + Switz + Nor + UK)	23921	77,7%	85278	36,3%	24,6%
Western Europe	23025	77,9%	82950	41,4%	23,9%
Germany	2376	42,8%	9651	29,1%	2,8%
United Kingdom	2992	50,1%	9591	40,0%	2,8%
Spain	2166	42,5%	8102	29,5%	2,3%
Italy	2425	49,6%	8851	36,9%	2,6%
France	6405	70,1%	25419	58,2%	7,3%
Belgium	1394	42,7%	3042	32,0%	0,9%
Netherlands	1425	47,9%	4131	46,7%	1,2%
Norway	927	71,5%	1894	71,0%	0,5%
Central Eastern Europe	1732	37,4%	3491	6,4%	1,0%
Poland	513	22,7%	864	7,2%	0,2%
Bulgaria	28	4,4%	51	1,6%	0,0%
Czech Republic	284	19,3%	492	8,4%	0,1%
Hungary	149	11,9%	267	4,7%	0,1%
Romania	100	15,1%	157	5,3%	0,0%
Slovakia	54	12,1%	95	5,1%	0,0%
Russian Federation	328	20,4%	699	5,9%	0,2%
Ukraine	52	7,7%	105	2,0%	0,0%
Latin America	2221	57,7%	3936	18,3%	1,1%
Brazil	1213	60,5%	1914	25,4%	0,6%
Argentina	146	16,6%	420	8,7%	0,1%
Mexico	394	36,1%	498	13,0%	0,1%
MEA	5990	75,8%	8339	40,8%	2,4%
Israel	857	42,1%	1071	18,1%	0,3%
Turkey	1580	69,7%	1989	35,4%	0,6%
South Africa	224	34,1%	482	18,8%	0,1%
Total (non-industry CTs)	**74544**	**82,3%**	**347043**	**44,4%**	**100,0%**

Table 6. Overview of non-industry CTs

Medical research prominence

A reliable, globally accepted benchmark of research prominence is H-index (28). It reflects both quantity and quality of research. The index can be applied to the productivity and impact of countries (29). Figure 25 summarizes the H-index in medicine ranking based on data from Scimago Journal (28). Insert in Figure 25 shows a comparison between another research excellence benchmark – net citations - against a global footprint of clinical trials (data from (28)). The results show that while Poland and CEE countries perform exceptionally well against their peers and rank among top countries in terms of global footprint of clinical trials as well as other parameters of industry CTs (accessibility and reputation) described elsewhere in this report, Poland and CEE in general underperform in terms of medical research prominence. The lack of medical research thought leadership may be an impediment in attracting the most innovative cutting edge clinical research which is primarily allocated to well-known medical researchers in a given therapeutic area.



Medical Research Prominence

Global Rank	Country	Net citations 1996-2019	Share of net citations
1	United States	68504844	23,26%
2	United Kingdom	27273856	9,26%
3	Germany	18708257	6,35%
4	Canada	15527373	5,27%
5	France	13682346	4,64%
6	Italy	12930945	4,39%
7	Japan	12718953	4,32%
8	Netherlands	11676507	3,96%
9	Australia	10217654	3,47%
10	Spain	7749717	2,63%
11	Switzerland	7664768	2,60%
12	Sweden	7156117	2,43%
13	China	6471651	2,20%
14	Belgium	5608771	1,90%
15	Denmark	4558589	1,55%
16	South Korea	4057620	1,38%
17	Austria	3411818	1,16%
18	India	3346963	1,14%
19	Brazil	3305581	1,12%
20	Finland	3267537	1,11%
21	Israel	3217360	1,09%
22	Norway	2899919	0,98%
23	Taiwan	2539398	0,86%
24	Turkey	2281660	0,77%
25	Greece	2242891	0,76%
26	Poland	2135587	0,72%
27	New Zealand	1860873	0,63%
28	Hong Kong	1747994	0,59%
29	Ireland	1747309	0,59%
30	Singapore	1457283	0,49%

Global Industry CT Footprint

Global Rank	Country	Active sites 2019	Share of active global sites
1	United States	149893	35,38%
2	Germany	23348	5,43%
3	Japan	21821	5,02%
4	Spain	18392	4,45%
5	France	17394	4,21%
6	Italy	14358	3,49%
7	United Kingdom	14094	3,31%
8	China	12361	3,26%
9	Canada	12116	2,86%
10	Russia	11364	2,58%
11	Poland	10719	2,57%
12	South Korea	9487	2,26%
13	Australia	8450	2,08%
14	Belgium	6296	1,49%
15	Brazil	5406	1,30%
16	Hungary	5373	1,24%
17	Czech Rep	5315	1,23%
18	Ukraine	5149	1,21%
19	Israel	4508	1,12%
20	Netherlands	4692	1,09%
21	Taiwan	4398	1,08%
22	Argentina	4296	1,02%
23	India	3787	0,87%
24	Turkey	3441	0,83%
25	Mexico	3438	0,77%
26	Bulgaria	3270	0,73%
27	Romania	2968	0,64%
28	Austria	2561	0,62%
29	Greece	2374	0,55%
30	Sweden	2229	0,49%

Figure 25. Medical research prominence – H-index 1996-2019, Top 30 countries. Insert: Net medical research citations (self-citations excluded) global share vs. share of global Industry CTs (% of all active sites in 2019).

Impact of COVID-19

In 2020, COVID-19 impacted clinical trials globally. A recent survey (30) found that the COVID-19 pandemic had affected 69% of the respondents in their conduct of ongoing clinical trials, and 78% reported that COVID-19 had affected the initiation of new trials.

This has resulted in a worldwide reliance and shift to digital technologies, data sources and virtual meeting capabilities.

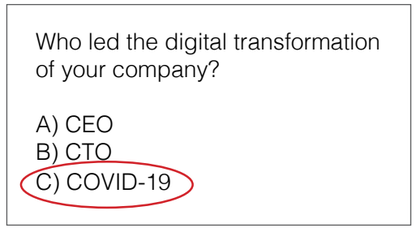


Figure 26. Digital Transformation Quiz, Source: Susanne Wolk (TWITTER)

As an example, 15 to 20% of providers reported using telemedicine pre-COVID, and now 90% of doctors plan on using telemedicine technology after the pandemic is over (31). The point being that COVID-19 has likely forever changed healthcare, how patients interact with their doctors and how patients are engaged and recruited to clinical trials. This presents an opportunity for the future of clinical trials in Poland as detailed in the chapter of this report on *Digitization of clinical trials and technology as future enablers of clinical trials Poland.*

Acute impact on clinical trials - globally and in Poland

	# new CTs	# new sites
Global annual average of new studies 2017-2019	4856	93081
Poland annual average of new studies 2017-2020	397	2899
Global studies 2020	5023	66006
% change vs prior 3 yrs	*3,4%*	*-29,1%*
Poland studies 2020	262	1642
% change vs prior 3 yrs	*-34,1%*	*-43,4%*
out of that:		
Global COVID-19 studies 2020	252	3269
Poland COVID-19 studies 2020	0	0
Net non-COVID-19 studies:		
Global non-COVID-19 studies 2020	4771	62737
% change vs prior 3 yrs	*-1,7%*	*-32,6%*
Poland non-COVID-19 studies 2020	262	1642
% change vs prior 3 yrs	*-34,1%*	*-43,4%*

Table 7. COVID-19 impact in Industry CTs: new studies and sites

Table 7 analyzes the impact of the COVID-19 pandemic on the iBPCTs, which have been substantially disrupted around the globe and in Poland. While globally the number of newly added iBPCTs in 2020 has grown by 3.4% vs the 2017-2019 average, Poland has seen a 34% decline of new iBPCTs vs the prior 3 year average. The net growth of the number of iBPCTs globally was driven by COVID-19 trials, however, when excluding these there was an approximately 2% decline the number of newly added iBPCTs in 2020 globally vs the 2017- 2019 average. It is very noticeable that Poland has not participated in any of the 252 COVID- 19 iBPCTs conducted globally in 2020 at nearly 3,000 sites.

Another factor impacting CTs during the COVID-19 pandemic were the delays and disruptions to the ongoing clinical trials caused by reduced patient visits to doctors' offices due to the pandemic fears and lock-downs, impacting both recruitment of new patients as well as missed patient visits in ongoing clinical trials. Not surprisingly, and based on anecdotal evidence, the least impacted were oncology CTs.

At the time of writing of this report, the worst impact on CTs appears to have been during Q2 and Q3 2020, and despite continuing intermitted lock-downs and other restrictions, most global sponsors and CROs resumed pre-pandemic level of activities since approximately Q4 2020.

However, the pandemic has brought a number of changes to the industry and accelerated adoption of remote processes (remote patient visits, remote monitoring visits, direct-to-patient delivery of study drug, home patient visits by study nurses and delivery) and virtual/de-centralized CTs technologies, detailed in the following chapter.

Lessons learned from the pandemic and market prognosis globally

A global survey of pharmaceutical and biotech sponsors (n=136), conducted in the autumn of 2020, regarding their outsourcing experience and general trends affecting the industry for 2021 and beyond provides important market insights (32). In addition to research on R&D expenditure trends, the survey assessed the short-term and longer-term implications of COVID-19, the use of site networks, and virtual trials.

Summary of key points:

- The lower-than-expected R&D expenditures in 2021 are likely a result of the operational challenges related to the ongoing pandemic,
- R&D Spend: expected R&D growth in the low- to mid-single-digit range in 2021, increasing to above 5.5% in 2022 and 2023. For comparison the R&D expenditures growth levels during the previous years were as follows: 7.6% in 2017, 10.7% in 2018, 5.1% in 2019, with 2020 estimated growth of 3.3%. (32),
- The R&D spend impact in 2021 is less severe than initially feared: the projected 2021 growth rate was a full point above 2021 estimates based on a survey of the same stakeholder group conducted in the spring 2020,
- 34% of respondents indicated that the pandemic caused them to increase their R&D budgets, compared to 27% of those who decreased R&D budgets,
- Active project growth is more normal compared to the spring 2020 survey, in which responses were more pessimistic when the pandemic took hold,
- COVID-19: based on the survey results it appears that the pandemic will likely be a longer- term positive for the industry,
- The pandemic is expected to increase the level of outsourcing in the next five years,
- Virtual clinical trials and site networks: 60% of respondents indicated that the pandemic would cause structural changes to virtual trials—particularly an increased use of virtual trials, remote monitoring/EHR access, and site networks (~50% respondents indicated expected higher use of site networks),
- According to the survey, the usage of virtual clinical trials has doubled (to 13% overall) from fall 2019 to spring 2020, and of the new trials, 20% is expected to be conducted (at least partially) as virtual,
- COVID-19 related CT delays: 65% of respondents indicated delays in CT timelines, with an average delay of 5 months.

Lessons learned from the pandemic in Poland

In Poland the following specific challenges have been reported during management of CTs during the pandemic:

- Remote source Data Review (rSDR), including Remote access to sites' EMRs: as per current legislation (law of 6 November 2008 on patient's rights and the Patient's Rights Ombudsman), patients' medical documentation can be reviewed only at the site, which makes remote SDR logistically complicated/impossible - no new guidance reflecting changed realities has been provided.
- Acceptability and guidelines for home patient care and DTP deliveries of study drug.
- Adoption of digital signatures to avoid delays due to wet ink signature requirements.

The lessons learned should be addressed not only to enable successful management of future crises but also because these elements will now become risk management and business continuity requirements of sponsors of clinical trials and lack of clear guidelines and/or inability to implement these may result in exclusion of country or sites during study planning.

Clinical trials - Opportunity for Poland to close the R&D gap on Sustainable Development Goals

According to the UNESCO Institute for Statistics, in 2019, Global spending on R&D has reached a record high of almost USD 1.7 trillion (33). About 10 countries account for approx. 80% of spending. As part of the Sustainable Development Goals (SDGs), countries have pledged to substantially increase public and private R&D spending as well as the number of researchers by 2030.

Not only in absolute terms of USD investment in R&D, but also in terms of R&D investment as a % of GDP, Poland and CEE in general (with the notable exception of Czech R and Slovenia) with less than 1% is lagging substantially behind North America and Western Europe as well as East Asia and the Pacific, which spend 2-3 times more in terms of % of GDP. According to the UNESCO report, Poland has an estimated USD 9.14 billion (0.9% of GDP at PPP) R&D spend and employs 2,064 researchers per million inhabitants or 78,000 R&D jobs in total. Industry CTs represented a significant portion of that amount with an estimated economic value of USD 1.35 billion representing 15% of the overall R&D investment in Poland and an estimated job creation of 9,000 (11% of total) in 2019. Further increasing Poland's attractiveness for sponsors of CTs represents a significant opportunity to close the existing R&D investment gap and creation of additional R&D jobs.

CONCLUSION

Growth of Industry CTs and reporting these activities as R&D represents a significant opportunity for the government of Poland to reduce existing gap against the UNESCO's Sustainable Development Goals (SDGs) to substantially increase public and private R&D spending as well as the number of researchers by 2030.

LEGISLATIVE ASSESSMENT OF CLINICAL TRIALS IN POLAND

CHAPTER 2

Chapter 2. Legislative Assessment of Clinical Trials in Poland

by Piotr Zięcik and Krystyna Miłowska

When analyzing the potential of the clinical research area in Poland, it is necessary to assess the current state of the legislation relating to clinical trials, as well as the changes that the legislator has made since the publication of the previous "Clinical Trials in Poland" report prepared by PwC in November 2015. The analysis of the current legal situation allows us to identify the main administrative and legal barriers which currently hinder the development of clinical trials in Poland. These barriers are summarized below. When discussing the clinical research area, it is also impossible not to draw attention to the factors which have significantly influenced the practice of conducting clinical trials in recent years and which are discussed in the next section of this chapter. In view of the European Commission's Decision No. 2021/1240 of 13 July 2021 to make the EU portal and EU database fully functional, which consequently means that the Regulation (EU) No. 536/2014 will become applicable from 31 January 2022, the last part of the chapter discusses the proposed changes to the legislation related to the implementation of the aforementioned Regulation.

2.1 Barriers

Barriers to the process of the conduct of clinical trials

1. Lack of precise rules for the financing of healthcare services in clinical trials, inconsistent positions of the NFZ [National Health Fund] Branches:
- introducing uniform and precise rules for sponsor's financing of clinical trials,
- introducing the compassionate use procedure,

2. Difficulties with remote monitoring and access to electronic source documents:
- introducing regulations allowing access to electronic medical records and medical records in electronic form for the purpose of clinical trials, including remote monitoring of trials,

Institutional barriers

3. Inconsistent practices pursued by ethics committees, lengthy proceedings before the Appeals Ethics Committee:
- creating an efficient ethical review system through the establishment of a Supreme Ethics Committee,
- a single fee for clinical trial authorization and ethical review,

4. Lack of a governmental authority permanently supporting the conduct of commercial clinical trials:
- appointing a public authority to support the conduct of commercial clinical trials or increasing ABM competencies in this area,

5. Defining the role of the research site in the conduct of a clinical trial as ancillary to the investigator:
- increasing the role of the research site in the conduct of a clinical trial by allowing research sites to control the entire process of conducting clinical trials (while maintaining the principle of responsibility of the principal investigator for the conduct of the clinical trial at the site),

Legislative barriers affecting patients' participation in clinical trials

6. Civil liability rules for entities involved in the process of conducting clinical trials are not adapted to the process of conducting clinical trials:
- making it easier for the participants to pursue claims for injury suffered in a clinical trial,

7. Lack of effective insurance for clinical research participants:
- creating new rules for participant insurance to allow rapid compensation of participants, as well as defining the insurance coverage and the sum assured depending on the nature of the trial and the scale of risk to participants, with particular emphasis on low-intervention trials.

2.2 Legislative changes in the area of clinical research - an overview of changes over the last 6 years

When assessing the legislative changes over the last 6 years, i.e., since the publication of the Clinical Trial in Poland report prepared by PwC, it should be noted that the Polish legislator, despite the fact that Regulation No. 536/2014 was enacted in 2014, has not made any significant changes in the legal environment for conducting clinical trials as compared to 2015. Only one legislative change, discussed in section 2 below, took into account the content of Regulation (EU) No. 536/2014 and introduced a solution identical to the provisions of the aforementioned Regulation. Other changes in the legal conditions for conducting clinical trials concerned clarification of issues giving rise to practical doubts (financing of clinical trials) or resulted from the introduction of legal regulations not directly related to clinical trials. It was not until the end of April 2021 that the long-awaited draft Act on Clinical Trials was published. The enactment of a new Act on Clinical Trials is necessary to ensure the application of Regulation No. 536/2014. According to the explanatory memorandum to the draft Act on Clinical Trials, the purpose of introducing new regulations on clinical trials is to increase Poland's competitiveness as a place for conduct of clinical trials by implementing transparent legal regulations enabling the application of European standards set out in Regulation No. 536/2014 and introducing additional facilitations and mechanisms to encourage the conduct of clinical trials, which would positively distinguish our country among the countries implementing only the minimum plan to apply the Regulation. The following section contains the changes in legislation that have taken place over the last 6 years, while a detailed discussion of the Regulation and the assumptions of the Act on Clinical Trials can be found in section IV.

Changes in the financing of clinical trials

The lack of application of uniform and precise rules for the financing of healthcare services in a clinical trial is a major barrier to the conducting of clinical trials. The application of Article 37 k (1) and (1a) of the Pharmaceutical Law which was introduced on 1 May 2011 raises many doubts. The provision stipulates that the sponsor shall finance healthcare services related to the clinical trial and covered by the clinical study protocol, which do not fall within the scope of guaranteed services, in particular it shall supply, free of charge, to the investigational medicinal products, the comparators and the devices used for their administration to the clinical research participants. Moreover, the sponsor shall finance guaranteed healthcare services when: (i) they are necessary to eliminate the effects of the occurring health complications arising from the use of the investigational medicinal product; (ii) they are required as a result of the use of the investigational medicinal product; (ii) they are necessary to qualify the patient to participate in the trial. Concerns have been raised about the interpretation of the phrase "health complications" (having no legal definition) and the absence of an obligation for the sponsor to finance the consequences of "health complications" resulting from procedures performed solely for the purposes of a trial. NFZ Branches interpret the above provision inconsistently, which leads in extreme cases to situations where the sponsor must finance guaranteed services at some research sites while at others the sponsor does not finance such services. In extreme cases, patients may be effectively excluded from access to guaranteed healthcare services because of their participation in a clinical trial. The financing of medicinal products for primary treatment, taken by the participant regardless of his/her participation in a clinical trial, also remains problematic. On 17 November 2015, an amendment to the Pharmaceutical Law came into effect setting forth a framework for the financing of non-commercial research, which in principle rests with the public payer. The application of the provisions discussed allows NFZ to finance healthcare services provided to participants of a non-commercial clinical trial who are beneficiaries within the meaning of the Act of 27 August 2004 on healthcare services financed from public funds. In addition, NFZ also finances medicinal products for participants if such products are included in the standard NFZ basket of services. This regulation allowed for creating a foundation for the development of non-commercial clinical research.

On 1 June 2019, in order to streamline and facilitate the identification of healthcare services provided to clinical research participants, an amendment to the Pharmaceutical Law was introduced under which the investigator or the research site is required to inform NFZ of the PESEL [Personal Identification] number of the clinical research participant, and if no such number is available, of the number of a document confirming the identity of the research participant within 14 days of the date of enrollment in a trial. Previously, a similar obligation applied only to non-commercial clinical research.

Revision of regulations with regard to the requirement to submit original agreements with the investigator and the research site to the President of the Office and ethics committees

For several years, the requirement to attach clinical trial agreements executed between the sponsor or CRO and the investigator and the research site to the application for authorization of a clinical trial submitted to the President of the Office for Registration and to the application for issuance of an opinion on a clinical trial by an ethics committee, was one of the key administrative barriers impeding the development of the market which was repeatedly pointed out to the legislator by the industry community. Poland remained one of the last European Union countries to have this requirement, which significantly limited Poland's competitiveness as a country of choice for study sponsors to conduct trials, particularly trials of short duration or with a short recruitment period. Postulates from all market participants to the Polish legislator to change the legal situation have had the desired effect. The obligation to attach such agreements was abolished on 18 October 2018 by the Regulation of the Minister of Health of 12 October 2018 on model document forms submitted in connection with a clinical trial of a medicinal product and the fees for submitting a clinical trial application. As a result, applications to the Office for Registration and the ethics committee can be submitted several or even more than twelve weeks earlier and the period for obtaining the authorization for a trial and a positive opinion from the ethics committee has been shortened by such time.

GDPR – the introduction of data protection legislation has changed the interpretation

The provisions of **Regulation (EU) 679/2016 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Processing Regulation)**, hereinafter referred to as the GDPR, came into effect on 25 May 2018. The provisions of the GDPR have given impetus to the structuring of the principles of protection of personal data of clinical research participants. The threat of high financial penalties has led the vast majority of entities involved in clinical research to implement the personal data protection principles required by GDPR. It is now undisputed that the sponsor is the controller of the research participants' personal data and, in most cases, the research participants' data are secured through pseudonymization. It is worth noting the position of the President of the Office for Personal Data Protection who in its communication of 17 August 2018 concerning the list of types of personal data processing operations that require a data protection impact assessment, indicated that organizations conducting clinical trials, in view of monitoring of health data, should perform personal data protection impact assessments ("Data Protection Impact Assessment", „DPIA").

The provisions of the GDPR allow for the identification of three grounds for processing of personal data in clinical trials. According to the European Commission's Directorate[6], the processing of personal data in clinical trials is lawful and falls under one of three legal bases depending on all the circumstances surrounding a particular clinical trial:

- a task carried out in the public interest pursuant to Article 6(1)(e) in conjunction with Article 9(2)(i) or (j) of the GDPR; or
- a legitimate interest pursued by the controller pursuant to Article 6(1)(f) in conjunction with Article 9(2)(j) of the GDPR; or
- in specific circumstances when all conditions have been met, an explicit consent of the data subject pursuant to Article 6(1)(a) and Article 9(2)(a) of the GDPR.

The above position was confirmed in the opinion of the European Data Protection Board (EROD) of 23/01/2019.[7] The implementing regulations to the Pharmaceutical Law impose an obligation on the sponsor to collect the consent of the clinical research participant for the processing of personal data and have not been adapted to the provisions of GDPR.

Amendments to the Act on the Professions of Physician and Dentist – new requirements for a medical experiment

On 1 January 2021, the amendment of the Act of 5 December 1996 on the Professions of Physician and Dentist concerning the conduct of medical experiments came into force. Among the many changes, those of practical importance for clinical trials are: lowering the age of participants who give concurrent consent to participate in a trial to 13 years, creating a legal framework for conducting trials involving persons incapable of giving consent to participate in clinical trials, the rules on the use of placebos, and the obligation to guarantee any necessary prophylactic, diagnostic, and therapeutic procedures to participants during a trial. The entry into force of the amendment to the Act has caused controversy with regard to the mandatory civil liability insurance for participants of medical experiments and any persons who may be affected by the consequences of the experiment. On 12 February 2021, the Ministry of Health issued a communication on applying the Regulation of the Minister of Finance, Regional Funds and Regional Policy of 23 December 2020 on mandatory third party liability insurance for entities conducting medical experiments. In the opinion of the Ministry of Health, in the case of clinical trials, only civil liability insurance as defined in the Pharmaceutical Law is applicable. The amendment to the Act has introduced the obligation to provide civil liability insurance for research on biological material to the same extent as for other medical experiments, which raises doubts and may significantly increase the cost of conducting scientific research.

Establishment of ABM - support for scientific research and development work in the field of medicine

Based on the Act of 21 February 2019, the Medical Research Agency (Agencja Badań Medycznych, ABM) was created. ABM is a state agency responsible for advancing research in the medical and health sciences and supporting the conduct of non-commercial research. ABM's activities to date in popularizing clinical research, facilitating patients' access to information on clinical trials, and the program for the establishment of Clinical Research Support Centers (Centra Wsparcia Badań Klinicznych, CWBK) are positively evaluated by participants in the clinical research market. ABM is implementing one of the first public grant programs with funding dedicated to non-commercial clinical trials. ABM aims to make use of the potential for medical research and health sciences development in Poland as regards non- commercial clinical trials, which accounted to date for about 2 percent of all registered trials. By comparison, the rate in Western European countries is about 40 percent, and ABM is working to increase the percentage of non-commercial clinical trials up to 20-30 percent. According to the declarations of ABM, at the end of 2020, about 60 non-commercial trials were granted authorizations or were in the process of obtaining such authorizations and, thanks to the activities of ABM, more than 20 thousand patients will participate in clinical trials financed by this institution in the coming years. The draft Act on Clinical Trials provides for an increased role of ABM in the conduct of commercial clinical trials, as the Supreme Ethics Committee and the Fund for Protection of Clinical Research Participants are to operate at ABM.

[6] Questions and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation, https://ec.europa.eu/health/sites/health/files/files/documents/qa_clinicaltrials_gdpr_en.pdf

[7] Opinion No. 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection Regulation (the GDPR) (Article 70(1)(b)) adopted on 23 January 2019, Section 14, https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_opinionctrq_a_final_pl.pdf

2.3. Current administrative and legal barriers to clinical research market development

When analyzing the practice of conducting clinical trials, it is necessary to present the key administrative and legal barriers hindering the development of the clinical research market. The barriers identified below affect the efficient conduct of clinical trials, as well as the safeguarding of the rights of patients participating in a clinical trial and thus encouraging their more active participation in clinical trials.

Financing of clinical trials

Barrier:

Lack of precise rules for the financing of healthcare services in a clinical trial, inconsistent positions of NFZ

Article 37k of the Pharmaceutical Law amended on 1 May 2011, which specifies which healthcare services related to clinical trials are financed by the sponsor and which are financed from public funds, has not brought the benefits expected by the market in terms of uniform positions of the National Health Fund Branches as the public payer. Sponsors still have no real ability to challenge the settlements made between research sites or investigators and NFZ. As a result, the common practice of shifting as much of the cost of guaranteed services as possible to sponsors still exists.

The ambiguity in the wording of Article 37k of the Pharmaceutical Law leads to a contradiction in the sponsor's obligation to provide the investigational medicinal products free of charge. On the one hand, sponsors are not obliged to pay the costs of the guaranteed services and, on the other hand, they are obliged to provide all medicinal products used in clinical trials, even those that are part of guaranteed services, e.g., reference products or comparators. Poland is one of the few European Union countries that has not introduced the "compassionate use" procedure which would regulate the rules for access to the medicinal product after the completion of the clinical trial and before sponsors obtain the marketing authorization. This situation raises ethical and legal issues and also discourages patients with chronic diseases from participating in clinical trials. Poland has not decided to use the compassionate use procedure despite the fact that such a mechanism has been provided for in Article 83 of Regulation (EC) No. 726/2004, after notification to the European Medicines Agency. The use of this mechanism does not slow down or prevent the continuation of clinical trials in any way. For patients requiring continuing treatment for medical reasons the sponsors, most often, choose to design and register a follow-up clinical trial, which involves the necessity to obtain all regulatory approvals and additional high costs. Draft Act on Clinical Trials of Medicinal Products for Human Use published on 30 April 2021 on the website of the Government Legislation Centre (https://legislacja.rcl.gov.pl/projekt/12346302/katalog/12784810#12784810) does not introduce any radical changes with regard to the rules for the financing of clinical trials currently in force. The term "health complications" has been removed and replaced by "adverse reactions to an investigational medicinal product or adverse events resulting from procedures performed solely for the purposes of a clinical trial". It has been clarified that the sponsor is obliged to finance the effects occurring both

after the use of the investigational medicinal product and following the procedures performed solely for the purposes of a clinical trial. Still, the sponsor, in case of the site's or the investigator's doubts as to who is to finance certain healthcare services, or in case of divergent interpretations of the facts or the legislation by the NFZ Branches, has no option to consult the state payer and resolve doubts about the rules for the financing of clinical trials. Uncertainty in this area may limit the activity of sponsors and sites. The draft Act also includes no provisions for a program for compassionate use of a medicinal product after the end of a clinical trial. Programs for compassionate use of a medicinal product after the end of a clinical trial are well established in other European countries and regulated at the level of EU law. These programs aim to protect the life and health of patients and clinical research participants when they are no longer participating in a clinical trial and no other therapeutic options exist on the market. The failure to introduce these provisions into the Polish legal system results in a different treatment of patients and clinical research participants in Poland compared with patients and clinical research participants in other EU countries.

Postulates:

- Introducing clear rules for the sponsor's financing of clinical trials,
- Introducing a procedure enabling the compassionate use of medicinal products following the conclusion of clinical trials.

Digitization of document flow in clinical trials

Barrier:

Difficulty with remote monitoring and access to electronic source documents

Legislation[8] provides for healthcare providers to maintain Electronic Medical Records ("EMR") and medical records in electronic form. However, there are no provisions specifying the rules for the use of EMR and medical records in electronic form for the purposes of clinical trials, including remote monitoring of trials and access to electronic source documents. Due to the development of digitization and the legal requirements, more and more healthcare institutions keep medical records in the form of electronic databases. Making medical records available for the purposes of conducting a clinical trial is therefore also done by granting access to these databases. During the pandemic, it was extremely difficult to oversee the progress of clinical trials and to monitor without reviewing medical records. Such arrangements exist in other countries, providing the opportunity to effectively oversee patient safety in clinical trials. The COVID-19 pandemic has posed new challenges for entities conducting clinical trials, including having to perform clinical trial activities remotely. However, the legislation does not correspond to the full use of EMR and medical records in electronic form for the conducting of a clinical trial. Pursuant to § 19 of the Regulation of the Minister of Health on Good Clinical Practice, Sponsors enter into written clinical trial agreements with investigators and research sites. This regulation does not require agreements to be made in writing under pain of nullity (ad solemnitatem), which allows the interpretation that the documentary form of the execution of a clinical trial agreement is acceptable. The regulations do not require that agreements with members of the research team or other agreements entered into for the purpose of conducting a clinical trial be in writing and nor that a particular form of this legal act be maintained for the effective execution of the agreement. An analysis of the current legal provisions of the Civil Code on the form of legal acts leads to the conclusion that it is possible, provided that certain conditions are met, to generally apply submission of declarations of intent in the form of an electronic document (other than qualified signature) when entering into clinical trial agreements as well as most of clinical trial-related agreements. At the same time, in agreements which contain provisions requiring a written form under pain of nullity (e.g., transfer of copyrights), the application of a documentary form of the act is not possible. It is reasonable to structure the new regulations in such a way as to enable parties to clinical trial agreements to exchange documents in electronic form. Currently, some of the entities involved in entering into clinical trial agreements indicate that clinical trials should be conducted in accordance with Good Clinical Practice, and since the Regulation on Good Clinical Practice mandates a written form for the agreement with the investigator, there is no basis for this agreement to be entered into in a simple electronic form. Sponsors and CROs annually negotiate over a dozen thousand agreements in Poland to conduct clinical trials. Enabling and popularizing execution of these agreements in electronic form (without a qualified signature), e.g., through electronic contracting platforms, would greatly facilitate the management and archiving of these documents. Companies operating in the pharmaceutical market successfully use existing IT solutions in this area, as they significantly speed up the process of signing a contract and reduce the costs of document archiving. The existence of such solutions also in the area of the clinical research law seems to be very necessary. Experience of conducting clinical trials in the era of the COVID-19 pandemic has indicated that the current requirement for such agreements to be concluded in writing is an unnecessary bureaucracy. It is also reasonable, as postulated by the clinical research industry organizations, to allow informed consents to be signed electronically by the patient. Regulation No. 536/2014 provides that informed consent should be in writing, which allows the national legislation to clarify that an acceptable form of the informed consent would be an electronic biometric signature.

[8] The Act on Information System in Health Services and the Regulation of the Minister of Health on the types of medical records, as well as the Act on Patient Rights and the Ombudsman of Patient Rights, and the Regulation of the Minister of Health concerning the types, scope and model forms of medical records and the method of their processing.

Postulates:

- Facilitating electronic document flow in a clinical trial and access to EMR and medical records maintained in electronic form,
- Introducing legislation allowing access to EMR and medical records in electronic form for the purposes of clinical trials, including remote monitoring of clinical trials,
- Allowing clinical trial agreements to be concluded in documentary form.

Ethics committees

Barrier:

Inconsistent practices pursued by ethics committees, lengthy procedures of the Appeals Ethics Committe

The ethical assessment of a clinical trial is currently carried out by the ethics committee designated according to the seat of the coordinator of a multi-center trial which, when issuing an opinion on a clinical trial, takes into account, among others, the legitimacy, feasibility and design of the clinical trial, the analysis of anticipated benefits and risks, the correctness of the study protocol, etc. One of the elements which a designated "central" ethics committee may take into account when issuing an opinion on a clinical trial are the positions of "local" ethics committees. It should be noted that the position of the "local" ethics committee is not binding for the "central" ethics committee (Article 37s(3) of the Pharmaceutical Law). Sometimes the "local" ethics committee raises objections that are incomprehensible, contradictory to the law, or factually incorrect – and in a situation such as this the "central" ethics committee is obliged to issue an opinion on the study assessing all the collected material, including the positions of all "local" ethics committees. Based on the content of § 10 of the Regulation of the Minister of Health and Social Welfare of 11 May 1999 on the detailed rules of appointing, financing and mode of operation of ethics committees (Journal of Laws No. 47, item 480, hereinafter the "Regulation on Committees"), the funds intended for financing the operations of ethics committees come from the fees paid by the entity intending to conduct a medical experiment and they cover the costs of ethics committee operations. The entity that intends to conduct a medical experiment pays such fees to the entity appointing the ethics committee, at its request, before the resolution expressing an opinion on the design of a medical experiment is adopted (§ 4). The Regulation on Committees does not include any regulations on other forms of expression of ethics committees, e.g., expression of a position or statement of objections, or rules for charging and collecting fees other than for an opinion on the design of a medical experiment. The Regulation on Committees provides that the fee shall be paid to the entity appointing the ethics committee which issues an opinion on the design of a medical experiment before the resolution expressing an opinion on the clinical trial is adopted (§ 10(2)), i.e., to the "central" ethics committee within the meaning of the provisions of the Pharmaceutical Law. In practice, the issue of financing "local" ethics committees has remained controversial for more than twelve years. The situation is not made easier by the fact that each ethics committee adopts its own regulations, and the rules of operation of the committee have never been formally standardized. Often, "local"

ethics committees condition their decision to raise or not raise an objection on sponsor's prior payment of a fee in the amount determined individually by each "local" committee. The committees argue that failure to pay the fee will prevent conducting of the clinical trial at a particular research site by the selected investigator. Failure by the legislator to indicate the source of financing for the "local" committees' "statement of objections" procedure in a situation where the Polish regulations require ethics committees to self-finance their operations results in discrepancies in the interpretation of the law and in the practice pursued by pharmaceutical companies as regards making payments to ethics committees. The Appeals Ethics Committee appointed by the Minister of Health and, as the only entity, financed from the state budget, only considers appeals against negative opinions of ethics committees, repeating the procedure for issuing an opinion on the design of a clinical trial. Although all ethics committees are required to provide timely opinions on clinical trials, the Appeals Ethics Committee very rarely convenes its meetings. The length of the appeals process and the time it takes to receive a final decision from the Appeals Ethics Committee that will allow for initiation of a clinical trial is often longer than the participants' recruitment period planned by the sponsor for the entire international clinical trial. The draft Act on Clinical Trials provides for the establishment of a Supreme Bioethics Committee at ABM which will be able to select a network of ethics committees authorized to draw up the ethical review of a clinical trial. There is no provision for the sponsor to appeal against an opinion on the ethical review of a clinical trial. The ethical review system proposed in the draft Act is quite new and it is currently difficult to assess its effectiveness. However, the legislator seems to have created the conditions for an efficient ethical review of trials within the deadlines imposed by Regulation (EU) No. 536/2014.

Postulates:

- **Efficient system for ethical review and appeals process, a single fee for ethical approval and review,**
- **Creating an efficient ethical review system through the establishment of a Supreme Ethics Committee,**
- **A single fee for clinical trial authorization and ethical review.**

Institutional support for commercial clinical trials

Barrier:

Lack of a governmental authority permanently supporting the conducting of commercial clinical trials

The positive assessment of the Medical Research Agency's efforts in the field of supporting non-commercial clinical trials allows us to express an opinion that it would be very helpful for the development of clinical research in Poland and for the benefit of patients if the Polish state also provided similar support to commercial clinical trials, which could significantly increase the number of clinical trials and patients participating in them. This support can be exemplified by the National Institute for Health Research (NIHR) in the UK, as well as the Danish government's activities. The potential tasks of ABM could be to look after the quality of research projects in Poland and to highlight their high quality internationally, to attract, develop and retain the best investigators, to facilitate the identification of specialists in given medical fields, to focus the research projects on improving healthcare, to develop the Clinical Research Support Centers in order to increase the number of clinical trials and to involve a larger number of patients. Such an authority could assist sponsors with planning trial locations, the available medical staff or the information on the potential patient population. The role of such an authority would be to reduce the complexity of administrative procedures, provide training for those involved in the conduct of clinical trials in order to improve their qualifications and the quality of trials, as well as to speed up initiation of the trial being carried out. Supporting the organization of clinical trials also seems justified, especially where reaching patients with a particular rare disease is difficult for individual sites, investigators and sponsors. NFZ has a huge database on the health of patients in Poland, so reaching the right people with a proposal to participate in a trial could be much easier. NFZ has the data not only on where the patients are but also who performs certain services and treats a given patient. Potentially, ABM in collaboration with NFZ could improve contacts between sponsors, sites, investigators and patient networks. ABM could also, by developing the Clinical Research Support Centers program, standardize the way public healthcare institutions conduct clinical trials.

Postulate:

- **Identifying a public authority to support the conduct of commercial clinical trials or increasing ABM competencies in this area.**

Research site

Barrier:

Specification of the role of research sites in the conduct of clinical trials as entities ancillary to investigators

With the issuance of the Regulation of 2 May 2012 on Good Clinical Practice (hereinafter "GCP Regulation), the legislator removed the open-ended directory of entities that are authorized to conduct clinical trials. Therefore, it is permissible for any legal entity to conduct a clinical trial even if the scope of its activities is not the same as the scope of activities performed by research sites in clinical trials.

The Polish legislation governing the conduct of clinical trials provides for an auxiliary role of sites in carrying out of clinical trials. Aside from making the premises and equipment necessary to carry out protocol-required diagnostic and therapeutic procedures available to the investigator and the research team, the research site being a healthcare provider maintains patients' medical records, including source documents. The only obligation of a research site being a hospital, indicated directly in the applicable laws, is the obligation of hospital pharmacies to maintain records of the investigational medicinal products (Article 86(4)(1) of the Pharmaceutical Law). It is the obligation of the investigator, and not of the research site, to provide adequate medical care to research participants, particularly in the event of a serious adverse event following use of the investigational medicinal product [§ 4(8) of the Regulation on Good Clinical Practice].

Consequently, the research site's obligations in a clinical trial, in most cases, are limited to allowing the investigator to conduct the trial at the premises of the research site by giving access to the facilities and equipment. This construction adopted by the Polish legislator creates many obstacles to efficient negotiation of clinical trial agreements based on international contract templates, as there is no definition of the relationship between the research site and the investigator, including financial, administrative, technical or personnel management. The investigator as an employee, often in public healthcare institutions, conducts clinical trials outside of his/her primary agreement with the site and, theoretically, outside of his/her working hours. A lack of unambiguous regulations in this respect impacts the conflict of interests of the research site and of the investigator, the uncertainty of entering into agreements, the length of negotiations and, consequently, the time for initiating clinical trials. At private research sites, on the other hand, the site usually controls the entire process of the conduct of a clinical trial and the investigator is employed solely to conduct the trial, which is in contradiction with the leading role of the investigator in the conduct of a clinical trial as stipulated by the provisions of the Pharmaceutical Law.

The Regulation (EU) No. 536/2014 contains a laconic regulation regarding research sites (the site where the clinical trial is to be conducted must be suitable for a clinical trial to be conducted there in accordance with the requirements set out in this Regulation). The draft Act on Clinical Trials does not introduce additional regulations in this respect. It seems that such an approach will allow for flexible solutions and, if necessary, for shaping the leading role of the site in clinical trial agreements involving taking over most of the responsibilities connected with the conduct of a clinical trial, other than the principal investigator's responsibility of conducting the trial. The legal relationship thus formed between the sponsor, the site and the investigator may correspond to the increasingly important role that research sites play in the process of conducting clinical trials.

Postulate:

- **Increasing the role of research sites in conducting clinical trials by allowing research sites to control the entire process (while maintaining responsibility of the principal investigator for conducting the clinical trial at the site), which will enable efficient operation public hospitals and private research institutions.**

Liability for damages in clinical trials

Barrier:

Civil liability principles are not adapted to the clinical trial process

Provisions of Article 37c in conjunction with Article 37j of the Pharmaceutical Law define the principles and the scope of sponsor's and investigator's liability for damages caused by a clinical trial. Despite the fact that the execution of a clinical trial involves many entities: sponsor, sponsors' clinical research organizations (CROs), investigator, site, members of the research team, who are interlinked through various legal relationships, Polish legislation defines the liability principles for only two of these participants - investigator and sponsor. Determining the principles of liability for damages caused in connection with clinical trials is in fact beyond the regulation of the Act, and therefore the provisions of the civil law apply, subject to Article 37j of the Pharmaceutical Law. The basis for liability for damages in this regard is the fault of the perpetrator in accordance with the general principle provided for in Article 415 of the Civil Code. This regulation is highly imperfect both in terms of proper protection of the interests of research participants and the quality of the legal wording used. According to these principles, it is very difficult for a participant injured in a clinical trial to prove that the sponsor or the investigator is at fault, which can have a negative impact on patients' decisions to participate in clinical trials. The draft Act on Clinical Trials provides for the liability of the investigator and the sponsor on general principles, i.e., the investigator and the sponsor are liable for culpable damage to clinical research participants. Such shaping of liability for damages means that it will continue to be difficult for participants to seek compensation before the general court of law, as it will require proof of the amount of damage, the perpetrator's fault and the causal link, which is complicated in the case of medical injury. However, the draft Act provides for the possibility of obtaining a limited benefit from the Fund for Protection of Clinical Research Participants in a simplified procedure before a committee of experts, once it has been demonstrated that the injury resulted from participation in a clinical trial.

Postulate:

- Making it easier for participants to pursue claims for injury suffered in clinical trials.

Clinical research insurance system

Barrier:

Lack of effective insurance of clinical research participants

The change in liability principles should be combined with the introduction of different categories of insurance adapted to the roles of the entities involved in conducting and participating in clinical trials, the nature of a trial and the scale of risk incurred. According to the current Regulation of the Minister of Finance[9] issued under Article 37b of the Pharmaceutical Law, insurance covers the liability of the sponsor and the investigator, whereas the research participant is not insured. Mandatory insurance covers investigator's and sponsor's civil liability for causing any bodily injury to, health disorder or death of a clinical research participant resulting from an act or omission of the insured (sponsor or investigator) or persons for whom the insured accepts liability during the period of coverage, as caused in connection with the conduct of a clinical trial. The current legal regulation on clinical trials insurance is widely criticized. In particular, it is pointed out that from the perspective of effective protection of clinical research participants, doubts arise with respect to insurance coverage of liability of the sponsor and the investigator based on the principle of fault. Participants are not the subjects of this insurance (i.e., the insured), and triggering the insurance generally requires that the research participant demonstrate that the injury is related to participation in the trial and that the sponsor or investigator is at fault. In the event of an apparent injury suffered by a research participant but not attributable to the investigator or sponsor, there may be no settlement of claims by the insurer despite the premiums paid by the sponsors of the trials. The draft Act on Clinical Trials provides for the possibility for a participant to obtain a benefit from the Fund for Protection of Clinical Research Participants in the event of an injury as a result of participation in a clinical trial. The benefit is to be paid based on the decision of the adjudicating committee at ABM. The maximum amount of benefit on account of participation in a clinical trial per participant is to be PLN 100,000 in the event of bodily injury or health disorder and PLN 300,000 in the event of death of the participant. According to the Act, the participant, irrespective of the benefit received from the Fund, will be able to claim compensation from the sponsor and the investigator on general principles, which liability for which will be covered by mandatory civil liability insurance.

Postulate:

- New insurance solutions in clinical trials,
- Introducing mandatory insurance in favor of participants allowing them to obtain compensation easily and quickly,
- Different and detailed definition of the insurance coverage and the sum assured depending on the nature of the trial and the scale of risk to participants, with particular emphasis on low-intervention trials.

[9] Regulation of the Minister of Finance on the Mandatory Third Party Liability Insurance of the Investigator and the Sponsor https://sip.legalis.pl/document-view.seam?documentId=mfrxilrvgayteojtheyc45tfoixdcmrzgu4a

2.4 Trends in the area of clinical research in Poland in recent years and the planned legislative changes

When discussing the state of the clinical research market in Poland in the administrative and legal areas, it is necessary to point out important factors affecting the practice of conducting clinical trials. The ABM efforts indicated below, the formation of a network of private research sites and the Clinical Research Support Centers in public hospitals will have a significant impact on the practice clinical trials in the coming years.

ABM activities – supporting non-commercial research activities, public awareness, building a network of clinical sites

ABM has funding from, among others, the state budget and grants from European funds, which allows for effective efforts to support non-commercial clinical research. It should be noted that ABM has been very active since the beginning of its operation in supporting non-commercial research. In particular, important projects that have been successfully completed are: creation of a network of Clinical Research Support Centers and support for projects using CAR-T technology (recombinant antibodies) as a therapy administered to clinical research participants, as well as creation of the website https://pacjentwbadaniach.abm.gov.pl which is a source of information on clinical trials in Poland.

ABM has been active in the establishment and development of the Clinical Research Support Centers (CCWBK). Under the first competition for the creation of CWBK, PLN 100 million was allocated to 10 selected entities. The emergence of the CWBK network is an opportunity for public entities to develop a uniform standard for clinical trials' execution and patient service. Implementation of the program may lead to centralization for public entities within the CWBK network for contract review and negotiations, standardization of medical procedure pricing, legal and accounting services, or design and implementation of non-commercial research. Plans for 2021 call for the network to be expanded by at least 5 more centers.

As part of ABM activities, a new website https://pacjentwbadaniach.abm.gov.pl/ was launched in February 2020. Thanks to this project, up-to-date knowledge about clinical trials was provided to Polish patients in a single service. The service provides content on clinical trials in an easy-to-understand manner, as well as a knowledge base on standards, procedures, and requirements for the process of entering into and participating clinical trials. In the future, establishment of a clinical trial search engine is planned to provide patients with information on specific clinical research sites recruiting patients for a particular disease entity.

According to the draft Act on Clinical Trials, the role of ABM will increase, as the Supreme Ethics Committee and the Fund for Protection of Research Participants are planned to be established at ABM. ABM's efforts to date are positively assessed in terms of developing the non-commercial research market, building positive public perception towards clinical trials and implementing beneficial organizational changes. In the coming years, ABM will have the opportunity to become a public entity that will initiate and support significant efforts in terms of increasing the number of clinical trials, increasing the number of patients and speeding up administrative procedures in completion of clinical trials.

Support for the establishment of (private and public) clinical research centers

Experience to date indicates that public entities conducting clinical trials present widely varying levels of preparation for cooperation with sponsors. The structure of the entities involved in the conduct of clinical trials varies. On the one hand, hospitals that have professionally organized clinical research centers are attractive for conducting research and they attract many research projects, for the benefit of their patients. However, on the other hand, there are public healthcare institutions where clinical trials are treated as a minor activity being of interest primarily to the investigators. Creating a broad network of clinical research centers would allow for making use of the potential for patient recruitment for clinical trials at public institutions. And implementing uniform legal and accounting procedures should make it much easier for sponsors to locate trials at these research sites. ABM's ongoing project to build a network of Clinical Research Support Centers partially addresses the demand described above, but is, for the time being, limited to the largest public hospitals. Supporting the establishment of clinical research centers at most of public healthcare institutions conducting clinical trials would allow for significantly removing the organizational barriers to conducting trials. Recent years have seen rapid growth of networks of private clinical research sites, some of which are even forming international networks of research sites. Private research sites are successfully implementing uniform quality procedures and standardization of legal and accounting services, electronic document flow, which results in good cooperation with sponsors. The barrier to the growth of private research sites is access to patients who mostly use public healthcare services. A solution worth considering is the cooperation of private networks of research sites under public-private partnership for the establishment of clinical research centers at public healthcare institutions. Such a solution would enable the combination of standardization and quality in clinical trials offered by private sites with the potential for patient recruitment that is still available at public healthcare institutions.

Creating hubs for clinical research and developing a network of clinical research sites

In recent years, several regional or global clinical research centers (hubs) have been located in Poland which administer and manage global clinical trials, deal with bioinformatics and support investigators by creating unique applications which allow, among other things, analysis of the data acquired in clinical trials or which support research on new substances. These centers create a knowledge-based economy and the results of the work conducted can also be used in other areas of the economy: biotechnology, information technology, etc. Innovative activities of clinical research centers and their cooperation with research sites contribute to building new competencies in the Polish medical community not only in the field of pharmacotherapy, but also diagnostics, knowledge exchange within the network of specialists and investigators or access to training resources.

Proposed legislative changes

Fearing that the competitiveness of the EU as a location for clinical trials would diminish, the European legislator decided to introduce a legal act that comprehensively and uniformly regulates the area of clinical research in all EU Member States, i.e., Regulation (EU) No. 536/2014.

Regulation (EU) No. 536/2014 - key assumptions

Regulation (EU) No. 536/2014 applies to all clinical trials conducted in the European Union which fulfil the new definition of a clinical trial set out in this legal act, whereas it does not apply to non-interventional research.

Formally, Regulation (EU) No. 536/2014 came into force 20 days after its publication in the Official Journal of the European Union, i.e., on 16 June 2014. It will not be applied in practice until 6 months after the date of publication by the European Commission of the notice on full functionality of the EU portal and the EU database on clinical research. The European Commission issued a decision on 13 July 2021 making the EU portal and EU database fully functional, which means that Regulation (EU) No. 536/2014 will become applicable from 31 January 2022. On the date of Regulation (EU) No. 536/2014 coming into application, Directive 2001/20/EC will be repealed.

The experience with the application of Directive 2001/20/EC has clearly shown that the process of transposition of Union law into national legal orders has resulted in discrepancies in the regulation on clinical trials. This problem was particularly noticeable in the discrepancies between Member States concerning, among other things, the process of obtaining clinical trial authorizations, safety data reporting, or investigational medicinal product labelling. Throughout the course of implementation of Directive 2001/20/EC, some countries abused the membership powers granted to them by introducing additional procedural requirements not applied by other Member States or Union institutions. Taking the above into account, the European Union decided to change the form of the legal act and replaced the existing Directive 2001/20/EC with Regulation (EU) No. 536/2014. A regulation shall have general application and shall be binding in its entirety and directly applicable in all Member States [Article 288 of the Treaty on the Functioning of the European Union]. Furthermore, the Regulation is binding in its entirety, so it cannot be applied in an incomplete, selective or partial manner.

New definitions

"Biomedical trial" and "clinical trial" • in Regulation (EU) 536/2014, the existing definition of a clinical trial provided in Directive 2001/20/EC was made more specific. To this end, the term clinical trial was defined by introducing a broader term, that is a "biomedical trial" of which a clinical trial is a category. This approach takes into account international guidelines and is in line with Union law governing medicinal products based on the distinction between "clinical trial" and "non-interventional trial", to which Regulation (EU) 536/2014 will not apply.

"Low-intervention clinical trial" • given that many clinical trials involve only a minimal additional risk to participant safety as compared to standard clinical practice, which is particularly the case where the investigational medicinal product is covered by a marketing authorization, a definition of a low-intervention trial was introduced in Regulation (EU) 536/2014. Low-intervention clinical trials, often non-commercial in nature, are often essential for the evaluation of standard treatments and diagnostics, thus enabling the optimal use of medicinal products and working towards a high level of public health. Therefore, clinical trials that fall into this category are subject to less stringent regulations, particularly with respect to monitoring, requirements for the content of the essential documents, or the process of obtaining informed consent. However, to ensure participant safety, they are subject to the same application process as any other clinical trial.

"Investigational medicinal product" and "auxiliary medicinal product" • new definitions adopted in Regulation (EU) No. 536/2014 were built on the existing understanding of an investigational medicinal product, with the proviso that the legislator explicitly indicated the possibility of using authorized products (so-called reference products) in a clinical trial. The experience with the application of Directive 2001/83/EC and the possibility to refer only to the Commission's recommendations [The rules governing medicinal products in the European Union Volume 10 – guidance documents applying to clinical trials guidance on international medical products and "non investigational medicinal products"] proved the necessity of introducing a definition of medicinal products so far qualified as so-called non-investigational medicinal products into the current legal act. Such products have become known as auxiliary medicinal products and, as used in clinical trials, they are subject to the relevant manufacturing and labelling rules set out in Regulation (EU) 536/2014.

New central procedure for obtaining clinical trial authorization

According to the analyses performed by the European Commission, after the entry into force of Directive 2001/83/EC, the time required to initiate a clinical trial increased by 90% (to 152 days on average), which significantly increased the cost of conducting trials in the Union and reduced the number of newly registered trials in the region. Therefore, in order to simplify the procedures while at the same time exploiting the recruitment potential and including as many Member States as possible, the European legislator decided to replace the multiple submissions of largely identical information in each Member State participating in the same clinical trial with a single marketing authorization application dossier submitted through the EU portal. The process of obtaining a single clinical trial authorization in all Member States can be divided into the following stages:

Submission of the application

In order to obtain authorization, the sponsor submits, through the portal referred to in Article 80 of Regulation (EU) No. 536/2014, the application dossier to the countries that are expected to be Member States. Sponsor proposes one of the relevant Member States concerned to act as rapporteur (also called "Reference Member State"). The content of the application dossier has been harmonized to ensure that all Member States have access to the same information and to simplify the application process.

Two-stage application assessment – validation and substantive assessment

The new central procedure for obtaining a clinical trial authorization in multiple Member States did not deprive those Member States which are not a reference Member State of the influence over the outcome of the procedure. After completion of the validation stage, the substantive assessment of the application is carried out in two independent and parallel stages: by the reference Member State and by each of the other Member States where the clinical trial in question is planned to be conducted. In the event of a public health emergency, Member States must be able to quickly assess and approve the application for clinical trial authorization. Thus, no minimum but only maximum deadlines have been established for issuing authorization.

Clinical trial authorization

The conclusion on the acceptability or unacceptability of a clinical trial issued by the rapporteur Member State shall be regarded as the conclusion of the Member State concerned. The procedure for central authorization of a clinical trial is therefore completed by a single administrative decision covering all Member States concerned.

The so-called "exit clause"

A Member State may disagree with the conclusion of the rapporteur Member State with regard to Part I of the assessment report (the so-called "exit clause") only on enumerated grounds, i.e., that the treatment received by the participant in the clinical trial is inferior to that which is standard clinical practice, that there is a breach of the national law, or that there are observations relating to participant safety and data robustness and reliability.

Implied consent

The time for the assessment of the application dossier for a clinical trial authorization should be sufficient to allow for the assessment of the documents while ensuring quick access to new innovative treatments and ensuring that the Union continues to be an attractive place to conduct clinical trials.

Refusal of authorization by the Member State concerned

The Member State concerned refuses to issue clinical trial authorization if it does not agree with the conclusion of the rapporteur Member State with regard to Part I of the assessment report on any of the grounds which entitle it to apply the 'exit clause', or if, on duly substantiated grounds, it finds a lack of compliance with the aspects covered by Part II of the assessment report, or where the ethics committee has issued a negative opinion which, according to the law of the Member State concerned, is valid throughout its territory.

Withdrawal and resubmission of an application

The sponsor has the option to withdraw an application for clinical trial authorization at any time and at any stage of the procedure. The only limitation on the sponsor's discretion in this regard is the right of withdrawal with respect to the entire clinical trial rather than selected Member States. After withdrawal of a prior application or obtaining a denial of authorization, the sponsor has the option to submit a new application for authorization of a clinical trial.

Adding a Member State concerned

Depending on the progress of clinical trial recruitment, in practice, sponsors may wish to extend the clinical trial to an additional Member State after the initial clinical trial authorization has been obtained. For this reason, Regulation (EU) No. 536/2014 introduced an authorization mechanism to allow for this extension while avoiding a re- assessment of the application by all the Member States concerned which were involved in issuing the initial clinical trial authorization.

Substantial amendment in clinical trials

In the concept applied by the European legislator, all that is needed is the probable and not the actual and direct impact of the amendment on the participant's rights or the reliability and robustness of the study data. Regulation (EU) No. 536/2014 indicates only

by way of example that a substantial amendment is an addition of a clinical research site or a change of the principal investigator. A substantial amendment can be introduced only after it has been approved in accordance with a procedure that mimics the procedure for the initial application for authorization of a clinical trial, however, shorter timelines for completing the various stages are set therein.

Solutions that are innovative or which change the current legal situation resulting from Regulation (EU) No. 536/2014

Informed consent

Regulation (EU) No. 536/2014 provides for both written form and for a form expressed and recorded via alternative means (e.g., audio, video recorder) in case the participant is unable to write. Bearing in mind that in some Member States the only person authorized under the national law to conduct an initial interview with a potential participant is a medical doctor, Regulation (EU) No. 536/2014 has given appropriate authority in this respect also to other members of the research team.

Simplified informed consent

In group randomized trials conducted within a single Member State, simplified consent has been allowed after the subject is provided with the required information and does not object to participating in the clinical trial. A simplified consent may be used in particular for Phase 4 clinical trials in which the investigational medicinal products are used in accordance with the marketing authorization and the individual participants receive standard treatment regardless of whether or not they agree to participate in the clinical trial.

Informed consent in emergency situations

Regulation (EU) No. 536/2014 also set clear rules for informed consent in emergency situations, which was necessary especially in trials involving unconscious patients, for example, experiencing a heart attack or stroke. By way of exception, the informed consent is obtained and the information on the clinical trial is provided subsequent to performance of the medical intervention, provided that such a decision is made at the time of the first intervention concerning the participant.

Co-sponsorships

The European legislator rightly noted that in practice there may be loose, informal networks of investigators or research institutions which jointly conduct a clinical trial. These networks should have the opportunity to be co-sponsors of a clinical trial. In order to prevent the weakening of the role of the sponsor and to ensure the fulfilment of sponsor's obligations in a clinical trial, where a clinical trial has more than one sponsor, all sponsors shall be subject to the sponsor's obligations set out in Regulation (EU) No. 536/2014. However, co-sponsors may, by written agreement, divide the obligations among themselves. Where the agreement does not specify which sponsor has the obligation, the obligation shall be shared by all sponsors.

Sponsor's legal representative in the European Union

The institution of a legal representative in the European Union has been retained to ensure that enforcement action is taken swiftly by Member States and that court and administrative proceedings can be initiated. This entity shall be responsible for ensuring that the sponsor's obligations under Regulation (EU) No. 536/2014 are complied with and shall be the person to whom all communications to the sponsor shall be directed. Member States may decide not to appoint a legal representatives, provided that they ensure that the sponsor in their territory has appointed at least a contact person for a given clinical trial who shall be responsible for all communication with the sponsor.

Extended archiving period for essential clinical trial documents

Regulation (EU) No. 536/2014 introduced a new period for archiving essential clinical trial documents. The sponsor and the investigator are required to maintain appropriate archiving for at least 25 years after the completion of a clinical trial, unless other Union laws require archiving for a longer period. It is notable that there is no explicit indication of the cut-off date from which the indicated period should begin.

Urgent safety measures

In the case of occurrence of an unexpected event that may materially affect the benefit/risk ratio, the sponsor and the investigator shall take appropriate urgent safety measures to protect participants. The sponsor shall notify the Member States concerned, through the EU portal, of the incident and the measures taken so that they can take appropriate action, for example within the territory of a given state. This notification shall be made without undue delay, but no later than seven days after the date on which the measures were taken.

EU portal and EU database

The European Medicines Agency, in collaboration with the Member States and the European Commission, will set up and maintain a portal providing a single common platform in the European Union through which data and information on clinical trials will be provided in accordance with Regulation (EU) No. 536/2014. The data and information provided through the EU portal are stored in the EU database. The EU database will enable the cooperation of the competent authorities of the Member States concerned, to the extent necessary for the application of Regulation (EU) No. 536/2014 and searching for individual clinical trials. It will also facilitate communication between sponsors and the Member States concerned and allow reference to previously submitted applications for authorization of a clinical trial or a substantial amendment. It will also allow Union citizens to access clinical information on medicinal products. The EU database will be publicly accessible, in all official languages of the Union, respecting the laws on protection of personal data, commercially sensitive information and confidentiality of communications between Member States.

Matters left to be regulated by Member States

Regulation (EU) No. 536/2014 stipulates that certain issues concerning clinical trials are to be regulated by the Member States concerned. It is left to the Member States to regulate, among other things, the system for ethical review of an application, specifying the language requirements for the application dossier, determining a legally designated representative of incapacitated persons and minors, the system for compensation for damages, fees, sanctions, civil and criminal liability, and how clinical trials are financed. The attractiveness of individual Member States for conducting clinical trials will depend on how EU Member States regulate the above issues.

Assessment of the draft Act on Clinical Trials of Medicinal Products for Human Use in anticipation of the new Clinical Trials Law

The enactment of a new national Act on Clinical Trials is necessary to ensure the application of Regulation No. 536/2014 by supplementing the content of the Regulation to the extent left to the Member States.

A team appointed by the Minister of Health prepared a draft Act on Clinical Trials regulating the issues left by the Regulation (EU) No. 536/2014 to be determined by the Member States.

The draft Act on Clinical Trials of Medicinal Products for Human Use, submitted by the Ministry of Health for public consultation on 30 April 2021, indicates the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products as the competent authority to conduct proceedings in respect of, among other things, the issuance of a clinical trial authorization.

No financial incentives or gratuities will be allowed in a clinical trial, with the exception of compensation for costs incurred, although Regulation (EU) No. 536/2014 does not impose such far-reaching restrictions by allowing, to a certain extent, the use of incentives that do not have any undue influence of a financial nature to induce participation in a trial, as well as compensation for loss of earnings related to participation in a clinical trial. It will be allowed to offer gratuities to adult, healthy and sick participants in a Phase 1 clinical trial, a bioequivalence or bioavailability trial.

The rules for conducting non-commercial clinical trials have been redefined, prohibiting the possibility of using data obtained during a non-commercial trial in order to obtain a marketing authorization for a medicinal product or to amend any existing authorization, or for marketing purposes, with the exception of non-commercial research funded entirely from public funds.

The draft Act provides for changes limiting the application of certain provisions of the GDPR taking into account the specificities of the conduct of clinical trials.

The draft Act provides for the establishment of the Supreme Ethics Committee at ABM. At the same time, it is assumed that this authority will not review all applications and some applications will be reviewed by ethics committees which will go through the accreditation process. The draft Act does not currently provide for an appeal against a negative opinion of the ethics committee.

The draft Act assumes the civil liability of the investigator and the sponsor for damages caused to the participant resulting from the conduct of the investigator or the sponsor. A new feature is the system for clinical trial insurance based on the Fund for Protection of Clinical Research Participants and the civil liability insurance of the investigator and the sponsor. Although, according to the draft Act, sponsors will be burdened with additional costs of participation in the fund, the costs of conducting research are to be reduced, e.g., by lowering the minimum sum assured under civil liability insurance.

The draft Act assumes that to examine specific claims of patients, the President of ABM will, each time, appoint a committee consisting of, among others, medical experts and lawyers, that would rule on the legitimacy of payment of any benefit to the patient if the damage resulted from participation in the trial irrespective of the fault of the sponsor or investigator. The Fund would be funded primarily by premiums paid by sponsors of clinical trials. The draft Act calls for cases to be processed within a maximum of four months, which should speed up obtaining finances for claims and increase the sense of security for patients.

Another change that is important from the patients' perspective is providing the ABM with access to the central research registry maintained by the URPL. This will enable the launch of a publicly accessible clinical trials database, from which patients will be able to draw information about ongoing trials.

As of the date of preparation of this report, the draft Act lacks provisions concerning the program of compassionate use of a medicinal product after the end of a clinical trial, facilitation of electronic document flow in a clinical trial and access to EMR and medical records maintained in electronic form, definition of the age limit for autonomous consent of a minor for a clinical trial (parallel or dual consent) and the proposed specification of rules for granting consent for minors (e.g., in the case of lack of contact with one of the parents), and identification of the governmental authority responsible for supporting commercial clinical research. The Association of Innovative Pharmaceutical Companies INFARMA, the Polish Association for Employers of Contract Research Organizations POLCRO, and the Association for Good Clinical Practice in Poland GCPpl have submitted comments to the draft Act postulating the introduction of, among other things, the aforementioned legal solutions.

The draft Act on Clinical Trials seems to be aimed at eliminating the barriers to conducting clinical trials by, among other things, establishing a new system for ethical review of clinical trial applications, clarifying the rules for sponsor's financing of clinical trials, increasing the safety of participants by facilitating compensation through the Fund for Protection of Clinical Research Participants, and introducing a single fee for processing applications for authorization of clinical trials. However, we should defer the final assessment of the detailed solutions until the determination of the final content of the Act which will complement Regulation (EU) No. 536/2014.

It should also be noted that even the best formulated legislation may be misapplied by public authorities and the entities involved in clinical trials, which may create further administrative and legal barriers to their completion. For these reasons, it seems particularly justified to postulate the appointment of a public authority (following the example of NIHR in the UK) whose task would be to provide ongoing support for the conduct of commercial clinical trials in Poland in order to reduce the complexity of administrative procedures and support the ongoing elimination of emerging barriers to conducting clinical trials.

BEST PRACTICES FROM OTHER COUNTRIES

CHAPTER 3

Chapter 3. Examples and best practices from other countries to be considered for implementation in Poland

by Vladimir Misik

In this chapter we introduce examples of some of the best practices for increasing country attractiveness towards sponsors of industry CTs which have been implemented by countries around the world and which should form the playbook of measures which Poland may want to consider implementing to retain and/or grow its share of global industry clinical trials.

As mentioned in the chapter *Participation in development vs participation in consumption of pharmaceuticals*, unless a country ranks among the large and/or high growth pharmaceutical markets it has to look for other ways to make itself attractive for industry sponsors of clinical trials.

The menu of measures can be broadly categorized into non-financial measures (ease of doing business) and financial measures (e.g., R&D tax rebates). Not to be underestimated are also promotional and marketing activities raising a country's profile among sponsors of clinical trials.

3.1. Non-financial measures

Below are examples of processes which we believe Poland should evaluate for implementation, some perhaps under the umbrella of the recently created ABM.

Country-level support for sponsors of CTs and site networks

UK: Established in 2006, the National Institute for Health Research (NIHR) was created to enable research and development within the National Health System (NHS) in order "to improve the health and wealth of the nation through research". At its core were five strategic goals (34):

- Establish the UK's NHS as an internationally recognised centre of research excellence,
- Attract, develop and retain the best research professionals to conduct people-based research,
- Commission research focused on improving health and social care,
- Manage our knowledge resources,
- Act as sound custodians of public money for public good.

One of the key pillars of NIHR is the **Clinical Research Network (CRN)** developed in response to a decrease in the UK's world share of clinical trials patients. CRN's role is to provide practical support across the NHS, increase clinical research and involve more patients. It consists of eight national networks with 103 local branches. Four hundred organizations are members of these networks which results in thousands of clinical research sites (including primary care). Each year it funds 7,800 NHS staff and trains more than 14,000 people. Over 1,200 research staff and clinicians are involved in research design, governance and delivery and 2,500 open studies recruit patients each year. In the area of study planning, it provides advice on available support staff and facilities, ideas to clinicians, and intelligence on patient populations. It provides national-level support to industry sponsors of clinical trials by helping to identify suitable sites with eligible patients utilizing EHR data from the NHS system across the country. CRN reduces complexity of administrative procedures and study start-up for sponsors of multi-centric studies, manages the approval process and speeds up start-up times. In the area of delivery of studies, it funds facilities and people to carry out the research, recruits patients and provides training. The researcher costs are paid by the clinical trials sponsors, the support costs are paid by the CRN and excess treatment costs are paid by the National Health System. As a consequence, 96% of all NHS sites have active patient recruitment into clinical trials. In 2019, more than 870,000 patients were recruited by CRN. (35)

Denmark: The country is positioning itself strongly to sponsors of industry CTs through their Trial Nation program (36) founded in 2018 and designed to "make Denmark the most attractive country for companies and other stakeholders to conduct clinical trials – for the benefit of patients, research and the economy".

Trial Nation offers a single, national entry point for global companies, patient organisations and clinical researchers wishing to conduct clinical trials in Denmark.

Acting as a single point of contact they offer the following support to sponsors of CTs and CROs:

- Identification of relevant specialists and clinical researchers,
- An expedited feasibility process with a collated, national response from hospital sites within five days,
- Access to a legal network, offering legal advice and national contract negotiation,
- Access to established clinical specialty centers and national networks within oncology, haematology, dermatology, pediatrics, respiratory diseases, infectious diseases and dementia,
- A national approach to increasing performance in clinical trials,
- Access to established partnerships with hospitals, scientists and patient networks.

The organisation is funded by the Ministry of Industry, Business and Financial Affairs, the Ministry of Health, several Danish life science companies and the five Danish Regions.

Canada: In 2014, it launched the Canadian Clinical Trials Coordinating Centre (CCTCC) as a joint project between industry, government and healthcare institutions to improve the operational environment for clinical trials in Canada and to address challenges identified through the 2011 Canadian Clinical Trial Summit to make Canada a destination of choice for clinical trials (19). Its key focus areas are:

- Marketing and promotion of Canada's clinical trial brand,
- Maintain an informing, influencing, and advocating role with regulators, funders, and governments,
- Facilitate the collection and sharing of national data,
- Operational efficiencies,
- Patient engagement in the clinical trial process.

In combination with these national-level initiatives, each province has also taken steps to improve the overall attractiveness for clinical trials (12).

Ireland: Clinical Research Coordination Ireland (CRCI) supports a number of clinical research networks (i.e., groups of clinicians and scientists from across Ireland who have come together around a particular disease, or clinical interest). Under the CRCI umbrella, clinical research networks are available on a national level in the following areas: Cancer, Cardiovascular and Stroke, Critical Care, Dementia, Diabetes, GI Diseases, Hematology, Hepatitis, Neurodegeneration, Neurology, Pediatric, Perinatal, Respiratory, Rheumatology, TBC, Rare Kidney Diseases, Primary Care (37).

Australia: Australian Clinical Trials Alliance (ACTA) is the "national peak body"[10] for 37 clinical trial networks operating in Australia, coordinating centers and quality registries conducting investigator-initiated clinical trials. These networks are led by highly experienced clinicians and can facilitate access to both patients and 'trial-ready' infrastructure. ACTA operates under the vision 'better health through best evidence' for a self-improving Australian healthcare system (38).

Australia has numerous biobanks, including cancer and brain banks, many include biological specimens with matching blood and patient records, providing a resource for organisations seeking to discover and validate new biomarkers. Biobanks are becoming an increasingly important tool for medical research. They give pharmaceutical and biotechnology companies the opportunity to conduct in vitro, proof-of-concept type studies before they commit to large-scale clinical trials (25).

South Korea: Since the early 2000s, Korea has continuously sought to improve its regulatory environment for clinical trials and has invested heavily in clinical trial infrastructure and technology. A strategic investment through the Korea National Enterprise for Clinical Trials (KoNECT) program began in 2007, and grew to encompass a network of regional clinical trial centers to promote clinical trial capabilities and to provide professional resources. In early 2014, KoNECT became a permanent organization focused on the advancement of the country's clinical trial industry. This was followed by the establishment of the Korea Clinical Trials Global Initiative (KCGI) and the KoNECT Collaboration Center for global clinical trials (KCC). Through KCGI and KCC, KoNECT promotes higher operational efficiency in the country's clinical trials. These new initiatives in clinical research are undertaking multichannel approaches to pursue an international collaboration model between government, industry and academia for the development of new treatments and improved patient care. (39)

Malaysia: Clinical Research Malaysia (CRM) was stablished by the Malaysian Ministry of Health in 2012. The mission of CRM is to fulfill the long-term focus by the Malaysian Government to make Malaysia a significant global player in clinical research. CRM exists to advance global health solutions for a brighter, more hopeful future for the people by providing speedy and reliable end-to-end clinical research support for quality studies. As these studies unfold, CRM works together with its partners to facilitate clinical trials in Malaysia for sponsors of clinical trials, while at the same time creating high skilled job opportunities (40).

For further examples on how to increase attractiveness of a country by creation of therapeutic networks focused on specific unmet or critical patient needs and how EHR systems can be effectively used to not only find existing patients within these networks but also patients that have not yet been correctly diagnosed for e.g., rare disease, see the chapter by Douglas Drake on how EHR mining can improve precision and speed of study planning in the *Stakeholders perspectives* part of this Report.

Digitization of clinical trials and technology as enablers of CTs

COVID-19 has accelerated adoption of technology-based solutions in clinical trials including virtual decentralized CTs, direct-to-patient IP deliveries, remote patient visits via telemedicine, remote monitoring visits with remote EHR access, e-consent, and has likely forever changed healthcare, how patients interact with their doctors and how patients are engaged and recruited to clinical trials. This presents an opportunity for countries which are early adopters of technology. The current technology trends in clinical trials and how Poland may benefit from their adoption is detailed in two chapters in the *Stakeholders perspectives* part of this report, one focused on how EHR mining can improve precision and speed of study planning (chapter by Douglas Drake) and one focused on other aspects on the use of technology in clinical trials (chapter by Tomasz Dąbrowski).

[10] Australian term for a non-government organisation whose membership consist of smaller organizations united with a shared purpose

Fostering international collaboration

As demonstrated in the chapter *Medical research prominence*, Poland's industry clinical research prominence is not matched by its overall medical research prominence. The absence of Poland's medical researchers and institutions from international collaborative networks and consortia may present a challenge in attracting early-stage cutting edge clinical research in novel treatment modalities for patient populations with unmet medical needs (e.g., ALS). Below are just a few examples demonstrating that **Poland needs to step-up its international exposure to enable access to the latest therapeutic modalities for difficult-to-treat patients and/or unmet medical needs:**

- REQUITE (requite.eu) is an international project drawn from leading research institutions from around Europe (France, UK, Germany, Belgium, Netherlands, Italy, Spain) and the US (none from Poland or CEE). It is conducting a longitudinal study of 5,300 patients aiming to determine which patients are more likely to have side effects from radio therapy,
- International Agency for Research in Cancer (iacr.fr): collaborating countries France, UK, Germany, Portugal, Switzerland, Spain, Austria, Belgium, Slovenia, Latvia, Finland, Italy, Norway, Belarus, (no representation from Poland),
- TRICALS (https://www.tricals.org/pharma/) consortium of leading international ALS-experts, patient advocacy groups and ALS foundations, aimed to accelerate clinical drug development for ALS. While Italy, UK, France and Spain combined have almost 30 representatives in the consortium, Poland only has one.

Educational activities for patients

Active involvement of patients and patient advocacy groups as a core resource in development of new medicines, regulatory deliberations, and other patient engagement initiatives have become synonymous with good product development practice. The European Patients Academy on Therapeutic Innovation (EUPATI) provides training for patients and patient representatives on the process of medicines research and development (41). Trained patient experts are the core resource for patient involvement in medicines R&D, regulatory deliberations, and other patient engagement initiatives. EUPATI supports patient engagement through patient education and is offering a range of training courses to patients and patient representatives (42). EUPATI offers a catalogue of modules to educate patients and patient advocates at both introductory and expert-level training in medicines research and development (42). The EUPATI Fellows have acquired skills and knowledge to make significant contributions in the process of patient involvement in medicines research and development in Europe and are actively involved in high levels of the process. There is no training material available to Polish patients through the Polish EUPATI page (https://pl.patientsacademy.eu/o-nas/#future-plans) and thus requires significant input in order to be able to involve patient advocacy groups in promotion of clinical trials in Poland.

One of the successful initiatives developed in recent years in Poland aimed at building public awareness and promoting knowledge about clinical trials and the development of new therapies, is the "Patient in Clinical Trials" portal. (43) The www.pacjentwbadaniach.abm.gov.pl portal was created thanks to the cooperation of non- governmental organizations, the scientific sector, public administration and the biotechnology and pharmaceutical industries. The site is a reliable source of information on clinical trials and all related procedures. (43)

3.2. Financial incentives

Tax treatment and tax credits

Canada: In addition to the structural measures mentioned above, Canada has created a number of financial incentives to industry sponsors of clinical trials (19):

- R&D tax treatment is one of the most favourable in the world,
- SRED program: up to 15% tax credit on eligible R&D expenditures,
- Total tax credits range from 15% to 32% on eligible R&D expenses,
- Individual provinces have additional tax incentives of 4.5% to 20%.

France: France offers one of the most generous R&D tax incentives among OECD economies. The generosity of R&D tax incentives has increased significantly over 2000-2019 period. In 2008, the French system became volume-based with a tax credit rate of 30% for eligible R&D expenditures up to Euro 100 million. (44)Importantly, CRO companies in France are also eligible for these tax incentives.

Australia: The Australian Government's R&D Tax Incentive gives companies with an annual aggregated turnover of less than USD 2 million a 43.5% refundable tax credit, and companies with an annual aggregated turnover of more than USD 20 million a 38.5% non- refundable tax credit on eligible R&D expenditures. (25) Unlike similar programs in other countries, there is no requirement for companies in Australia to demonstrate year-on-year growth in their R&D expenditure in order to claim a tax benefit. There is also no requirement for intellectual property from eligible R&D projects to be held in Australia. This recognises the inherent value of the research and development process itself, regardless of the eventual 'location' of ownership of the resulting intellectual property. The R&D Tax Incentive is available for both domestic and foreign-owned companies to conduct R&D activities in Australia. To be eligible for the R&D Tax Incentive, a clinical trial must meet the definition of a 'core' R&D activity or a 'supporting' R&D activity under Australian law. An eligible claim must have at least one 'core' R&D activity, which must be an experimental activity that meets certain criteria. In general, while there are some exclusions to eligible core and supporting activities, activities conducted in early-stage development or clinical trials (Phase 1, 2 and 3) undertaken in Australia are likely to meet the criteria for eligibility. Phase 4 clinical trials are not eligible as core R&D activities if they are being carried out to meet regulatory requirements or are for other purposes. However, where trials are being carried out as experiments for the purpose of resolving further scientific unknowns, and eligibility requirements are met, Phase 4 clinical trials may be eligible. For example, testing the interaction of a developed drug with an existing commercial drug is an example of an activity that may be eligible. (25)

Government R&D funding

Canada: The government disburses approximately CAD 30 billion in R&D funding on an annual basis (19).

Germany: The German government has identified life sciences as a decisive economic factor in the 21st century. In line with this, a number of programs – financed through public resources at national and regional levels – have been made available to the pharmaceutical industry. The German government invests approximately EUR 4 billion in its "High-Tech Strategy" each year and provided EUR 1.2 billion for R&D projects within the health care and biotechnology industries in 2019 (45) (46).

STAKEHOLDERS PERSPECTIVES

CHAPTER 4

Chapter 4. Stakeholders perspectives

The Stakeholder perspectives section of the report complements the global benchmarking part of the report by providing insights about the CT market in Poland, written by clinical trial industry professionals with years of experience in international clinical trials and with intimate knowledge of the clinical trial market in Poland. It provides unique vantage points: industry start-up expert, site/SMO perspectives, including academic research, clinical research organizations, and experts in clinical research technology.

4.1. Start-up process: strengths, limitations and recommendations

Impact on perception of Polish clinical trial trends and requirements in the start-up phase of clinical research (Phase 2-4).

by Bartłomiej Jarosz

Given its complexity and time-sensitivity, the start-up phase of clinical research can easily be considered as one of the most rate-limiting factors of a trial, potentially limiting opportunities for countries with less-than-ideal start-up requirements, timelines and procedures (mostly resulting from legislation in force), but also for non-responsive sites or those with unusual document/contract requirements. At the same time, it can be a significant opportunity if an environment for fast and efficient start-up is created specifically at the local level. Countries with less demanding start-up procedures and requirements continue to be a more viable option for a sponsor/CRO who needs their sites up and running faster. Given an increase in research competitiveness, the number of new drugs constantly increasing and constant pressure to be more cost effective, opportunities such as these will be taken into greater consideration. Nevertheless, it is important to remember that quick start-up with its short turnaround cycles is not the single or most important factor in selecting a particular country or site. Other factors such as the attractiveness of a market from the future sales perspective, availability of a specific patient population (including a positive enrollment track record), or location of a particularly important key opinion leader(s) (KOL) will always be taken into serious consideration by a pharmaceutical company planning to put its trial on the map (see Spain where start-up process can take more time, mostly due to complex site contracting, but this does not discourage sponsors from placing most of their pipeline in the country). Since start-up is among these factors and its impact cannot be underestimated, it is essential to take a deeper look into its specifics, and position Poland as a market for clinical research through this perspective.

The first piece for review and at the same time the first element on start-up timeline is feasibility. According to a survey (47), more than 80% of 253 respondents agreed that they are much more likely to select a trial site if all the relevant investigator and site-specific information is made easily available to them. This indicates that uncertainty and opinion- based practices are still prevalent in the feasibility assessment process. The ongoing need for information sufficient to make informed decisions during feasibility evaluations is crucial in attracting sponsors of clinical trials to sites and countries. (20).

In terms of speed of return of feasibility questionnaires, Polish sites usually perform well[2]: Polish sites, whether public or private, very often turn around feasibility questionnaires much faster in comparison with others (setting aside CDA related matters, which can slow down the process at sites which require thorough CDA review). Reasons for this may be understood in different ways, but most of them are likely driven by competitiveness of the market itself and willingness to be the first for consideration. On top of that, provided that Polish research centers have been historically strong in terms of patient recruitment, with many of them maintaining excellent patient databases, Poland and its sites look very appealing at this early stage of the start-up process. The initial availability of equipment required by protocol at sites returning feasibility questionnaires will also influence the decision-making process at this stage. Over the last 5 years Polish research sites have made substantial investments in this space, trying to become more attractive for sponsors of CTs and CROs, and this trend needs to continue for the sites to maintain their research-ready image. Investments in more specialized professional equipment frequently required in iBPCTs (e.g., centrifuges or -80^{o}C freezers) will be yet another step towards making their mark and demonstrating research-readiness. Furthermore, although many sponsors offer equipment for the duration of the trial at no cost, sites with their own devices and machines which are allowed to be used for commercial clinical research purposes are likely to look more appealing in comparison to the sites without all required equipment.

Another important factor for clinical research sites to focus on during feasibility is to demonstrate the availability, education, and experience of their investigators. Per World Bank data in 2019, there were 90,440 physicians in Poland (or 149,222 according to GUS data), while there were 12,037 active research sites[11] in Poland. This would seem to suggest there is still a large untapped source of potential CT investigators. However, as explained by Magda Czarnecka in her *Execution of Clinical Trials in Poland* chapter, Poland may experience a saturation threshold in clinical research at lower levels than expected, predominantly driven by shortages in medical personnel.

A sign of the increasing awareness of clinical research and its benefits (whether professional or financial) is the growing number of doctors in Poland who include clinical trials in their portfolios. For many doctors, clinical research is an opportunity to achieve recognition outside of their own country, and they try to grow their international profile through active professional networking and maintaining positive relationships with foreign pharmaceutical companies and CROs, as well as writing publications or attending international conferences.

However, as shown in the chapter on Medical Research Prominence in this Report, Poland needs to do more to grow its international profile in terms of medical thought leadership and participation in international research and therapeutic networks as these are important factors to international sponsors of clinical trials for allocation of clinical trials.

Summarizing the first part and impact that Polish sites maintain during the selection process, it is important to mention that despite quick feasibility turnaround times, the availability of professional and internationally recognized investigators, access to patients and positive enrollment figures – each sponsor may have different selection criteria encompassing all or just some of these elements. Very often their selection criteria will vary by a therapeutic indication or by clinical trial phase. In order to increase their presence in international clinical research, management of research sites needs to be mindful of such diverse landscape and be able to tailor their approach depending on sponsor, study, phase, indication or other factors influencing study allocation. The ability to highlight strengths, investment in infrastructure as well as in research staff is just one key factor to success.

Logically, another stage to look at during start-up process evaluation would be the Ethics Committees' and Regulatory Authority's requirements and timelines. Given that Poland is an EU country and therefore has similar requirements to other states, country specific differences have a minor impact on start-up timelines (i.e., sponsor registration timelines or sworn translation requirements). For this reason, it is more reasonable to focus on certain factors which do make start-up in Poland more time and effort consuming, and to understand the reasons behind these rate limiting aspects, as well as focusing on recommendations to overcome them. The first element to review from a time and turnaround perspective is contracting of research sites. Unfortunately, Poland has a long history in this area and improvements are required if cycle times in site contracting (very often influencing the overall start-up cycle) are about to get shorter (see Chapter on start-up timelines in this Report). Before 2018, fully executed clinical trial agreements had to be submitted together with other documents to Regulatory Authorities. This was an obvious factor prolonging start-up in Poland as it stripped the process of a possibility for a parallel course of EC/RA submission-approval from one hand and contract negotiations from the other. Since implementation of this change by Polish regulators, this obstacle is no longer an issue. However, negotiations in Poland still struggle with a lack of knowledge regarding the nature of research and potential legal risks associated with it (especially visible at public hospitals outsourcing legal services to external law firms who see the issue solely from the civil law perspective), and very often from overloaded resources taking care of the matter (at sites, CROs, and often also on Sponsors' end). One particularly problematic legal issue is coming to the fore during the legal discussions, namely the position of many public hospitals (or rather of their lawyers) that institutions are not responsible for clinical trial conduct, but in-

[2] Based on author's 15+ year experience in managing clinical trials in Poland, subjective

[11] For the avoidance of doubt: these are not unique sites – a single site running 3 trials counts as 3 sites

vestigators are (to the fullest extent). This misunderstanding results from the conservative approach to ICH GCP where it states that 'Sponsor and investigator are responsible for clinical research conduct'. Since the institution (in fact employer of the investigator) is not mentioned in that chapter of ICH GCP, it is a common position among lawyers that institutions do not bear any responsibility. The same ICH GCP is understood very differently across all countries in Western Europe and many Eastern European ones too – in those countries the contracts are concluded with institutions, investigators very often not being a contracting party at all. This kind of mismatch is very often overlooked by sponsors and may cause negotiations to stall in certain situations.

Additionally, further unusual requirements presented by Polish sites can often complicate start-ups, such as pre-agreements requested for signature before formal negotiations start, detailed commercial registry excerpts requested from well-established international pharma companies (i.e., Hoffmann La-Roche, Eli Lilly or Pfizer), power of attorney documents requested from CROs to prove that contracting has been delegated properly by sponsors, insurance certificates and even policies requested prior to contract signature – all of this is just a sign that lawyers in Poland do not trust that the process is well maintained or controlled by organizations conducting clinical trials. Moreover, each site's unusual and unjustified request adds days, weeks and months to the process and causes divergence from the recruitment timeline or results in the elimination of a site from consideration. It would be therefore a step in a positive direction if sites (public or private) were to invest in their clinical research departments to hire dedicated contract managers, trained to manage these types of agreements instead of outsourcing this part to a research-naïve legal firms.

Last but not least – very often signature turnaround times at public sites may add significant time to the overall cycle, although it is worth emphasizing that considerable improvement has been observed in this area. A factor compounding this problem is the lack of validity of electronic signatures in contracts to make them legally binding, which is now a norm with the majority of North American and West European institutions and sponsors. This needs to change with Polish regulators specifically and in Poland generally to align with the rest of the developed world.

Yet another challenge causing misunderstanding are insurance matters, or rather lack thereof. This remains an area of concern affecting start-up timelines and adding unnecessary confusion in discussions between CROs/sponsors and research sites. ICH GCP section 5.8.1 states that "*Sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence*". That last part from the word "except" was not present in the earlier versions of ICH GCP, and very often sites claim that sponsors shall insure them against any and all damages resulting from clinical trial conduct, regardless of the nature of such damage. At the same time, research sites (including but not limited to public hospitals) deny securing any research-specific insurance themselves, which would cover that exact malpractice and/or negligence on their part. For many sponsors this is not a deal-breaker since they know that most advanced legal systems will protect them from damage caused by another party (although lack of financial coverage might pose a risk), but for smaller pharma companies, and especially small biotechs located in North America or Asia, this issue will not be easily resolved and may cause them to withdraw a trial from Poland once confronted with the issue. At the same time, the Polish insurance market has yet to recognize clinical research as a specific standalone industry and finally start offering products tailored to the industry needs.

The final element (and final stage) of the start-up process to be assessed, is the time spent between site readiness for initiation (IP pack approved) and actual initiation visit (including availability of the drug being tested). This is not specific to Poland, but improvements in this area could shave off what is often a noticeable period, making Polish cycle times more appealing in comparison to other countries (from a perspective that from an overall start-up timeline, Poland still must catch up with faster countries). Coordination of start-up activities is a challenging task, where all elements must be completed towards the same timepoint, making sites ready to start screening patients. However, despite many efforts, very often time between site readiness and actual initiation visit adds several weeks to the overall cycle time (which is often not measured at that point as many companies measure start-up up to IP pack approval date). This is because Site Initiation Visits (SIVs) are in majority instances performed only once: a) a CRA is available, b) an acceptable date could be agreed upon with the site, and c) the study drug is available at the site. Sponsors and CROs managing projects at Polish sites need to understand that coordination between start-up and clinical teams (where applicable) is critical to achieving success in this area, and to ensure sites can be activated immediately after such activation is possible, without losing time for SIV planning in a more reactive rather than proactive manner. Moreover, implementation of this specific fragmented metric (from IP pack approved to SIV) would enable Sponsors and CROs proper assessment of that last period which is often missing from the overall picture.

In conclusion, start-up timelines in Poland compared to other countries in Europe and across the world still present significant room for improvement (see chapter on start-up timelines in this Report). At the same time, fast and effective feasibility cycle times (including content), improvements made by Polish regulators in recent years (i.e. eliminating the requirement of having fully executed contracts submitted to Regulatory Authorities), as well as the dedication of Polish research sites to getting ready as soon as practically possible (at this moment this is not the case for the majority of public hospitals), make the start-up process less cumbersome for sponsors considering Poland for their clinical trials. Nevertheless, any improvements coming from the regulators, or the sites at which their current requirements make them difficult to work with, would surely help the country to avoid potential red flags signaling start-up inefficiencies.

Conclusions: The feasibility process in Poland usually works well and is frequently faster in comparison with other European counties. This should be used as a strong argument to promote Poland for selection in more feasibility reviews which could open the door to more trials. Any potential CDA-related delays in this space should be flagged upfront and taken into account for operational planning regarding turnaround times (CDAs are low risk contracts which are almost immediately replaced by confidentiality matters included in clinical trial agreements executed during the start-up process). On the other hand, a significant effort is still required to ensure that public sites, historically slow in contract negotiations, consider that a very conservative legal approach (very often applied unnecessarily) will hinder their access to many clinical trials and may discourage sponsors from utilizing their services, favoring more flexible private clinics instead.

4.2. Research Site Landscape in Poland

by Łukasz Bęczkowski

Patient population and healthcare system overview

Poland, with its population of 38.4 million is ranked as the 5th largest country in Europe and 36th worldwide. There is a well-established healthcare system in Poland which has both public and private components. Generally, healthcare services are provided as:

- stationary (24 hours a day)

e.g., at hospital and outside of hospital (oriented more to general care rather than treatment)

e.g., hospices or rehabilitation

- ambulatory

e.g., primary health care or ambulatory specialist care

Medical services can be provided by entities as regulated by law (Medical Services Act, dated 15th April 2011, as amended), the key ones are:

- Enterprise
- Independent public healthcare centers
- Public offices e.g., dependent on Defense Ministry, Home Office etc.
- Research Institutes
- Foundations or associations

Medical professionals can provide their services at organized entities (as above) as well as individual or group professional practices.

There are a total of 22 universities in Poland (including 9 dedicated medical universities) with medical faculties. According to official statistics 4,638 medical doctors graduated in Poland in 2020.[12]. In 2017 there were a reported 90,284 active medics[13], which is the 6th largest number across EU countries and the United Kingdom (Figure 27).

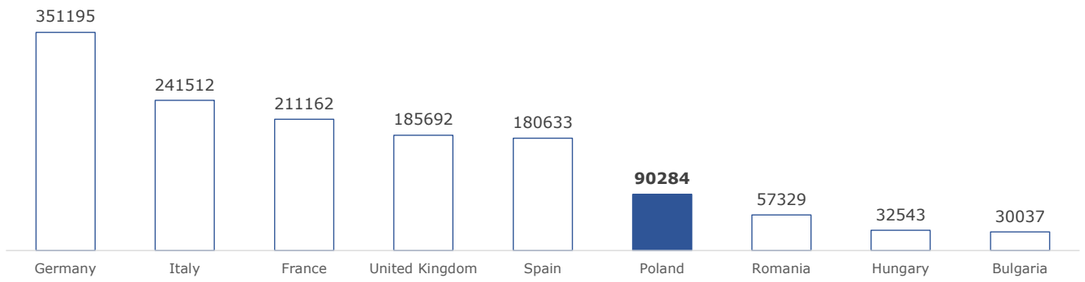


Figure 27. Active medical doctors in 2017. Selected European countries.
Source: OECD.org (https://stats.oecd.org/Index.aspx?DataSetCode=SHA), 2017 data

[12] https://stat.gov.pl/en/topics/education/education/higher-education-in-the-202021-academic-year-preliminary-data,10,7.html
[13] Eurostat – Health personnel (excluding nursing and care professionals) – https://ec.europa.eu/eurostat/databrowser/view/HLTH_RS_PRS1/default/table?lang=en

When comparing indicators of medics per 1,000 citizens[14] Poland with value 2.4 is ranked below the EU average of 3.7 (Figure 28).

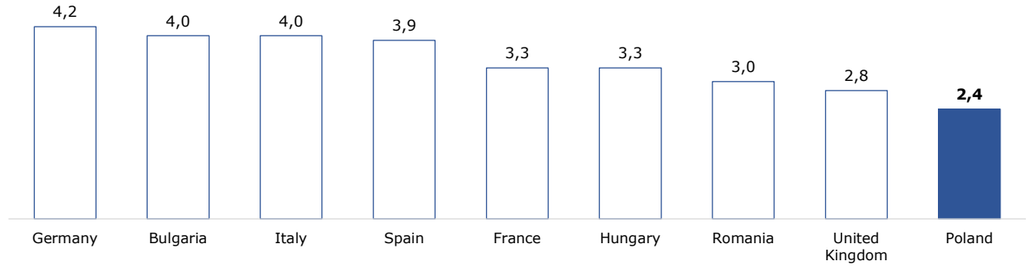


Figure 28. Physicians per 1,000 citizens in 2017. Selected European countries.
Source: https://ec.europa.eu/eurostat/databrowser/view/HLTH_RS_PRS1__custom_1528079/default/table?lang=en

Looking into healthcare financing expenditure as a percentage of gross domestic product, by country, Poland ranks behind the biggest European economies as well as several CEE countries (Figure 29).

Figure 29. Healthcare expenditure as GDP percentage in 2018. Selected European countries.
Source: https://ec.europa.eu/eurostat/databrowser/view/tps00207/default/table?lang=en 2018 data

This brief snapshot of the patient population and healthcare system confirms why Poland is considered one of the most important clinical trials markets in Europe. This is due to several driving factors outlined in this report, including:

- Availability of patients willing to participate in clinical trials and with the relevant disease profile
- Availability of qualified investigators willing and available to conduct the trials
- Willingness of patients to participate in trials due to trial facilitating access to higher standard of care or medications not otherwise available to them
- Poland offers one of the biggest patient populations in Europe and a significant number of well-educated investigators

At the same time, however, the existing healthcare system suffers from medical personnel understaffing and insufficient public healthcare financing in some areas. Both factors limit patients' access to medical care and new therapies, thus clinical trials provide an interesting alternative to many patients. All of the above contributes to the high ranking of Polish sites in terms of number of enrolled patients (see the site productivity metrics in the main part of this report).

[14] World Health Organization's Global Health Workforce Statistics – Medical doctors in 2017 (Bulgaria indicator dated 2014, the most recent available)

Research site models

For the purpose of this report, the research sites in Poland are classified into three general categories driven by facility type and study process organization. These are hospitals, ambulatory sites and dedicated research sites, or SMOs.

Hospitals

This category consists of university hospitals, general public and private hospitals, hospital-based institutes, and hospitals governed by particular governmental bodies e.g., Ministry of defense or Interior ministry. The biggest number of sites conducting clinical research in Poland belongs to this category. Hospitals are engaged in all phases of clinical research projects spanning from early phases to post marketing authorization projects. Typically, they offer very good access to both patient populations across multiple therapeutic areas and experienced investigators. Usually, the downside of this model has been a lack of study administrative support resources, longer than average clinical trial agreement negotiation timelines and the primary focus on statutory healthcare activities which continuously competes for resources. Historically, the pain point of clinical trial administration at hospitals was that in a vast majority of cases it remained with medical staff; however, in recent years, the development of clinical research support units has begun at hospitals. These units are expected to support hospital staff training, study registration and ethics submissions, contracting process, study documents maintenance and data entry. It is worth mentioning that hospitals and academic institutions in particular are the main habitat of non-commercial research. As shown in elsewhere in this report, the percentage of non-commercial studies registered in Poland remained at 2% in 2019, significantly below the benchmark of Western European countries. A proactive measure was taken in 2019, whereby the Medical Research Agency (ABM) was established by the government with the mission to support research in the field of medicine and health sciences as well as non-commercial research. One of the projects founded by the ABM was the creation of specialized Clinical Research Support Centers as a shared service ensuring complex and systemic support of both non-commercial and commercial studies. In the same year, the ABM began developing the Polish Clinical Research Infrastructure Network (POLCRIN) and joined the European Clinical Research Infrastructure Network (ECRIN) with observer status.

Ambulatory sites (non-dedicated)

This group includes ambulatory facilities (outpatient clinics) which are primarily focused on healthcare, with clinical research remaining an add-on activity for them. Organization-wise, these are ambulatory (multi)specialty clinics, less frequently primary care practices, individual or group physician practices. These types of sites can be characterized by good access to patient populations, however they are usually limited to practice specialty. As most of these sites are privately owned, site contracting processes are usually faster compared to large public hospitals due to a shorter approval pathway and quicker turnaround of documents. Typically, clinical research administration processes at these sites are supported by mid-level medical or administrative staff, however this is typically in addition to their primary healthcare duties and very often only part-time. Patient capacity and limited resources dedicated to research are often limiting factors of these research sites. The advantage of these sites is the patient-doctor relationship which usually exists before the study and continues post study participation.

Dedicated research sites/Site Management Organizations

This type of the research site organization model is the smallest in number, however rapidly growing in recent years. Into this category we allocated the standalone or network sites (ambulatory in most of the cases) where clinical research activities constitute not less than 50% of site activities. A typical dedicated research site demonstrates continuous engagement into clinical trial projects. The site may (or may not) provide regular healthcare services, however, in contrast to the previously described model, the proportion of healthcare proportion in overall activities is less than 50%. Dedicated sites which do not provide regular healthcare activities usually require proactive patient recruitment tactics or established cooperation with non-resident investigators to ensure achievement of expected enrollment targets. These sites usually offer dedicated administrative study support teams in the field of study start-up, project coordination, data entry, patient recruitment, and quality control.

Site management organizations in this category increasingly partner with hospitals in hybrid models, combining medical resources and diagnostic potential of the hospital with professional organization of study administrative processes by dedicated study teams brought by the SMO.

For many years there have been dedicated sites in Poland specializing predominantly in human (FIH) and bioequivalence and pharmacokinetic studies. Depending on the study type, these sites enroll either patients or healthy volunteers. Although these early phase sites in Poland exist primarily within a hospital setting due to their dedicated facilities and personnel, these early phase sites are classified as dedicated research sites/SMO.

Figure 30 below provides an overview of research site types in Poland with consideration of their focus, study type (commercial/non-commercial focus) and study phases.

		Hospitals	Ambulatory sites (non-dedicated)	Dedicted sites / Site Management Organisations
primary focus	healthcare	●●●	●●●	●○○
	clinical research	●○○	●○○	●●●
study type	commercial	●●●	●●●	●●●
	non-commerical	◐○○	○○○	○○○
study phase	Phase 1	◔○○	○○○	◐○○
	Phase 2	●○○	●○○	●○○
	Phase 3	●●○	●●●	●●●
	Phase 4	◐○○	◐○○	◐○○

Figure 30. Visualization of research site types in Poland with consideration of their focus, study type and study phases.

As the data in Table 8 show, the number of active sites in Poland between 2009 and 2020 has grown significantly, which reflects growing interest in Poland as a clinical trial destination as described in this report. As the data in Table 8 and Figure 31 show, while the hospital sites dominated during 2009-2012 (more than 50% of all active sites), both ambulatory and dedicated research sites were the fastest growing site types in recent years. This tendency, in the opinion of the author, reflects the shift of investigators' preferences towards conducting commercial research outside of the traditional hospital environment (whenever possible due to the nature of therapeutic indication and protocol design) due to several reasons including:

- Availability of experienced, dedicated study administrative support teams
- Organization of the study-related processes ensuring better PI oversight
- Faster contracting process enabling investigators more time for patient enrollment

Research sites market dynamics in the period of 2009-2020*

active sites in Poland	2009-2012	2013-2016	2017-2020
total number	7066	8742	10553
hospital	51%	42%	40%
ambulatory (non-dedicated)	23%	27%	31%
dedicated sites / SMO	2%	5%	7%
other	24%	27%	23%

Table 8. Representation of site types among active sites in Poland between 2009 and 2020. Number of active sites number were provided in line with methodology presented in Annex 1 to this report. Active sites number for a period means average sites number for all years in a particular period. Data by LongTaal (www.longtaal.com).

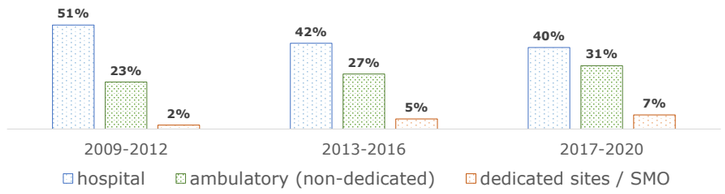


Figure 31. Contribution of site types among active sites in Poland between 2009 and 2020.
Number of and active sites were provided in line with methodology presented in Annex 1 to this report. Data by LongTaal (www.longtaal.com).

Nevertheless, as seen from Table 8 and Figure 31, hospitals retained the largest share among research sites. It is worth repeating the analysis of the research sites landscape in Poland in subsequent years to document evolving preferences of study sponsors as well as maturity of research sites.

Thanks to the substantial growth of the volume of clinical trials in Poland over the previous three decades, the number of experienced investigators, sites and clinical trial professionals has grown significantly. This human capital, reinforced by continued professionalization of research sites, and government-triggered initiatives (e.g., establishment of the ABM) will play an important role in further development of the clinical trial market in Poland.

An obvious deficiency, as also pointed out in the *Recommendations* section of this Report, is the fact that while the focus of the ABM is support of non-commercial clinical research, it is the industry sponsored studies which drive the market in Poland and also have the potential to deliver the greatest socio-economic value. In the opinion of the author, the efforts to continuously improve standards and processes of industry sponsored studies are of no less importance than the non-commercial studies initiatives.

This is particularly relevant in the hospital environment as this site model remains the primary choice for commercial studies by the industry.

It is worth considering how to effectively combine the research know-how of dedicated sites/SMOs with hospital site potential. Dedicated sites/SMOs are well known for strong process optimalization and are usually more advanced in the adoption of new digital technologies which are becoming a new standard for study delivery nowadays.

There is a robust experience of successful combination of both dedicated and hospital models across other European countries including but not limited to the United Kingdom, Bulgaria, Ukraine, and Spain. The modern clinical research site requires not only experienced investigators and availability of eligible patients, but also a professional research-dedicated study team. Research sites of the future will only be able to meet the increasingly metrics-driven sponsors demands through research professionalization of site staff resulting in improved sponsor site experience, from the early stages of site engagement and contracting and enhanced by adoption of new digital technologies (see technology chapters below, written by T. Dabrowski and D. Drake).

4.3. Challenges Ahead of Research Sites and Networks

by Wojciech Szczepanik

As shown in the *Clinical trials market in Poland* chapter, in the recent years, the number of clinical trials in Poland has increased, reaching a record number of 603 registered projects in 2019 (in 2020, this number decreased due to the COVID-19 pandemic, resulting from a short halt in the registration of new trials, particularly in the second quarter).

As also shown in the *Clinical trials market in Poland* chapter, the largest number of studies are Phase 3 studies (more than 50% of all projects), hence these require availability of many sites with a large pool of patients. **This creates a great opportunity for development of a potential network of research centers in Poland**, in which both inpatient as well as private outpatient clinics would participate. Hospitals, especially large academic units, form centralized in-house departments with clinical research management. These departments accumulate activities dedicated to research contracting, project coordination and even quality control. This enables investigators in hospital wards to be relieved of certain time-consuming research-related duties and to improve clinical research logistics. The growth of new clinical research sites in Poland came primarily from dedicated outpatient sites and SMOs, while very few new investigators were found at public hospitals where research conduct was not their focus area. The number of dedicated outpatient sites and SMOs in Poland has been growing visibly over the past decade. Some of these dedicated research sites are associated with international networks while many act as individual medical practices specialized in clinical trials. As many of these specialized sites have learned the hard way, opening of a new research-focused center and its management presents many challenges. Below we summarized some of the most frequently reported problems.

Research site team

The most important concept to start with is access to experienced medical specialists, willing and able to act as principal investigators. If they have already worked in this role previously, there is a high probability that they would be contacted again for a new trial by CROs/pharmaceutical companies with whom they worked previously, otherwise a potential investigator may never be approached for a new project.

The types of research projects have also changed significantly in recent years. Indications with an abundant patient pool such as hypertension, type 2 diabetes or osteoporosis, which dominated the 1990s and the first decade of this century and recruited well, and in which an intern could play the role of an investigator, have been replaced by indications which are difficult to recruit for. Nowadays, a lot of new research is focused on biological drugs in rheumatology, neurology, dermatology, and a fast-growing volume of research is in gastroenterology, especially Crohn's disease and ulcerative colitis. There is also a lot of research in Alzheimer's disease and other neurological diseases, as well as hematology and oncology. These indications require access to specialists in those medical fields, and often require two investigators with a given specialization due to the roles of a rater, unblinded assessor, etc. Very often the sites have to reject a new study during the feasibility process due to the lack of sufficient specialist capacity.

Unfortunately, however, the reason for rejection is often perception by the site physicians performing the feasibility of the lack of adequate general research capacity, much of which can be delegated to and performed by experienced and research-trained study coordinators or trial nurses. Dedicated study coordinators enable the investigator to focus on identification of suitable patients and treatment procedures, while delegating the bulk of the management of the other study-required administration, e.g., cooperation with the CRAs, entering data into eCRF, planning patients' appointments, communication with study vendors, etc.

Recommendation:
Summarizing the above, when opening a new research-focused site it is important to hire investigators experienced in clinical trials, with existing working relationships with CROs and pharmaceutical companies[15]. Of equal importance is also hiring or preparing study coordinators and trial nurses who will effectively manage the study from feasibility, through study start-up to the end of the study.

Research site base and equipment

It goes without saying that research sites must have adequate facilities in order to perform procedures such as physical examination, collection and processing of biological material, an investigational drug room, documentation storage, as well as working rooms for CRAs. Facilities for interventions such as biopsies or imaging (CT, MR, X-ray) are also extremely important. These types of procedures may of course be outsourced but this requires appropriate contracts and training on the part of the vendor which usually takes precious time from the overall tight start-up period. At a minimum, research sites should have basic equipment to store IMP and biological samples, such as refrigerators and freezers.

In order to be well equipped, research sites should also create a document archiving room (now increasingly outsourced to third party vendors), and a local laboratory, which will also allow monitoring the health of patients outside clinical trials, e.g., in pre-screening or between trials. Not to be forgotten is access to vendors for imaging, sophisticated medical procedures, IMP destruction, recycling of biological waste, as well as a pharmacy often required in psychiatry, neurology, or haemato-oncology studies.

Recommendation:
Clinical research facilities at sites need to be appropriately designed to accommodate rooms related to study procedures and for study documentation. However, in order not to have to invest too much in the beginning, many of these facilities and procedures can be outsourced to vendors to avoid incurring a significant initial fixed cost. The cost of these outsourced procedures can be fully covered from the study budgets. A word of caution: clinical research sites with multiple vendor agreements may be seen as a deterrent to sponsors/ CROs as they add to the complexity of site contracting and study payments.

Access to patients

When receiving a protocol feasibility questionnaire, a research site needs to have certain experience to complete this properly, highlighting its capabilities (keeping in mind the stiff competition among research sites currently on the market), as well as its ability to access and recruit patients with the required profiles.

This information is verified during qualification / pre-study visits. If the research sites do not have their own patient database, they need to provide contracted GPs or specialists able to bring patients from their external practices. Both solutions present many challenges. Building your own database requires knowledge of the principles of communication with patients in clinical trials and the related legal restrictions, while contracting GPs or specialists is not always possible for several reasons. Firstly, payments to them will be a significant cost to the site, secondly GPs are not always aware of the benefits for patients in clinical trials and hence may be reluctant to refer them and thirdly, many of them may already have contracts of this type with other research sites.

In recent years, Poland has observed a significant turn towards online patient recruitment, as well as through dedicated websites run by public agencies or private companies. Social media is also becoming an important source of research patients, but not all centers have been successful at utilizing these patient recruitment tools (success depends very much on the type of study). Currently, there are successful examples of recruitment for lifestyle research such as cellulite or smoking cessation, which were widely advertised on Facebook, but it is difficult to find information about patient recruitment for rare disease trials on social media. Nevertheless, the number of social media advertisements directed to potential clinical trial patients and submitted for approval by Ethics Committees is steadily increasing.

Recommendation:
The patient databases alone of even the best investigators may be insufficient for complex and specialized research. Recruitment success at sites will therefore depend on the ability of the site to mobilize potential new study patients. In addition, hiring a marketing specialist who understands the specifics of communicating with patients may be advisable. When doing so, sites should not forget about management of patient data in accordance with GDPR requirements.

[15] While hiring experienced investigators is the ideal strategy when opening a new research site in cannot be the growth strategy for the country: the pool of investigators in Poland needs to be continuously expanded by investment in training and awareness programs for new investigators and research sites.

Procedures and quality control

In Poland, the frequency of sponsor audits and regulatory inspections including EMA, US FDA and Polish regulatory inspections is increasing (see more on the topic in the Quality: Site inspection findings chapter). In addition, at professional research sites with sponsor Master Services Agreements across multiple studies, sponsors also perform routine system audits.

To make a mistake is human, but lessons should be learned from such cases and should not be repeated. A set of basic SOPs that will describe in an accessible and controlled form all aspects of clinical trial conduct, including IMP management, record keeping, safety reporting, ICF process, staff training, or handling of quality failures/CAPA creation, will allow research sites not only to improve the quality level at the center, but also to deal with uncertainties that arise during monitoring, audits, and inspections. In addition, it is vital that sites have a dedicated individual to verify whether research staff follow implemented procedures, and if and how they report errors. This is one of the key investments that the sponsors expect from research sites serving the industry today.

Recommendation:
An investment that will surely pay off is hiring an external quality specialist or a company that will help to write the site's SOPs, and hiring a dedicated person responsible for quality and compliance. At the beginning, the quality and compliance specialists could be hired on a part-time basis. There is a growing number of specialists on the market with this type of experience working as freelancers.

Changing the therapeutic landscape

Another critical success factor for professional CT sites is their **readiness to adapt to the changing therapeutic area needs of sponsors**. It is no secret that the work of one sponsor on a drug in a given indication often triggers work on a similar drug developed by their competitor(s).

This has changed the therapeutic demands of sponsors several times in the past, such as a wave of research with osteoporosis drugs in the first decade of this century which allowed many private sites with DEXA machines to establish their market presence. The wave of diabetes and cardiology research in the second decade of the 21st century resulted in the creation of many research sites focused on metabolic diseases. A recent increase in the amount of biosimilar research in rheumatology and dermatology has also changed the picture of this market, giving specialist practitioners an opportunity to develop a solid base for conducting clinical trials. More recently, the race has started to develop drugs against cancer, Alzheimer's, and Crohn's disease. Therefore, professional research sites must be aware that in a few years, specific research types may no longer exist or be minimized, hence their flexibility and quick adaptation to new industry trends is essential.

Oncology and hemato-oncology are currently very interesting areas for research sites and, given the magnitude of the therapeutic challenge, are here for the foreseeable future. In Poland in 2019, this accounted for almost 50% of all studies and 35% of all sites (please refer to the Poland's market share by Disease area and by Diseases and Conditions chapter of this report). As a result, the vast majority of research sites (including private sites) are getting ready to perform such studies, with the market leaders already having studied the area for some time.

Oncology is not an easy research area, and although sponsors are actively looking for new oncology sites, because the current base of public hospitals with oncology departments is quite saturated and is a limiting factor, the choice of private sites or private research networks is not always obvious. The biggest challenge is the access to appropriate patients and moreover, access to specialized equipment necessary for these studies.

Both are within the reach of large academic or public hospitals, but not of private sites. This barrier effectively prevents sponsors from qualifying such research sites in these studies. Another important obstacle is the lack of credible assurance of patient safety in oncology trials or access to registered therapy in the event of trial drug failure. These obstacles combined mean that neither sponsors nor ethic committees afford private sites a chance to enter this research area, which would effectively expand the pool of oncology research sites in Poland. However, there are some initial examples of successful private oncology sites built and operated in cooperation with KOLs in Poland.

Decentralized CTs

The ability of sites to successfully navigate the growing number of decentralized CTs presents another challenge. The COVID-19 pandemic has changed the face of the CT market to one where the very flexible sites will do the best job. Accelerated by the pandemic, the percentage of studies in the decentralized model in which clinical site staff visit patients at home is growing. When recruiting patients from remote regions, sites need to contract vendors such as "flying nurses" able to provide home-care to patients. Virtual trials often do not require physical patient site visits at all, while patients are monitored remotely by a number of wearable devices and applications. This creates challenges of a completely different nature for the sites, many related to the use of IT technologies and the remote support of patients.

Recommendation:
Professional CT sites can cope with dynamically changing therapeutic area trends by building and maintaining extensive networks of KOLs and specialists - maintaining regular contact with key study sponsors and CROs communicating with them proactively. Keeping up-to-date with literature and industry news, following R&D conferences and having access to dashboards of new studies (e.g., Citeline - https://pharmaintelligence.informa.com/products-and-services/data-and-analysis/citeline), GlobalData - www.globaldata.com/industries-we-cover/pharmaceutical/, or LongTaal – https://longtaal.com) is also of great importance, but an open mind and going-with-the-flow is essential.

In summary, starting a professional clinical trial site, regardless of whether a research medical entity already exists or a new one has been created, requires great investment of money, time and energy, including time needed to train the research staff and advertise the site to sponsors. However, it is an investment worth making, due to the continuing growth of CT sites in Poland (see the *Clinical trials market in Poland* chapter of the report), with concomitantly growing demand for professional research-focused sites. In the future, however, doing-it-alone will not be sufficient and consolidation of research sites into site networks is inevitable and desirable (see the *Recommendations* part of this report as well as the chapter on *Harnessing the power of Electronic Health Records* to increase speed and precision of Clinical Trials).

Conclusion: Steady growth of the number of active research sites in Poland (50% growth during 2009-2020), as well as a significant increase in the percentage of research-dedicated sites from 2% in 2009 to 7% in 2020 (see *Research Sites Landscape in Poland* chapter by Łukasz Bęczkowski) clearly indicate the significant increase in the share of dedicated sites in this market. Most of these research-dedicated sites managed to navigate challenges faced by them and were able to adapt to the dynamic changes in the industry's demands. Evidence of the growing business interest in the professional sites and research networks is in recent ownership changes at these sites as well as the presence of the largest global SMOs in Poland. This demonstrates that professional CT sites are a buoyant sector in Poland and given the growing industry's demands on their trial sites requiring professionalization, this segment of sites in Poland is likely to grow in the years to come.

4.4. Execution of Clinical Trials in Poland

by Magda Czarnecka

As demonstrated in this report (see the *Clinical trials market in Poland* chapter), Poland has a strong position in global industry clinical trials and is highly recognizable as the candidate country for study placement among sponsors of CTs and CROs.

However, Poland cannot rest on its laurels: outlined below are areas which in the opinion of this author, writing from the perspective of a seasoned clinical research professional, require national attention to maintain and grow Poland's profile on the global clinical trial scene.

Poland as a European Union (EU) member

Poland being a European Union member is subject to identical regulations and directives related to clinical trials placed by the European Commission which shape the unified clinical trial environment in the EU area. This environment makes the regulatory scene more transparent and stable for clinical trial conduct. We are on the verge of making this space even more harmonized as we are expecting the Clinical Trial Regulation no. 536/2014 to come into realization. Its full enforcement would bring simplification of clinical trial execution in Europe, as it is anticipated that many country-level procedures will retire and be replaced with centralized submissions. The new order will be more comparable to circumstances in the US. Current advantages of Poland being in the EU experienced by study sponsors include: comparable regulatory law, regulatory proceedings and timelines, no customs duties (a single import license for the EU area).

In addition, EU members continue to keep their healthcare systems under individual supervision and jurisdiction, thus substantial differences, or nuances in the standards of medical care as well as national laws governing CTs exist between the EU countries, complicating execution of the same clinical protocols. Subsequently, unless more alignment is introduced to minimize the differences, country-level protocol versions will remain the core remedy. With increasing interest to enable decentralized clinical trials, aspects of country-level medical practice need to adapt, e.g., the scope of responsibilities defined by law for the so-called "flying nurses" differs significantly between countries with Poland, unfortunately, granting them less medical independence and responsibility. Similarly, there are limitations to patient home-care, with pharmacists whose licenses do not include for, e.g., the right to perform injections. For these reasons, a significant portion of medical professionals (nurses, pharmacists) cannot be deployed optimally in the context of clinical trials and decentralized clinical trials, leaving much space for regulatory and operational improvements in this respect.

Recommendation:
here is that Poland make all effort to optimize its input into the implementation of EU legislation. More attention should be paid to the implementation of directives and inter-country analysis should possibly be carried out to drive the establishment of optimal legislation. Of importance is the review of currently binding legislation regarding non-physician medical professionals to review and consider the enhancements in their scope of responsibilities, in order to enable them to support clinical research (including decentralized clinical trials) and medical practice in general.

Poland as a country with straightforward organization of its healthcare system

Most of the Polish population is under compulsory health insurance (91%). "The 9% of the population not covered is mainly the result of casual or atypical work contracts."[16] The market of private healthcare insurance or private medical entities is growing, but it still functions more as a supplement to the national healthcare system (providing predominantly outpatient or ambulatory care) rather than an alternative or parallel systemic solution. The majority of specialized medical procedures and treatments (e.g., oncology) can only be accessed via the national healthcare system. Consequently, most patients are being concentrated around the centralized public medical system. Public hospitals and ambulatory sites (as mentioned in earlier chapters) are becoming increasingly aware of clinical research and are gradually creating clinical trial departments with administrative staff dedicated to contracting non-commercial and commercial projects. This change is further fueled in select public institutions by developmental grants from the ABM to establish professional clinical research centers predominantly specializing in non-commercial projects to drive the optimization of country level medical expertise and practice.

Recommendation
to manage this further is to:
1) introduce effective coordination between public and private medical institutions including medical records transfer
2) ensure that basic information on clinical research, its value for evidence-based medicine and fundamentals of management has been introduced into the curricula of all medical professionals and increases their exposure to clinical research already at university-level.

Poland as a country with highly educated healthcare professionals but low in numbers

The educational system for potential medical professionals is very demanding. Medical students attend medical schools for 6 years followed up by post-graduate obligatory 13-month internships. Subsequently, medical graduates can consider a medical specialization. It is estimated that an educational pathway to become a specialized physician takes between 15 to 20 years beginning with the commencement of medical school. High professional standards apply also to nurses, pharmacists, and dentists – all of whom need a university degree (which takes 5 years to obtain) to be allowed to practice. Most medical institutions in Poland have either been renovated or recently built, most equipped with certified EU-standard technology and the medical personnel is very well educated and qualified. The indirect confirmation of the high quality of medical services is provided by growing medical tourism in Poland, driven by patients from other European countries or USA, seeking medical care in Poland due to its attractive value for money.

For various reasons, however, Poland has the lowest numbers of physicians and nurses per capita in the European Union[17]. As described above, this self-imposes limitations on the volume of medical care to be provided to patients within both the healthcare system as well as clinical research. That is, Poland may experience a saturation threshold in clinical research at lower levels than expected, predominantly driven by shortages in medical personnel. Further to this, considering a high qualification of medical personnel and shortages in medical staff, this translates into higher investigator fees, driven by high demand and low supply. Therefore, site investigator grants for Polish sites are often comparable or falling short of selected Western European counterparts.

Recommendation:
To fully utilize Poland's capacity in clinical research, it is of great urgency to increase the number of medical practitioners in Poland. One recommendation would be to increase the number of medical professionals to be trained, to ease the procedures for foreigners to be licensed as medical professionals, or, perhaps most importantly, to increase the scope of responsibilities for non-physician medical professionals.

[16] https://www.euro.who.int/__data/assets/pdf_file/0006/355992/Health-Profile-Poland-Eng.pdf
[17] https://ec.europa.eu/health/sites/health/files/state/docs/2019_chp_poland_english.pdf
[18] https://ec.europa.eu/health/sites/health/files/state/docs/2019_chp_poland_english.pdf

Poland as a country with patient population interested in participation in clinical trials

As mentioned in another section, Poland has relatively low public expenditure on healthcare compared to other EU member states (**Figure 29**). A financial cap results in financial restrictions with regards to the volume of medical procedures and care to be provided to Polish patients. "In 2017, the share of the Polish population reporting unmet needs for medical examinations due to either costs, distance or waiting times was 3.3%, compared with the EU average of 1.8%. Waiting times explained most of these unmet needs across all income groups (70% compared to 40% in the EU where cost was the main reason for reported unmet medical needs)".[18] The second tangible item for the underperformance of the national healthcare system is significant out-of-pocket expenditure on pharmaceuticals. Access to expensive pharmaceuticals, if these are granted with the positive recommendation for reimbursement status, is made available through the so-called "drug programs" to which entry is guarded by patient eligibility criteria.

Considering all challenges listed above, which include shortages of medical specialists, long waiting times, considerable out-of-pocket expenses for medicines, and uncertainty of guided medical practice (covered in the section on central databases), a growing number of patients see clinical research as a remedy to some or all these problems.

Of note, as access to (expensive) innovative medicines (such as immuno-therapeutics) is delayed until the drug prices become affordable for the system and can be reimbursed, this disassociates the patient population into two strata – patients treated with innovative medicine (e.g., under the drug program) and treatment-naïve patients. Consequently, Poland has access to higher numbers of treatment-naïve patients in comparison with Western European countries.

Recommendation
in this area would be to introduce parallel measures to gradually improve the stressed healthcare system, e.g., by extension of medical personnel's responsibilities (in particular nurses and pharmacists) to reduce the burden on physicians, as well as to establish educational platforms for patients about the benefits of clinical research in general on access to ongoing clinical trials in relevant indications and which are available near them (more on that below) (benchmark: NIH and clinicaltrials.gov).

Poland as a country with growing digitalization but a low number of centralized medical databases

As outlined in the chapters on the use of technology and digitalization, Poland needs to master a revolution in eHealth solutions, which would be available not only to medical personnel and patients but also to sponsors of CTs.

Unfortunately, Poland still has not managed to launch even a low-tech solution: a publicly available platform capturing all clinical trials ongoing in Poland, to be available in Polish for both medical professionals as well as patients. No progress has been made in this regard despite the agreements made between ABM and URPL in 2019 to fix this issue. This leaves patients and their medical professionals roaming for information on matching clinical trials via media, social-media networks, or international databases. There is also much room for improvement to compile the disparate epidemiological registries into one conglomerate of national epidemiological data, cross-validated and supplemented with National Health Fund data on healthcare resources (treatment, medical procedures) utilization (benchmark: SEER in USA). For example, this would allow potential study sponsors to confirm the availability of target study populations as well as core medical procedures and based on that they would be able to make data-driven decisions about the placement of a trial in Poland.

Similarly, there is a growing need to cumulate and systematize the information on treatment algorithms, to counteract medical misinformation and to curate medical information available in the public domain for both patients and medical professionals. As exemplified by NCCN cancer guidelines, it can be also utilized to highlight the level of recommendation behind every therapeutic option and indicate the positioning of clinical trials in the treatment algorithm.

Recommendation:
Collection of dispersed databases (e.g., epidemiology) and creation of new information databases currently lacking (e.g., clinical trials database, rare disease registries), in order to establish a curated space for medical information, for use by patients and medical professionals alike, as well as for potential study sponsors assessing the suitability of Poland for a clinical research program, would help to increase attractiveness of Poland among sponsors of CTs and CROs. Please refer also to additional e-health technology solutions presented in the chapter on *Harnessing the power of Electronic Health Records*.

Availability of talent of clinical research professionals

Over the past 30 years many global pharmaceutical companies as well as all major CROs and many mid-sized and local CROs have set up and grown their clinical research organizations in Poland, which has helped to position Poland as a strong global player renowned for its operational excellence.

This success of clinical operations in Poland would not be possible without the continuous inflow of life sciences educated personnel. As Poland offers public higher education at no admission or tuition fees, the data from 2018 show that 44 percent of young adults in Poland have completed higher education.[19] This gives the clinical research environment a promise of access to the pool of well-educated personnel to support the execution of clinical trials in Poland. In addition, numerous organizations, private higher education schools recognize the significance of clinical trials and they offer post-graduate classes in clinical trials. At the same time, due to the market growth in Poland, the competition for experienced clinical research professionals has intensified and is driving the cost of labor force up and personnel retention down.

Recommendation:

One way of overcoming these problems is thinking longer-term and offering the prospect of a life-long career in clinical research to qualified individuals without pre-existing experience in clinical research by providing them with continuous professional training, starting from research site coordinator, to CRA, to clinical project manager or clinical research data scientist. Such pro-active training if done on a large scale would achieve the following:

- provide a large pool of trained study site coordinators who could be deployed across many clinical trial sites without professional and fully study-dedicated study personnel (currently only available at a minority of CT sites in Poland),
- with 3-5 years of experience as professional study coordinator, additional training as a CRA or data analyst would be provided, thus creating a pool of junior CRAs and data analysts with significant experience in clinical research which after successful completion of their role-specific training, could be ready for project deployment,
- after further 4-8 years of experience as CRAs further professional development for e.g., into clinical project management would be offered.

This could be coordinated nationally (e.g., by the ABM) and if done on a large scale would result in easing the existing labor cost pressures and qualified labor shortages among clinical research organizations (pharmaceutical companies, CROs and SMOs). The first pilot of its kind of this model is currently underway within the NEUCA group in collaboration with a professional training academy VIARES (www.theviares.com)

Summary:

- Poland is a member of European Union (EU). For this reason, Poland is subject to and follows identical regulatory proceedings and timelines set by the European Commission to other EU member states. Thus, the regulatory environment in Poland is structured and predictable.
- Poland has a clear organization of healthcare provision, and most of the Polish population is covered by national health insurance. As a result, the healthcare system in Poland is well-structured and centrally administered (National Health Fund, Ministry ofHealth).
- Polish medical personnel are highly educated and trained but due to systemic problems (exodus of doctors and nurses abroad), low in numbers in relation to population's needs and in comparison to average numbers in other EU member states.
- Increasing interest in clinical trial participation is observed in Poland driven predominantly by the following factors: medical specialist shortages, long waiting lists, out-of-pocket expenditure for medicines and uncertainty of guided medical practice.
- Centralized capture and provision of medical information to the public (including among others treatment guidelines, epidemiology data, ongoing clinical trials) is only partially functioning in Poland – mainly in oncology, while other therapeutic areas are not adequately represented.
- Clinical research is still booming in Poland as the country is being recognized for its operational excellence and a sizeable population (38+ million) and more companies are taking strategic decisions to open their local or regional offices and centralized operation centers there. Therefore, proactive measures need to be adopted to counter the competition for experienced clinical research professionals which is a driving the cost of labor up and personnel retention down.

[19] https://www.gov.pl/web/science/report-the-percentage-of-poles-with-higher-education-is-close-to-the-oecd-average

4.5. How Technology and Data Digitization are Bringing Revolutionary Changes to the World of Clinical Trials

by Tomasz Dąbrowski

The lessons-learned from COVID-19 pandemic offered an opportunity for the healthcare sector to accelerate digital transformation. Many experts believe that Poland has caught up on the development of broadly defined e-health services by as much as three to five years. With solutions such as e-Prescription (eRecepta), Online Patient Accounts (IKP) or remote appointments, Poland is now ahead of Western European countries such as Germany, where the adaptation process of remote health services during the pandemic is less efficient. The COVID-19 pandemic has significantly catalyzed the development of 'digital healthcare'. Market participants – patients and doctors alike – are becoming acquainted with the new solutions and technologies. Clinical trials have followed this trend and appear to have benefited from it.

Electronic health records in clinical trials

The basic legal act which stipulates the rules of using electronic health records in Poland is the Act of 28 April 2011 on the Healthcare Information System, which specifies that electronic health records are documents created in electronic form, bearing a qualified digital signature, a trusted signature, a personal signature or signed using the method of certification of data origin and integrity available in the ICT system provided free of charge by the Social Insurance Institution[20]:

- prescriptions,
- documents defined in provisions issued under Article 13a,
- referrals defined in provisions issued under Article 59a section 2 of the Act of 27 August 2004 on Publicly Funded Healthcare Services.

While the statutory requirement of healthcare providers to keep health records is still not fully compulsory (currently, there are exceptions which allow health records to be kept in paper form, such as organizational and technical limitations to keeping digital records), many components of the patient care process in Poland are already digitalized. On the date of this report, these included:

- prescriptions,
- referrals,
- descriptions of diagnostic tests other than laboratory tests,
- as of 25 April 2021, this will apply to laboratory tests as well.

Currently, more and more providers in Poland keep their health records in electronic form and it is only a matter of the next few months before we no longer see a traditional 'patient file' when we come to a doctor's appointment.

With the increasing digitization of healthcare providers within the clinical trial community, initiatives to design systems to maintain electronic health records in clinical trials are becoming more common. As the procedures involved in a medical experiment often differ significantly from a routine appointment, most electronic health record systems are not suitable for these types of projects. According to the current standard, a healthcare provider should have a single source of health records, and therefore there should be one system of electronic health records covering both clinical trials and the routine healthcare services of the provider. Therefore, either a very extensive end-to-end healthcare facility management system with functionalities adapted to conduct clinical trials, or two separate systems that use API (application programming interface) to exchange health records may be an appropriate solution. While the former seems to be the preferred alternative, building a 'do-it-all' system may require a lot of trade-offs at the expense of some medical activities. The challenge seems to be easier for dedicated clinical trial centers, where the conduct and management of clinical trial projects are a core business. In this situation, these centers may choose professional solutions for conducting medical experiments.

[20] a) Regulation of the Minister of Health of 8 May 2018 regarding electronic medical records
b) The Act of 28 April 2011 on the information system in healthcare

The functions performed by systems of electronic health records in clinical trials are a barrier to the implementation and deployment of solutions

Currently, there are few comprehensive solutions on the market that would include an EMR system to conduct clinical trials and simultaneously support the entire clinical project management process, including Remote Monitoring, eTMF, or CTMS. The biggest challenge is to create a system that can be implemented and used across many countries, while meeting the requirements of local regulations as regards health record keeping and conducting of clinical trials.

Key specific features of a complete solution, apart from the electronic health records module itself, include:

- Compliance with FDA 21 CFR Part 11
- Compliance with GDPR (GDPR in Poland, HIPAA in the US) in respect of processing sensitive data
- A system capability enabling the selective provision of blinded health records to third parties in track change mode for the purposes of remote or local source data monitoring
- Two-factor user authentication on the side of the study team (site) and the clinical trial monitor
- Capability to maintain records for mixed study teams (blinded and unblinded with predefined trial file viewing privileges)
- Capability to implement complex 'study flow charts' in system graphics along with a procedure settlement system
- Data conformity to HL7 standard

Despite the multitude of available solutions which include 'eSource', CTMS, eRegulators for clinical trial sites, if we take a closer look at each of them individually, we may conclude that at the moment, they are all lacking functionality and they are fragmentary, offering only one or some of the features that are necessary for the effective management of clinical trials at site level. Since most solutions originate from the US market, they do not comply with local, European, and Polish regulations governing the production and maintenance of electronic health records.

However, the market associated with the digital transformation of clinical trial centers is growing at a fast pace and it seems that the existing tools will be tweaked and new complete solutions for the industry will emerge within a year or so. The obligation which is soon to be imposed on Polish healthcare providers to maintain electronic health records will additionally force them to keep electronic health records in clinical trials, which will accelerate the digital transformation of the industry and the development of tools to support this process.

Currently, several IT companies in Poland are working on solutions for sites dedicated to clinical trials. The ongoing activities initiated by the Medical Research Agency to establish clinical trial support centers (which are aimed, inter alia, at digitization of research at site level) and the fact that Poland is home to Europe's largest independent clinical research networks, may turn Poland into a hub of innovation driving the digital transformation of the industry.

The HL7 protocol as a guarantee of health data integrity in Poland

The e-Health Centre (CSIOZ) of the Ministry of Health has been working on business and validation rules for various types of electronic health records. Their work has resulted in the release of the Polish National Implementation of HL7, which is the Polish implementation of the HL7 standard for electronic health records.

The HL7 standard (standard for electronic transfer of data in medical communities) is a guideline (framework) for the creation and exchange of health records, owing to which systems generating health data in conformity with the above standard ensure the integrity of data exchange between systems. Therefore, electronic health records in a clinical trial drawn up according to HL7 should considerably facilitate any future integrations with vendors and clinical trial co-organizers, such as central laboratories, data management, telemedicine, or with wearables[21].

For more practical insights on how de-identified EMR-based technology can be effectively deployed to accelerate clinical trials, please refer to the next chapter by Douglas Drake from Clinerion (*Harnessing the power of Electronic Health Records to increase speed and precision of Clinical Trials*), who have recently networked several hospitals in Poland into their global Patient Network Explorer site network with de-identified data available for data mining by study sponsors.

[21] Wearables: a category of electronic devices that can be worn as accessories, embedded in clothing, implanted in the user's body, or even tattooed on the skin. The devices are hands-free gadgets with practical uses, powered by microprocessors and enhanced with the ability to send and receive data via the Internet.
[22] CRF – case report form
[23] rSDV – remote source data verification
[24] Guidance on the management of Clinical Trials during the COVID19 (Coronavirus) pandemic, part 11
[25] Guidance on the management of Clinical Trials during the COVID19 (Coronavirus) pandemic, part 11
[26] Decentralized Clinical Trials – clinical trials conducted at the patient's home with the use of remote communication means

The future of Remote Monitoring

Remote digital source data analysis based on Risk Based Quality Monitoring (RBQM) has been used in large international clinical trials for years. Both clinical trial sponsors and CROs have moved away from 100% data verification to scalable solutions based on big data analytics. The introduction of RBQM was only possible due to the digitalization (via eCRF) of data entered by clinical trial centers. Since most clinical trial projects globally and in Poland are still paper-based, the only source of data with remote access is the information entered into the eCRF[22].

Today, traditional paper-based health records are the main and apparently only barrier to the introduction of fully-fledged remote monitoring of clinical trial health records (rSDV[23]). With the onset of the pandemic, which has significantly restricted or prevented on-site visits by clinical trial monitors, companies started to rush with new hybrid solutions enabling remote access to clinical trial records. Such solutions, which typically involve scanning health records, binding them, and uploading them to temporary cloud drives to make them available for monitoring, are inefficient and often insufficiently validated, which can lead to erroneous conclusions.

On 4 February 2021, the EMA updated its guidance applicable to European Union member states which sets out the requirements and options for remote monitoring of patient source data in a clinical trial. The update introduces additional obligations and indicates how such records should be prepared as well as what can be done remotely and when:

> "Remote source data verification (rSDV) can be justified in clinical trials. Remote SDV can be considered only during the COVID-19 pandemic related public health crisis and when in line with EU and national law (or temporary national emergency measures). Remote SDV may be considered for trials[24]:
>
> - involving COVID-19 treatment or prevention
> - investigating serious or life-threatening conditions
> - where the absence of SDV for critical data may likely pose unacceptable risks to participants' safety or the reliability/integrity of trial results
> - involving particularly vulnerable participants such as children or those temporarily (e.g., trials in emergency situations) or permanently (e.g., trials in patients with advanced dementia) incapable of giving their informed consent or in pivotal trials."

In addition, the regulator specifies that where the source documentation is pseudonymized and thus cannot be considered as original source documents, a re-monitoring visit should be conducted when it is possible to do so:
"Data subject to remote source data verification are likely to require re-monitoring, in particular if it was based on pseudonymized documents, which cannot be considered as source documents, and considering that remote monitoring is expected to only have focused on the most critical information."[25]
Despite the continuing restrictions imposed by the European regulator, which are mainly due to the lack of standardized electronic health records and effective solutions for remote SDV monitoring, it appears that once fully functional solutions are implemented, sponsors and CROs will be able to conduct remote monitoring visits to verify the source documents of the trial (SDV) also after the pandemic has ended. The emergence of reliable solutions on the market is both a precondition for and a restraint to the development of rSDV. Things are more or less the same from the perspective of the FDA, the US regulator, but the United States seem to be more open to a faster implementation of solutions involving so-called Decentralized Trials models[26] and Remote Monitoring. As in the case of the implementation of electronic health records and digitalization of clinical trial sites, Poland may become a beneficiary and a role model in the implementation of remote monitoring of clinical trial source documentation.

We can take advantage of this opportunity if:

a) ABM, as part of its activities aimed at the digitalization of major public clinical trial centers in Poland, will define the requirements for Remote Monitoring functionalities and eSource specifications for IT system vendors. This will enforce the implementation of appropriate standards for the digitalization of these entities,

b) The clinical research community and IT system vendors will contribute to education on remote monitoring and requirements which must be met by a system to provide remote monitoring of source documentation in the framework of international clinical projects,

c) Providers of electronic health (hospital) record systems, together with providers of clinical trial solutions, will open a dialogue to integrate their solutions which will result in providing better quality source data. The most desirable way would be to force this type of integration in the design phase of the solutions by law,

d) Sponsors will include the possibility of remote monitoring of source documentation in the study protocol prior to submission of the required trial file in Poland (and other countries). A project registered in this way can be monitored both in a traditional and remote manner (or a hybrid of both) without any additional annexes,

e) The solution will be approved by the regulator (URPL), which would necessitate some legislative changes.

Telemedicine as an originator of decentralized clinical trials and new business models

In both the US and Europe, telemedicine is beginning to expand into the realm of clinical trials. Between 2000 and 2020, the number of clinical trials increased from 181,238 to 325,817 in 2020.[27] Clinical projects are growing both in numbers and in complexity. It seems to be natural that digitalization of this area may result in many benefits for the R&D sector and, perhaps most importantly, for the subjects, or patients, themselves.

The year 2020 was marked by fast changes across the entire industry in the development of telemedicine platforms and various alliances for remote decentralized clinical trials[28], from leading CROs such as Labcorp, ICON/PRA, IQVIA, PPD, to financially robust technology companies such as Castor (the Netherlands), hyggio (Poland), Medable (US), Science37 (US), Thread (US) or VirTrials (US). Several international initiatives emerged aimed at harnessing telemedicine to conduct clinical trials at patients' homes (which means a fully virtual clinical trial) or, where impossible, to conduct 'hybrid' clinical trials, where the number of visits to the clinical trial site is minimized. Such solutions are not only more comfortable for patients, but also have a direct impact on the enrollment rates of the required study population, better data quality (as 100% of data in such projects is digital) and, consequently, faster market launch of the investigational product.

Sponsors, i.e., pharmaceutical and biotechnology companies, are also involved in the decentralization of clinical trials. Trials at Home, Europe's largest project involving the promotion of virtual clinical trials (www.trialsathome.com), brings together several medical universities (including Oxford University) and pharmaceutical companies such as Allergan, AstraZeneca, Medtronic, Merck, Novartis, Pfizer, and Sanofi.

The market of virtual clinical trials is estimated to have been worth USD 7.0 billion in 2019, with an expected annual growth rate (CAGR) of 5.1% between 2020 and 2027.[29] The unrelenting COVID-19 pandemic, global digital transformation of healthcare, increasingly accessible communication tools and wearables will undoubtedly accelerate the development of virtual clinical trials and change our current approach to collecting health data for R&D purposes. Decentralized clinical trials are also part of a global trend toward patient-centered care and greater patient involvement early in the development of the study protocol, which enable tailoring the solutions to patient needs.

Poland has been one of the few European countries that have implemented nationwide telemedicine solutions relatively quickly. Solutions such as e-prescription, e-referral, remote doctor appointments, remote case conferences, remote rehabilitation, digital descriptions of diagnostic and laboratory tests,[30] the HL7 data exchange protocol or the Polish patient portal patient.gov.pl (IKP) have made every doctor and citizen aware of available e-health solutions. While before the pandemic there might have been some opinions challenging the legitimacy of telemedicine and remote appointments, today we can definitely say that these solutions will stay with us permanently. It seems that in a community that is so well-prepared and informed, from the perspective of both patients and doctors (investigators), Poland may become a pilot country implementing the best practices in telemedicine and virtual clinical trials.

The transformation should be driven by:

a) the Medical Research Agency (which, as already stated, should define the requirements for platforms to digitize the existing network of clinical trial sites),

b) local representatives of CROs and Sponsors, who should promote Poland as a country that is prepared in terms of technology and, more importantly, legislation to launch pilot projects of virtual trials, including those with remote source data monitoring,

c) local clinical trial sites and operational independent research networks which already have the technology to conduct such projects.

[27] Source: clinicaltrials.gov
[28] Remote Decentralized Clinical Trials (RDCTs) – definition adopted from trialsathome.com: make use of new, digital innovations and enable participants to visit a clinical trial centre less frequently, if at all.
[29] Grand View Research – Virtual Clinical Trials Market Size, Share and Trends Analysis Report. According to another independent report - Polaris Market Research - the virtual CT market value in 2027 will reach USD 13.78 billion with a CAGR of 12.6% (2020 to 2027).
[30] Obligation to introduce electronic documentation of laboratory test results by the end of April 2021.

4.6. Harnessing the Power of Electronic Health Records to Increase Speed and Precision of Clinical Trials

by Douglas Drake

In the previous chapter on *How digital technologies have revolutionized world of clinical trials* Tomasz Dabrowski provided an excellent overview of the latest trends in applications of digital technologies in CTs, including opportunities for broader use of EMR-based technologies, an area still mostly untapped in Poland. Clinerion has started this journey in Poland by having networked several hospitals in Poland into our global site network with de-identified EHR-based data available for data mining by study sponsors.

In this chapter we will outline the opportunities for using real-world data (RWD) from anonymized Electronic Health Records (EHR[31]) together with modern cloud, interoperability, and analytics technologies to unlock major improvements in clinical research processes to save time, reduce costs, and make processes more efficient. Being able to query anonymized EHR across many hospitals at once allows sponsors of clinical trials to work on protocol design using real patient data and identify patient cohorts for the purpose of site selection. Within hospitals, trial staff may use high-level data analytics for patient stratification to identify and contact patients for screening and recruitment.

Specifically, we will make recommendations as to how Poland can create data networks between hospitals and regional affiliates that will better aid collaborative research, patient referrals, recruitment for clinical trials and better global visibility to Poland's expertise and capabilities. Also, we suggest that Poland can also use a digital network capability across the healthcare network to create disease expertise and referral centers for specialized care and diagnostics. This can also create international awareness of specialty care expertise in the country that will result in collaborative research, publications and clinical research and trial investment.

Effective use of EHR: broader use of digital data instead of traditional patient profiling

EHRs are the digital data records of patients and their diagnostic and treatment journeys. These systems have become common over the last 20 years and provide extensive longitudinal metrics as well as immediate updates on the patient as they are seen and their cases reviewed. The anonymized records can be indexed and made searchable from outside the hospital in a cloud-based architecture.

Systems that facilitate use of hospital EHR data remotely will allow study sponsors to examine and probe Polish hospital patient care metrics, and specific care expertise, as well as highlight potential sites with available patients for clinical research and trial recruitment. These digital systems have been shown to be highly effective in replacing or supplementing traditional study recruitment and outreach methodologies (48):

- Prototype multiple scenarios and better understand the patient population for a given indication, determining possible factors impacting study design.
- Increase confidence that real patients exist who satisfy target protocol conditions.
- Reduce costly protocol amendments.
- Increase predictability of trial enrollment, identifying & pre-screening patients earlier.

Data driven solutions have been shown to supplement traditional recruitment efforts effectively speed up patient recruitment, and aid patient identification for therapeutic studies, for example for cardiovascular diseases, where many of the study-required biomarker values can be obtained from laboratory values and procedure codes available in the patient EHR (48). In order to increase speed of study planning (identification of sites) and patient recruitment and thus attract sponsors of clinical trials, several countries including the UK, South Korea, and Switzerland, have enabled national anonymized EHR data visibility for sponsors of clinical trials. Let us examine here the Swiss model: the Swiss Personalized Health Network (SPHN) connects various regional and cultural healthcare systems together so they can share care metrics and standards of care across the country. Starting with

[31] The term EHR (Electronic health records) is used as higher-level term than EMR: EHR contains the patient's records (EMRs) from multiple doctors and provides a more holistic, long-term view of a patient's health

the major academic hospitals, the SPHN is creating a private data network using Swiss technology to connect the different hospitals and enable anonymized EHR data visibility and connectivity across these leading institutions in the four Swiss national languages as well as English (49). Such initiative is designed specifically to increase cooperation between all the country's institutions and create more open care standards and access across the country. This in turn will enable more clinical research cooperation and joint efforts, such as clinical trials, whereby patients and protocols can be managed and directed across multiple sites and remotely in tandem instead of through single sites, as done traditionally.

The Swiss model appears relevant for Poland and the creation of an EHR data-sharing platform would help to overcome the fragmentation of the public health care system between the Ministry of Health and the three levels of territorial government.

Therapeutic networks

A further recommendation would be to create therapeutic consortia (networks) across Poland, focused on specific unmet or critical patient needs. Rare diseases comprise over 7,000 diseases and often have high impact on patients, the families, support systems and the care system. It is estimated that over 50% of rare disease patients are never correctly diagnosed or treated. Recent studies suggest that due to the heterogenous nature of many of these diseases, more training is needed for caregivers, in addition to a better referral system so that patients, especially, newborns, can be referenced as soon as possible to care centers and experts able to provide specialized diagnostic as well as expertise. An example of this in the United States is the Rady Children's Institute in San Diego, which has become a major referral, treatment and education center for early diagnosis and treatment of newborns with rare but also debilitating disease conditions (50). Another example in the United States is the network of (currently) seven Comprehensive Care Centers dotted around the country, which are dedicated centers of expertise for Congenital Adrenal Hyperplasia (CAH). (51) In Europe, the Share4Rare platform exists to link rare disease patients, carers and researchers, allowing them to share information and participate in scientific research. (52) EHR systems can be readily used to not only find existing patients but also patients that have not yet been correctly diagnosed for rare diseases. By applying sponsor-based disease symptom models to identify potential patients that match associated disease conditions and unsuccessful treatment modalities, potential patients can be identified through their anonymized EHR records within networked hospitals. These patients, in turn, can be referred through their treating hospital for an approved study to be tested, correctly diagnosed, and referred for the appropriate treatment. This is being successfully applied in Turkey and the United Arab Emirates with interest also in the Kingdom of Saudi Arabia, with the next expected development the application of artificial intelligence and machine learning (AI/ML) algorithms to these modeling efforts. By deploying digital technologies, **Poland can accelerate the creation of healthcare networks** within the country, enabling better visibility to care, access to care and specialized care across the country. This will also result in better visibility to sponsors and research CROs focused on clinical research and trials, thus better enabling them to enable projects and efforts across the country in a more effective and digitally enabled manner.

Summary: Poland has historically evolved into a strong global player in clinical research, however, to retain its position, going forward, acceleration of adoption of digital healthcare technologies will be required. COVID-19 has accelerated demand for adoption of new technologies that enable digital healthcare, and their availability is now expected by sponsors of clinical trials and CROs.

What Poland needs to do: Using digital technology, Poland can accelerate creation of the healthcare networks within the country, enabling better visibility to care, access to care and specialized care across the country. The same technology can be applied to identify high-potential research sites for sponsors of clinical trials and CROs, which would increase the precision and speed of clinical trials conducted in Poland thus creating a very attractive digitally-enabled clinical trial market attracting more clinical trials to Poland.

4.7. Non-commercial Clinical Trials in Poland

by Przemysław Magielski

In recent years, the structure of the clinical trial market has changed considerably. We are seeing an increase in the number of non-commercial projects defined, in accordance with Article 37ia of the Pharmaceutical Law of 6 September 2001, as trials aimed exclusively at improving knowledge and changing clinical practice, which as a rule do not lead to any commercial use of trial outcomes. Unlike in the case of commercial projects, the data obtained in a trial is owned by the Sponsor, which is a university or a federation of higher education and science system entities, a healthcare provider, a patient organization, an investigator, an investigator organization, another natural person, a legal person or organization without legal personality which has a non-profit making aim with respect to the conduct or organization of clinical trials or manufacture of or trade in medicinal products.

There have been no stable sources of financing for non-commercial projects so far in Poland that would enable large multicenter clinical trials. Such projects have been implemented using own funds of medical universities and scientific research institutes. As a result of this financing structure, the size and territorial range of projects, including the number of sites or patient populations recruited, have been naturally limited. In most cases, own resources provided by universities have been insufficient to set up IT structures dedicated to supporting major multicenter projects, or to contract relevant services (eTMF, eCRF/IVRS, pharmacovigilance, monitoring etc.) from third parties providing such services commercially. The difficulty in analyzing data associated with these types of projects also lies in the fact that there are no cumulative data on projects sponsored by grants from pharmaceutical companies and implemented by state-funded scientific research bodies.

The structure of research projects in 'old EU' member states was different. While commercial projects were a slight majority, it should be emphasized that almost 50% of them were academic and non-commercial projects. Between 2011 and 2019, mainly commercial clinical trials were conducted in Poland, and the percentage of non-commercial projects registered with the URPL was in the range of 0.5% to 5% (Figure 32).

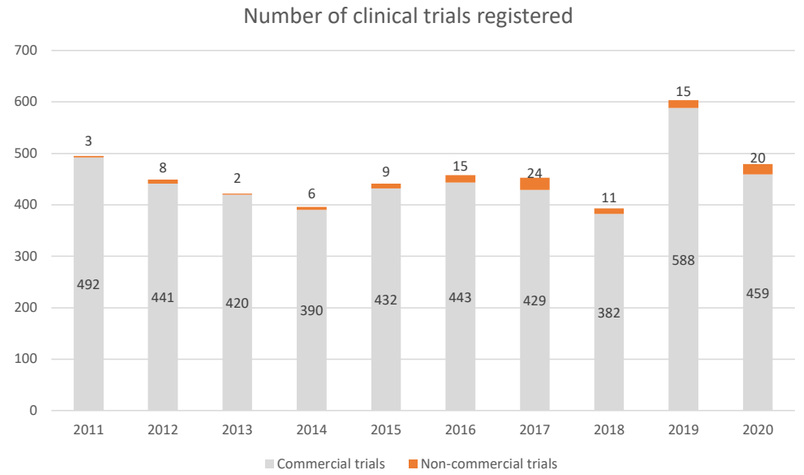


Figure 32. Number of registered trials in Poland between 2011 and 2020. Source: URPL

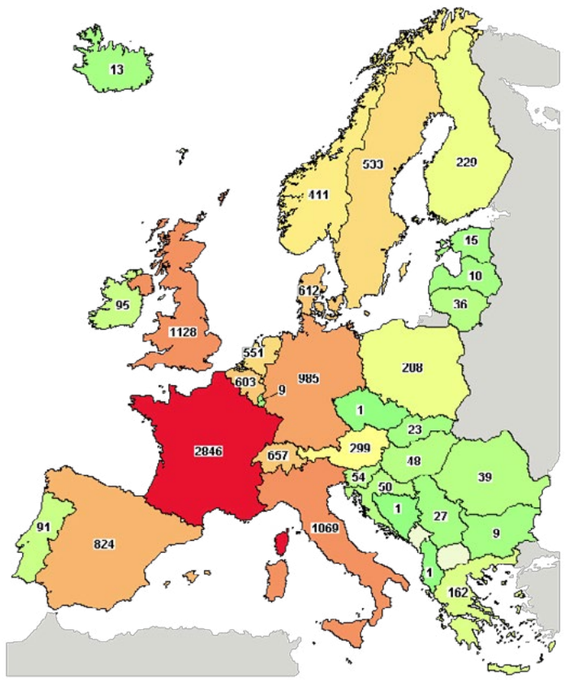


Figure 33. Number of recruiting trials registered in ClinicalTrials.gov sponsored by U.S. government agencies [including NIH] and other non-commercial entities between 2010 and 2021.

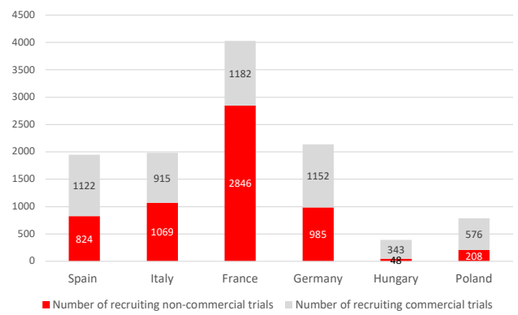


Figure 34. Proportion of recruiting commercial and non-commercial trials registered in ClinicalTrials.gov between 2010 and 2020.

If we analyze the current data based on content available in ClinicalTrials.gov, we will notice a huge disproportion between Poland and countries with a comparable R&D capacity (Figure 33).

In the reference period, there were 1,122 commercial projects and as many as 824 non-commercial projects in Spain (42%). A similar pattern is observed for Italy and Germany. The ratio of the two types of trials in the French market is noteworthy, as the proportion is reversed, and the number of non-commercial projects is more than double the number of commercial trials. In the case of France, it is interesting to note the high number of projects carried out in the pediatric population (474), which indicates that a very effective support system exists for research projects in this area.

It should be pointed out that in the previous years, a substantial number of single-center research projects was implemented in Poland, mostly in the framework of own statutory activities. These projects of high scientific significance were not included in the general statistics. This was because the legislator allowed the aforementioned trials to be conducted only on the basis of favorable opinions obtained from local ethics committees. This situation changed dramatically upon the establishment of the Medical Research Agency (ABM) and the launch of competitions for the conduct of non-commercial research.

As part of its activities between 2019 and 2021, the ABM carried out four competitive procedures, one in 2019 and one consisting of three rounds in 2020, in 2021 a competition was completed for research on rare diseases and further competitions were announced in the area of psychiatry, neurology and diseases of affluence. Additionally, targeted procedures were conducted for the development of a Polish CAR/CAR-T therapy and prevention of COVID-19 (Figure 35).

The total value of funds granted for project implementation in 2019 exceeded PLN 544 million, while in 2020 a total of PLN 376 million was granted over three rounds.

Grants were provided to as many as 26 oncology projects (including 8 in haemato-oncology) and 21 cardiovascular disease projects (Figure 36). Additionally, it should be emphasized that as many as 14 projects will be implemented in the pediatric population.

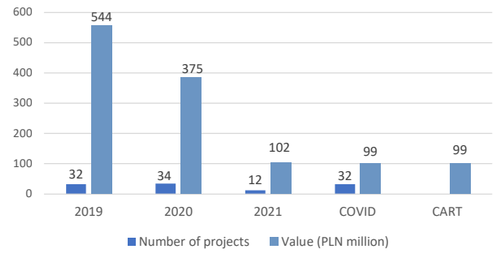


Figure 35. Number and funding of projects in Medical Research Agency competitions in Poland from 2019 to 2021. Source: ABM.

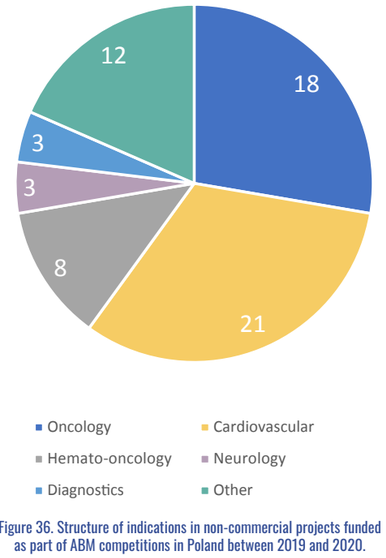


Figure 36. Structure of indications in non-commercial projects funded as part of ABM competitions in Poland between 2019 and 2020.

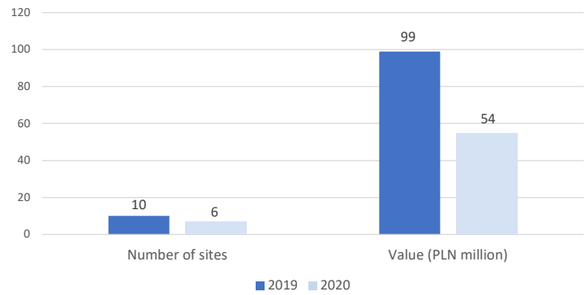


Figure 37. Financial support for development of Clinical Trial Support Centers.

Conclusions for the development of clinical trials in Poland

The support system for non-commercial trials operated by the Medical Research Agency is mainly based on the transfer of the financial resources necessary for the implementation of non-commercial research projects, but this also includes the provision of training for study teams (the POWER project), establishment of competence centers within universities (Clinical Trial Support Centers) (Figure 37), site network development (POLCRIN), or educational activities addressed to potential trial subjects (the "Patient in Clinical Trials" portal).

The outcome of implementation of the support system for academic projects will be seen in a few years, but it is already possible to forecast their impact on the entire market of clinical trials in Poland and to predict their future role in the development of the particular area of non-commercial projects.

1. Impact on non-commercial projects

The systematically emerging financing options and competitions offer a strong stimulus for the formation of new consortia of scientific research bodies and creation of young and ambitious research teams providing more capacity for multicenter projects, and developing the competences of project leaders. This change involves both the absolute number of projects and the expected patient recruitment levels. Most of these are multicenter projects, and the expected study population often exceeds 1,000 randomized patients. For the first time, the registration and initiation of more than 30 non-commercial multicenter projects are almost simultaneous. This poses a challenge to the entire clinical trial authorization system, as there is an increased number of applications to be evaluated which inherently entail a higher risk of error or inferior level of detail. As a result, demand has been emerging for new types of services for non-commercial trials, such as CRO services focused on the execution of such projects, sourcing of comparators and concomitant medications, production of placebos, or logistics services involving storage and delivery of investigational products, which opens the market for new players. It should be stressed that the total number of all non-commercial trial applications submitted, as many as 166, is just as important as the number of projects which received funding. The applicants (investigators) prepared complete clinical trial plans which, in addition to the scientific basis, included financial calculations and plans for investigational product logistics and additional equipment required for the implementation of multicenter projects. This creates awareness among study teams and their leaders, and the improved quality of project plans will support the acquisition of European or global projects in the future. Projects in the pediatric population are particularly important – the projects which are implemented/receive funding will broaden our knowledge in this area, which has been tremendously underfunded so far, while providing access to new therapeutic options. The funding will support the activities of numerous associations or organizations which have until now supported small projects, such as the DKMS Foundation, which is an example of an independent sponsor providing funding for this type of research.

2. Impact on the clinical trials market

Interesting observations in the coming years will concern the structure of sites implementing non-commercial projects. In a vast majority of cases, project funding is provided to highly specialized hospital-based bodies, which are most often affiliated with universities. For the first time there will be competition for patients between non-commercial projects, generally less funded in this respect, and commercial projects. Ambitious recruitment plans, especially for projects with similar indications, will put academic centers under heavy pressure to redirect the patient flow towards scientific projects. ABM-funded trials are estimated to involve 40,000 patients. On the other hand, there is a noteworthy positive effect for the entire patient community, consisting of an increase in the absolute number of research projects and thus the possibility of participation of further patient groups in clinical trials.

3. Clinical Trial Support Centers

Financing of the establishment and development of Clinical Trial Support Centers by the Medical Research Agency will stimulate the development of competencies of universities and project teams, including legal and IT departments as well as scientific and management staff, in respect of running entire R&D projects independently. By improving the availability of highly qualified staff and infrastructure, the newly established Centers should drive a significant increase in the number of all types of projects implemented in teaching hospitals in the coming years. There is also a separate focus on supporting the construction or development of existing early phase trial sites. Improvement of quality will enable the transfer of such projects from other countries to Poland, while opening up opportunities for end-to-end management of entire projects for commercial sponsors from early phases to registration studies. The development of spin-offs established at universities is also noteworthy – the system of grants from the National Science Centre, the Medical Research Agency and the National Centre for Research and Development as well as the newly established infrastructure of Clinical Trial Support Centers should enable the development of ambitious projects devised by Polish research centers and support their implementation from concept stage all the way to commercialization.

LOOKING AHEAD

CHAPTER 5

Chapter 5. Looking ahead

by Vladimir Misik

5.1 Assessment of growth potential of clinical trial market in Poland

Market growth scenario: In order to assess the growth potential of the CT market in Poland, the methodology explained in the chapter on Patient accessibility to clinical trials (patient accessibility to CTs is expressed as number of active CT sites per 1m population relative to the US) has been utilized. **Poland with 63% Accessibility levels in 2019** ranks 12th globally, with Hungary, Belgium, Israel and the Czech Republic each having accessibility levels more than 100%. These countries are all relatively small relative to Poland, thus we feel that a more meaningful benchmark would be Spain, with 88% accessibility levels. Thus, we propose to assume the achievement of 90% accessibility levels within 10 years as a realistic target for Poland – this would require an average annual growth of active CT sites in Poland of approximately 3.5% (see Figure 38). We consider such a target challenging but not unrealistic.

One of the ways to achieve such growth could be increasing the average number of CT sites per trial in Poland: as we have demonstrated in the chapters *Utilization of Poland by industry sponsors of CTs* and *Patient accessibility to industry clinical trials*, Poland, given its size, has a proportionally low average number of sites per active trial (an average of 6.3 in 2019) thus increasing it to 9.8 per trial appears realistic (e.g., Ukraine population 44 million has an average of 8.3 sites/trial and Slovakia population 5.4 million with average of 5.5 sites per trial).

An ideal vehicle to achieving a high number of sites per trial will be creation of large networks of competent and willing sites which would interact with the industry sponsors as a network rather than individual sites.

Market correction scenario:
However, it is important to discuss here an alternative scenario of CT market size reduction in Poland. There are several reasons to consider this possibility as plausible:

1. CEE as a region, for the first time since its opening for international clinical trials in the mid 90's and followed by continuous growth, started losing market share from 2015
2. Germany has been losing market share since 2012
3. Poland has one of the largest imbalances (7th globally) between pharmaceutical market share and share of clinical trials (with an almost a 4x research bias)

Thus, unless Poland adopts government-supported and government-led bold measures to increase country attractiveness to sponsors of clinical trials, a 25% loss of global market share over the next 10 years is an entirely realistic scenario for Poland (see Figure 38).

The delta between the Market growth scenario and Market correction scenario during 2021-2030 period would be USD 6.3 billion, with an annual impact of USD 1.32 billion in 2030 (see Figure 38).

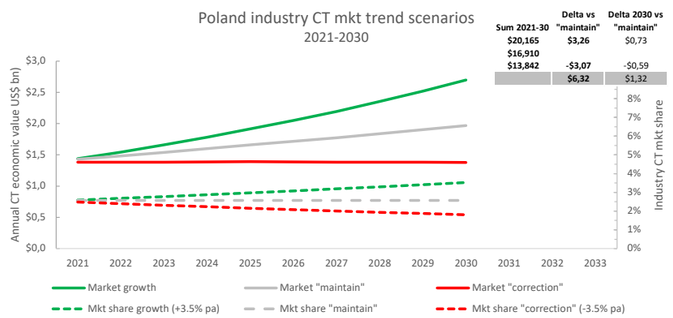


Figure 38. Poland Industry CT market trend scenarios 2021-2030

It is the delta which is the opportunity prize to go after by adopting bold growth-focused measures (examples of which are described below). Given the very significant socio-economic impact of industry CTs in Poland,[32] the identification and adoption of effective measures in support of the Growth scenario should become one of the government's priority focus areas.

5.2 Recommendations

This report identified substantial benefits for Poland's healthcare system and the Polish economy deriving from industry clinical trials in Poland. In order for Poland to remain an attractive location for sponsors of clinical trials, emphasis should be placed on the following focus areas:

- Support for sponsors of CTs through CT Infrastructure and Technology
- International promotion of Poland as an attractive location for CTs
- Raising profile of Poland through international collaborations
- Financial incentives to reward R&D activity not just innovation

Create support office for sponsors of CTs (both industry and academic): we recommend that the current scope of ABM be expanded to include support for commercial clinical trials.[33] A support office would help commercial and academic sponsors of CTs with the following process and data:

1. Identify sites and patients for clinical trials by creating a Digital platform capable of data mining for de-identified EHR data from major hospitals around Poland to enable digital patient mining and improve speed and reliability of study planning. In addition to supporting study planning, providing access to this **data mining platform to sponsors of clinical trials could be monetized which would provide required funding for creation and maintenance of such system**.

2. **Support sponsors of CTs with study set-up and study conduct following examples of the UK, Denmark and South Korea outlined in this report**. CT support offices should be staffed with contract specialist and study coordinators. The support offices would charge participating sites transparent fees for their services.

Available structural options:

Scheme	Pros	Cons
A single national CT support office (eg., under the ABM)	- Single point of contact for sponsors - Performance overview across Poland	- Support of sites would be virtual
Geographically aligned CT support offices to support CTs within their geographic area	- Better able to support sites through physical proximity	- Lack of national-level performance oversight
Therapeutic network-aligned CT support offices (see below)	- Single point of contact for sponsors in each major therapy area - Performance overview across Poland in each therapy area	- Support of sites would be virtual
Hybrid CT support: centralized office with study coordinating staff based locally across Poland	- This would provide the benefit of centralized approach with local support of sites	

[32] In the Growth scenario, the CT related economic value would grow 7% p.a. relative to the expected GDP growth of less than 2%. As a result, CT investment could rise up to 24% of the total R&D investment in the country, with incremental 3400 new R&D jobs created during 2021-30 to a total of more than 12,000 in 2030. On the other hand, the Correction scenario would represent a cumulative opportunity loss of USD 15 billion during 2021-2030 relative to the Maintain scenario and USD 32 billion relative to the Growth scenario. The Correction scenario would also mean a loss of 2700 jobs during 2021-2030 from the 2019 levels and an opportunity job loss of 6,000 jobs relative to the Growth scenario.
[33] Alternatively, a new organization could be established tasked with support of commercial CTs.

Promotional activities and materials

Task an organization (e.g., ABM with an expanded mandate would be most likely the most suitable) with increasing the profile of Poland among sponsors of clinical trials by regularly participating in and speaking at leading industry events in Europe, North America, China, and Japan, highlighting Poland's profile and promoting adoption of new measures to increase attractiveness of Poland to sponsors of CTs.

Performance indicators

In order to enable effective and up-to-date promotional material for the above-mentioned promotional activities, we recommend collecting and maintaining data about the performance of Polish sites in international studies. Towards that objective we recommend the creation of a data analytics team within ABM maintaining up-to-date performance data for Poland:

1. Productivity data: Upon study closure, sponsors would be required to submit (e.g., to ABM) information about study completion and provide a list of participating countries, with number of sites and number patients recruited in each country. This would enable maintaining up-to-date productivity data analogous to those shown in this report.

2. Study start-up data: de-identified global benchmarks to be submitted annually by large sponsors and CROs active in Poland (e.g., member companies of POLCRO and INFARMA)

Educational activities

Training of site staff and patient groups, which are activities typically performed by sponsors of CTs, vary substantially in terms of their quality and rigor. These educational activities could be streamlined and standardized e.g., under ABM or the Patient Obmudsman (https://www.gov.pl/web/rpp).

- Provide easy access to high-quality certified training for investigators and sites staff
- Engage and train representatives of Polish patient organizations to enable their active engagement of their patient communities

Therapeutic Networks and international collaboration

1. The Ministry of Health should be tasked with formalizing the creation of therapeutic networks in major therapeutic areas with large development pipelines (oncology/hemato-oncology, neurology, psychiatry, metabolic/endocrinology, cardiovascular), which could provide access to large patient populations in these disease areas cross Poland. The therapeutic networks should become virtual SMOs with professional CT support (see recommendation on CT support offices above). Special focus should also be paid to pediatric clinical trials with their C4C program. (53)

Representatives of these networks should regularly participate at leading therapeutic events and actively engage with international therapeutic networks and consortia in Europe and the US, and actively participate in CTs led by international therapeutic networks and consortia.

2. Therapeutic networks to establish or broaden collaboration with academic clinical research organizations (AROs) (e.g., Duke Clinical Research Institute, TIMI, Berman Center for Outcomes in Clinical Research, Julius Clinical) and consortia (e.g., TRICALS) frequently tasked with identification of centers for sponsor trials.

Establish regulatory thought-leadership

URPL to identify focus areas in which Poland has existing regulatory competencies and/or plans to develop them in order to be able act on behalf of other Member States as a reporting Member State (as per REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL from 16 April 2014). Currently, within the CEE region it is the Czech and Hungarian authorities which are viewed as the strongest and have acted repeatedly as Rapporteur authorities under the VHP process under the EU Directive 2001/20/EC.

Academic incentives to physicians for their participation in CTs

Universities/ research centers to introduce academic incentives as part of academic promotion, and professional recognition, by recognizing participation in CTs as an equivalent/part-equivalent to a in-extenso research publication in terms of academic merit assessment. The lack of such academic incentives has been identified as a barrier to greater participation in CTs by physicians at academic centers. (54)

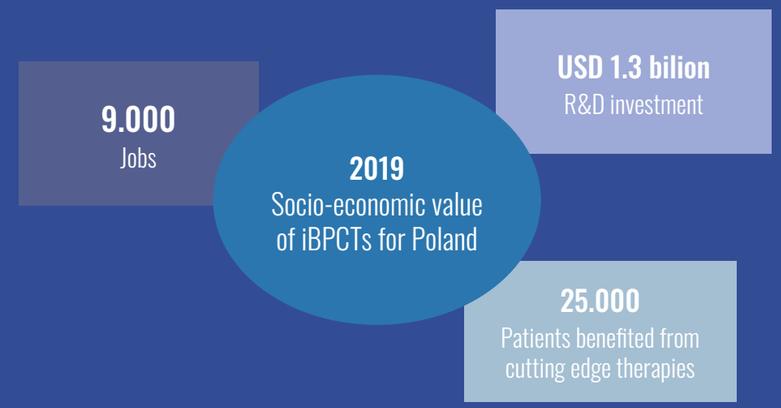
Create attractive R&D tax incentives/tax rebates

Ministry of Finance to allow CROs to claim R&D credit and incentivise multinational biopharma sponsors to set-up and/or expand their regional or global product development hubs, thus creating high-end R&D jobs in the country (e.g., global/regional study management) which has the potential to substantially increase the number of high-end R&D jobs in the country as well as raise the profile of the country from patient recruitment hub to, more broadly, a product development hub.

The recently introduced IP Box has been established in Poland to reward innovation. The limitation is that it does not reward R&D process *per-se* - it rewards only the innovation. Given the high socioeconiomic value of the R&D process, financial incentives should be provided to all organizations which carry out commercial CT activities (pharmaceutical companies, CROs, SMOs). Examples to follow in that regard would be e.g., France and the UK – both countries offering significant tax incentives which can be claimed also by CROs, not just innovative pharma. Broad incentives on the R&D process (not just the innovation part) would help to create additional R&D jobs in Poland and increase Poland's profile in global iBPCTs, as innovative pharmaceutical companies and CROs would be rewarded not only to carry our clinical trials at sites in Poland but also to create global/ regional R&D hubs responsible for coordination CTs in other countries.

Conclusions

Since the mid 1990s Poland, has grown into a powerhouse of innovative biopharmaceutical industry clinical trials (iBPCTs): in 2019 it ranked 11th globally in terms of iBPCT market share, and during the 2014-2019 period posted 5th largest iBPCT market share gain globally, behind China, Spain, South Korea and Taiwan. The socioeconomic impact of this market share is very significant: in 2019 the economic value of iBPCTs represented more than USD 1.3 billion (15% of total R&D investment in Poland), some nine thousand jobs in Poland were related to iBPCT, and more than 25,000 Polish patients gained access to cutting edge experimental therapies in 2019 alone. In 2019, Poland ranked 12th globally in terms of population-adjusted accessibility to experimental therapies, and ranked 7th in terms of industry-country reputation index.



Going forward, continuing success is not guaranteed as evidenced by recent market share declines in the neighboring countries (Germany as well as most of the CEE countries). Therefore, for Poland to retain or even grow these socio-economic benefits of iBPCTs amidst intensifying global competition, adopting bold, growth-focused measures will be essential and should become government's priority areas (e.g., building CT infrastructure supported by technology, promotional activities (both international and national), growing international medical research collaborations, financial incentives for sponsors of iBPCTs and contract research organizations). In the absence of such bold actions aimed at increasing attractiveness of Poland to sponsors of global iBPCTs, there is a very realistic risk of significant market share decline, driven by one of the largest imbalances (#7 globally) between pharmaceutical market share and share of clinical trials.

Glossary of terms

CTs – clinical trials
CDA – a Confidential Disclosure Agreement: a legal contract that protects proprietary information and binds the parties to hold information in confidence for a set period of time
CRO – contract research organization (a company providing support to the pharmaceutical, biotechnology, and medical device companies in the form of research services outsourced on a contract basis)
iBPCTs – innovative biopharmaceutical industry clinical trials (does not include clinical trials of generic manufacturers and academic CTs)
ABM - Medical Research Agency (Agencja Badań Medycznych)
NFZ - National Health Fund (Narodowy Fundusz Zdrowia)
URPL - Urzad Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych
RPP – Rzecznik Praw Pacjenta (Patient Obmudsman) https://www.gov.pl/web/rpp
EHR – Electronic Health Records. Sometimes incorrectly used interchangeably with the term EMR (Electronic Medical Record) which is a digital version of a patient's chart. EMR contains the patient's medical and treatment history from one practice. By contrast, an EHR contains the patient's records from multiple doctors and provides a more holistic, long-term view of a patient's health.
EMR - Electronic Medical Record. A digital version of a patient's medical chart. EMR contains the patient's medical and treatment history from one practice.
MeSH terms - Medical Subject Headings (MeSH) is used by ClinicalTrials.gov registry to classify which diseases are studied by trials registered in the registry
MAA - Marketing authorization application
eTMF - electronic trial master file
eCRF/IVRS - electronic case report form/ interactive voice response system

ANNEX 1. Methodology, data sources and model assumptions

For the purposes of this analysis, LongTaal CT Informatics: proprietary big-data clinical trial informatics platform (www.longtaal.com), which allows preparing bespoke comparative benchmarks for clinical trial markets globally, has been utilized as the primary data source for comparative benchmarking purposes. This big data platform has been specifically designed for countries' and sponsors' benchmarking purposes and has been utilized for providing market insights to multiple governmental organizations, medical institutions or professional organizations in several countries including Canada, Germany, Turkey, Saudi Arabia, UAE, as well as to several leading clinical research organizations.

The following data sources and model assumptions have been used in this report:
iBPCT: Biopharmaceutical-sponsored R&D clinical trials:[i] unless explicitly specified differently, in the context of this report only active industry-sponsored Phase 2 and Phase 3 trials have been considered.
LongTaal informatics combines information downloaded from ClinicalTrials.gov (55), EUDRACT (56).

Clinical Trials Market share

Previous reports on clinical trials in Poland (1) (2) were the primary source of information on clinical trial trends was based on the number and type of clinical trials reported by the Competent Authority in Poland and based on the data published by the EMA as part of the MAA approvals (3). Such reference data do not adequately answer the following questions:

- Is Poland gaining or losing market share of global industry clinical trials?
- Is Poland adequately represented in development of new products across all phases and all indications?
- What are the financial and socio-economic impacts of the measured market share changes?

Therefore, in this report a different methodology has been utilized to provide answers to the questions above. These are the reasons why evaluating country-level CT market based on global market share rather than changes in the number of new trials approved in a country is more reliable method of gauging the market trends:

1. Global iBPCTs are funded centrally thus countries compete for a finite slice of the global cake (USD 140 billion in 2019) and it is a zero-sum game: i.e., market share growth in one country goes at the expense of other countries.

2. There are year-on-year variations in terms of number of newly approved studies but there is a steady growth in terms of USD spent on development of new products.

3. Number of clinical trials a country is just one dimension for the assessment of the market size in a country: the other, just as important, dimension is the number of sites participating in a clinical study.[34]

In order to overcome the limitation of CT market assessment based on number of clinical trials, several authors have utilized the number of new sites added over a defined period using ClinicalTrials.gov registry as a data source to analyze geographic iBPCT trends previously (57) (7) (8) (58) (59). However, such methodology based on assessment of global market iBPCT share suffers from two limitations:
1. There is a considerable year-on-year variation in terms of new sites added, caused by initiation of studies with large number of sites in some years. For countries with relatively low number of clinical trial sites this can lead to a significant year-on-year under-/overestimation of clinical trial market share, and/or market share gains/losses, unless new sites added are aggregated over several years.
2. Global spent on running clinical trials of new drugs is funding all active sites in all active clinical trials (rather than those newly added in a given year).

In order to overcome these limitations LongTaal has developed a novel methodology allowing determination of active trials and active sites in each year (60), rather than only new sites added, which was the methodology used by other authors previously (57) (7) (8) (58) (59). Such methodology based on assessment of active clinical trials in each country and globally was utilized in this paper of assessment of Poland's global market share.

The following algorithms and assumptions were applied to arrive at number of active CT sites: to determine whether sites in a study were active in a given calendar year the start and completion date associated with the study record in clinicaltrials.gov were used. Based on our analysis, less than 3% of studies do not have a completion date entered in their record. For these, the study completion date was replaced with either study last update date or start

[34] It is similar to assessment of growth of a city's size based on number of houses built each year: such information is meaningless without specifying whether those were single family houses or high-rises with hundreds of flats and without specifying how many houses and of what type have been torn down.

date plus five years, whichever is less. Number of active sites in a country represents the sum of all site locations for all active studies in that country.

This methodology was further improved by combining data from clinicaltrials.gov registry with data downloaded from EU Clinical Trials Register and using proprietary algorithms to eliminate duplicate entries and enrich data content.

A country's iBPCT market share was determined as the percentage of active iBPCT sites in a country relative to the global (60).

Unless specified differently, clinical trials market share refers to the number of active industry-sponsored Phase 2 and 3 sites in each country/region during any given period, relative to the number of such active sites globally. Country/regional percentage of global BPCT sites (industry-sponsored Phase 2 and 3 only) has been assumed equal to iBPCT sites market share of those countries/regions.

Accessibility to Clinical Trials

Patient accessibility to clinical trials has been calculated as described previously (60): accessibility to CTs is defined as the number of Phase 2 and Phase 3 iBPCT sites per 1 million population. For comparative purposes, iBPCT accessibility is expressed relative to the US levels (US iBPCT accessibility level being 100%) (60).

Market share of pharmaceutical consumption

Market share pharmaceutical consumption of countries and regions has been calculated based on published pharmaceutical sales data, i.e., BMI pharmaceutical sales data (61). Source of the population data was the World Bank population databank (62)

Calculation of financial revenues related to patient recruitment and management in industry CTs

Global biopharma R&D spend in 2019 was USD 194 billion (32), out of that the spend on development was USD 130 billion (67% of R&D) (32). Approximately 40% of development spend is linked to patient recruitment (63) (59), thus in 2019 the annual patient-recruitment related spent in clinical trials was approximately USD 52 billion (this includes patient-related hospital and investigator grants, patient expenses, costs of investigational product provided to patient, national regulatory fees, ethics committees/IRB fees, local safety laboratory fees, salaries of hospital clinical trial staff, eg study coordinators/nurse, in-country CRO fees, customs fees & logistics of study material, courier fees). Thus, the dollar value of 1% market share of Industry R&D CTs in 2019 was approximately USD 520 million of pharma R&D investment. The average y-y growth of Development spend during 2017-2019 has been more than 7%, and historically more than 3%. The forecasted growth 2019 – 2025 is more than 3.5%, thus the forecasted 2025 development spend is USD 161 billion (32) resulting in an economic estimated value of the 1% market share of USD 640 million.

ANNEX 2. Report Contributors

For the report preparation, a unique multidisciplinary team of experts has been assembled with decades of experience in management of global clinical trials who served in senior international roles at large multinational corporations, combined with local clinical trial experts with intimate insights about the clinical trial market in Poland.

Lead author:
Vladimir Misik, PhD.

Partner & Founder at LongTaal (www.longtaal.com),
Partner & Co-Founder at VIARES (www.viares.at);
Board Member at SanaClis (www.sanaclis.eu).

Author of more than 60 research articles and book chapters in peer-reviewed journals, editorial board member at Applied Clinical Research, Clinical Trials and Regulatory Affairs journal, board member of DIA Core committee for clinical research.His current research focuses on various aspects of globalization of industry clinical trials. As a lead author of the Report Vladimir was not only able to tap into his experience of more than 30 years in biomedical R&D, during which he worked and served in multiple senior roles in North America, Europe, Middle East and Africa, and Asia, but also provided objective external global benchmarks utilizing big data analytics of LongTaal (www.longtaal.com) a clinical trial informatics company, which he founded and is managing.

Lead author Poland:
Bartłomiej Jarosz

Independent Clinical Research Consultant

Bartek brings almost 20 years of experience in clinical trial start-up and site contracting with multiple senior-level global and regional roles st Quintiles and INC Research and multiple global pharmaceutical leadership project roles (Teva/Nuvelution, Celgene, UCB Biosciences GmbH). For this report Bartek was the lead editor of the Stakeholder perspectives section of this report, providing key stakeholder insights about clinical trials in Poland from the perspectives of a site managemenet organization, clinical research organization, academic research, in which Bartek contributed a chapter on start-up process of clinical trials in Poland.

Other Report authors are shown below in alphabetical order:

Łukasz Bęczkowski, MBA

Chief Operating Officer
at Pratia Site Network

Łukasz brings more than 15 years of experience in the clinical research industry, both on the side of CT sponsors (Pfizer) and large site management organizations: Synexus (now Accelerated Enrollment Solutions) and Pratia. For more than 10 years, he has co-created and managed research sites operating in various models across multiple European countries and the US. For this Report Łukasz contributed a chapter on clinical research sites' landscape in Poland in the Stakeholder perspectives section in which he focused on the role of dedicated clinical research sites and networks.

Magda Czarnecka

Proposal and Strategy Manager
at Clinscience

Magda brings altogether more than 10 years of experience in pre-clinical research, health technology analysis, consultancy, clinical operations, and strategizing activities. Over years, she has contributed into numerous scientific publications, clinical analyses reports and consulting projects. For this report, she has construed a chapter on general considerations regarding the "Execution of Clinical Trials in Poland".

Tomasz Dąbrowski

Head of Clinical Trials
at Neuca Capital Group SA;
CEO of Neuca's parent companies Pratia SA; Clinscience, Hyggio (www.neuca.pl), Member of Business Council of Polish Clinical Trials Network at Agencja Badań Medycznych.

As an entrepreneur he built multiple healthcare, telemedicine, and clinical trial businesses, leveraging this experience in M&A, digital transformations, business strategy, and patient engagement processes in the healthcare industry. During his tenure, Pratia became the largest European Research Site Organization in terms of the number of ongoing studies (600), and Oncology and Ambulatory Sites coverage (90). Hyggio, which he also oversees as a CEO, plays is enabling decentralized clinical trials and digital transformation of the industry. For this Report Tomasz contributed chapter in the Stakeholder perspectives on technology and data digitization in clinical trials.

Douglas Drake, MS, MBA

Senior Director,
Client Solutions,
Clinerion (www.clinerion.com)

Originally a life science researcher with a passion for digital enablement of better patient care. With over 30 years of experience working in various aspects of diagnostics, therapeutic research and drug discovery, Douglas has broad experience in transformative technologies, data sciences, global business development and applying these to improving patient engagement and the patient journey. Douglas has contributed chapter on best practices in the use of anonymized EHR.

Przemysław Magielski, M.D. Ph.D.

Medical Director,
Independent clinical research consultant

Two decades of experience in CRO integration and mergers, managing strategy, business development, budgets, resourcing and compliance, management of CROs. Directed QA and Medical Information department, Strategy of international expansion at Pratia. Previously served in senior roles at PRA Health Sciences, Poland and the Executive VP at Clinscience. Currently academic lecturer and Medical Director in Scientia Research Institute. In the context of the report Przemysław contributed chapter on academic research landscape in Poland in the Stakeholder perspectives section.

Krystyna Miłowska and Piotr Zięcik

Managing Partners,
Kancelaria Prawna „ZFLegal" Zięcik, Miłowska i Partnerzy

Partners at Law Firm providing comprehensive services for Polish and foreign entities operating on the Polish pharmaceutical market for 17 years. The Law Firm has negotiated thousand of contracts for clinical trials, represented clients in reimbursement proceedings, and provided general legal services to pharmaceutical companies and CROs.
The Law Firm advises, and actively participates in conferences and conducts trainings and practical workshops for industry organizations operating on the clinical trials market (the Polish Association of Clinical Research Organizations POLCRO, the Association for Good Clinical Practice in Poland (GCPpl)).
The Law Firm's partners are co-authors of scientific publications recognized on the clinical trials market "Pharmaceutical law. Commentary 'Wolters Kluwer, 2016; "Clinical trials" CeDeWu.pl, 2015; "Contracts in Clinical Trials" series of comments from C.H. practitioners Beck, 2009.
For this report Krystyna Miłowska and Piotr Zięcik contributed chapter on Legislative analysis – conditions for conducting clinical trials in Poland.

Wojciech Szczepanik, PhD.

VP of International Site Network
at Pratia SA

Wojciech has more than 15 years of experience in various aspects of international clinical trials. Started in AstraZeneca as a CRA then continued his career at Synexus advancing from the Site Manager to the Head of EMEA sites. Currently is responsible for expanding and integrating Pratia sites network outside of Poland. In the context of the report Wojciech contributed a chapter on perspectives of the site research networks: Challenges ahead of research sites and networks.

Collaborating Companies

(shown in alphabetical order)

Clinerion

Clinerion provides leading real-world data solutions based on live data queried and aggregated from the anonymized electronic health records (EHRs) of millions of patients around the world on the Patient Network Explorer platform. Data from our network of partner hospitals in our Clinerion Community enable detailed data analysis of patient journeys and outcomes, and support the generation of real-world evidence (RWE), while complying with international patient privacy and data security regulations. Patients and physicians at our partner hospitals gain access to leading-edge sponsored trials. Clinicians at trial sites and pharma clients improve efficiency in patient search and identification for clinical trial recruitment to save time and costs.

Clinscience

Clinscience is a global CRO company offering smart (end-to-end) CRO services, i.e., protocol creation to final study report development. The company has offices in Poland, Spain, Italy, Germany, and the USA and provides its services in 6 European countries. More than 150 clients of Biotechnology companies in Europe and the USA trust the Clinscience brand. Our procedures and Data-driven approach harnessed with Genius Suite™ technology allow us to be agile in meeting Our Clients' needs. In 2021, the company has invested in Italian-German company EXOM GROUP, thanks to which it can continuously expand its services. By uniting a multicultural team's expertise with the technology based on Genius Suite, we offer a unique solution within Clinical Trials. Since Clinscience is part of a publicly-traded parent company Neuca Plc. – an organization in the pharmaceutical wholesaling and the healthcare industry - it provides the structure to meet the needs in commercial and non-commercial studies.

LongTaal

LongTaal has been providing advanced clinical trials analytics since 2012 (www.longtaal.com) utilizing data from multiple public domain sources including, but not limited to: clinicaltrials.gov, World Bank data, US FDA inspection results, PubMed, Medline

Customized reports and market trend analyses have been utilized by policy advocates across Europe and the Middle East, senior managers of large pharmaceutical companies and CROs, presented at international conferences, and published in peer-reviewed journals

Customers include: large biopharmaceutical companies, CROs, regulatory bodies, as well as academic medical institutions.

Pratia SA

Pratia is the independent site network which consists of more than 90 research sites (including professional ambulatory sites, embedded hospital sites and dedicated oncology research units) across 6 European countries. Pratia offers a platform connecting patients and experienced investigators with innovative therapies available as Clinical trials. Its mission is to enable Patients access to healthcare in order to improve their quality of life and wellbeing. Mixed site model enables both – projects delivery across majority of therapeutic areas (more than 85% of TAs coverage) as well as meets requirements of complex protocols and medical procedures. Since 2012 the network has conducted over 700 clinical trial projects. Pratia develops and implements digital solutions that significantly support study data quality as well as decentralized trials model. Pratia joined Neuca capital group in 2014.

VIARES

Clinical research talent organization since 2019 training industry standards-ready standards (JTCRC) with over 2,000 trainees, VIARES virtual talent bench, trained in 71 countries on five continents. Supported clinical research industry's training needs having successfully placed almost 600 of its trainees within clinical research industry across biopharma, CROs and SMOs.

Kancelaria Prawna „ZFLegal" Zięcik, Miłowska i Partnerzy - Solicitors and Legal Advisors

The Law Firm is a professional partnership that for 16 years has been providing comprehensive services for Polish and foreign entities operating on the pharmaceutical market. The clients for whom the Law Firm has rendered services in recent years are the largest international pharmaceutical companies (sponsors), companies conducting clinical trials commissioned by sponsors (CRO), networks of clinical sites (SMO), study sites as well as individual investigators and subcontractors. Clinical Trials Department is managed jointly by Managing Partners - attorney Piotr Zięcik and legal advisor Krystyna Miłowska.

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Possibilities to increase number and scope of trials in Poland

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