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Clinical Trials in Poland



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Foreword

Please find below a report on the current state of clinical trials in Poland, which has been developed by PwC upon request and in collaboration with the Employers' Union of Innovative Pharmaceutical Companies (INFARMA), Association for Good Clinical Practice in Poland (GCPpl) and Polish Association of Clinical Research Organizations (POLCRO).

Clinical trials are the foundation of the contemporary medical science and a pre-condition of patients' access to modern therapies, while simultaneously greatly contributing to doctors' professional knowledge. Currently, the European Community is preparing for the implementation of the Regulation No. 536/2014 of the European Parliament and of the Council (EU) on clinical trials on medicinal products for human use. The Regulation, which is to become applicable most likely in March 2017, will significantly change the existing procedures of clinical trial authorization. The European Union Member States vary in the degree of their legislative and administrative preparations for the application thereof. These differences will influence the distribution of clinical trials across the European Union. Therefore, it is in Poland's interest to best prepare for the changes ahead in both legislative and administrative terms within a relatively short time.

In this report you will find an analysis of the current state of affairs in the clinical research industry in Poland as well as discussion of three potential scenarios of the development of the sector. Realization of a scenario in which Poland's activity will be limited to commencing the application of the Regulation No. 536/2014 without attempting any adaptive actions in the areas not directly regulated by the EU legislation would lead to the collapse of the clinical trials market in Poland. The negative consequences of such development would be borne not only by patients, but also healthcare professionals and facilities. This would also negatively affect the state budget and the innovativeness of the Polish economy.

In more optimistic scenarios, in which the key administrative and legislative barriers will be fully or partially eliminated, Poland's clinical trials market would have a chance to stabilize or even grow significantly. This option would bring the biggest benefits to patients, whose well-being is the most important factor. It would be beneficial to doctors, healthcare facilities and the state budget, as well.

We would like to thank all the persons involved in the development of this report. We believe that it will become the basis for an informed dialogue on the development of the commercial and non-commercial clinical trials market in Poland.

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Summary

In the era of numerous civilization diseases and other threats to human life and health, patients worldwide expect new therapies which are effective and safe at the same time

In the era of numerous civilization diseases and other threats to human life and health, patients worldwide expect new therapies which are effective and safe at the same time. However, access to modern drugs would not be possible without clinical trials, which are a necessary element of the drug marketing authorization process.

In this report, we attempted a comprehensive analysis of the clinical research industry, accounting for both regulatory and market aspects. The study, which was developed by PwC upon request of three organizations (i.e. INFARMA, GCPpl and POLCRO), is a follow-up to our Clinical Trials in Poland – Key Challenges report published in November 2010. The latter considered four scenarios of the evolution of Poland's clinical trials market in the years to follow (from the most pessimistic to the most optimistic, involving not only improvements in the administrative environment but also introduction of additional incentives to encourage clinical trials). Determining which of the scenarios considered in our previous report did in fact materialize became the starting point for the analysis and evaluation of the current shape of the clinical trials market.

Our analysis has shown that in 2011–2014 Poland failed to use the potential existing in the clinical trials market. Furthermore, the market has seen a slow decline recently.

Clinical trials are a major opportunity for patients, especially those suffering from severe diseases in the treatment of which all standard therapies have failed.

- Patients taking part in clinical trials freely receive cutting-edge therapies combined with a higher standard of medical care.
- Sometimes clinical trials offer terminally ill patients the only chance of access to a medicine which may improve their condition.
- Even participation in the process of enrollment into a clinical trial offers a chance to undergo free screening tests, which often result in early diagnosis of other dangerous conditions.

Choosing Poland as a country for the conduct of clinical trials generates tangible savings for the state budget and the National Health Fund (NHF).

- In 2014 alone, the state budget received over PLN 300m in taxes and fees paid in connection with clinical trials carried out in Poland.
- In just one therapeutic area, i.e. oncology, NHF could save even PLN 600m in the same year.

Clinical trials are a strictly innovative activity, which contributes to the emergence of a new modern reality in the Polish medicine.

- The investigators and researchers involved in clinical trials get an opportunity to gain unique knowledge and gather experience in particular areas of medical science through access to new treatments, increased possibility of operating modern medical equipment (e.g. PET diagnostics), facilitated know-how sharing among a network of specialists and investigators, as well as access to additional materials and training.

- The ultimate beneficiary is patients, who remain in the care of highly qualified staff.

Poland is still perceived as a country with huge potential for the conduct of clinical trials owing to a large population of patients, well-qualified specialists and relatively low costs.

Despite obvious benefits and high growth potential, the number of clinical trials conducted in Poland has been declining. While a total of 469 clinical trials were registered in Poland in 2009, the figure dropped to 396 in 2014. The number of clinical trial participants fell accordingly. In addition, it should be a matter of concern that in Poland the ratio of the volume of clinical trials to the population is significantly lower than in comparable European countries, such as the Czech Republic or Hungary.

The existing legal and administrative barriers should be considered the underlying cause of the current state of affairs.

- The sponsor needs to complete a number of formalities in order to launch a commercial trial. One of the most burdensome requirements is the obligation to submit contracts between the sponsor and the investigator and/or the site when filing a clinical trial application.
- While conducting clinical trials in Poland, it is difficult to estimate the ultimate costs of particular projects due to unclear division of obligations between the sponsor and NHF with respect to financing of healthcare services.
- Lack of social awareness and knowledge of clinical trials is also a major issue. At present, due to legal restrictions, there is no platform through which patients could get full information about clinical trials being conducted in Poland.

The declining attractiveness of European countries as a location for clinical trials became the starting point for the Regulation No. 536/2014. This is to replace the Directive 2001/20, currently in force, which has been much criticized by the community. The new regulations, which will be directly applicable in all EU countries, provide for a number of improvements and lower requirements in the process of the registration and conduct of clinical trials within the European Union.

Awaiting the application of the Regulation No. 536/2014, Poland is on the verge of major changes.

Using the potential of the new regulations will depend primarily on the actions undertaken on the national level, as the Regulation does not address the most problematic issues related to the official practice, ethical assessment system, insurance system and clinical trial financing.

Like in 2010, based on the surveys and studies conducted, in our report we drafted three alternative scenarios of Poland's clinical trials market evolution.

- **Passive implementation of the Regulation No. 536/2014.** In case of failing to adopt a proactive approach to lower the existing barriers and limiting to passive application of the community regulations, Poland may become an even less attractive country for the sponsors of clinical trials.
- **Elimination of obvious barriers.** Undertaking efforts aimed at removing the drawbacks in the clinical trials market in parallel with the application of the Regulation No. 536/2014 may result in Poland becoming a country offering conditions similar to those in other EU countries.
- **Active promotion of Poland as a friendly country to clinical trials.** Only the elimination of administrative drawbacks and a change of Polish regulations aimed at maximizing the potential of the Regulation No. 536/2014, accompanied by additional efforts to increase the attractiveness of Poland as a location for clinical trials may create conditions for Poland achieving the highest growth rate in the region and strengthening its position as the largest market for clinical trials in the CEE region.

Achievement of the optimistic forecasts depends on a number of factors, the most important being focus on changes in legal regulations, official practices and social awareness.

In particular, the key changes should be as follows:

- To exclude the obligation to submit the contracts with investigators and/or sites from the clinical trial registration process – this cosmetic change will significantly contribute to reducing the time to start a clinical trial; as a result, Poland will become a more attractive country for this type of activity;
- To provide patients with access to the drug upon completion of a clinical trial, so that the effective therapy may be continued also after the clinical trial;
- To introduce the compassionate use procedure – it authorizes the use of selected categories of drugs on an individual basis with respect to patients in a particularly difficult condition or those who cannot be successfully treated with any of the authorized medicinal products;
- To introduce a possibility of and define clear rules for payment of compensation and remuneration to patients or healthy volunteers for participation in clinical trials which bring them no therapeutic benefits (phase I clinical trials, bioequivalence studies);
- To facilitate patients' access to knowledge about innovative therapies and the terms of conduct of clinical trials by developing a public independent information platform dedicated to clinical trials in Poland – such a solution could become a tool for initial patient qualification for particular projects (currently, this scheme is not possible);
- To improve the functioning of the ethical assessment system by developing an efficient chain of Ethics Committees, which will ensure that opinions about clinical trials are issued within the timelines set out in the Regulation No. 536/2014;
- To enable patients to gain compensation for damage resulting from their participation in a clinical trial by introducing sponsor's liability on a strict or culpability basis and establishing a dedicated insurance fund – under the current legal regime, claiming compensation for damage related to clinical trials is troublesome;
- To increase transparency in division of obligations between the sponsor and the public payer with respect to financing of healthcare services provided in connection with a clinical trial – under the current legal regime, due to all the ambiguities, the burden of financing of the healthcare services guaranteed to be financed from public funds is transferred from the public payer onto the sponsor;
- To take efforts aimed at supporting non-commercial clinical trials by reducing financial burden related to their commencement (official fees, insurance) and providing technical support with respect to the organization of such an activity;
- To introduce legal, tax and investment incentives to encourage sponsors to conduct clinical trials in Poland – these may include solutions modeled on other countries, such as R&D tax relief or tax grant programs.

1.



Clinical trials market in Poland: Key characteristics

What are clinical trials?

Clinical trials are necessary to ensure efficacy and safety of medicines

Positive outcome of clinical trials is a precondition of drug registration and introduction in to the market

Drug route to the market

The key purpose of clinical trials is to confirm that a new medicine which is to be handed over to doctors and patients is safe and effective.

Clinical trials are a major component of the drug development process: approximately two-thirds of the average cost of the molecule route to the market is allocated to clinical trials.

Owing to the growing complexity of medical technologies used in modern medicines and the necessity to adapt to increasingly strict standards of the safety of use of medicinal products, the role of clinical trials and the related costs have been steadily growing, and this trend may be expected to continue in the nearest future.

A clinical trial is a series of medical studies conducted in patients and/or healthy volunteers and aimed to determine whether a particular medicine or treatment brings the expected medical benefits, while being effective and safe for patients. Clinical trials are an important factor driving progress in medical science.

A typical process consists of four phases of clinical trials (preceded by a phase of preclinical trials, when the concept of a new therapeutic method is tested on cellular and animal models). According to Good Clinical Practice (GCP) standards, these phases are as follows:

- Phase I:** Initial testing of drug safety and pharmacological properties, involving c. 50-100 healthy volunteers;
- Phase II:** Dose-ranging tests and initial analysis of drug safety and efficacy, involving c. 300-600 patients with specific types of ailments;
- Phase III:** The lengthiest and costliest part of trials, involving from c. 1,000 to c. 3,000 patients, which aims to confirm the safety and efficacy of a drug to enable its registration and introduction in the market;
- Phase IV:** Additional post-registration testing aimed to confirm the long-term safety and efficacy of a drug.

Drug registration based on the results of phase III trials means that patients get a proven and effective medicinal product, which addresses some specific health needs of the particular population. There would be no new medicines without clinical trials.

Non-commercial trials are an important component of the market

Non-commercial trials

Non-commercial clinical trials are also an important component of the market. Such trials are carried out by entities which are not involved in the manufacture and marketing of medicines or trial organization on a contract basis. These include: healthcare centers, research facilities as well as investigators themselves (or their organizations).

Typically, non-commercial trials do not aim at introducing a new drug into the market, but concern medicines which have already been authorized for marketing. Non-commercial trials focus on the analysis of drug efficacy with respect to various groups of patients (e.g. in pediatrics), different dosage or off-label use.

Clinical trials involve a number of stakeholders representing various segments of the market

Key players in the clinical trials market

Conduct of clinical trials is a complex process involving a number of stakeholders.

Each group of stakeholders involved in the clinical trial process is responsible for a different component of the market.

- **Sponsors:** Pharmaceutical companies, biotechnological companies, academic institutions and research centers, which finance testing of their prospective medicinal products, are the most common sponsors of clinical trials. Pharmaceutical companies can run clinical trials in-house or outsource them to independent CROs.
- **CROs (Contract Research Organizations):** Independent specialist organizations which carry out clinical trials upon request of sponsors, including pharmaceutical and biotechnological companies or non-commercial sponsors.
- **Participants/Patients:** Healthy volunteers or patients suffering from a specific disease who have met the inclusion criteria and given their informed consent to taking part in the clinical trial.
- **Sites:** Clinical research sites where clinical trials are actually conducted; depending on the nature and therapeutic area of a clinical trial, research can be carried out on an out-patient and/or in-patient basis.
- **Investigators/Doctors:** Key persons in the clinical trial process, who have direct contact with patients and work individually or with a research team (other doctors, nurses, administration personnel).
- **Public authorities:** Institutions supervising, reviewing and approving clinical trials, as well as ensuring compliance with legal regulations and International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) requirements. In Poland, this is, in particular, a responsibility of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL).
- **Ethics committees:** Independent institutions providing opinion on clinical trials, supervising their conduct and ensuring protection of the rights of clinical trial participants.



Why are clinical trials worth supporting?

Clinical trials bring a number of benefits to both clinical trial market stakeholders and the state budget

Importance of clinical trials

Clinical trials are not only a way of collecting data required for the registration of a new drug, but also one of the most complex research processes in the field of advanced technologies.

In order to successfully complete a clinical trial, one has to determine its methodology, terms and scope of diagnostics, patient recruitment procedure, methods for verifying and supervising the conduct of the trial, etc.

It is not possible without thorough preparation and training of people who are to conduct a clinical trial. Consequently, the countries and sites in which clinical trials are conducted obtain not only knowledge of the latest medical technologies but also get access to know-how in management and research procedures.

Taking into account the importance of the time factor (the cost of a clinical trial is a function of its duration), great focus on maximizing the efficiency of actions and interventions and optimizing processes and procedures (while ensuring patient safety) should not be surprising. This offers an element of improvement of the entire system, much needed in healthcare, which should subsequently be reflected also in standard medical procedures.

In this respect, a particularly important role is played by non-commercial trials, which owing to their nature most frequently contribute to improvements in the efficacy and safety of diagnostic and therapeutic regimens used by doctors in their daily clinical practice. As a result, they also contribute to the development of knowledge, science and medical practice – in treatment of both common and rare diseases. Therefore, they have a virtually direct effect on the patient care and treatment standards.

Furthermore, the results of clinical trials, including non-commercial ones, may be useful for e.g. public authorities in making decisions on the reimbursement of drugs available in the market from the state budget.

Finally, participation in a clinical trial brings a number of tangible and intangible benefits to all the parties involved, that is patients/participants, investigators, sites, etc., as well as to the entire economy of the country.

“It is the academic research which has solidified the role of adjunctive treatment in a number of oncological diseases and enabled the verification of the efficacy of breast/larynx conserving therapy, while demonstrating the inefficacy of several procedures previously considered to be a standard treatment”.

Investigator

Clinical trials bring special benefits to patients

Benefits to patients

- **Registration of modern drugs.** The key and most obvious benefit of clinical trials is a possibility to use a new medicine once it is registered. In other words, the ultimate and main beneficiary of clinical trials is the patient, who, following the positive outcome thereof and the drug registration, gets an effective and proven medicinal product.
- **Best possible treatment.** For some patients, participation in a clinical trial may turn out to be the best available treatment, especially if the therapeutic options available as part of standard medical services are limited.

If the currently available range of therapies is insufficiently effective, participation in a clinical trial can be often the patient's only hope of undergoing an effective treatment. It is particularly clear in case of rare diseases, when participation in clinical trials is frequently the only chance to get access to therapy.

- **Higher standards of care.** Owing to their nature, clinical trials require improved diagnosing and monitoring of diseases and treatment efficacy. It means enhanced frequency and quality of patient's interaction with doctors, additional diagnostics, more rapid response to potential deterioration of patient's condition, etc.
- **Chance to prolong life.** Patients affected by a terminal disease can get a chance to prolong their life through participation in a clinical trial. This can be related not only to the characteristics of the investigated drug itself, but also to the level/scope of medical care offered in a trial.
- **Benefits to patients not included into a trial.** Benefits are not limited to the participants who have actually received the investigated medicinal product. Screening and diagnostic tests which precede patient enrollment often reveal diseases which would not have been revealed otherwise. Thus, even if such patients are excluded from a particular trial, they can start treatment for the diagnosed disease earlier, which is often decisive for the treatment efficacy.

Pharmaceutical companies are increasingly fostering dialogue with patients to better understand their needs

Owing to the fact that patients are the most important in any clinical trial, at present the entities conducting clinical trials focus increasingly on understanding their needs and opinions related to the intended study in terms of life comfort, practical aspects and feeling of safety, so that participation in a trial is the least interfering with patients' normal life routine, while offering them a chance for positive effects of treatment. Relations with patient associations, including cooperation and sharing opinions and suggestions, are particularly valuable for sponsors and CROs in obtaining such information.

Moreover, these organizations are getting increasingly involved in developing innovative treatments and raising patients' awareness of clinical trials. One of the examples is a platform provided by the European Patients' Academy on Therapeutic Innovation (EUPATI), which aims to provide patients with scientifically confirmed information about clinical trials. As a result, patients can increase their knowledge of the research and development activity of the pharmaceutical industry and participate in a decision-making process related to pharmaceutical innovations, drug safety and availability of particular treatments.

Investigators can use know-how and the latest research tools

Benefits to investigators

- **Expertise and experience.** For doctors involved in clinical trials, the latter provide an opportunity to obtain unique knowledge and gather experience in particular areas of medical science through access to new treatments, increased possibility of operating modern medical equipment (e.g. PET diagnostics), facilitated know-how sharing among a network of specialists and investigators, as well as access to additional materials and training.
- **Access to research tools.** Owing to the nature of clinical trials, which are based on the latest scientific methodology, investigators get access to best practices, methodologies and systemized data collections – and these can be subsequently used in their daily medical practice, contributing to improvements in the quality of functioning of the healthcare system in the country.

Clinical trials market in Poland contributes to the establishment of know-how in the use of innovative drugs and therapies and to improvements in the infrastructure used by clinical research sites

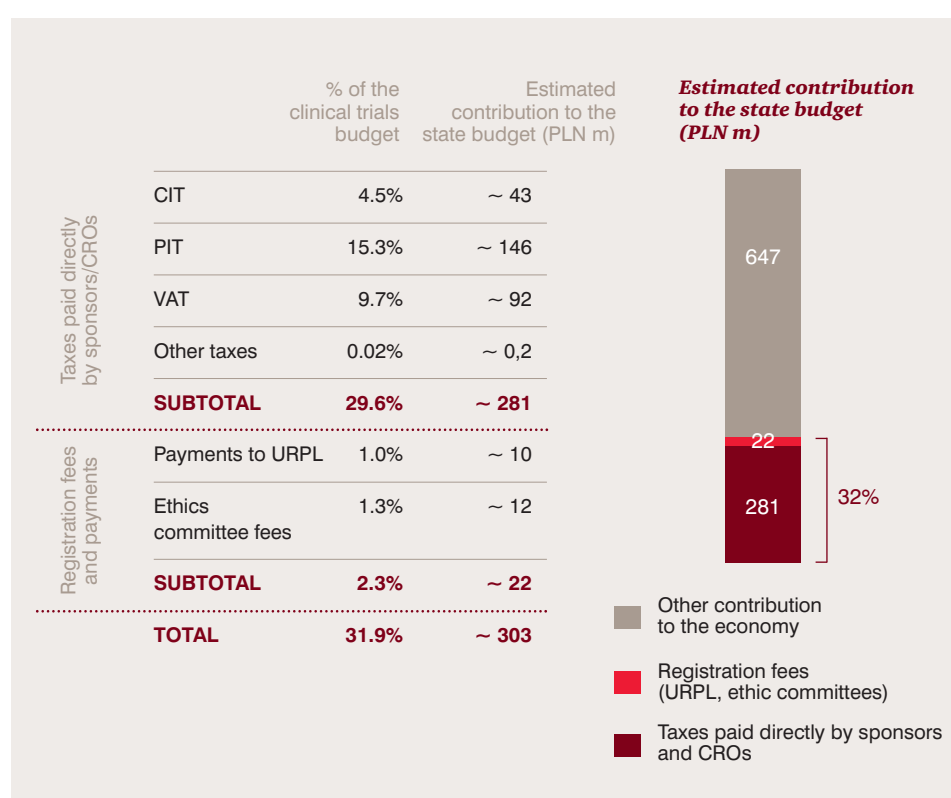
Benefits to other market stakeholders

- **Establishment of know-how.** The data and information obtained during clinical trials constitute a major contribution to the development of medical knowledge with respect to the efficacy and safety of drug therapies. The knowledge increase is not limited to clinical trials with positive outcome. The very fact of the conduct of a clinical trial enables better understanding of the nature and mechanisms of particular diseases, which improves the efficacy of their treatment, including the efficacy of the existing and commonly available therapies.
- **Additional source of hospital financing.** Hospitals receive fees for the conduct of clinical trials. Importantly, it is one of few available sources of financing of hospital operation in Poland which is not related to contracts with NHF. As a result, hospitals have additional funds at their disposal, which they can spend on modern technology purchases, infrastructure replacement, etc.
- **Development of new treatment standards.** Conduct of clinical trials and innovative therapies frequently leads to the development of new treatment standards. As a result of clinical trials, new forms of treatment are implemented and new, more effective medicines are introduced. This is to the benefit of patients, doctors and the scientific community.
- **Gains in medical technology.** The existence of the clinical trials market influences the scope and manner of use of medical equipment, improving the general quality of technical facilities of clinical research sites. This is a consequence of the investigators' obligation to use certified technologies and equipment meeting the specified technical requirements.
- **Growth of knowledge-based economy.** Most countries aspire to develop the economic sectors which use the intellectual potential, knowledge and invention of people (rather than e.g. raw materials sectors) and which have a great potential for rapid growth in the future. In this context, it is hard to overestimate the role of clinical trials in the development of medical knowledge and technology which can be used in a number of innovative industries (biotechnology, information and communication technology, etc.)
- **Scientific conferences.** Clinical trials and their results are typically the subject of scientific conferences, whose participants share knowledge and conclusions. Such exchange of experience is the key to developing an innovative approach to the therapeutic process itself as well as the methodology, scope and size of research carried out in a particular site/country.

In 2014, clinical trials contributed c. PLN 300 m to the state budget

Benefits to the state budget

- **Tax receipts.** Based on the available market data, one can estimate the benefits to the state budget resulting from clinical trials conducted in Poland. The analysis indicates that one third of clinical trial spending is contributed to the state budget through taxes and fees paid. These summed up to PLN 300m in 2014. The size of this contribution may be illustrated by the fact that spending this amount on wages would result in creating c. 5,500 new jobs* (which corresponds e.g. to the total number of registered unemployed persons in the City of Gdynia).
- **Indirect benefits.** It should be noted that the aforementioned estimate accounts only for direct contribution, that is taxes paid by sponsors and CROs plus fees to the Registration Office (URPL) and ethics committees, while excluding any indirect effects (PIT and VAT paid by investigators, company's employees and any other persons earning income as a result of involvement in clinical trials; taxes paid by companies providing services to sponsors and CROs; etc.).



* Average wage cost for the employer per annum in Poland in 2014, according to GUS (c. PLN 55k/year)

Source: GUS, PwC Survey, PwC Analysis

Owing to research in oncology, the largest segment of clinical trials, NHF saved c. PLN 160m in 2014

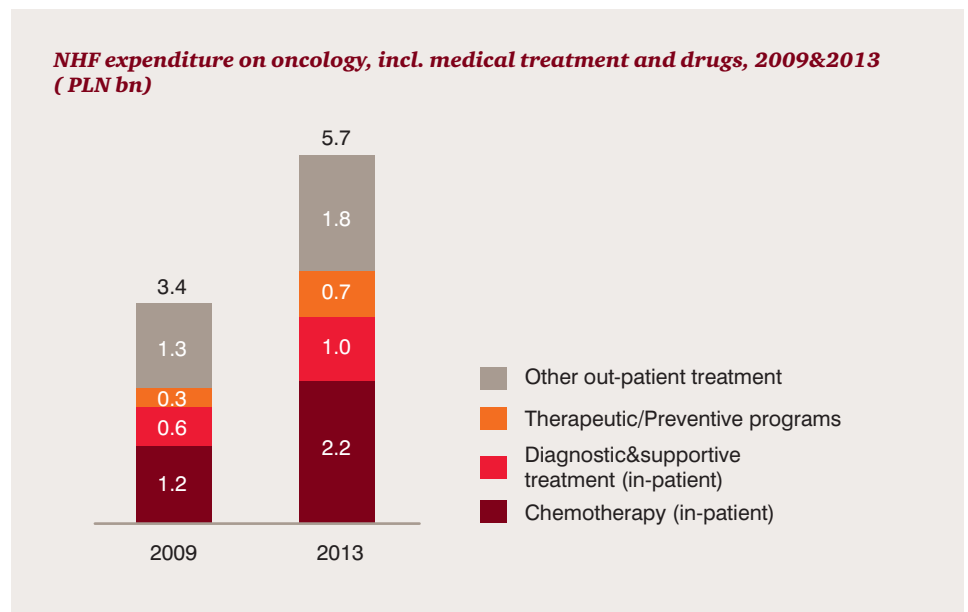
Benefits to NHF

- **Cost reduction.** Clinical trials executed by entities operating in the Polish market significantly reduce NHF costs as a result of the following:
 - Complex diagnostic tests are conducted as part of clinical trials; otherwise, the costs of such tests would be borne by NHF;
 - Owing to the number and scope of additional tests, it is often possible to diagnose concomitant diseases and start the relevant treatment, which increases the safety of patients and eliminates potential hospitalization. This leads to a reduction in NHF future spending on such patients;
 - In clinical trials, patients/participants may undergo long-term treatment in healthcare centers of upgraded standard, receiving more intense care – without an increase in NHF spending.

Case study 1: NHF savings generated by clinical trials in oncology

In Poland, c. 4% of patients suffering from oncological diseases take part in clinical trials. As their treatment is financed by sponsors, cost savings for NHF totaled c. PLN 160 m in 2014 alone. This estimate is rather conservative, as the standard of treatment and the advancement of therapies is typically much higher than of therapies financed by NHF. Thus, the alternative cost savings are in fact higher.

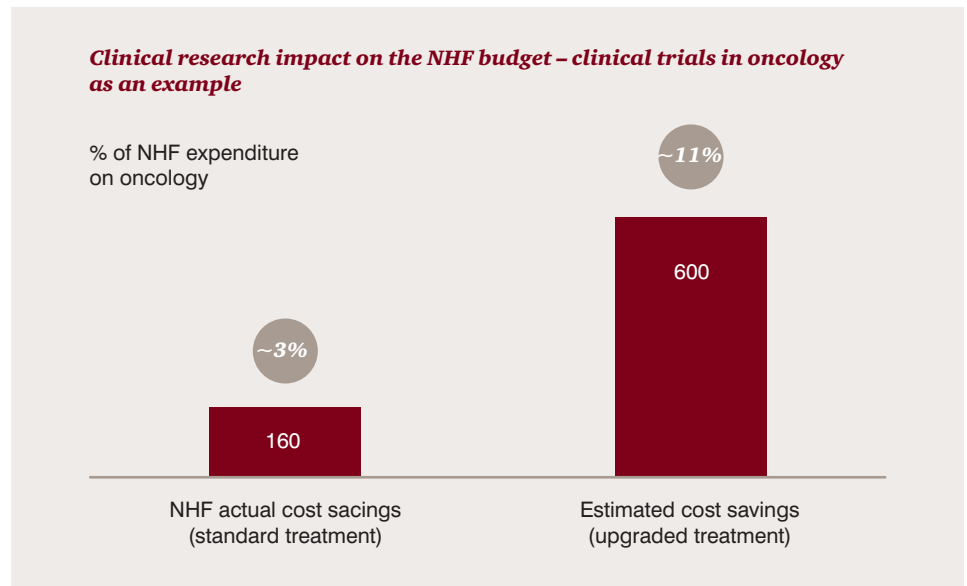
Mean expenditure on oncology drugs per capita in more developed countries – which is, on the average, 5-fold higher than in Poland – is a good proxy of the quality of treatment differential between standard treatment reimbursed by NHF and therapies provided in clinical trials.



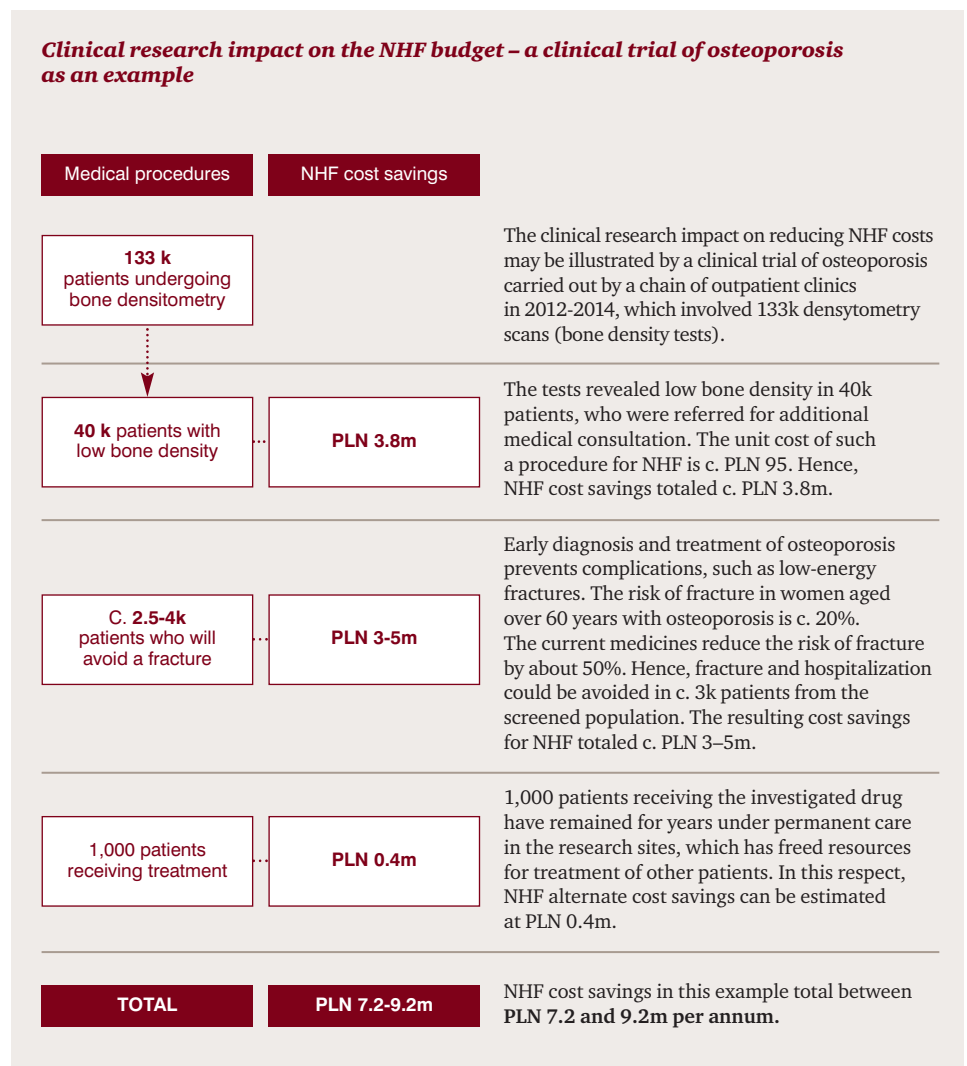
Note: Figures exclude cancer treatment of patients in wards other than oncology, e.g. lung diseases, surgery, neurosurgery, etc.
Source: NHF, Ministry of Health, DiA, PwC Analysis

Owing to a single clinical trial of osteoporosis conducted in one research site, NHF saved c. PLN 7-9 m in 2012-2014

If differences in the quality and advancement of therapies are taken into account, the actual value of treatment financed from clinical trial budgets may amount even up to PLN 600m, which constitutes c. 11% of NHF expenditure on oncology.



Case study 2: Clinical trials of osteoporosis



Analysis of the clinical trials market in Poland

In recent years, Poland's clinical trials market saw slight growth, to c. PLN 950m in 2014, though the number of trials decreased

Size of the clinical trials market in Poland

Poland's clinical trials market has been stagnant in recent years.

Between 2012 and 2014, there was a drop in the number of new clinical trial registrations, which can be attributed to a number of both local and global factors. These included:

- Lengthy administrative procedures and a large number of formal requirements in Poland;
- Less friendly regulations than in other European countries, where additional allowances and incentives are typically offered to clinical trial sponsors;
- Implementation of the provisions of the Directive 2001/20, which has made EU countries less competitive vs. the rest of the world in the clinical trials sector;
- Consolidation of the global pharmaceutical market and, consequently, a decrease in the number of sponsors.

In the same period, the costs of conduct of clinical trials increased due to the following factors:

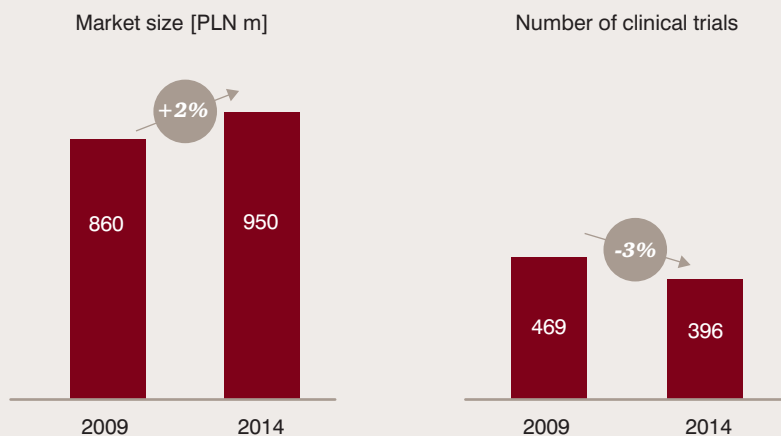
- Growing complexity of clinical trials, resulting from e.g. increased diagnostic requirements;
- A drop in the percentage of patients ultimately enrolled to clinical trials (due to more detailed requirements concerning the type of ailment, resulting from a growing share of clinical trials of targeted therapies, one has to screen larger populations), which can hinder recruitment and lead to an increase in the number of sites required to reach the target number of patients;
- An increase in formal requirements, generating additional costs.

According to our estimates, the clinical trials market was worth c. PLN 950 m in 2014, growing at a mean annual rate of 2.0% (CAGR '09:'14), i.e. below the GDP growth rate in the same period (2.9%). The number of clinical trials decreased from 469 to 396 between 2009 and 2014.

“Over recent years, the market has been growing at a relatively low rate, mainly due to decreasing number of clinical trials.”

CRO

Market size and number of clinical trials in Poland, 2009-2014
 [PLN m, no. of trials]



Note: Market size is defined as total expenditure on clinical trials
 Source: PwC Analysis

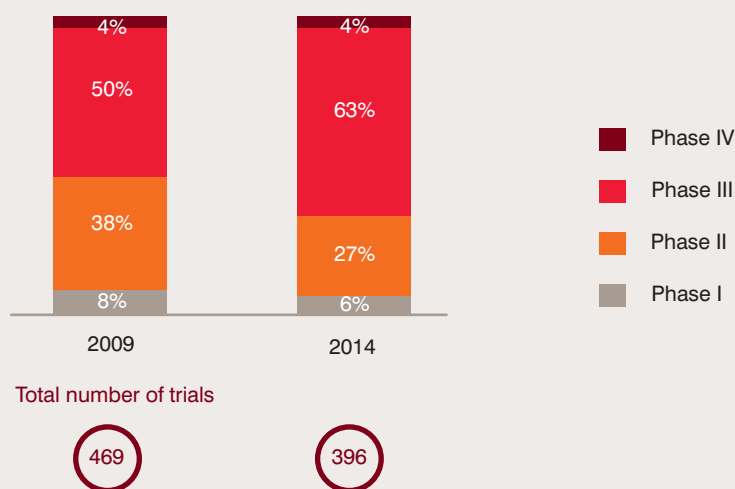
Phase III clinical trials dominate in the Polish market...

Structure of the clinical trials market in Poland

Despite a drop in new clinical trial registrations in Poland, between 2009 and 2014 the number of phase III trials increased (from 235 to 251), driving their share from 50% to 63%. A large share of phase III clinical trials is typical of CEE countries.

Notably, phase II clinical trials were the hardest hit by a decline in volume – their number decreased by 71 over the 5-year period; as a result, their share in the mix shrank from 38% in 2009 to 27% in 2014. It should be noted that time is crucial in phase II. The faster the process of clinical trial registration and patient recruitment in a particular country, the more likely it is to attract sponsors of phase II projects. As the time between the development of a protocol and the clinical trial registration in Poland is longer than in the majority of European countries, Poland is not seen as an attractive country for early phase clinical research.

Structure of clinical trials in Poland, phases I-IV, 2009 & 2014

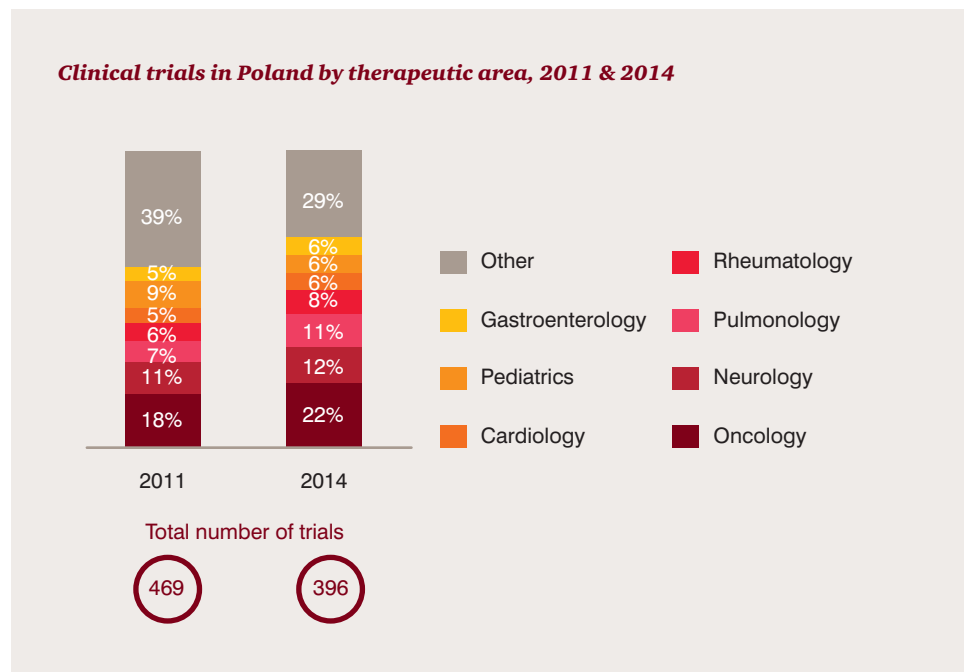


Source: URPL

...and are largely related to oncology

Oncology has remained the leading therapeutic area, increasing its share in the volume of clinical trials by 4 percentage points (to 22% in 2014).

In general, there has been growing concentration in the largest therapeutic areas. In 2011, the three dominating therapeutic areas (oncology, neurology and pediatrics) accounted for nearly 40% of the total number of clinical trials, while in 2014, the three dominating therapeutic areas (oncology, neurology and pulmonology) accounted for as much as 45% of the mix.



Source: URPL

Evaluation of Poland's potential as a site of clinical trials

Poland's key advantage is a large population of patients and strong medical background: research staff and experienced clinical research assistants

Attractiveness of the clinical trials market in Poland

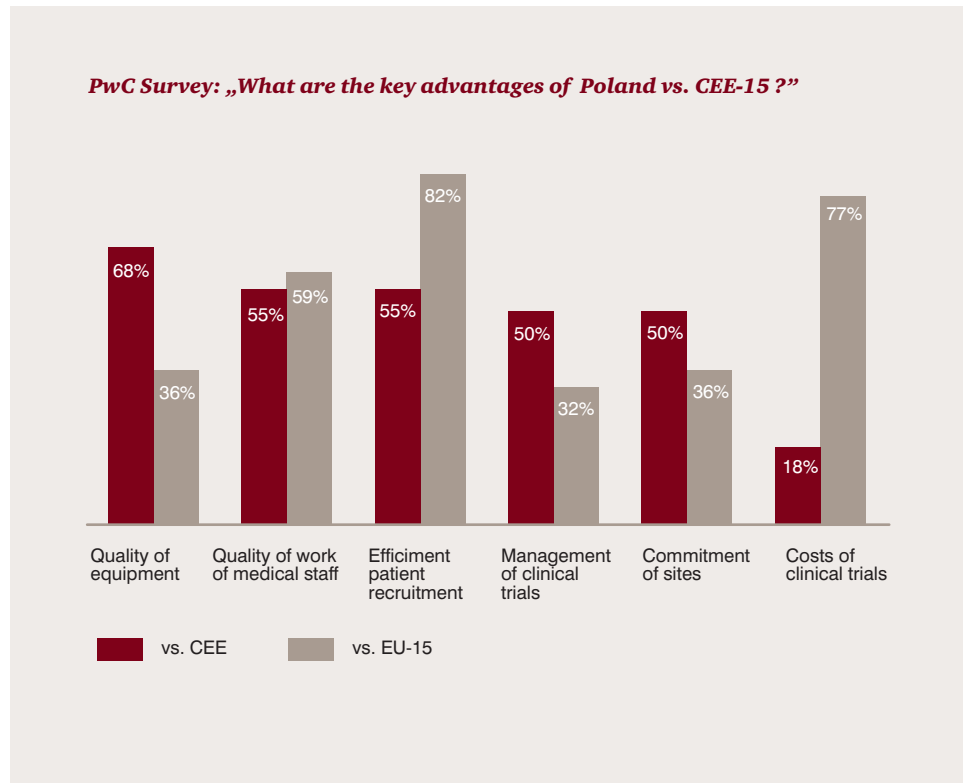
The clinical trials market in Poland is still expanding, with potential for future growth. It has six key advantages, which make it attractive for clinical trial sponsors. These are:

- Large population of patients;
- Size and maturity of the market, experience of market stakeholders and good organization of work;
- Qualified medical staff;
- Well-organized and specialist research sites;
- Strong sponsor/CRO market and qualified and experienced CRAs;
- Attractive level of clinical trial costs vis-à-vis WE or even some CEE countries.

In a survey conducted by PwC, respondents have indicated the areas in which Poland is the leader in the CEE region. These are: quality of medical equipment and staff, as well as high commitment of clinical research sites. According to the survey, the key competitive advantages of Poland versus EU-15 countries are still efficient patient recruitment and lower costs of clinical trials.

“Poland is an attractive market with very well qualified medical staff (doctors), which is characterized by highly efficient patient recruitment.”

Pharmaceutical company



Source: PwC Survey

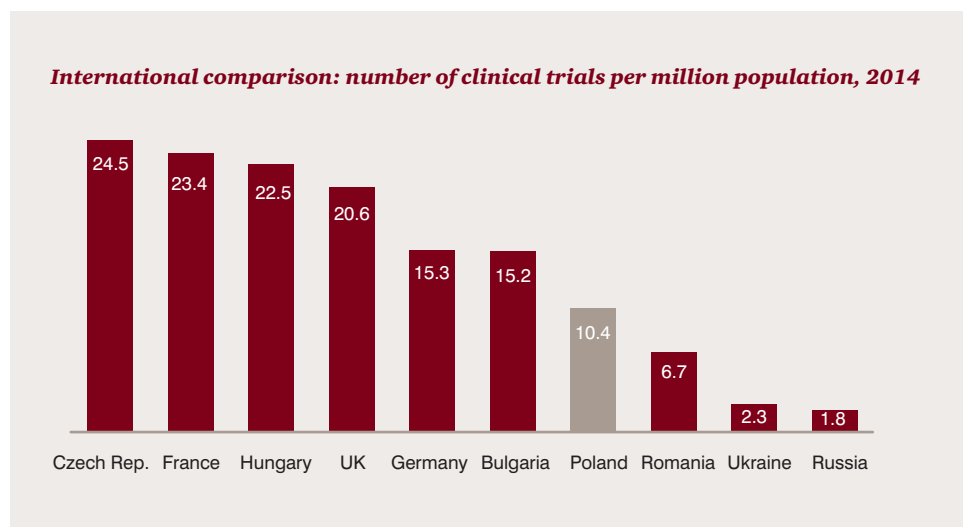
The number of clinical trials conducted in Poland could double

Potential for further growth of the clinical trials market in Poland

The future of Poland’s clinical trials market may seem much more optimistic. Data comparison with other countries in the region indicates that Poland could significantly increase the number of clinical trials.

There is still room for further growth, mainly owing to a difference in the clinical trials market penetration. The market penetration in Poland could increase at least to that in the leading CEE countries, such as Hungary and the Czech Republic.

In Poland, the number of clinical trials per million population is 10.4, that is two times less than in the aforementioned most effective countries of the region. It means that if similar conditions for growth in clinical trials were established in Poland, the penetration rate could converge towards the levels observed in the Czech Republic (24.5) or Hungary (22.5 per million population).

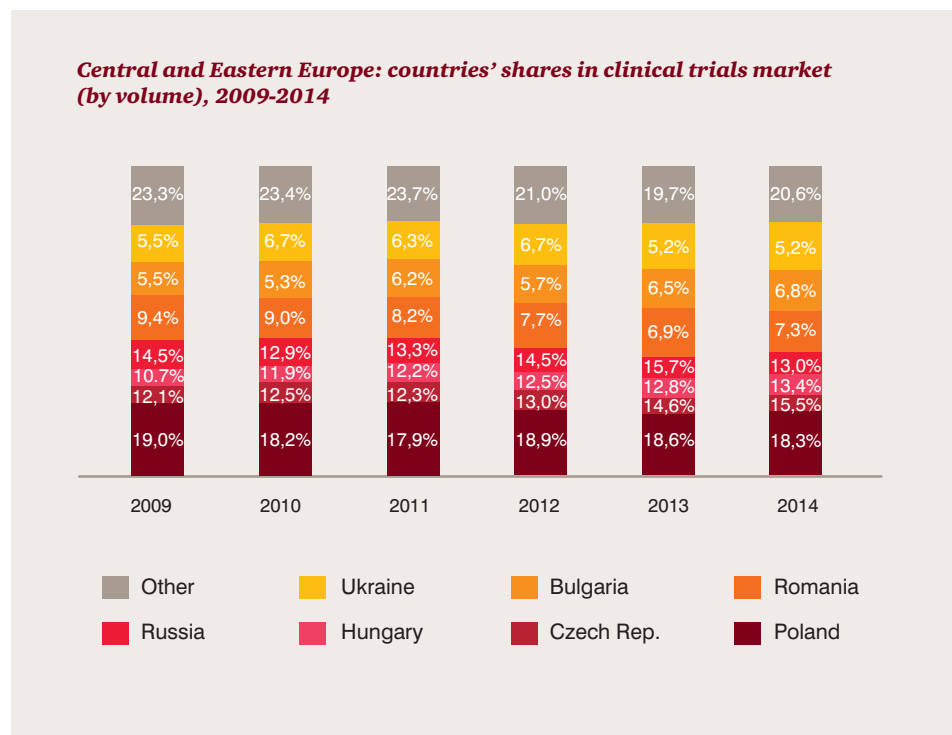


Source: URPL, ClinicalTrials.gov, PwC Analysis

Poland retains the largest share in the volume of clinical trials conducted in CEE (primarily owing to the largest population).

In 2009-2014, a share of clinical trials in Poland in all clinical trials in the CEE region remained fairly stable, ranging from 18% to 19%. However, as shown by some other countries, this share could have grown in that period.

The Czech Republic increased its share from 12.1% to 15.5%, that is by 3.4 percentage points. Hungary experienced similar growth, from 10.7% to 13.4%, in the same period.



Note: "Other" includes: Croatia, Estonia, Lithuania, Latvia, Serbia, Slovakia and Slovenia

Source: ClinicalTrials.gov

Poland's potential remains unused...

Both the Czech Republic and Hungary have successfully implemented some mechanisms to encourage clinical trials

One of the elements that may have influenced the aforementioned trends is positive attitude of public authorities in these countries to the clinical trials sector. In a survey, respondents have specified countries which have made efforts to make their clinical trials markets more attractive. The key conclusions, which could be an inspiration for changes in Poland, are presented below.

Perception of the clinical trials market in Hungary

Sponsors positively assess the attitude of public authorities in a process of clinical trial authorization. The authorities make efforts to facilitate this process and support the sponsor.

Also a solution with one central ethics committee has been positively assessed. In this scheme, the application is reviewed in parallel by all the bodies involved in the clinical trial authorization process and the authorization is granted through a single decision.

Furthermore, Hungary paid much attention to lower administrative barriers, which the respondents have also assessed as a positive step contributing to the market growth.

Perception of the clinical trials market in the Czech Republic

In the Czech market, a process of clinical trial authorization is also assessed very positively, owing to clear rules and good cooperation with public authorities.

A possibility to file documents electronically is a major advantage. Sponsors have positively commented on the terms of financing of medical services provided in connection with a clinical trial. The process is considered as transparent and facilitating the clinical trial cost estimation. Also the issue of tax and financial incentives for clinical trials has been regulated in the Czech Republic.

As a result of friendly legislation environment, there is much interest among sponsors in the clinical trials market in the Czech Republic, leading to high penetration rate in this regard.

Unfortunately, the existing growth opportunities for the clinical trials market in Poland have not been used over the last several years

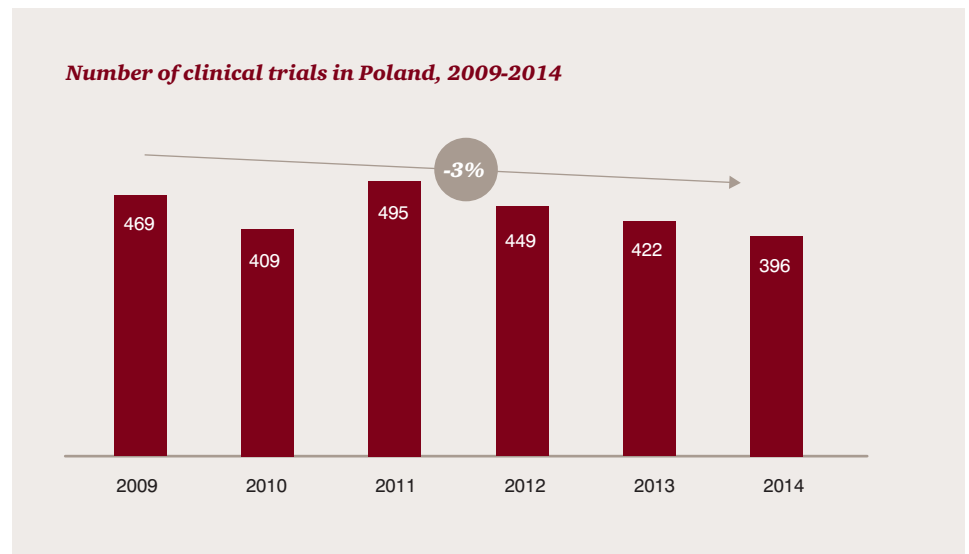
The developments in the clinical trials sector in Poland over the last five years can be rather easily identified.

In particular, the market evolution could be referred to the four scenarios presented in our report of 2010, “Clinical Trials in Poland – Key Challenges”, which described potential paths of development of the clinical trials market in Poland:

- **“Status quo”** – No major changes in the clinical trials legislative and administrative environment;
- **“Admin improvement”** – Shortening of the time required to register a clinical trial and other administrative improvements;
- **“Additional incentives”** – Introduction of favorable tax regulations, additional grants, etc., resulting in a significant increase in the volume of clinical trials;
- **“Restrictive legislation”** – Introduction of additional restrictive legislation, reducing Poland’s competitiveness and leading to outflow of clinical trials to other geographies.

From today’s perspective, it may be concluded that an opportunity to increase the potential of this market in Poland has not been used.

The clinical trials market has followed the “Status quo” path over the recent years, performing as if no major changes had been introduced. Despite slight improvements in the functioning of public authorities, there has been no reduction in the overall registration time (which had been assumed in the “Admin improvement” scenario).



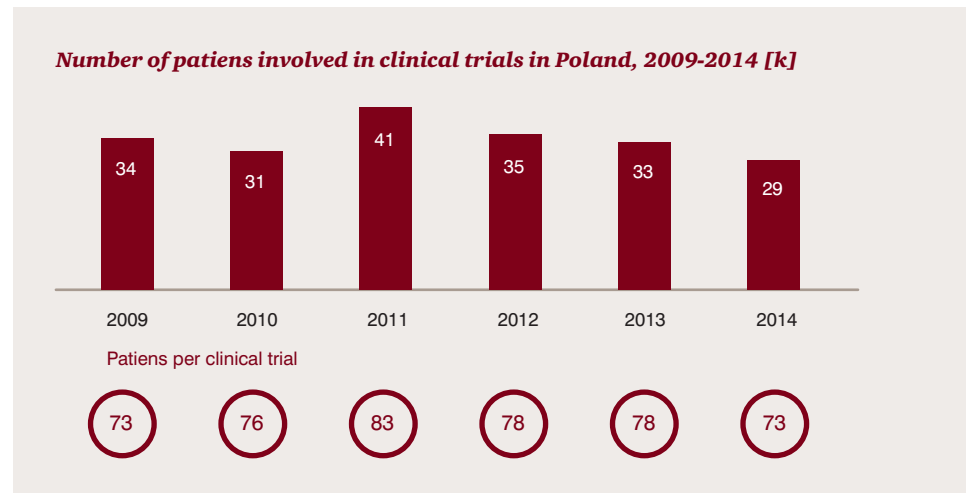
Source: URPL

“2010 was an unfavorable year for both Polish and global clinical trials market. A number of sponsors decided to suspend or delay clinical trials due to the market climate”.

Pharmaceutical company

There has been a drop in the number of both patients and investigators involved in clinical trials

The volume decrease was accompanied by a declining number of patients (at a rate of c. 2% per annum).



Source: URPL, PwC Survey

A similar downward trend may be observed with respect to the number of investigators and the number of patients per investigator.



Source: URPL, PwC Survey

*Non-commercial trials
are a negligible component of the
clinical trials market in Poland*

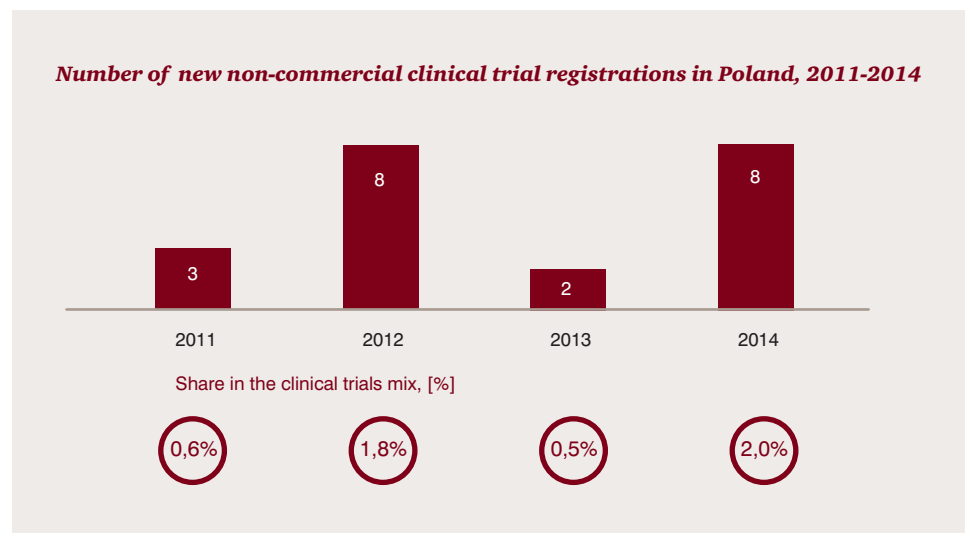
Non-commercial clinical trials

Moreover, the potential of non-commercial clinical trials is still unused in Poland, as their number remains very low.

Non-commercial clinical trials are conducted by research or medical centers and aim at seeking treatments for rare diseases or general progress in medical knowledge and science.

Such trials may also be launched to assess the efficacy of the existing medicines. Such assessment may be useful to e.g. public authorities in making decisions on the reimbursement of drugs available in the market from the state budget. Non-commercial clinical trials are a negligible component of the Polish market: only 6 such trials were registered in 2014, which accounted for less than 2% of all clinical trials in Poland.

Poland's comparison with WE countries, where such projects constitute even 40% of the clinical trials mix, only confirms the scale of the problem in Poland.



Source: Ministry of Health

Causes of the current state of the clinical trials market in Poland

Changes in the scope of the required dossier decreased Poland's attractiveness as a country for clinical trials and to a large extent inhibited the market growth

Legislative changes – perspective over the last 5 years

While analyzing why Poland has failed to utilize its potential in the clinical trials area over the last few years, one should mention the legal environment and unstable regulations.

Already in 2009 and 2010 the Polish legislator identified some then existing barriers and made an attempt to remove them. The legislative process was halted in 2011 upon development of a draft act on clinical trials of medicinal products and veterinary medicinal products (due to information about the European Union's intention to issue a regulation in the same area). However, the draft bill in the wording proposed in 2010 raised serious concerns, as it included some provisions that could lead to a collapse of the clinical trials market in Poland.

Despite discontinuation of works on the aforementioned clinical trials act, over the last five years the Polish legislator admittedly made some attempts to improve the regulations related to this market. On May 1, 2011, a process of clinical trial authorization was simplified, that is both the application assessment and the final decision are now issued by a single agency, namely URPL (in the former scheme, the final decision was issued by the Minister of Health). Furthermore, one should commend the Polish legislator for its efforts concerning non-commercial clinical trials. A recent amendment to the Pharmaceutical Law should bring about a significant decrease in the costs of such trials, particularly with respect to the costs of healthcare services provided to the participants of non-commercial clinical trials. As a result, the amendment may contribute to an increase in the number of such trials in Poland.

Furthermore, the PwC Survey indicates that in the said period sponsors observed more flexibility on behalf of URPL. In particular, the exchange of letters and comments was made possible via electronic means of communication, which radically facilitated a dialog with the URPL and accelerated the clinical trial authorization process.

On the other hand, in the last 5 years Poland implemented some provisions whose assessment is definitely negative. These significantly increased the barriers existing in the clinical trials market and, according to a common opinion, to a great extent inhibited its growth.

Key administrative barriers to the market development

- **The requirement to submit original contracts with the investigator and the site when filing the clinical trial dossier.** These documents should be submitted together with the application; they cannot be provided at a later date (like it was possible before the amendment). Bulgaria is the only other country in the European Union which still has such a requirement.

The scope of guaranteed medical services to be financed by sponsors is not accurately defined, so their cost is hard to predict

As a result, a clinical trial application can now be filed only after the aforementioned contracts with the investigator and the site for the given particular clinical trial are concluded. Hence, the time to obtain a clinical trial authorization has increased by the time required for negotiating, finalizing and executing these contracts (often by up to several months). Consequently, a possibility to conduct quick short-term clinical trials or trials which require rapid patient recruitment is very limited.

- **Financing of healthcare services in clinical trials.** On May 1, 2011, Article 37k(1) of the Pharmaceutical Law, determining which procedures are to be financed by the sponsor and the public payer, was clarified. According to this article, the sponsor shall finance the procedures which are included in the scope of guaranteed medical services. In addition, the sponsor shall also finance some non-guaranteed services, which are: (i) required to counter the effects of any health complications resulting from the use of the investigated medicinal product, (ii) necessary to provide due to administration of the investigated medicinal product, or (iii) required to enroll patients into the clinical trial.

As there is no real procedure for challenging the settlements between the public payer and a site, as a rule any doubts concerning the aforementioned costs are decided to the detriment of the sponsor:

- NHF differently interprets the provisions of the article and often tries to offload the costs of guaranteed medical services onto the sponsor. Sites, which fear that NHF will not finance the relevant healthcare services, also try to shift any costs to the clinical trial sponsor;
- this may lead to discrimination of clinical trial subjects by excluding financing of guaranteed services with respect to this group and by restricting patients' constitutional right of equal access to guaranteed services simply because they take part in a clinical trial.

For years, the terms of financing of healthcare services remained a major barrier also to non-commercial trials. This matter was particularly difficult for non-commercial sponsors who had to plan and allocate a budget for financing the costs of healthcare services (including guaranteed services related e.g. to potential complications, which had to be financed by such sponsors pursuant to the Pharmaceutical Law). Fortunately, this matter has been recently regulated in a manner favorable to sponsors, at least in case of clinical trials of a non-commercial character.

- **Changes in the field of non-commercial clinical trials.** On May 1, 2011, a ban on commercial use (including registration of new medicines) of the data gathered in non-commercial clinical trials was incorporated into the Polish legal system. This resulted from the transposition of the community law.

Social awareness is a major factor affecting the current state of the clinical trials market in Poland

Issue of social awareness and attitude of institutions

The presented examples of regulations which have affected the clinical trials sector in Poland do not exhaust the matter. It is worth noting that a psychological factor plays the key role in a process of shaping both legal regulations and actual practices. Arguably, without significantly raising awareness of the role and importance of clinical trials (both with respect to both the development of new medicines and the development of medical science in general) it is impossible to improve the existing state of affairs and any attempts to reform or amend the existing regulations will be doomed to failure. Only a concerted effort of all market stakeholders aimed at raising social awareness and changing the attitude of the legislator can bring about major improvements in the legal environment. Such initiatives can lead to the successful implementation of the proposals of the clinical trials community, elimination of barriers and development of the clinical trials market in Poland.

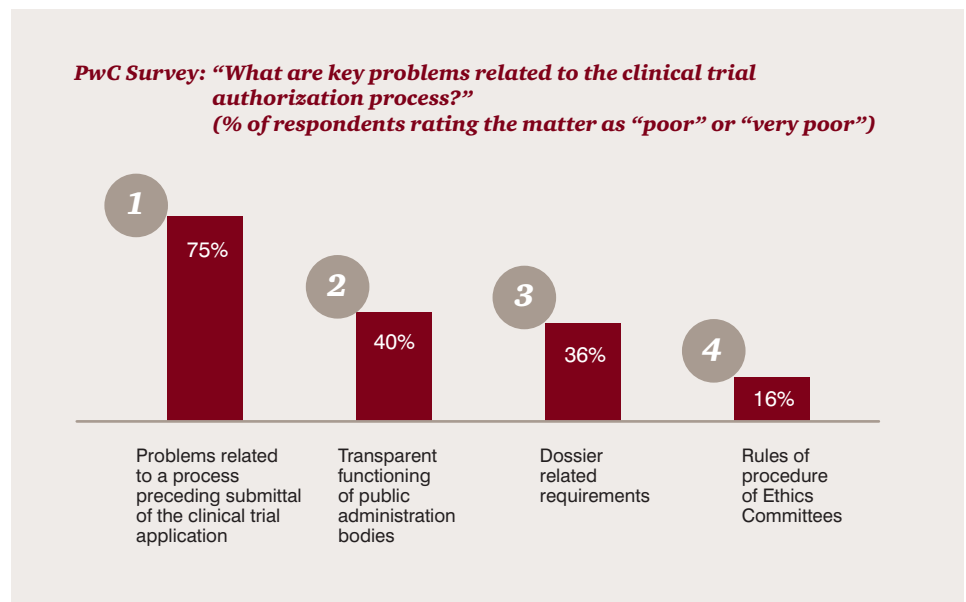
Administrative issues, mainly clinical trial registration time and procedures, remain major obstacles

PwC Survey results

The state of affairs described above was reflected in the results of a survey conducted by PwC and the interviews with parties involved in clinical trials. Based on the gathered opinions, one may conclude that the most important factors which constitute barriers to the development of the clinical trials market in Poland include:

- Requirement to submit contracts with the site and the principal investigator as a condition of filing a complete dossier when applying for clinical trial registration;
- Lack (in a number of hospitals) of transparent procedures for document flow and making decisions related to contract negotiation and conclusion. This happens even if sites have specialist units which coordinate the process of concluding contracts with sponsors (due to limited resources and lack of specialist training in project management);
- Lack of clear rules for financing by NHF of medical services provided to clinical trial subjects;
- No standardization of ethics committees' operating procedures and no detailed regulations concerning payment of fees to local ethics committees.

The Survey specified 8 barriers typically met by sponsors and CROs. These were divided into administrative matters and matters related to the conduct of clinical trials. The key conclusions and comments formulated by the PwC survey respondents are presented below.

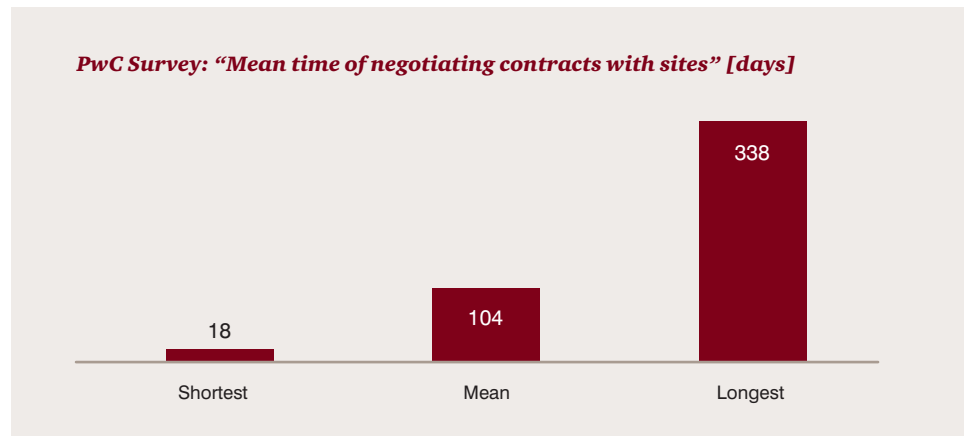


Source: PwC Survey

The main problem related to clinical trial approval is a lengthy process of negotiating contracts with hospitals

1

Problems related to a process preceding submission of the clinical trial application. The matter was negatively assessed by 75% of respondents.



Source: PwC Survey

"The requirement to attach the negotiated contract with a site to the clinical trial application is the most important problem. It takes a lot of time for a site to make a decision and sign a contract. This applies particularly to public hospitals, which play the key role owing to access to large populations of patients."

Pharmaceutical company

"The mean time of negotiations with a hospital is 4 months, but these can take even 11 months. With private-owned sites, this process is much quicker and takes about a month."

Pharmaceutical company

"Private-owned sites benefit most from the situation, as they are more flexible and efficient."

Investigator

This state of affairs may be primarily attributed to the lack of a business unit that would effectively and efficiently coordinate the relevant administrative processes in individual sites (mainly public healthcare facilities).

The long time of clinical trial registration is also a major problem. Over the five years, the whole process has got even longer due to significant changes in the requirements concerning the clinical trial application dossier. In this respect, Poland compares unfavorably with other CEE countries.

"Cooperation with sites would be better and more efficient if they had a person coordinating the process of negotiations and contract conclusion."

CRO

"No major changes are required to make an improvement, as often the problem lies in lack of efficiency and the fact that documents are held back by one of the site departments."

Investigator

Also the way of functioning of Ethics Committees is a source of problems in obtaining approvals

PwC Survey: Mean time of clinical trial registration in CEE countries, 2014 [days]



Time between adoption of the final version of the protocol and the clinical trial registration
Source: PwC Survey

2

Transparent functioning of public administration bodies. Lack of clear division of competence between URPL and Ethics Committees.

“There is no clear division of competence between public administration bodies. In particular, there is double assessment by URPL and Ethics Committees.”

Pharmaceutical company

3

Dossier related requirements. The current formal requirements introduce artificial restrictions, which are non-existent in other EU countries and could be easily avoided.

“The requirement to attach an excerpt from the National Court Register to an application restricts foreign companies with no branches in Poland.”

CRO

4

Rules of procedure of Ethics Committees. The way of functioning of Ethics Committees hinders the process of commencing a clinical trial, mainly due to lack of standardization of their internal regulations.

“Lack of uniform rules of procedure of Ethics Committees results in a lot of unnecessary and arduous work on studying each committee’s own regulations and price list.”

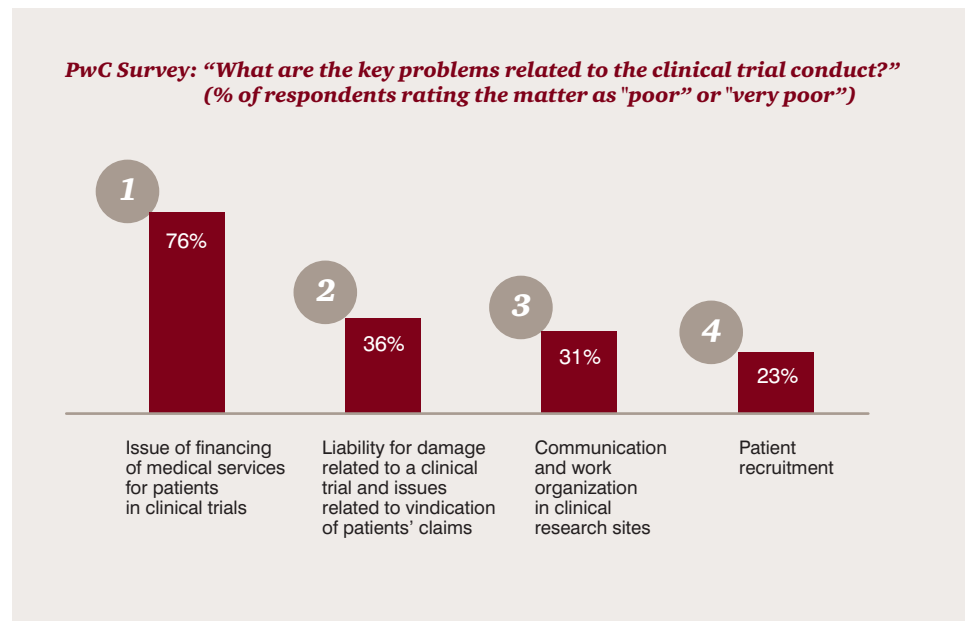
Pharmaceutical company

“Some committees do not have any websites. Furthermore, in the holiday season, committees have virtually no meetings, so application processes get suspended.”

Investigator

Issues related to clinical trial conduct

Lack of certainty with respect to financing by NHF of procedures from the basket of guaranteed medical services is a major problem



Note: Multiple answers available – results do not sum up to 100%

Source: PwC Survey

1

Issue of financing of medical services for patients in clinical trials.

Despite the existing regulations, the parties' share in financing of clinical trials and the related costs was unpredictable in the analyzed period.

"In Poland, it is difficult to determine whether the cost of a particular diagnostic test from the basket of guaranteed services (which are eligible to all the insured) will be financed by NHF or not, as NHF frequently does not consider a particular clinical trial to be justified. As a result, some sponsors choose other countries with higher costs yet easier to predict share of services financed by the public payer."

Pharmaceutical company

2

Liability for damage suffered in connection with a clinical trial and issues related to vindication of patients' claims. Liability insurance schemes available in Poland do not adequately protect patients, sponsors or investigators involved in a clinical trial, as compensation payment depends on proving the sponsor or investigator's fault. A patient who has suffered harm yet cannot prove anybody's guilt, can only raise claims in court against the sponsor and/or investigator, but such claims are not covered by the liability insurance policy.

"Currently, patients have little chances to receive compensation as they have to prove one's guilt."

CRO

3

Communication and work organization in clinical research sites. In a number of sites, there are no teams of doctors and nurses dedicated to clinical trials.

“From the investigator’s point of view, it is important to have a team of nurses dedicated to a clinical trial. It is good if their duties focus on a single area of activity.”

Investigator

Broader access to comprehensive and coordinated information in the media would definitely attract new patients to clinical trials

4

Patient recruitment. There are numerous tools which could be introduced to facilitate access to information for the people concerned, thus contributing to more efficient patient recruitment.

There is a number of dedicated Internet portals which help patients, their relatives and doctors to find a clinical trial offering effective treatment. However, most of these portals are available in English only and do not account for Polish clinical research sites. Also the clinical trials database operated by the INFARMA Employers’ Union of Innovative Pharmaceutical Companies at <http://www.badaniaklinicznepolsce.pl/> is not aimed at contacting patients with sites. Under the current Polish regulations, URPL cannot publish data of registered clinical trials.

“At present, there is no independent platform providing patients with knowledge about on-going clinical trials. Such a platform could be established e.g. at URPL.”

Patient association

“It would be a good idea to develop an information platform offering patients initial qualification for a clinical trial.”

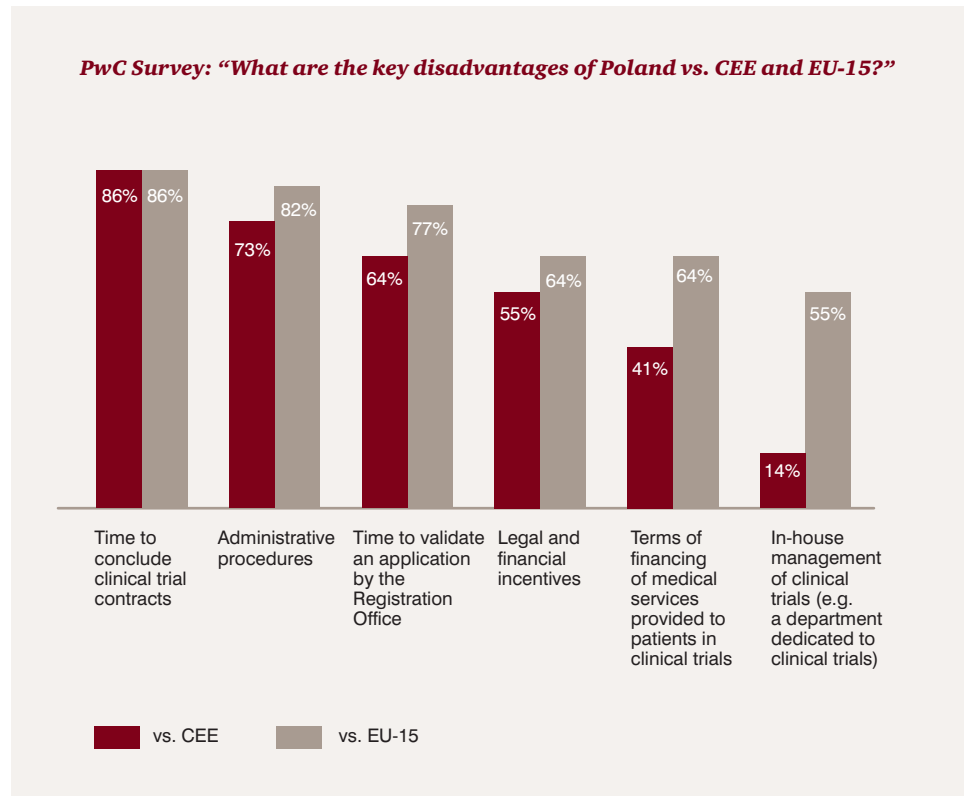
CRO

Poland compares unfavorably with other countries in administrative issues which are important for the clinical trial conduct

PwC Survey summary

The barriers listed by the PwC Survey respondents negatively affect the perception of Poland’s market among sponsors, decreasing access to innovative therapies for Polish patients and reducing Poland’s competitiveness vis-à-vis CEE and WE countries.

The key issues indicated by all the respondents which need to be improved versus CEE and WE countries include, above all, (i) cancelling the requirement to attach signed contracts with a site and investigator to a clinical trial application, and (ii) reducing the time to validate the clinical trial dossier submitted to URPL (the current regulations do not set any deadline for URPL to complete the validation process).



Source: PwC Survey

It is necessary to further facilitate the conduct of non-commercial clinical trials

Non-commercial clinical trials

Until recently, non-commercial clinical trials in Poland were subject to the same legal restrictions as commercial ones. An amendment to the Pharmaceutical Law passed in the second half of 2015 facilitated financing of non-commercial clinical trials by partly transferring to NHF the obligation to finance healthcare services provided to patients involved in such projects. However, non-commercial sponsors still have to meet the same formal requirements which are imposed on commercial sponsors.

Acknowledging the existing problems with financing of non-commercial trials, the Polish legislator has reduced fees to be paid by non-commercial sponsors for a clinical trial application. Similarly, a number of Ethics Committees charge lower fees for ethical assessment of non-commercial clinical trials. However, the obligation to hold a liability insurance policy remains a major burden for sponsors of non-commercial trials. Even though the latter typically concern already registered medicines and pose the minimal risk for patients, there are no special clauses in this respect in the Polish regulations. The regulations which remained in force in recent years contributed to the establishment of unfavorable conditions for the conduct of non-commercial clinical trials in Poland.

Another major barrier to non-commercial clinical trials is related to lack of know-how among non-commercial sponsors with respect to trial organization (e.g. protocol development), securing funds (access to sources of financing, awareness of Polish and international grant programs) and legal handling of the clinical trial registration and execution process (in case of commercial sponsors, these matters are often handled by dedicated departments responsible for the legal and organizational aspects of clinical trials).

Costs and effects of the lost opportunities

Nearly 70 clinical trials worth c. PLN 170m were not conducted in Poland in 2014 due to administrative drawbacks

Due to sponsors' perception of Poland as a less attractive country (despite its obvious potential), in case of some clinical trials Poland is not even considered as a country for the conduct thereof. Moreover, sponsors sometimes discontinue the trial registration procedure in Poland due to its lengthiness. This state of affairs results in losses related to the lost opportunities for the market development and growth of the volume of clinical trials.

According to a survey conducted by PwC, in 2014 alone c. 70 clinical trials (corresponding to 18% of the Polish market) were not conducted in Poland due to the existing drawbacks. Namely:

- c. 40 clinical trials were not conducted due to problems occurring in a process of negotiating contracts with investigators and sites; and
- c. 30 clinical trials were not registered due to a lengthy process of application validation/ /trial registration or tiresome procedures to patients. As a result, the Polish market and the state budget might have lost even c. PLN 170m and c. PLN 54m, respectively.

In the long-term perspective (e.g. 2011-2014), the losses suffered by the Polish economy might have been even bigger. These include lost receipts and other tangible benefits (e.g. related to creation of jobs, investments, development of the supporting services sector, etc.), as well as intangible benefits (development of medical knowledge, growth of experience, know-how transfer, etc.). Furthermore, the perception of Poland as a country which is not engaged in actively supporting innovative industries (which include the clinical trials sector and the related innovative pharmacy and medicine sector) may in the future negatively affect the general opinion about Poland as a non-attractive country for prospective investors.

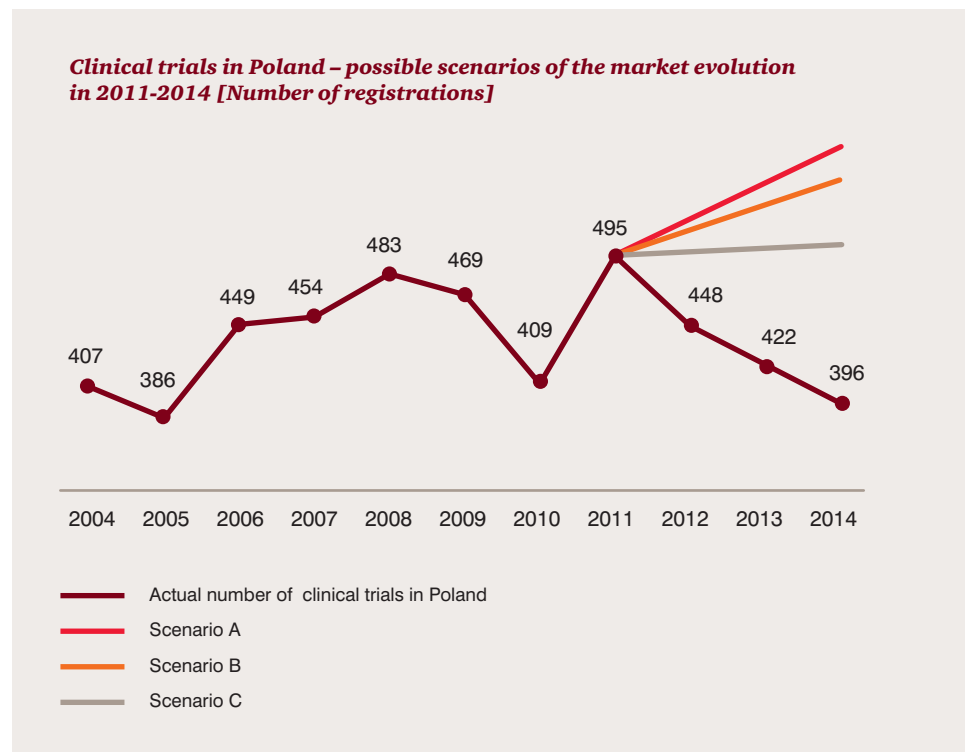
Comparison of the effects of the barriers existing in the clinical trials market in 2011-2014 on the relative position of Poland versus its peer markets in the region, the Czech Republic and Hungary, is not optimistic, either. For the purpose of such comparison, one may attempt to draft alternative scenarios of market evolution and refer them to the actual data for the clinical trials market in Poland.

Poland could have completed 300-450 additional clinical trials of the total value of PLN 0.6 to 1.0 bn in 2011-2014. The state budget could have gained PLN 200-350 m.

Alternative scenarios of Poland's clinical trials market evolution

Below, we present three possible scenarios of evolution of the clinical trials market in Poland together with the actual data for 2011–2014 as a reference. The scenarios are based on the following assumptions:

- **Alternative scenario A:** Path of convergence to Hungary – It assumes that the number of clinical trials per million population would reach Hungary's level within 8 years (from 2011). The key driver of growth would be an active role of the legislator and public authorities in removing the existing barriers, particularly through lifting the obligation to submit signed contracts with investigators and sites while filing a clinical trial application;
- **Alternative scenario B:** Growth rate like in the Czech Republic – It assumes implementation of positive changes in regulations with respect to clinical trial financing (following the example of the Czech Republic) and lifting the aforementioned obligation. As a result, it would be possible for the Polish market to experience a similar growth rate to that seen in the Czech Republic;
- **Alternative scenario C:** Status quo – It assumes that the requirement to submit signed contracts with investigators and sites while filing a clinical trial application was not introduced in 2012. In this scenario, the market could have grown at a rate of 2% per annum.



Note: Number of trials per capita assumed to reach the level in Hungary within 8 years (from 2011)
Source : URPL, ClinicalTrials.gov, PwC Survey

The above comparison indicates that the clinical trials market in Poland not only failed to follow a path of convergence to its CEE peer markets, but also, due to persistent drawbacks (e.g. registration time) and new barriers (e.g. the requirements introduced in 2014), began to shrink.

Using the opportunities related to new EU regulations is the most important challenge for the clinical trials market in Poland

Depending on the scenario, the lost gains* for the Polish market in 2011-2014 may total:

- **From 300 to 450 clinical trials lost;**
- **From PLN 0.6 to 1.0bn** lost in the value of the clinical trials market;
- **From PLN 200 to 350m** not received by the state budget.

These figures indicate that in the future Poland's clinical trials market could grow 20% to 35% faster than in the 2011-2014 period.

Identification of a catalogue of actions required to change the existing state of affairs and attract additional clinical trials to Poland is fundamental to the rate and scale of future growth of the clinical trials market in Poland. It is all the more important as we face the introduction of very important regulatory changes in the functioning of the clinical trials market across the European Union.

The new regulations, which harmonize procedures and unify interpretations, may result in a considerable increase or decrease in the attractiveness of markets in individual countries (e.g. in connection with the quality of provisions drafted on the local level, which are to accompany the implementation of the Regulation No. 536/2014).

Furthermore, the harmonization of the conditions of clinical trial authorization and centralization of processes may lead to the loss of advantage related to the size/population of Poland (as the ease to obtain a harmonized authorization in several smaller markets at the same time may become the deciding factor). In this context, it is important to analyze the effect of the new regulations on the situation of clinical trials in Poland and determine the character, scale and schedule of adaptive actions.

The aim is not only not to worsen the conditions of functioning of the entities involved in clinical trials in Poland but, above all, to use the said changes to make Poland as attractive as possible as a site of future clinical trials.

As indicated before, this would be possible only if some concerted efforts are undertaken in order to raise the social awareness of the role and importance of clinical trials and change the mentality of the institutions which are to set and apply new regulations (so they account for the benefits of maximizing the volume of clinical trials in Poland).

* The loss estimate accounts for the sum of lost gains in 2011–2014, determined separately for each year in accordance with the presented scenarios.

Potential market evolution scenarios

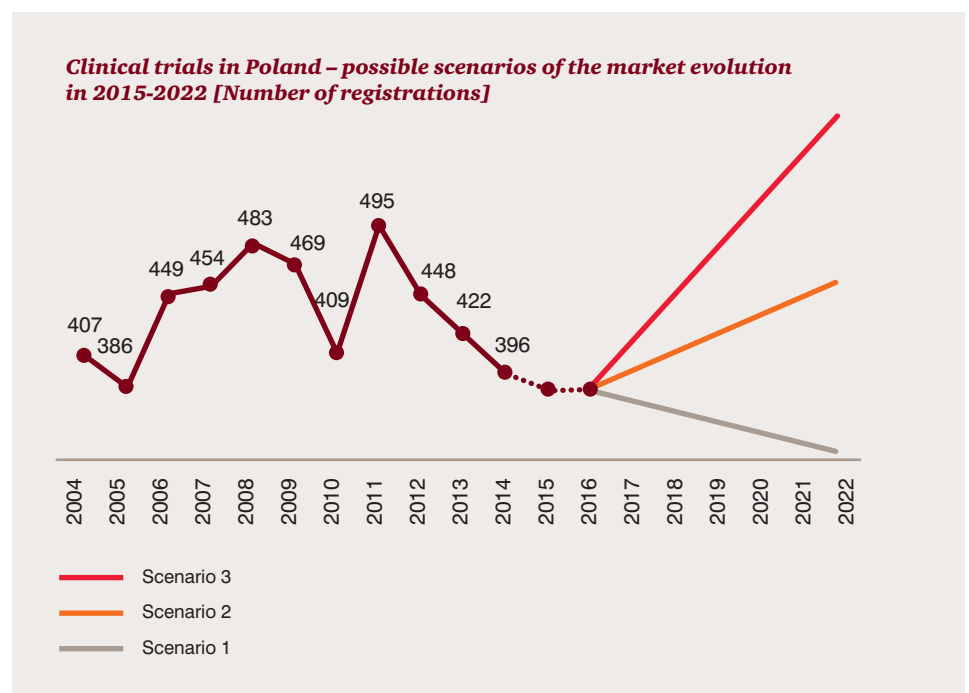
Inactivity of the Polish legislator will have a negative effect on the clinical trials market in Poland

Provisions of the Regulation No. 536/2014* will not be applied before 2017. By then, Poland has to adjust its legal system to the community requirements.

On the one hand, the Regulation No. 536/2014 is an opportunity for the Polish market, on the other hand it puts Poland in a position in which failure to harmonize its regulations with EU requirements will have negative effects on Poland's clinical trials market. Moreover, not only the fact of undertaking harmonization efforts, but also their quality and prudence (accounting for the benefits to all market stakeholders resulting from an increase in the volume of clinical trials in Poland) will matter.

Our analysis indicates that there are three main scenarios of the evolution of the situation in Poland:

- **Scenario 1:** Launch of the Regulation No. 536/2014 without any actions to adapt the legal environment in Poland;
- **Scenario 2:** Supplementing the Regulation No. 536/2014 with prudent domestic regulations to maximize its positive effect on the market;
- **Scenario 3:** Active support through a system of incentives and instruments offered to all market stakeholders.



Source : URPL, ClinicalTrials.gov, PwC Survey

* The effects of its implementation and the implications of this fact for the Polish market are discussed in detail in Section 2 below.

Active support will significantly improve the functioning of the clinical trials market, enabling Poland to achieve the dominating position in the CEE region

Scenario	Effect	Assumptions
Scenario 1: Regulation only	Negative	<ul style="list-style-type: none"> Poland's actions are limited to commencing the application of the Regulation No. 536/2014; there are no adaptive actions in the area not directly regulated by the EU legislation. Poland becomes an even less attractive country (in the wake of the unification and standardization of processes, the restrictions and requirements existing in Poland will decisively contribute to a negative opinion among sponsors). As a result, this leads to further decline in the volume of clinical trials in Poland at a rate similar to that observed in recent years.
Scenario 2: Supplementary regulations	Negative	<ul style="list-style-type: none"> Transposition of the Regulation No. 536/2014 to the Polish legal system are accompanied by actions to adapt/modify local regulations in the areas not directly governed by the Regulation. Poland becomes a country similar to other EU countries in terms of conditions for the conduct of clinical trials; some existing administrative drawbacks are eliminated and the time to commence a clinical trial is shortened; As a result, the Polish market grows at a similar or slightly higher rate than the European benchmark (like up to 2009) owing to Poland's potential (particularly large population of patients and qualified medical staff).
Scenario 3: Active support	Positive	<ul style="list-style-type: none"> Implementation of the Regulation No. 536/2014 and removal of the key barriers. In addition, implementation of solutions aimed to enhance the attractiveness of the Polish market versus CEE and WE countries, particularly by introducing financial and tax incentives, developing information platforms for patients, supporting hospitals involved in clinical trials, encouraging healthcare centers to introduce coordinators for relations with clinical trial sponsors, etc. Growth rate reaches a level comparable to that seen recently in the Czech Republic, which had benefited from a number of positive changes ensuring high penetration with clinical trials and attractive position in the clinical trials market in the CEE region. As a result, Poland achieves the highest growth rate in the region and strengthens its position as the largest market for clinical trials in CEE.

2.



Clinical trials in the wake of the Regulation No. 536/2014

EU's path to the Regulation No. 536/2014

European Commission: barriers to the development of the clinical trials market on the EU level are of administrative and legal nature and should be removed

Assessment of the current Directive 2001/20

The key documents regulating the field of clinical trials in the European Union are the Directive 2001/20 of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, and the supplementary Commission Directive 2005/28 of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products. These documents were introduced to ensure uniform legal framework across EU Member States with respect to the key issues related to the conduct of clinical trials, particularly:

- To ensure protection of the health and safety of subjects participating in clinical trials;
- To legally determine the ethical standards required in clinical trials;
- To ensure the validity and reliability of data obtained in clinical trials;
- To simplify and unify the administrative obligations related to clinical trials (particularly with respect to the clinical trial authorization procedure).

The goals of the Directive 2001/20 and the concept solutions contained therein should be, as a rule, positively assessed, but the European Commission's review of the functioning of the Directive 2001/20 indicated that these solutions – implemented into the national legal systems of the Member States – did not function correctly in practice and did not lead to the achievement of the intended objectives.

The data gathered by the Commission indicate that the number of clinical trials conducted in the European Union declined in a period after the full implementation of the Directive 2001/20 into the legal systems of the Member States (2006), as compared to a period before the implementation.

The European Commission carried out a broad public consultation in order to investigate the public assessment of the key provisions of the Directive 2001/20 as well as seek opinions on its weaknesses and ideas to address them. Based on the information obtained, the Commission concluded that the identified barriers to the development of the clinical trials market on the European level – like in Poland – are of administrative and legal nature and should be removed.

*Regulation No. 536/2014
as a remedy for a decline
in the number of clinical trials
conducted in Europe*

Differences in the implementation of the Directive 2001/20 across the Member States were identified as the main source of problems. This was particularly important because approximately 24% of all clinical trials applied for in the EU in the reviewed period were multinational clinical trials, i.e. clinical trials intended to be performed in at least two Member States. Those multinational clinical trials involved approximately 67% of all subjects enrolled in clinical trials*, while mono-national clinical trials were limited to small studies with low recruitment targets.

Fearing a reduction in the competitiveness of Europe as a base of clinical trials, the European legislator decided to introduce a new legislation (in lieu of the Directive 2001/20), i.e. Regulation No. 536/2014, to regulate the field of clinical research in a comprehensive and uniform manner in all the EU Member States.

In recognition of the importance of extensive harmonization of procedures, the new provisions were introduced as a regulation rather than a directive, because the former is directly applicable in all Member States without the need for implementation into the national legal system.

The Regulation No. 536/2014 shall apply as from six months after the publication of the notice of the full functionality of the EU portal (i.e. a new communication platform for clinical trials) and the EU database, but no earlier than 28 May 2016. It is known by now that the launch of the EU portal will be delayed at least to March 2017, which means that the Regulation will not be applicable before September 2017.

A temporary solution to the aforementioned problems related to the application of the Directive 2001/20 was attempted in 2009 by the Heads of Medicines Agencies (HMAs) in the form of a voluntary procedure for joint assessment of dossiers of clinical trials on medicinal products, Voluntary Harmonisation Procedure (VHP), which could, and can, be joined by EU Member States. VHP is a major step towards harmonization of clinical trial authorization procedures. It will lose its validity (and cease to exist) once the Regulation No. 536/2014 becomes applicable. Poland joined VHP in 2015.

* Memorandum on a proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, COM(2012) 369 final, Brussels 2012, p. 2.

Key legal concepts of the Regulation No. 536/2014

A new uniform procedure for clinical trial authorization applications was established

New clinical trial authorization procedure

The key change introduced by the Regulation No. 536/2014 is related to a uniform procedure for clinical trial authorization based on cooperation between the Member States in which a clinical trial is to be conducted.

This concept is based on the following assumptions:

- **One procedure.** Regulation No. 536/2014 lays down uniform legal framework for clinical trial authorization in all EU Member States for both multinational and national clinical trials (commercial or non-commercial).
- **Two-aspect review of clinical trials.** Clinical trial applications shall be subject to scientific and ethical review. The ethical issues shall remain a national competence. The ethical review shall be carried out by the Ethics Committee (termed 'Bioethics Committee' in Poland) in accordance with the law of the Member State concerned, taking account the timelines and procedures set out in the Regulation No. 536/2014.
- **One communication platform for sponsors.** At the EU level, there shall be a special portal as a single entry point for the submission of data and information relating to clinical trials (the 'EU portal').
- **One dossier.** The sponsor shall submit through the EU portal one application dossier to all the Member States where a clinical trial is to be conducted (the 'Member States concerned'); the scope of dossier is set out in an annex to the Regulation No. 536/2014.
- **One authorization/one decision.** The authorization to conduct a clinical trial should be contained in a single administrative decision (issued by each Member State concerned), which should address all the matters related to the subject safety and data reliability and robustness.
- **One fee.** In connection with the assessment procedure, a Member State shall not require multiple payments to different bodies involved in that Member State in the assessment of a clinical trial application.
- **One contact point.** Regardless of the number of bodies involved in the authorization of clinical trials within a particular Member State, each Member State should designate one contact point.

New clinical trial regulations, important mainly from the patient's perspective, were introduced

Other major changes related to the conduct of clinical trials

In addition to the matters related to the clinical trial authorization procedure, the Regulation No. 536/2014 governs a number of other issues related to the conduct of clinical trials, which are discussed below.

- **Publicly accessible EU portal and EU database.** Regulation No. 536/2014 provides for establishing IT solutions for submitting and storing data and information relating to clinical trials, namely the publicly accessible EU portal and EU database. These tools shall be used for communication between sponsors and the Member States concerned, particularly for the submission of documents required to initiate clinical trials. These solutions shall be also accessible to EU citizens, enabling them to have access to information about intended, on-going and completed clinical trials and their results. All data shall be held in an easily searchable and viewable format. Also the summary of the results of the clinical trial and the summary of the results of the clinical trial for laypersons will be made available in the EU database (there is an obligation to inform clinical trial subjects about this fact, specifying when the summaries become available).
- **Modifications with respect to the safety of clinical trial participants.** Regulation No. 536/2014 introduces some modifications (extensions) with respect to the scope of information which should be provided to participants prior to obtaining their informed consent (willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the participant's decision to participate). The Regulation introduces special provisions concerning clinical trials involving pregnant or breastfeeding women. The current Polish regulations in this respect are not clear, especially with respect to research experiments (i.e. clinical trials conducted to broaden medical knowledge, that is to benefit a particular population rather than specific participants).
- **New rules for obtaining informed consent by simplified means or in emergency situations.** Regulation No. 536/2014 introduces a possibility to obtain informed consent to participate in the clinical trial by simplified means and special rules for obtaining such consent in emergency situations.
- **Rules for remuneration and compensation of expenses of clinical trial subjects.** Under the current Polish legislation, remuneration for participating in a clinical trial can be paid exclusively to healthy adults who are capable of giving informed consent. In case of other groups (adult patients, minors or incapacitated persons, incapable of giving informed consent), only compensation for expenses can be provided. With respect to these special groups of subjects and their representatives, the Regulation No. 536/2014 introduces a possibility of broader compensation, which may also include loss of earnings. On the other hand, the Regulation specifies that a clinical trial can be conducted if no undue influence, including that of a financial nature, is exerted on subjects to participate in the clinical trial. This provision undermines the current possibility which exists in Poland to pay remuneration for participating in early phase clinical trials to healthy volunteers.
- **Co-sponsorship.** Regulation No. 536/2014 introduces a possibility for a clinical trial to have several sponsors.
- **Regulations for non-commercial clinical trials.** Regulation No. 536/2014 provides that the clinical trial conduct procedures, restrictions and authorization requirements shall be the same for commercial and non-commercial clinical trials. However, the Regulation includes a general guideline on the preferred attitude of EU Member States towards non-commercial clinical trials:

“In order to maximise the valuable contribution of non-commercial sponsors and to further stimulate their research but without compromising the quality of clinical trials, measures should be taken by Member States to encourage clinical trials conducted by those sponsors.”

Tiret (81), Regulation No. 536/2014

The Regulation changes the rules for remuneration and compensation of expenses to clinical trial subjects

Regulation No. 536/2014 confirms the need to support the development of non-commercial clinical trials

In fact, the only provision of the Regulation No. 536/2014 which reduces formal requirements for non-commercial trials is lack of obligation to develop and submit the clinical study report (in addition to the summary of the results of the clinical trial and the summary of the results of the clinical trial for laypersons) to the EU portal, as this requirement applies exclusively to sponsors of clinical trials aimed at registration of a new medicinal product.

Nevertheless, the Regulation No. 536/2014 provides that fees for procedures set out therein may be reduced for non-commercial sponsors; in particular, inspections fees, if any, may be waived for them.

Regulation No. 536/2014 leaves a number of important issues to national legislation

Areas left to national competence

The Regulation No. 536/2014 lays down uniform legal framework for clinical trial authorization and conduct. However, this framework is not exhaustive, as a number of issues is left to be governed by additional legislation at the national level. In particular, these issues include:

- **Competent body and contact point.** Designation of the competent national body to perform the scientific review of clinical trial applications and the organization thereof, as well as designation of one national contact point in the Member State. In addition, the establishment of a procedure for further transfer of information to bodies involved in the procedures set out in the Regulation No. 536/2014 is also governed by national law.
- **System of ethical review.** Organization of a system of the ethical review of clinical trials (assessment of applications for clinical trial initial authorization or substantial modification, formulation of opinions on adverse events, etc.), including designation of the bodies involved, procedures and scope of review, providing for the involvement of patients' organizations.
- **Informed consent.** Supplementary rules to the Regulation No. 536/2014 with respect to obtaining informed consent to participate in the clinical trial (the determination of legally designated representatives; definitions of a minor and a person incapable of giving informed consent; rules concerning assent by a minor) as well as safety of clinical trial participants (persons authorized to provide information about the clinical trial and perform a prior interview; indication of populations in which clinical trials are not allowed; specific protective measures for persons in a situation of subordination, e.g. prisoners).
- **Independent assessment.** Ensuring that the persons assessing the application and dossier are independent.
- **Fees.** Determination of the amount of fee(s) in the clinical trial authorization process and the terms of payment thereof.
- **Civil or criminal liability.** Conditions for civil liability or criminal liability (sanctions) of the sponsor, investigator or, potentially, site for damage caused in the course of a clinical trial.
- **Insurance system.** Establishment of a clinical trial insurance system and determination of the rules of its functioning with respect to compensation for any damage suffered by a subject resulting from participation in a clinical trial.
- **Support for non-commercial clinical trials.** A system of financing, insurance and fees for non-commercial clinical trials.

Expected effects of application of the Regulation No. 536/2014

From the patient's perspective, broader access to information about clinical trials is the key change

Analysis of the potential impact of the Regulation No. 536/2014 on different stakeholders of the clinical trials market in Poland

Patients

Regulation No. 536/2014 clearly indicates that in a clinical trial the rights, safety, dignity and well-being of subjects should be protected and the interests of the subjects should always take priority over all other interests – this is the superior value.

From the clinical trial participants' perspective, the intended establishment of the EU portal and EU database are of great importance. Owing to these solutions, it will be much easier than now to obtain information about intended, on-going and completed clinical trials and their results. This may have a positive influence on patients' awareness of clinical trials.

Increased participation of patients in the review of clinical trials will be definitely an effect of the application of the Regulation No. 536/2014, as it provides for the involvement of patients' organizations in Ethics Committees.

Pursuant to the Regulation, clinical trial participants can obtain broader compensation, which is not limited to the reimbursement of expenses related to the participation in the clinical trial, but can also cover loss of earnings (also by legally designated representatives of subjects from particularly vulnerable groups).

Introduction of a possibility to obtain consent ex post in emergency situations makes it possible to apply innovative therapies in case of a hardly predictable course of disease or if the potential participant, due to his or her medical condition, is not capable of giving informed consent, which may occur in case of multiple traumas, stroke or heart attack. Under current legislation, in emergency situations patient's informed consent may be substituted by consent of the guardianship court, which in practice precludes intervention within a clinical trial in such cases.

Investigators

Regulation No. 536/2014 broadens the scope of information which the investigator should provide to potential participant prior to obtaining their consent.

On the other hand, lower requirements for low-intervention clinical trials (concerning already registered drugs used in accordance with the summary of product characteristics) may stimulate more active involvement of investigators from the scientific community and increase the volume of non-commercial clinical trials (with investigators as sponsors thereof).

In case of investigators acting as non-commercial sponsors, increased transparency of clinical trial data and results may facilitate their subsequent use for the purpose of designing new non-commercial clinical trials.

Sites

Regulation No. 536/2014 does not clearly decide the issues which are at present identified as problematic, that is in particular (i) the sponsor's obligation to submit signed contracts with investigators and sites while filing a clinical trial application, and (ii) relations between the site and the investigator. Hence, in this respect, the national legislation complementing the Regulation as well as the practice and relations between clinical trials market stakeholders will matter most.

Simplification and unification of administrative obligations are the main reason for sponsors to conduct clinical trials in Europe

Sponsors/CROs (commercial sponsors of national/international clinical trials and non-commercial sponsors)

In the context of the administrative obligations of sponsors/CROs, the Regulation No. 536/2014 will definitely contribute to their simplification and unification, primarily with respect to the clinical trial authorization (one contact point, one communication platform, one dossier, one fee, etc.), introduction of substantial modifications to the clinical trial protocol, reporting of SUSARs and conditions of obtaining informed consent.

The aforementioned changes may bring about shortened time to commence a clinical trial, higher predictability of the clinical trial authorization process and, consequently, reduced costs of clinical trials related to the administrative procedure.

It may encourage sponsors to carry out a larger number of clinical trials in the European Union, but, above all, it will result in the establishment of a single system of legal rules across all Member States, enabling the conduct of clinical trials in the entire EU population on the basis of one legal system. In this way, EU will be able to compete for sponsors with e.g. China or other large countries in Asia.

Simultaneously, entering into force of the Regulation No. 536/2014 will result in the more accurate determination (either directly in the Regulation or through delegation to the national legislation) of several issues which raise doubts and/or have been differently interpreted by the agencies in various Member States. In particular, these issues include substantial modifications to clinical trials, differences between investigational medicinal products and other substances used in clinical trials, as well as the import and marking of investigational medicinal products.

Regulation No. 536/2014 introduces an option of co-sponsorship of a clinical trial. This solution may become an impulse to more active involvement and cooperation of the scientific community with respect to the conduct of clinical trials, particularly through participation in the costs thereof and use of shared resources (i.e. staff, laboratories, etc.).

The current model of ethical review functioning in Poland must be thoroughly redesigned

Ethics Committees

Regulation No. 536/2014 confirms that the ethical review of a clinical trial is equally important as the scientific review thereof.

Application of the Regulation No. 536/2014 will require reorganizing of the current system of functioning of Ethics Committees in Poland in order to assure that the timelines and procedures for the ethical assessment by the latter will comply with the timelines and procedures set out in the Regulation with respect to the assessment of a clinical trial application.

At the same time, like in case of URPL, from the Ethics Committees' perspective the application of the Regulation No. 536/2014 will mean a radical change in the legal background of their activity, particularly with respect to the ethical review of a clinical trial, introduction of substantial modifications to the clinical trial protocol and reporting of SUSARs.

In practice, one will have to carry out training for Ethics Committee members and introduce new internal operating procedures. An opinion of Ethics Committees will be crucial in the cases when URPL inclines towards refusing clinical trial authorization. Under the new Regulation, this will be one of few ways to block a clinical trial which meets all legal requirements. Hence, it is particularly important to assure that the process of formulating ethical opinions complies with the timelines set out in the Regulation No. 536/2014.

The Regulation introduces a principle of one fee for a clinical trial application. The division of income from such fees between URPL and Ethics Committees will have to be determined. Once a general rule for dividing the aforementioned amounts is adopted at the central level, it will be no longer possible for Ethics Committees to charge different fees.

Regulatory body (in Poland, most likely URPL)

From the perspective of the national body for the scientific review of clinical trials (in Poland, according to the Ministry of Health' declarations, this will be URPL), the application of the Regulation No. 536/2014 will mean a radical change in the legal background of its activity, particularly with respect to the clinical trial authorization, introduction of substantial modifications to the clinical trial protocol, reporting of SUSARs and conditions of obtaining informed consent.

Furthermore, the Regulation No. 536/2014 will result in new duties of URPL, particularly the necessity to closely cooperate with similar bodies in other EU Member States, quickly respond to their queries and actively participate in the clinical trial authorization process.

Furthermore, the new Regulation will to some extent restrict URPL's powers as compared to the current state of affairs (e.g. by eliminating a possibility to demand an additional clinical trial dossier).

In consideration of the above, it will be necessary to implement new internal operating procedures in URPL, which will account for the rules of procedure, rights and timelines resulting from the Regulation No. 536/2014. In practice, one will also have to carry out training for URPL employees, review their scope of duties and verify the number of positions.

Preparation for the application of the Regulation No. 536/2014 will be a great challenge for the national legislator and public authorities

State (legislator, public authorities, economy, healthcare system, etc.)

One of the key positive effects of the unification of the procedures and timelines of the clinical trial authorization and conduct in all EU countries and, consequently, establishment of similar legal framework across Europe, may be an increase in the competitiveness (attractiveness) of the European Union for sponsors.

Undoubtedly, Poland as a country of significant and unused potential may benefit from it. However, in order to seize this opportunity Poland will need to have a range of arguments to effectively compete with other EU countries and become a country frequently chosen by sponsors to carry out clinical trials (investments).

Regulation No. 536/2014 requires Member States to introduce legislation which will enable the functioning of the new system (e.g. to determine the rules of operation and financing of Ethics Committees).

At the same time, one should bear in mind that failure to adhere to procedural timelines may pose certain risk, especially for patients. In the worst case, it may become necessary to grant authorization of a clinical trial despite a negative conclusion in Part II of the assessment report (non-compliance with legal requirements for informed consent, staff qualifications or personal data protection) or a negative opinion of the Ethics Committee. This may happen in case of failure to notify the sponsor within the relevant period of a decision whether the clinical trial authorization is granted or refused (where the conclusion of Part I of the assessment report is that the clinical trial is acceptable).

Whether Poland makes use of an opportunity to improve the state of the clinical trials market or whether new barriers will emerge will depend on the legislation initiatives of the Polish legislator.

It is also up to the Polish legislator to undertake additional legislation initiatives extending beyond the scope of the Regulation No. 536/2014 and the delegations contained therein. This could establish a friendly climate for clinical trials in Poland and increase the competitiveness and attractiveness of Poland as a base for clinical trials.

Whether an opportunity to change the state of the clinical trials market in Poland is seized will depend on the national legislator

Introduction of such additional solutions could enable Poland to positively differentiate from other EU countries implementing just the minimum plan (i.e. the legislation required by the Regulation No. 536/2014) and change Poland's perception (i.e. solidify an opinion about Poland as a friendly country for clinical trials, which has a lot to offer). All this should ultimately stimulate growth of the volume of clinical trials in Poland.

Hence, the future state of Poland's clinical trials market and, consequently, the degree of innovativeness of Poland's economy, will depend on the nature and scope of the legislation initiatives taken by the Polish legislator.

Furthermore, in order to enable efficient and effective cooperation between Member States and facilitate the functioning of the procedures referred to in the Chapter II (authorization procedure for a clinical trial) and Chapter III (authorization procedure for a substantial modification of a clinical trial) of the Regulation No. 536/2014, each Member State shall designate one contact point. Poland has declared the Ministry of Health as its contact point.

It should be assumed that this declaration can be attributed to the role played by the Ministry of Health in shaping the health policy of the State. However, a question arises about the justification for this decision and potential delays in the execution of the aforementioned procedures due to the fact that another body, i.e. URPK, has not been chosen.

Failure to undertake adaptive actions after the implementation of the Regulation may decrease the attractiveness of Poland's clinical trials market

Effects of potential negligence and a chance of success

The implementation of the Regulation No. 536/2014 into the Polish legal system without necessary adaptive actions in the areas beyond its scope will significantly worsen the situation of entities operating in the clinical trials market.

From the point of view of people making decisions whether to conduct a clinical trial in Poland or not, certain factors may push Poland to the bottom of the list of countries considered attractive for this type of activity. These factors include: lack of transparent processes, lengthy procedures and unpredictable outcome thereof, as well as unclear division of administrative powers. All of them may result from failure to take adaptive actions.

This may result not only in the continuation, but even acceleration, of the downward trend in the volume of clinical trials conducted in Poland, leading to a further decrease in the attractiveness of the Polish market (as a lower number of clinical trials means smaller experience of investigators and the need for additional training to update their knowledge, etc.).

On the other hand, the Regulation No. 536/2014 arguably creates an opportunity and stimulus for clarifying the state of affairs in the field of clinical trials. While enforcing thorough analysis of the scale and scope of necessary adaptive actions, it offers a unique opportunity to engage all market stakeholders in the process of their planning and subsequent implementation. Such an approach would not only facilitate the identification of the areas which require the legislator's intervention, but also assure that no major issue which constitutes a barrier to the market development is overlooked. On the other hand, improving Poland's image as an attractive country for clinical trials will be possible only as a result of active participation of all the stakeholders in the development of new solutions.

Moreover, it should be Poland's ambition to become a regional center for managing clinical trials in neighboring countries. It seems justified by its geographical and demographical characteristics and the fact that multinational companies often locate their regional decision-making hubs in Poland. However, such an ambitious goal can only be achieved if all stakeholders get involved in deliberate actions aimed at changing the climate around clinical trials, establishing legal background for unrestrained market growth and offering prospective investors a system of incentives (e.g. tax exemption). This will make Poland stand out as a very attractive country vis-à-vis its neighbors.

It should be noted that even if the aforementioned concerted actions are not undertaken, as long as the effects of the Regulation No. 536/2014 in terms of the unification of the clinical trial authorization procedure are not thwarted by adverse legislation left for national competence or unfavorable interpretations, Poland – owing to its large population, qualified investigators, well prepared clinical research centers and lower costs of clinical trials vs. WE – can still become an attractive location for clinical trials.

Poland has a real chance to benefit from the application of, the Regulation No. 536/2014

3.



How to use Poland's potential

An opportunity to change the state of the clinical trials market in Poland

We need a comprehensive analysis of the scale and scope of the necessary adaptation and a strategy to use an opportunity offered to Poland by the Regulation No. 536/2014

Regulation No. 536/2014 undoubtedly offers a new quality in the field of legal regulations concerning clinical trials, as it unifies, clarifies and harmonizes a number of important issues related to clinical trials in all Member States. Nevertheless, one should bear in mind that this Regulation is not exhaustive, leaving certain issues for national legislation and still others unregulated at all.

The matters related to legal interpretations and practice, particularly relations between market stakeholders and their mutual perception, remain intrinsically beyond the scope of the Regulation No. 536/2014.

Regulation nr 536/2014 addresses only a section of the clinical trials domain, including just a fraction of legal issues which make up the legal environment in which the clinical trials market stakeholders operate. This leaves a number of important issues, including those currently identified in Poland as the key barriers to the clinical trials market development, to regulation at the national level.

One of the major implications of the aforementioned Regulation is the fact that it creates a chance to change the status quo in the clinical trials market in Poland. This situation serves as a perfect pretext for listening to the opinions of the market stakeholders and passing new legislation (addressing the issues left by the Regulation No. 536/2014 for national law and introducing additional solutions with respect to the matters not governed by the Regulation), which will make Poland an attractive country for conducting clinical trials.

Owing to the fact that clinical trials are an indispensable element of a process of development of new therapies and they bring tangible benefits to patients, the healthcare system, the public finance and economy, the clinical trials market stakeholders need to undertake multifaceted cooperation in order to maximize the benefits from clinical trials.

Poland's path to fully use the potential of the Regulation No. 536/2014



Directions of changes suggested by Poland's clinical trials market stakeholders

Regulation No. 536/2014 is a perfect opportunity to review and improve the functioning of the clinical trials market in Poland.

It is crucial to establish foundation for stable growth in clinical trials, which is possible, provided that the safety of clinical trial subjects is ensured and the cooperation between the entities and institutions operating in this area is strengthened.

The main identified barrier to the development of the clinical trials market in Poland is related to the requirement to submit signed contracts with sites and investigators when filing a clinical trial application, which extends the time of preparations for submission of the application by the time required to carry out negotiations. Currently, negotiations with large medical entities, often critical for a clinical trial, last between a few and a few dozen months in Poland.

Annex I to the Regulation No. 536/2014, which specifies documents which should be filed with a clinical trial application, mentions information on financial transactions and compensation paid to subjects and investigators/ sites for participating in the clinical trial, as well as description of any other agreements between the sponsor and the site. The Regulation does not introduce a direct requirement to submit signed contracts with investigators and sites, but the meaning of the term 'description of agreements' is unclear. The adopted interpretation of the provisions of the Regulation will be crucial in this respect.

Access to the drug after the clinical trial and the compassionate use procedure

What matters for patients is access to an effective, innovative therapy after the clinical trial completion

- To provide patients with access to the drug upon completion of a clinical trial, so that the effective therapy may be continued also after the clinical trial;
- To introduce instruments for financing innovative medicinal products after the completion of a clinical trial;
- To introduce a possibility of drug reimbursement for patients who have benefited from the therapy in the completed clinical trial;
- To introduce the compassionate use procedure, enabling use of a drug prior to its registration. This solution is dedicated to patients with special therapeutic needs and those who were not able to take part in a clinical trial;
- To remove tax barriers related to transfer of drugs free of charge by the sponsor, including a tax exemption for patients' income from receiving free drugs;
- To enhance the safety of patients.

Access to the drug upon completion of a clinical trial and the compassionate use procedure have already been introduced in a number of EU countries, including Germany, France and Italy.

One should establish clear rules for compensation and remuneration payments

Remuneration and compensation

- To introduce a possibility of remunerating patients or healthy volunteers for participation in a clinical trial which brings them no therapeutic benefits (phase I clinical trials, bioequivalence studies);
- To determine a catalogue of entities eligible for compensation for loss of earnings;
- To provide tax exemption for compensation for expenses related to the participation in a clinical trial.

It is necessary to provide easy access to knowledge about innovative treatments and the rules of conduct of clinical trials

Access to information about clinical trials

- To improve patients' access to information about potential participation in innovative therapies;
- To establish a public independent information platform for patients concerning clinical trials in Poland. The project should be coordinated by a renowned and trusted independent agency (e.g. URPL or MoH in Poland);
- A public knowledge platform about clinical trials could become a tool for initial patient qualification for particular projects. Under current legal regime, this is not possible due to personal data protection regulations;
- To carry out an informational campaign for patients, enabling them to gain basic knowledge about clinical trials (subjects' rights, liability and compensation for damage, benefits from participation in clinical trials) and aiming to improve perception of clinical trials.

More efficient functioning of the ethical review system and improved patient safety are necessary

System of ethical review

- To develop an efficient chain of Ethics Committees, ensuring that opinions about clinical trials are issued within the timelines set out in the Regulation No. 536/2014;
- To enhance transparency of the functioning and financing of Ethics Committees and to assure independence of their members.
- To ensure high level of safety of clinical trial subjects through:
 - engaging experts with hands-on experience as well as lawyers and patients' representatives to Ethics Committees;
 - organizing mandatory training for Ethics Committee members.

The sponsor should bear liability on the strict and culpability basis

Liability and insurance system

- To enable clinical trial participant to gain compensation for damage resulting from participation in a clinical trial;
- To introduce various categories of insurance, corresponding to the character and scale of risks involved in a clinical trial and consistent with the provisions of the Regulation No. 536/2014;
- To introduce sponsor's liability, partly on a strict basis (for damage caused by the investigational medicinal product) and partly on a culpability basis (other damage, e.g. resulting from procedures conducted in line with the protocol);
- To keep liability of the investigator and site on a culpability basis, and to develop adequate solutions related to insurance of subjects themselves.

One may consider introducing an insurance fund for clinical trial participants. Such a solution has been implemented in Denmark, where the establishment of an insurance fund at the government level has reduced costs of insurance and enhanced patient protection.

Clear rules of division of financial obligations between the commercial sponsor and the public payer should be set out

Financing of healthcare services

- To increase transparency in division of financial obligations between the sponsor and the public payer with respect to healthcare services provided in connection with a commercial clinical trial;
- To prevent situations when the burden of financing of the healthcare services guaranteed to be financed from public funds is transferred onto the sponsor;
- To introduce an appellate procedure for commercial clinical trial sponsors questioning the actual division of costs as well as a possibility to recover by the public payer of the healthcare services which should be financed by the sponsor.

One may consider a solution which involves the introduction of a nationwide price list for procedures in clinical trials to facilitate contract negotiations (such a solution has been implemented in the UK).

There should be one fee charged to the sponsor

Fees

- A single fee for the scientific and ethical review, set in a clear and transparent manner (a fee for the Ethics Committee should be included);
- The amount of the fee should correspond to the actual costs and workload related to the assessment.

One should establish favorable conditions for non-commercial clinical trials...

Support for non-commercial clinical trials

- To lower administrative barriers;
- To provide investigators with necessary training and technical support with respect to designing clinical trials and obtaining authorization;
- To reduce financial burden related to the clinical trial commencement (official fees, insurance);
- To create sources of financing to support the conduct of non-commercial clinical trials (similarly to StrategMed and Innomed programs, which allow for supporting commercial trials);
- To facilitate participation of non-commercial entities in such projects and introduce special solutions for supplying the investigational drug.

...to encourage sponsors to conduct clinical trials in Poland

Legal, tax and investment incentives

- Currently, there are no such instruments dedicated to clinical trial sponsors in Poland. Such solutions would play a very important role in promoting Poland as an attractive location for clinical trials.

Legal and tax incentives in other EU countries:

- Patent box – a set of legal and tax regulations to encourage innovative activity (UK);
- Biomedical Catalyst grant contest addressed to scientists and small to medium enterprises, which aims at quick commercialization of innovative solutions; funds are awarded in the contest (UK);
- Introduction of a system of programs aimed at providing financial support for the conduct of clinical trials (e.g. NIHR's Research Programmes in the UK);
- Introduction of grants for academic research and support for non-commercial clinical trials from public funds (Italy);
- Introduction of tax exemptions for R&D activity (Hungary).

Using the issues not governed by the Regulation No. 536/2014

Other solutions indicated by clinical trials market stakeholders are worth implementing

While drafting national legislation, one should consider the solutions successfully implemented by other EU Member States.

Clinical trials market stakeholders, referring also to positive solutions in other countries, have indicated the following issues and solutions as important and worth implementing or clarifying in the Polish legislation:

- **Establishment of an agency for the development and promotion of clinical trials** (e.g. UK-based *National Institute for Health Research* (NIHR) is a public institution supporting the development of clinical trials, particularly those of transnational importance); in particular, the agency would carry out informational campaigns for patients about clinical trials (e.g. "OK to ask" campaign in the UK, which aimed at raising patient awareness and developing positive conditions for asking about taking part in clinical trials).
- **Development of a platform for the sponsors vs. state authorities dialogue** (e.g. the Ministerial Industry Strategy Group in the UK, which consists of representatives of the State and the pharmaceutical industry and aims at creating attractive environment for entities involved in clinical trials).
- **Introduction of 'scientific advice' on the national level**, i.e. an opportunity for dialogue with the Ministry of Health and/or URPL prior to the application with respect to the directions of clinical trials and medicinal product development as well as terms of the clinical trial conduct. Such a solution is intended e.g. in the UK and Germany. In the UK, it is in the form of a pre-approval, that is a binding opinion issued in doubtful formal and medical matters which may arise in the clinical trial authorization process. The Medicines and Healthcare Products Regulatory Agency (MHRA) issues binding recommendations to the sponsor with respect to the matters of doubt, and the sponsor is guaranteed that the solution agreed upon with the agency will not be challenged.
- **Division of duties between the site and the investigator.** Regulation No. 536/2014 does not address this issue. As a result, the doubts as to the division of functions/duties and other relations between the site and the investigation team will continue.
- **Initial recruitment of patients to clinical trials.** Regulation No. 536/2014 includes no clauses or guidelines concerning patient recruitment. One of the ideas which have been suggested to improve the recruitment process and facilitate participation in clinical trials is to introduce initial patient verification with e.g. a questionnaire on a web portal. The patient would answer questions and then verify whether he or she meets the boundary conditions for inclusion in a clinical trial.

4.



Conclusions and recommendations

Conclusions and recommendations

The challenges faced by the healthcare system require innovative drugs, whose efficacy and safety have to be confirmed in clinical trials

The healthcare systems worldwide face a number of challenges related to rapid demographic, epidemic and economic processes occurring on the global level. Aging societies needing intensified care and adjusted therapies, growing incidence of civilization diseases, antimicrobial resistance and intensive search for healthcare cost savings in the wake of the global crisis – these are only some of the problems which give healthcare decision-makers sleepless nights.

It means growing problems for increasingly aware and organized patients, who expect better, cheaper and more effective therapeutic solutions, particularly drugs, which remain the key component of most therapies.

In order to successfully respond to the aforementioned challenges, patients need new, groundbreaking and innovative drugs, offering high efficacy and safety of therapeutic processes accompanied by cost effectiveness. These goals cannot be achieved without coordinated and intensive efforts of all stakeholders involved in a process of medicinal product development and marketing.

This particularly applies to the clinical research phase of this process. Clinical trials remain the most time-consuming and costly element in the development of new therapeutic solutions and involve the highest risk of failure. On the other hand, without thorough verification of the safety, efficacy and efficiency of a medicinal product during clinical trials, it is not possible to offer it to patients.

Notably, the clinical research phase already offers a number of benefits to all the parties involved in the process. For patients, these include access to the latest therapeutic solutions, upgraded standard of treatment and diagnostics, etc., while investigators enjoy access to the latest medical knowledge and innovative treatment standards. The public payer also benefits from the process.

Growth in the volume of clinical trials concerning new drugs will not be possible without legislative support

Therefore, it is hardly a surprise that the market stakeholders make intensive efforts to increase the number of drugs which are subject of clinical trials. Simultaneously, they try to streamline and shorten the clinical research process itself, so as to offer innovative treatments to the largest possible population as quickly as possible (sometimes, like in the UK, conditionally before the completion of a clinical trial).

However, these efforts will be unsuccessful without active involvement of the legislator and the relevant public administration bodies. This connection has been noticed also by the community legislator, which decided to intervene in the clinical trials market in Europe and issued the Regulation No. 536/2014.

By unifying the requirements, processes and standards of the clinical trial registration and conduct across EU countries the Regulation should, in the authors' intention, stimulate growth in clinical trials conducted within the European Union (to the benefit of both patients and healthcare systems).

Faced with changes in the European clinical trials market triggered by the Regulation, Poland will have to take firm adaptive actions

By choosing the legal form of regulation (i.e. the supreme act, which does not need to be transposed into the legal systems of the Member States), the community legislator made a clear indication that the adopted legislation aimed at the strongest integration of the clinical trials market in the EU as soon as possible. From the Member States' perspective, this may become a major impulse to rapid growth of the said market and, consequently, providing patients with broader access to innovative drugs at earlier stages of their development.

This is a good news for Poland, whose clinical trials market has been stagnant over the recent years and whose demographic and scientific potential, existing infrastructure and gathered experience have not been fully utilized (*vis-à-vis* neighboring countries).

As the main barriers to the development of the said market in Poland have been of administrative character (e.g. excessively strict regulations or complicated official routines), and thus should be removed by the harmonized regulations, this optimism may seem all the more justified.

Unfortunately, a closer analysis of the situation which will occur upon entering into force of the new Regulation indicates that the latter will not automatically solve all the existing problems related to clinical trials in Poland. In order to achieve it, the Polish legislator will have to undertake a number of initiatives and actions to adapt the areas of the clinical trials market which remain beyond the scope of the Regulation No. 536/2014. Failure to act decisively in this respect while counting on the effects of the Regulation alone will not improve Poland's position in competing to attract as much clinical trials as possible, but – in the face of unification of procedures in the rest of the European single market – may even lead to Poland's market marginalization and exclusion from a decision-making process related to clinical trials.

This risk is present in the following areas of the functioning of the clinical trials market in Poland, which require immediate intervention:

- Removal of the requirement to submit original contracts with the investigator and the site when filing the clinical trial dossier;
- Easier access to the drug after the clinical trial and the establishment of the compassionate use procedure in Poland;
- Determination of the terms of remuneration and compensation for selected groups of subjects;
- Improved accessibility of information about clinical trials;
- Enhanced functioning of the system of ethical review (Ethics Committees);
- Modification of the principles of liability and the system of insurance (of entities conducting clinical trials and patients);
- Enhanced transparency of financing of healthcare services provided to clinical trial subjects;
- Modification and unification of the system of fees for the scientific and ethical review of clinical trial applications.

Clarification of the doubts in the aforementioned areas and introduction of friendly legislative solutions should contribute to creating conditions for the conduct of clinical trials in Poland comparable to those which exist, or will exist, in the majority of other Member States. Unfortunately, this will be insufficient to actively encourage sponsors of clinical trials to conduct them in Poland. In order to achieve it, Poland has to develop a comprehensive long-term program to support clinical trials. Such a program should be developed by the Ministry of Health, URPL, Ministry of Finance, NCBiR and other entities, and should address the following strategic priorities:

- Introduction of a system of tax incentives (e.g. in the form of income tax deductions for some qualified expenses incurred by sponsors);
- Introduction of a system of scientific grants to support clinical trials in selected therapeutic areas;
- Development of a long-term program for the clinical trials market monitoring, constant improvement and transformation (i.e. Polish equivalent of NIHR);

Polish legislator's failure to attempt firm actions will weaken the competitiveness of Poland's clinical trials market

- Introduction of a program for supporting non-commercial clinical trials;
- Development of a platform for the sponsors vs. state authorities dialogue aimed at discussing the means of supporting the clinical trials market in Poland;
- Enhanced possibilities of the initial recruitment of patients to clinical trials;
- Clear division of duties between the site and the investigator;
- Introduction of 'scientific advice' on the national level.

Based on the scenarios of the potential developments in Poland's clinical trials market, one may assume three possible following models of functioning of this market in the next few years' perspective.

Scenario 1: Negative

In this scenario, Poland's actions will be restricted to passive application of the Regulation No. 536/2014, which will replace the selected national legislation. In particular, no adaptive actions will be undertaken in the areas not directly regulated by the EU legislation.

As a result, the persisting doubts and peculiar requirements will be decisive in making Poland even less attractive. Consequently, the number of clinical trials in Poland will drop and the clinical trials market will shrink.

Scenario 2: Neutral

In this scenario, the introduction of the Regulation No. 536/2014 in the Polish legal system will be accompanied by efforts to adapt/modify the national legislation in the areas not directly governed by the Regulation (as required to eliminate the existing barriers and drawbacks).

As a result of these efforts, Poland may become a country with similar conditions for the clinical trial conduct to those in other EU countries. In particular, it may be expected that the majority of the existing administrative barriers will be removed and the time to commence a clinical trial will be reduced.

As a result, Poland's market will grow at a similar or slightly higher rate than the European benchmark (like up to 2009) owing to Poland's potential (particularly large population of patients and qualified medical staff).

Scenario 3: Positive

This scenario is based on an assumption that the application of the Regulation No. 536/2014 and the removal of the key barriers will be connected with a change in the attitude towards clinical trials in Poland.

This will involve the implementation of solutions aimed to enhance the attractiveness of the Polish market versus CEE and WE countries, particularly by introducing financial and tax incentives, developing information platforms for patients, supporting hospitals involved in clinical trials, encouraging healthcare centers to introduce coordinators for relations with clinical trial sponsors, etc. As a result, Poland may become one of the market growth leaders within the EU and strengthen its position as the largest market for clinical trials in CEE.

Access to innovative therapies is of fundamental importance for the health of citizens of a country (and thus its macroeconomic situation). A huge role in the development of such therapies and making them available to patient populations affected by diseases is played by clinical trials. Therefore, one should wish that Poland's opportunities related to the unification of the European clinical trials market are not lost and that the most optimistic scenario is fulfilled. Despite concerns, one should remain hopeful of this outcome, as the decision-makers in Poland declare their commitment to make it a truly innovative country, participating in the research and development activity to the extent corresponding to its potential. Another positive factor is a growing range of conscious patients/clinical trial subjects, who expect further development of the opportunities in this respect.

There is a possible scenario in which Poland will become one of the EU leaders in clinical trials – to the benefit of patients, the healthcare system and the state budget

Glossary

Term	Definition
bn	Billion
c.	Circa
CARG	Compound Annual Growth Rate
CEE	Central and Eastern Europe; in this report this includes: Poland, Czech Republic, Slovakia, Hungary, Estonia, Latvia and Lithuania
CIT	Corporate Income Tax
CRA	Clinical Research Associate
CRO	Contract Research Organization
DiA	Dane-i-Analzy.pl Sp. z o.o.
Directive 2001/20	Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (<i>Official Journal</i> L.2001.121.34)
Directive 2005/28	Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (Text with EEA relevance) (<i>Official Journal</i> L.2005.91.13)
EU	European Union – an economic and political union of democratic European countries
EU-15	15 Member States of the European Union before May 2004
EUPATI	European Patients' Academy on Therapeutic Innovation
GCP	Good Clinical Practice
GUS	Central Statistical Office
HMA	Heads of Medicines Agencies
ICH	International Conference on Harmonization
INFARMA	INFARMA Employers' Union of Innovative Pharmaceutical Companies
k	Thousand

Glossary

Term	Definition
m	Million
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MoH	Ministry of Health
NCBiR	National Centre for Research and Development
NHF	National Health Fund
NIHR	National Institute for Health Research (UK)
PET	Positron emission tomography
Pharmaceutical Law	Act of 6 September 2001 – Pharmaceutical Law (<i>Journal of Law</i> 2008.45.271, as amended)
PIT	Personal Income Tax
PLN	New Polish zloty
PwC	PricewaterhouseCoopers Sp. z o.o.
Regulation No. 536/2014	Regulation No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance) (<i>Official Journal</i> L.2014.158.1)
SUSAR	Suspected Unexpected Serious Adverse Reaction
URPL	Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products
VAT	Value Added Tax
VHP	Voluntary Harmonisation Procedure
WE	Western Europe
ZOZ	Healthcare Center



Employers' Union of Innovative Pharmaceutical Companies (INFARMA)

represents 28 leading pharmaceutical companies engaged in research and development activities and the production of innovative medicines. INFARMA is a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA) – an international organization of the innovative pharmaceutical industry, the Employers of Poland and the Polish Chamber of Commerce.



Association for Good Clinical Practice in Poland (GCPpl)

was established in 1997. Since the beginning, the mission of GCPpl has been to develop and support initiatives aimed at the implementation of the procedures for the ethical and reliable conduct of clinical trials. The Association plays a major role in the clinical trials community in Poland. It carries out an educational and training activity, develops and promotes good standards, takes part in public consultation of new legal regulations and supports the positive image of clinical trials among the public. Owing to voluntary work of its members, GCPpl successfully integrates the efforts of the entire community, acting towards the development of clinical trials in Poland.



Polish Association of Clinical Research Organizations (POLCRO)

was established in September 2012. The Association was formed in order to develop the unified and, above all, legally established representation of the interests of the clinical research industry in Poland. At present, 15 Clinical Research Organizations (CROs) have the membership status. In POLCRO, there are three working groups, namely for legislation, training and quality of standards, which are composed of both employees of the member companies and independent consultants working for the Association.



PwC

It is a global organization operating in the world for over 150 years, and in Poland since 1990. Using the knowledge and skills of more than 208,000 employees in 157 countries, PwC provides with professional services in audit, business advisory, tax and legal. PwC in Poland employs over 2000 specialists and support staff in seven cities: in Gdansk, Katowice, Krakow, Lodz, Poznan, Wroclaw and Warsaw. The company's offer is directed to entities operating in all sectors – both major corporations and local family businesses.

