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# Clinical Trials in Poland – Key Challenges



## Table of Contents

1. Summary	1
2. Introduction: A global view	7
3. Clinical trials in Poland:	
Key characteristics	25
4. Benefits and risks of clinical trials	42
5. Barriers to market development	55
6. Conclusions	71

## Appendix

1. Glossary	83
2. PwC Contact	86

# Section 1 Summary

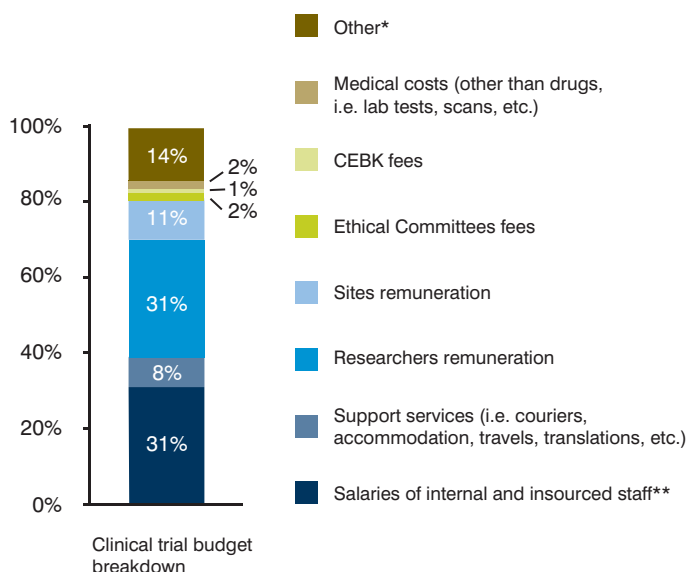


**Summary: Key messages**

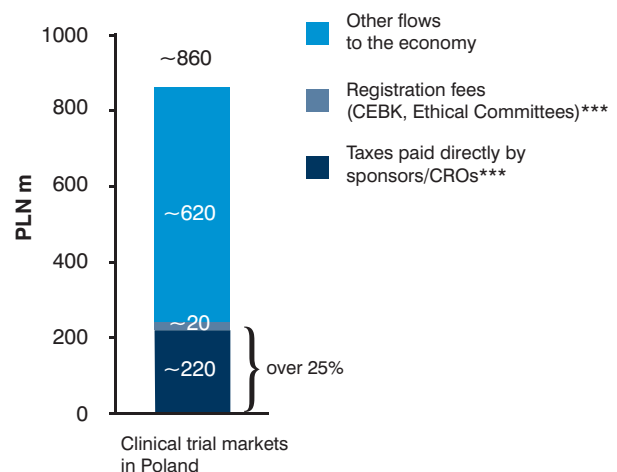
- *Clinical trials are necessary to ensure efficacy and safety of newly developed medicine.*
- *Sponsors seek for increased operational (and cost) efficiency primary by outsourcing trials to CROs and considering new locations for research projects, e.g. CEE-based, due to constant developments in pharmaceutical industry, such as declining productivity of R&D spent caused among others by upcoming patent expiry of blockbusters as well as expected shortening of drug development.*
- *Poland remains the largest clinical trials market in CEE/CIS, however, both patient participation and site penetration rates indicate a potential for growth.*
- *The clinical trials market in Poland is worth c. PLN 860 m.*
- *Clinical trials in Poland imply a number of tangible and intangible contributions to Polish society and economy:*
  - *Provide access to advanced therapies for patients, combined with better standard of medical care;*
  - *Contribute to human capital growth in terms of know-how sharing and professional development opportunities for medical staff;*
  - *Contribute to the Polish economy with c. PLN 860 m of which vast majority is a cash inflow and the state budget with c. PLN 240 m of taxes paid by sponsors/CROs, CEBK fees and Ethical Committee fees as well as provide alternative cost savings that can relieve the public healthcare system.*
- *Launching a number of initiatives will accelerate the market growth and maximize the potential benefits to the economy:*
  - *Improvement of timing/feasibility of administration procedures, which is expected to increase the trials volume by c. 20%-30%;*
  - *Improvement of the level of transparency, especially in terms of clear competency split between different regulatory and approval bodies (e.g. CEBK and Ethical Committees) as well as the relationship between the sponsor, the researcher and the site;*
  - *Establishing administrative processes improving cooperation between sponsors and sites.*

- Clinical trials are necessary to ensure efficacy and safety of newly developed medicine. Since they are key in the drug development process, they appear to be an increasingly hot topic;
  - Global clinical research market is worth c. USD 50-80 bn (depending on the source of information). In 2009, over 17k clinical trials were newly registered worldwide.
- Sponsors seek for increased operational (and cost) efficiency primary by outsourcing trials to CROs and considering new locations for research projects, e.g. CEE-based, due to constant developments in pharmaceutical industry, such as declining productivity of R&D spent, upcoming patent expiry of blockbusters as well as expected of shortening of drug development.
- Poland remains the largest clinical trials market in CEE/SEE/CIS, however, both patient participation and site penetration rates indicate a potential for growth. The clinical trials market in Poland is worth c. PLN 860 m. With 469 new clinical trials registrations in 2009, Poland accounts for c. 2.5%-3.0% of the world market by registration volumes. Still the largest geographies where clinical trials are held are US and Western Europe.
- Clinical trials in Poland imply a number of tangible and intangible contributions to Polish society and economy:
  - Contribute to the Polish economy, including significant cash flows into the state budget via different taxes paid by sponsors/CRO as well as all types of registration fees (Ethical Committees, CEBK fees);
    - > This contribution is estimated at is c. PLN 240 m and that amount excludes taxes paid by suppliers and as a result of consumer spends of the employees and researchers – what corresponds to the fact that every 1 PLN invested in clinical trials is finally allocated to the state budget;
    - > Also hospitals and other sites where the trials are executed benefited from more than 10% of the total market size (i.e. c. PLN 85 m). One should remember that clinical trials heavily involve other parties like laboratories, translators, couriers and many other service providers which benefit from clinical trials conducted in Poland;

Estimated clinical trial budget breakdown



Clinical trials market in Poland (2009)



\*Other involves any miscellaneous category as indicated by survey respondents

\*\*Includes also "in-sourced" employees

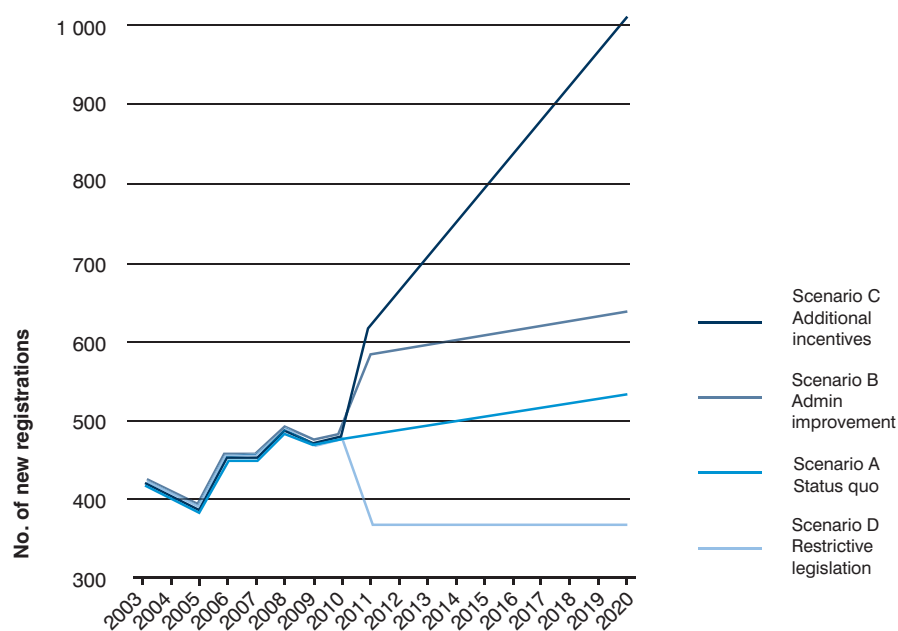
\*\*\*Cash flows to the state budget

Source: PwC Survey, PwC Analysis



- Clinical trials provide alternative cost savings for the National Health Fund (NHF) as there are a number of patients who are participants of clinical trial projects and are actually co-financed by the sponsors rather than by the public funds;
- > Our estimation for oncology for example, which captures approximately one-third of clinical trial participants in Poland, suggests that in 2009 NHF saved c. PLN 130m this way;
- > Moreover, as participants typically obtain therapies that are beyond standard treatment, the value of oncology treatment under clinical research may amount up to c.PLN 0.5bn. This appears to be a significant amount compared to total NHF budget on oncology treatment, amounting c.PLN 3.4bn in 2009;
- Access to advanced therapies for patients, combined with better standard of medical care;
- Contribute to human capital growth in terms of know-how sharing and professional development opportunities for medical staff, which is a vital issue in the light of scarcity of doctors and other medical workforce in Poland.
- However, it appears that there due to several barriers, the number of clinical research projects executed in Poland has potential to be larger. The evolution of clinical trials volumes will certainly have impact on the total economy as well.

#### Clinical trials market in Poland – potential development



Note: PwC Analysis based on historic data of CEBK and EMA.  
Source: PwC Analysis

- In this report we present four scenarios in which clinical trials in Poland have potential to evolve:
  - If Scenario C materializes, therefore admin improvements as well as a set of additional incentives are implemented in order to attract an increased trials volumes, the contribution to the state budget can increase by two-thirds, or c.PLN 160m, over the next five-year period, i.e. reach c.PLN 400m;
  - > Only the admin improvement (Scenario B), primarily referring to enhancement of administration procedures (including inter alia shortening of registration period), is expected to increase the trials volume by 20-30% and increase contribution to the budget by c.PLN 45-65m quite immediately;
  - > It is worth mentioning that the total realized budget of the Registration Office (URPLWMPB) amounted c.PLN 52.5m in 2008, while the Office contributed to the state budget with c.PLN 108m of inflow earned through drug registration and clinical trials fees, in this year;
  - Conversely however, if excessively restrictive legislation is introduced (Scenario D), this can lead to significant drop in the market size. For example decrease by c.30% which corresponds to c.PLN 200m decline of the clinical trials market would result in decrease of the contribution to the state budget by c.PLN 55m per annum.
- Hence, in order to ensure the more thorough exploitation of benefits, a number of initiatives have to be launched. This would primarily include:
  - Introduction of more plausible regulatory framework. This would include improvement of timing/feasibility of administration procedures;
  - Improvement of the level of transparency, especially in terms of clear competency split between different regulatory and approval bodies (e.g. CEBK and Ethical Committees), which would help them to ensure that there are no overlaps in work;
  - More transparency in contracting between the sponsor/CRO, the researcher and the site is also desirable. The introduction of tripartite contracting sounds as a plausible solution to all stakeholder groups;
  - Tailoring the administrative processes to improve day to day cooperation between sponsors and sites. Introduction of higher standards in sites in relation to management of the clinical trials and contacts with sponsors. Development of dedicated units responsible for clinical trials affairs established by some hospitals provided examples of significant improvement in the quality of cooperation, efficiency and transparency of the process;
  - Overall, clinical trials in Poland require operational and regulatory rationalization. However, this rationalization should not lead to excessive and unnecessary regulations which may significantly limit the overall benefits.

*We have surveyed c.80 companies as well as interviewed c.30 market insiders from all major stakeholder groups to obtain an objective view over the clinical research industry in Poland*

## Acknowledgements and methodology

### Acknowledgements

- We would like to thank all clinical trials market stakeholders who generously donated their time and effort to the project. We would also like to express our particular gratitude to entities, which actively participated in our PwC Survey as well as all interviewees who shared their valuable views on the current state and future prospects of clinical research industry in Poland.
- Finally, we would like to express our appreciation for the input from many people at PricewaterhouseCoopers who helped us develop this report and contributed to the content.

### Methodology

- We based our report on three main streams of information, which are:
  - PwC Survey: We have issued a questionnaire to c. 80 companies engaged in clinical trials in Poland and obtained a representative sample of responses for the analyses presented in the report;
  - PwC Interviews: We have interviewed c.30 respectable market observers, including all key stakeholder groups engaged in the industry, such as sponsors (pharmaceutical companies and academic society representatives), CROs, sites, researchers, representatives of the authority bodies (i.e., Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products, the CEBK unit and Ethical Committees) as well as patient organizations;
  - Externally provided and publicly available data: We have used relevant data from these sources to which PricewaterhouseCoopers has commercial rights.
- We used verified PricewaterhouseCoopers' models for all sizing and estimation modeling exercises presented in the report.



# Section 2

## Introduction: A global view



**Introduction: A global view**

- *Clinical trials are necessary to ensure efficacy and safety of newly developed medicine. The process of drug development evolves and is expected to be more refined, as more emphasis is put on pre-trial molecule development.*
- *Sponsors seek for increased operational (and cost) efficiency primary by outsourcing trials to CROs and considering new locations for research projects, e.g. CEE-based.*
- *Poland is ranked 10th in the world and 1st among emerging (and CEE) markets in terms of number of clinical trials sites. The structure of Polish clinical trials market differs from global and leads the modern tendencies – CROs operates the majority (70% by volume; 53% by value) of trials.*

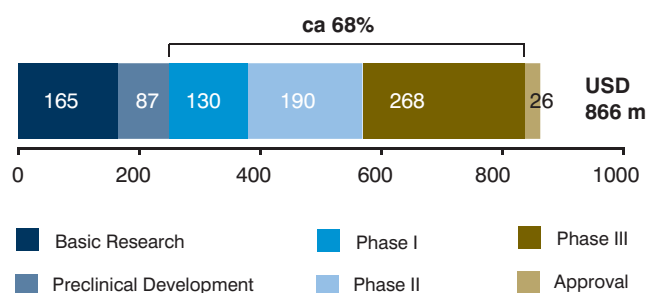
## What are the clinical trials?

### Drug route to the market

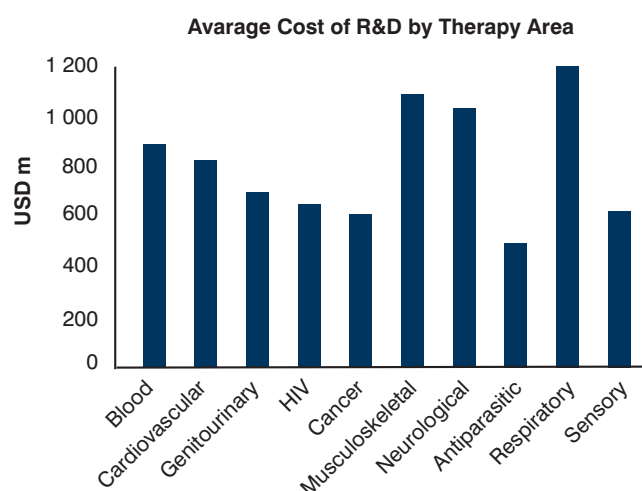
- The key aim of conducting clinical research is to ensure safety and efficacy of a health intervention that is expected to be routed to the market and thus serve patients as end-users.
- As they are lengthy and costly, clinical trials constitute a very important component of the drug development process – approximately two-third (i.e., c. USD 590m) of average cost of molecule route to market is allocated to clinical trials.
- Drug developing company (a sponsor) has the right to exclusive sales over a specified period after the drug is registered. This exclusive period is typically between 10 and 15 years of patent protection.
- When patent protection expires, the drug is exposed to competition from generics.

*Clinical trials are necessary to ensure efficacy and safety of newly developed medicine. They remain to be the core stage of drug development process*

### Average cost of molecule route to market (USD m)



### Costs per drug for medicines in selected therapeutic areas



Source: Federal Trade Commission, PwC Analysis

*Averaging c.USD 866m, the cost of molecule route to market varies between the therapeutic areas*

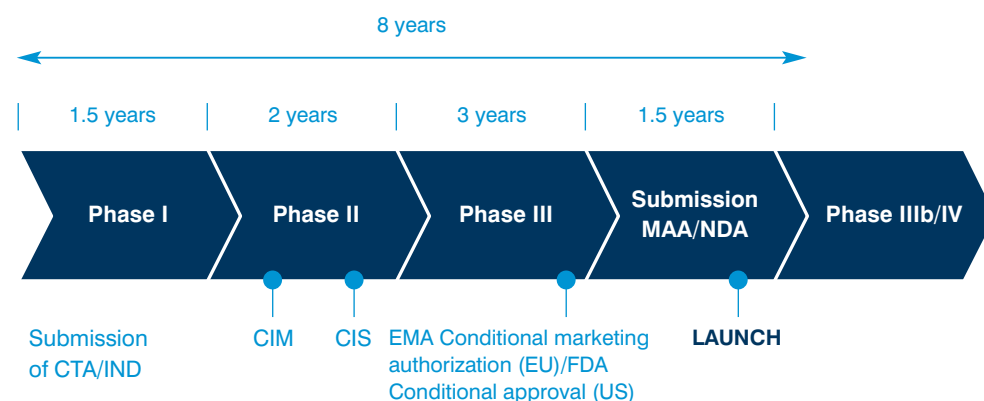
*In a typical development path, the satisfactory completion of a three-phase process is a prerequisite for a drug to be launched*

*As the patent protection period usually starts at the molecule development stage, the aim of sponsors is to minimize the length of clinical research and speed up the drug route to market*

### Clinical trials process

- In a typical process, by means of four-phase investigation, a sponsoring entity (usually a pharmaceutical company), after a promising pre-clinical development, conducts a series of clinical trials according to Good Clinical Practice (GCP) standards on patients who volunteer to undergo such clinical trials.
  - **Phase I:** Initial testing of drug safety, metabolism, and the drug's reaction and impact on digestive system. At this stage, typically a rather small number of healthy patients take part in the trial (50-100 patients, on an average);
  - **Phase II:** More detailed testing on drug dosing and safety vis-à-vis initial efficacy results. In phase II, first comparative trials are conducted (application of new substance versus standard treatment and placebo). Confidence in Mechanism (CIM) and Confidence in Safety (CIS), which are the key milestones for a drug to be tested on a larger population sample, are expected to be met at this stage. Typically, a randomized selection is applied to patients with specific types of ailments (c.300-600 patients, on average);
  - **Phase III:** The lengthiest and costliest part of trials, where the final efficacy of the drug is expected to be confirmed. Patient selection and recruitment are similar to those in Phase II. However, patient population can range from hundreds to up to a couple of thousands people. Successful completion of Phase III trial allows the drug to be registered and introduced in the market ("Launch");
  - **Phase IIIb/IV:** Additional, post-launch testing aimed at confirming drug efficacy in additional treatments, applications, etc. as well as assuring the validity of previously completed phases and long-term efficacy of drug.

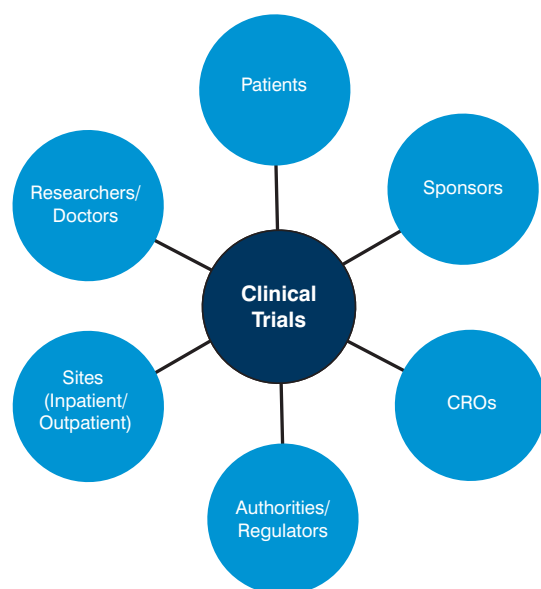
### The current clinical trials development process



CIM Confidence in Mechanism  
 CIS Confidence in Safety  
 IND Investigational New Drug (US)  
 CTA Clinical Trial Application (EU)  
 MAA Marketing Authorisation Application (EU)  
 NDA New Drug Application (US)  
 Source: PwC Analysis

## Stakeholders involved

### Key groups of stakeholders involved in clinical trials



Source: PwC Analysis

- **Sponsors:** Pharmaceutical companies are the most common sponsors of clinical trials, however some projects are financed by academic institutions or research centers. In the former case, clinical trials are run in-house by pharmaceutical companies and/or can be outsourced to independent CROs.
- **CROs (Contract Research Organizations):** Unlike integrated pharmaceutical companies, independent CROs are solely focused on clinical trials. CROs and pharmaceutical companies hire contract research associates (CRAs) – the qualified staff responsible for monitoring of the process and cooperation with researchers.
- **Sites:** Depending on the nature and medical specification of a clinical trial, the research can be run in out-patient and/or in-patient medical entities. Hospital directors are key decision makers in the latter case.
- **Researchers/Doctors:** Doctors have direct contact with patients, thus they are the leaders of clinical trial conduction in a particular site. They work individually or with a team of assistants.
- **Patients:** By means of individual consent, patients of specific ailments voluntarily agree to take part in the clinical trial. This can be done in both out-patient and in-patient modes.
- **Authorities:** National regulatory offices and ethical committees are expected to provide opinion and approve/reject the launch of a clinical trial. They are also bound to ensure that International Conference on Harmonization (ICH)- GCP compliance requirements are satisfied.

*Various stakeholders impact the clinical trials process and the drug development path*

*Clinical trials can be operated inhouse by pharmaceutical companies and/or outsourced to independent CROs*

*Clinical trials market is dependent on a number of key global phenomena...*

*...and thus it is implied to accommodate*

## Global perspective

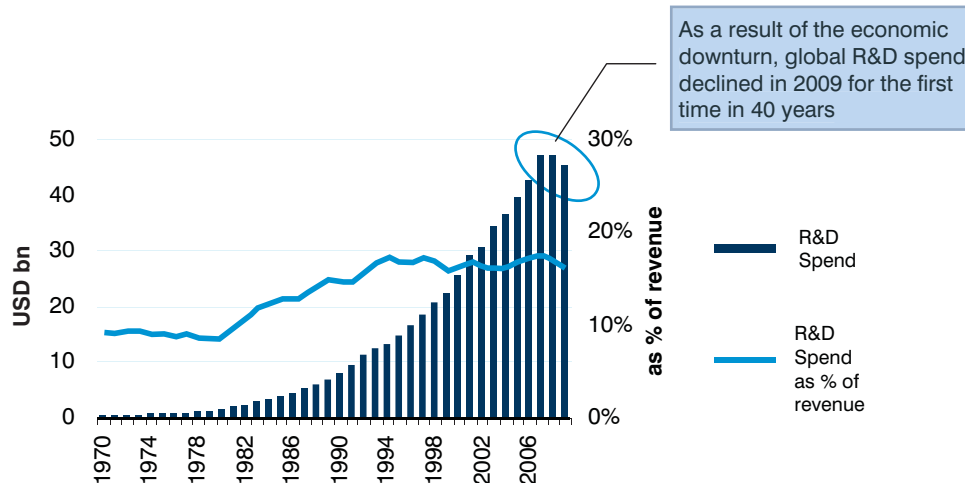
Key global market influencers	
Pharma R&D spend	<ul style="list-style-type: none"> <li>Pharmaceutical companies' R&amp;D spend is directly linked to the budget allocated to clinical trials.</li> <li>Overall pharmaceutical and biotechnological companies' R&amp;D spend historically exhibited continuous, long-term growth. However, recently R&amp;D productivity declined.</li> </ul>
Disease prevalence	<ul style="list-style-type: none"> <li>Forecasted trends in disease prevalence and death causes may indicate therapeutic areas where demand for drugs, and thus clinical trials, will increase.</li> <li>Therefore, areas such as oncology and cardiology appear to have potential to attract more clinical trial projects in the future.</li> </ul>
Blockbuster patent expiry	<ul style="list-style-type: none"> <li>The leading pharmaceutical companies will be exposed to revenue declines as a result of patent expiries until 2012.</li> <li>This decline will demand from sponsors to revise their policy over new clinical trial launches and perhaps recalibrate their execution (e.g., decide whether it should be implemented inhouse or outsourced).</li> </ul>
Shorter drug development path	<ul style="list-style-type: none"> <li>The future drug development process is expected to be more refined, as more emphasis is put on pre-trial molecule development.</li> <li>Interview feedback suggests that this is something inevitable as sponsors need to lower high cost of trials, especially during phase III.</li> </ul>
Increased focus on process efficiency	<ul style="list-style-type: none"> <li>Sponsors seek for increased operational (and cost) efficiency, primarily by outsourcing trials to CROs and considering new locations for research projects.</li> <li>The sponsors shift the execution of clinical trials to emerging markets (former CIS*/Asia), where cost is lower and patient recruitment is easier. However, as quality, predictability, and assurance of procedural standards is important, large part of clinical research projects is still retained within the mature markets (US/WE). Also marketing issues as well as the fact that these are the largest markets for innovative drugs influence execution of clinical trials in these markets.</li> </ul>

\*CIS – Commonwealth of Independent States



## Pharmaceutical companies' R&amp;D spend

## Pharma R&amp;D spend over time



Source: FDA/CDER, PhRMA, PwC Analysis

- Depending on the source, global clinical trials market is estimated to be worth c.USD 50-80bn. Despite the uncertainty over the future growth of R&D spend of big pharmaceutical companies, the market is expected to maintain historical positive growth trend in the future.

– “As healthcare development will continue anyway and given that we are heading towards genetics-based, so-called ‘personalized medicine’, clinical trials will still be key to new drugs development.”

*Pharmaceutical company, Poland*

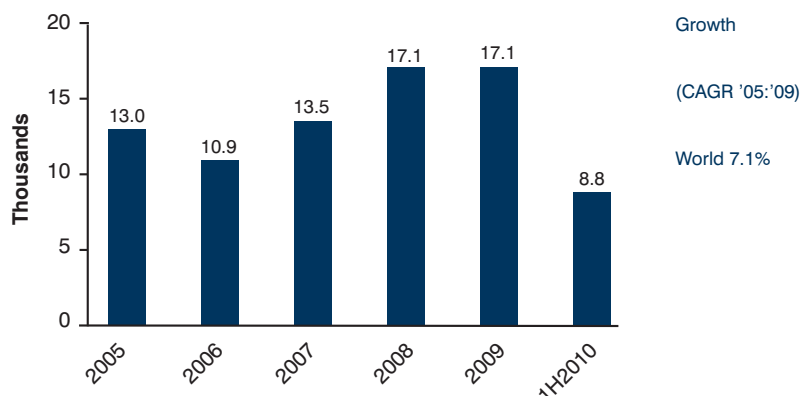
– “The global market will certainly grow overall, it is rather a question which countries would attract more trials and benefit from this growth.”

*CRO, Poland*

*Historically, overall pharmaceutical companies' R&D spend exhibited continuous, long-term growth*

*Estimated at c.USD 50-80bn, global clinical trials market has been growing. Interview feedback suggests that this trend is expected to continue*

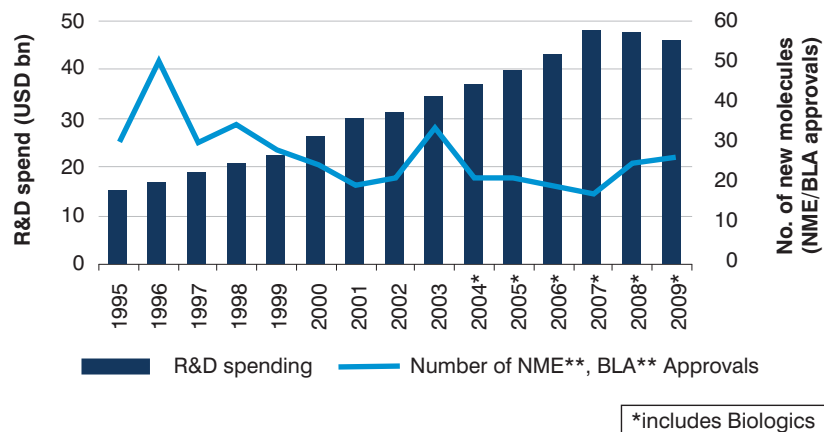
## Global, Number of registered clinical trials



Note: CAGR – Compound annual growth rate  
Source: ClinicalTrials.gov

*R&D productivity continues to decline...*

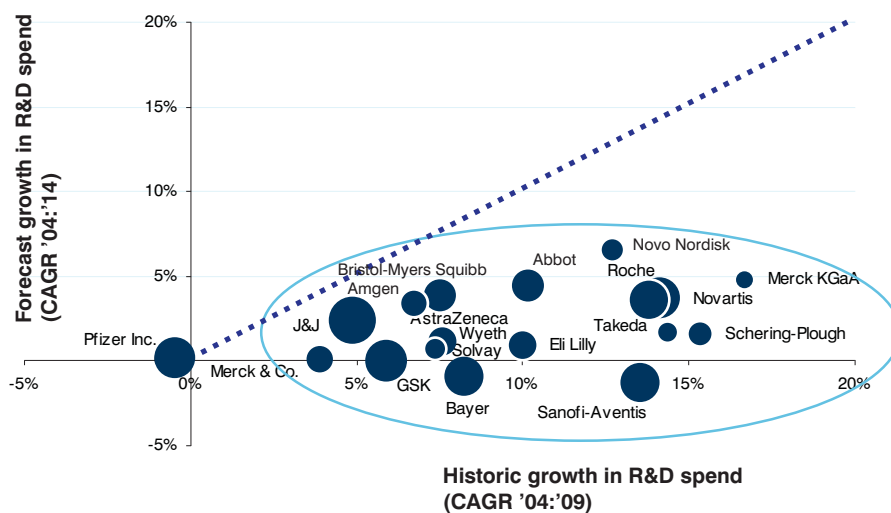
**R&D productivity of pharmaceutical industry**



Note: \*\*NME – new molecular entities; BLA – biologic license application; New chemical or biological prescription therapeutic: Excludes vaccines, antigens, and combination therapies, which do not include at least one new constituent  
Source: FDA/CDER, PhRMA, PwC Analysis

*...and it appears that forecast R&D spend will likely grow at a much slower pace than historically*

**Top 20 pharma companies: Historical versus Forecasted R&D spend**

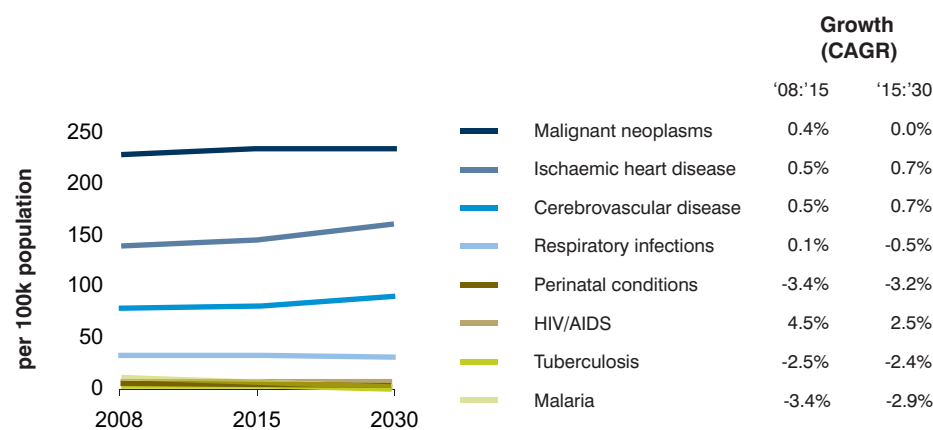


Note: Bubble size indicates R&D spend in 2009; CAGR – Compound annual growth rate  
Source: Datamonitor, PwC Analysis

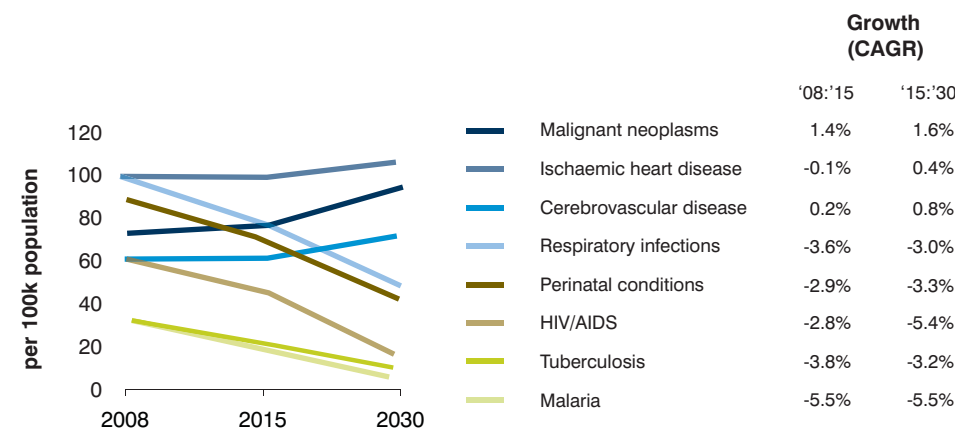
### Disease prevalence

- WHO has forecasted that in high income countries, civilization diseases such as malignant neoplasms, ischaemic heart as well as cerebrovascular disease will remain to be the most common mortality causes, and all three will maintain forecasted positive growth to this regard over the next 20 years. This is expected to drive demand for the relevant type of drugs.
- Due to different average health condition of societies in low income countries, the dynamics of mortality causes are somewhat contrasting. However, one needs to bear in mind that disease detection is typically worse in those geographies.

### High income countries, Forecasted mortality causes (per 100k population)



### Low income countries, Forecasted mortality causes (per 100k population)



Note: CAGR – Compound annual growth rate  
Source: WHO

*In high income countries, oncology and cardiology related diseases exhibit the highest relative mortality rates. In low income countries, converging trend towards wealthier geographies is expected in the long-term*

*Forecasted trends in disease prevalence and death causes may indicate therapeutic areas where demand for drugs, and thus clinical trials, will increase*

*The leading pharmaceutical companies will lose between 14% and 41% of their existing revenues as a result of patent expiries until 2012*

#### Blockbuster patent expiry

##### Upcoming patent expiries of large pharma companies

Company		2010	2011	2012	Share of Revenues (%)
AstraZeneca	Arimidex	(\$2.2bn)*	Seroquel (\$4.7bn)	Symbicort (\$3.7bn)	38**
BMS			US Plavix (\$4.8bn) Avapro (\$1.3bn)	Abilify (\$2.1bn)	30
GSK	Advair	(\$3.8bn)		Avandia (\$2.5bn)	23
Eli Lilly			Zyprexa (\$4.8bn)		22
Merck	Cozaar/Hyzaar	(\$3.2bn)		Singulair (\$4.5bn)	22
Novartis	Femara	(\$1.1bn)		Diovan (\$6.0)	14
Pfizer	Aricept	(\$800m)	Lipitor (\$12.1bn) Xalatan (\$1.6bn)	Viagra (\$1.7bn) Detrol (\$860m) Geodon (\$1.1bn)	41
sanofi-aventis	Taxotere	(\$2bn)	US plavix (\$3.8bn) Avapro (\$2.1bn)	Lovenox (\$3.1bn)	34

Note: \*Estimate of global sales in 12 months prior to patent signing;

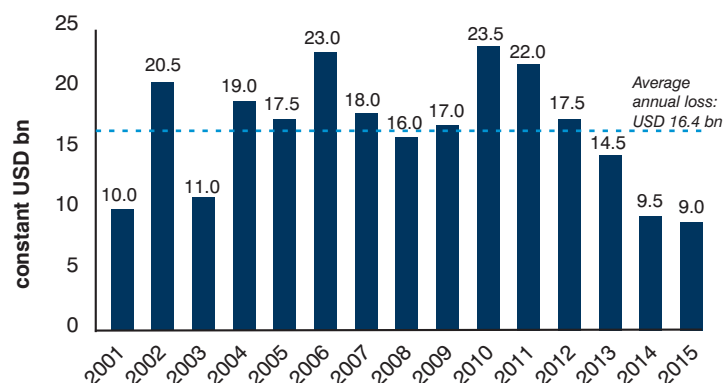
\*\*Value of products losing patent protection as a percentage of total company sales over next five years

Source: PwC Analysis, AXA Framlington

- Increase in cost-cutting on the sponsors' side appears inevitable and clinical research expenditure might be negatively impacted in the next four to five years.
- As the innovative pharmaceutical market consolidation progresses, small R&D oriented companies are acquired by larger players. As a result, pressure for efficiency and searching for synergies may decrease the overall net R&D spend.
- However, this might be favorable for less costly CROs (e.g., CEE-based), which could benefit from increased outsourcing of clinical research activity – as outsourcing is believed to provide more cost flexibility.

*USD 96bn sales is exposed to generic competition in 2010-2015*

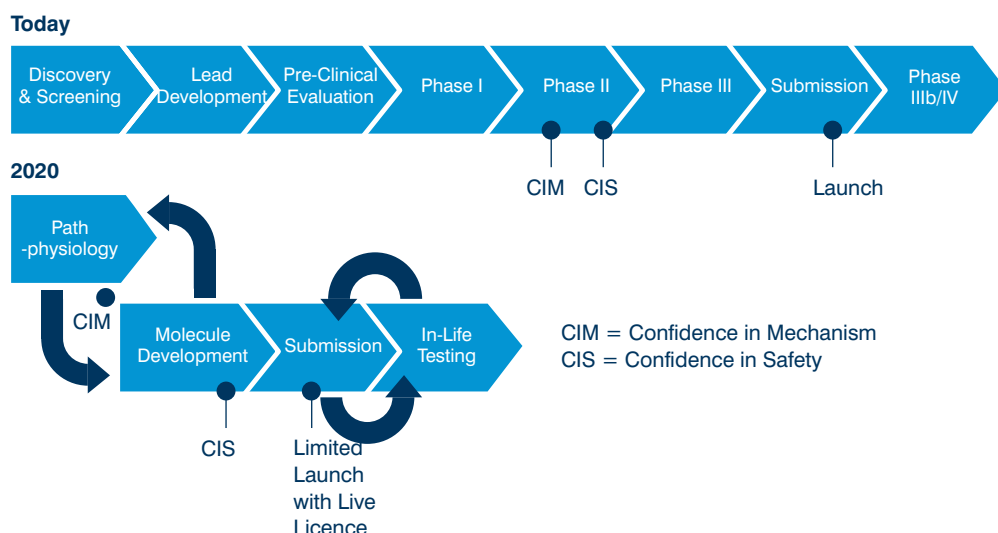
#### Value of patent expiries 2001-2015



Source: IMS Health Midas

## Shorter drug development path

## Drug development process – current and expected for the future



Source: PwC "Pharma 2020: The Vision" Report

- The new drug development process is expected to be shorter and less costly in the long-term;
  - “We expect shortening of clinical trials process as drug development path overall is expected to be enhanced – more emphasis will be put on laboratory research (molecules) and clinical trials will be more focused on particular group of patients. Phase III is costly and the industry needs to cut down on this cost!”

*Pharmaceutical company, Poland*

- The drug developer will first secure and launch “in-life testing”, that is a series of small, highly targeted clinical studies. Upon the regulatory agency’s conditional approval, the company will be allowed to market the drug on a restricted basis (to a narrow group of patients).
- In the long-term, it might culminate in the complete integration of clinical trials with clinical practice (already starting to happen in the treatment of cancer). In effect, should the expectations materialize, clinical trial participation would become part of normal care.
  - Market insiders claim that there is increased pressure on authorities to support R&D and allow for shorter drug development path (and thus cost), while maintaining appropriate safety measures. As an example, the EU has already introduced conditional registration principle for innovative medicinal products, which appears to put even more pressure on preclinical trials during the drug development stage.
- However, a more thorough fulfillment of those expectations is expected within next 10 or 20 years rather than shortly.

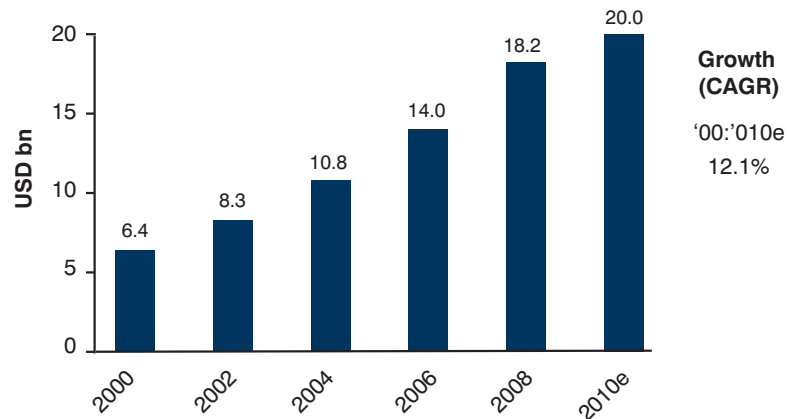
*The drug development process is expected to be more refined in the long-term as more emphasis will be put on pre-trial molecule development and conditional approval*

*Interview feedback suggests that this is something inevitable as sponsors need to lower high costs of trials, especially during Phase III*

*Global CRO market has grown dynamically in the last 10 years...*

#### Increased focus on process efficiency – Outsourcing

##### Global CRO market (USD bn)

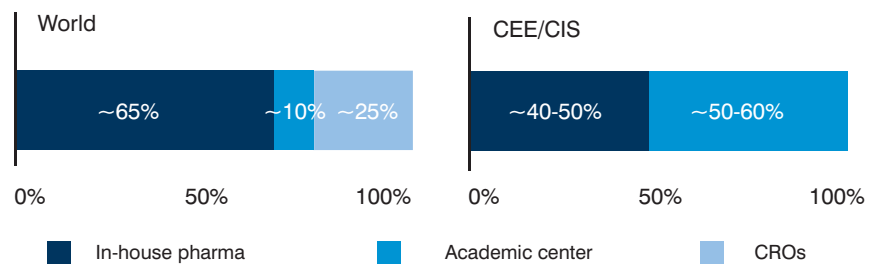


Note: CAGR – Compound annual growth rate  
Source: Business Insights

- Outsourcing trend globally gained significance in the last decades, especially in the markets where pharmaceutical companies are strategically present to a lesser extent or operation of trial is more complex.
  - “In the light of the downturn pharma companies became even more aware of their financials. They focus on their core activity and outsource R&D to other companies – this brings flexibility of cost. Only recently, some of the leading pharmaceutical companies lowered their R&D spend and rather maintain outsourcing trend in clinical trials.”  
*CRO, Poland*
  - “But it also depends on particular company strategic goals. Sometimes you’d expect less outsourcing in III/IV phase, as pharma companies aim at maintaining continuous presence and relations with sites management and researchers.”  
*Pharmaceutical company, Poland*

*...but roughly two-thirds of global clinical trials are still conducted inhouse by pharmaceutical companies*

##### Clinical trials market structure (by value, estimated)

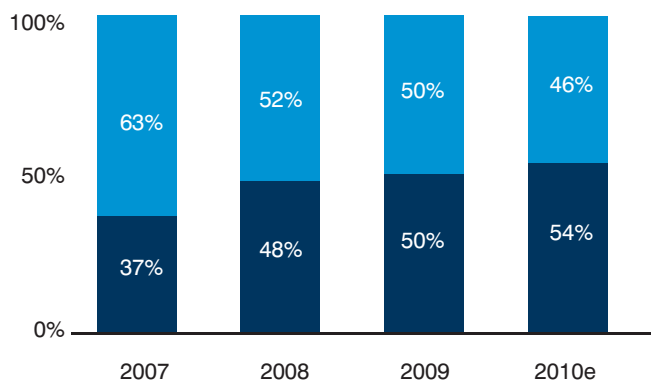


Source: World: Business Insight, CEE/CIS: PwC Interviews

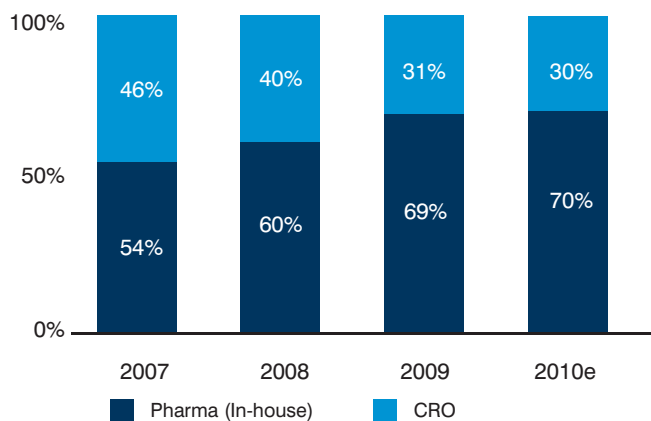


- Generally, the sponsor's headquarters decide on the selection of particular CRO for a project execution.
  - “Although we are free to share our recommendations with our headquarters on which subcontractors are best performers here in Poland, the final decision is rather centralized in big pharma companies. This centralization trend has gained on significance in recent years.”  
*Pharmaceutical company, Poland*
- In CEE, CRO appear to have earned larger market share than in-house pharmaceutical operations, as compared to the global trend.
  - “In Poland, the majority of trials is run by CRO as pharma companies have limited presence here. Locally active CROs have settled down here quite firmly.”  
*Pharmaceutical company, Poland*
- Analysis based on PwC Survey confirms that in Poland the number of clinical trials outsourced to CRO has been increasing.
  - “We have also developed some ‘in-sourcing’ practice, where clinical trials staff is leased to us from CROs. These people work at our premises on temporary basis and they are usually assigned to a specific project.”  
*Pharmaceutical company, Poland*

Poland, Clinical trials market structure (by value)



Poland, Clinical trials market structure (by volume)



Analysis based on PwC Surveys shows CROs have maintained increasing market share both in value and volume terms – this confirms the increasing outsourcing trend.

It also appears that CROs operate the smaller size trials (of lower budget).

*In Poland, CROs operate the majority of trials and appear to have gained gradually increasing market share.*

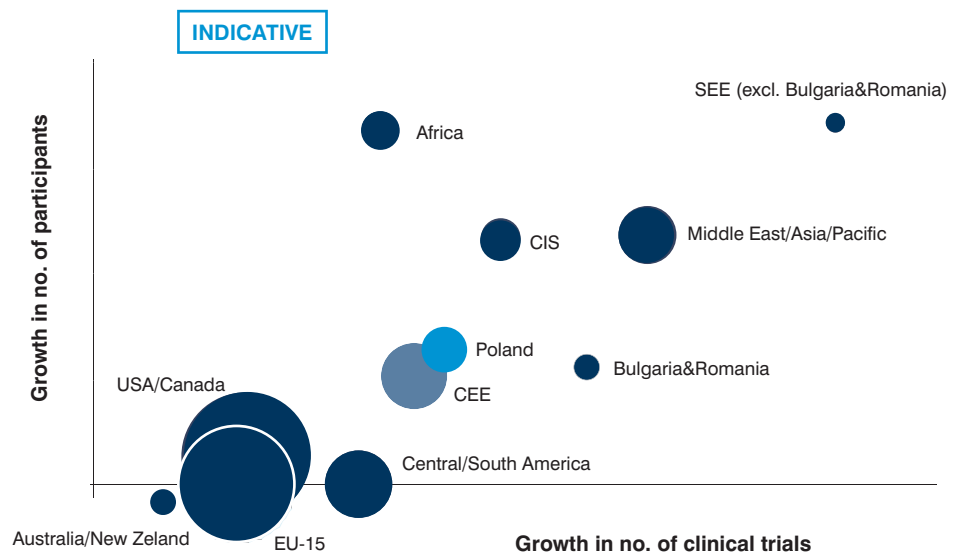
Source: PwC Survey

*Despite the fact that location of clinical trials moves towards emerging markets...*

#### Increased focus on process efficiency – Geographical shift

- North America (USA and Canada) and WE are traditional clinical trials market. Over the last two decades, an increasing shift to CEE/SEE/CIS as well as Central/South America or Middle East has been observed, as sponsors were attracted by lower cost and time-efficient patient recruitment.
  - “In fact, CEE has proved to be more attractive location than CIS, as value for money was higher and EU accession path assured greater extent of certainty over legislative and procedural standards.”  
*Pharmaceutical company, Poland*
- Sponsors of clinical trials are expected, to a greater extent, to search for low-cost and large population locations in the future.
  - “Everybody expects that China, India and Middle East will be increasingly penetrated, however there are still some obstacles to more aggressive expansion into those markets – for example, I am not sure about the quality of patent protection system in China.”  
*CRO, Poland*

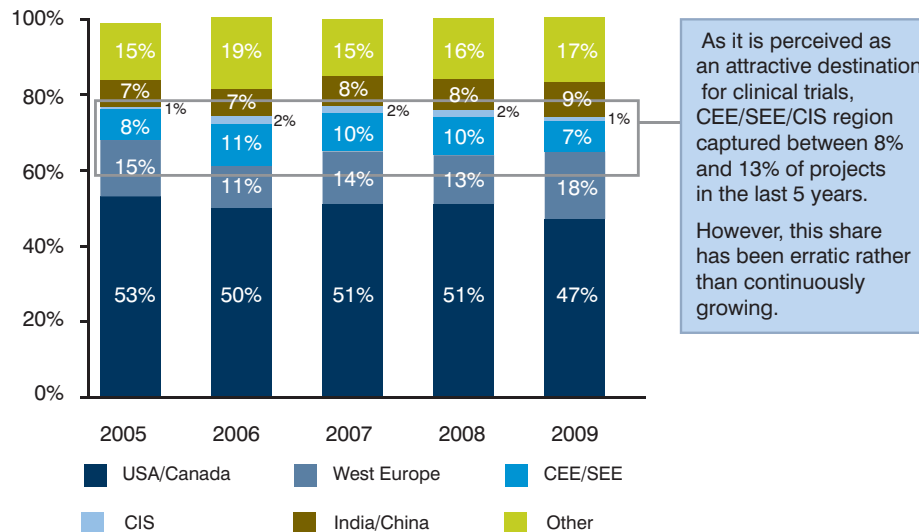
#### Pivotal clinical trials submitted in MAAs registered at EMA



Note: Indicative; Analysis based on a sample of clinical trials, i.e. pivotal clinical trials submitted in MAAs registered at EMA; Bubble size indicates average per annum number of participants in 2005-2008  
Source: EMA

- Nevertheless, traditional markets remain to be the leading geographies.
  - “Clinical trials indeed are shifting to the East, but North America and West Europe are still the core markets. US is not a market you don’t want to be in!”  
*Pharmaceutical company, Poland*
  - “Especially in the light of the downturn, it appears that sponsors to greater extent focus on their domestic markets.”  
*CRO, Poland*

## Shares of registered clinical trials, by region



Source: ClinicalTrials.gov

- CEE is still perceived as a prospective clinical trials market and it is expected to be maintained as long as currently observed attractors are valid. However, market insiders emphasize emerging role of alternative locations, such as Latin America and Middle East.
  - “Brazil, Argentina and a number of Middle East countries appear to be winning the increasing number of trials because factors such as population size and efficient patient recruitment are attractive there. CEE has to maintain its well respected quality of clinical research execution and eliminate currently existing drawbacks in order to compete successfully with “new markets.”  
*Pharmaceutical company, Poland*

*...still approximately two-thirds of worldwide projects are registered in North America and WE*

*CEE/SEE/CIS is an attractive region with further growth potential. However, it also faces increased competition from other emerging regions*

*Poland is ranked tenth in the world and first among emerging (and CEE/SEE) markets in terms of number of clinical trials sites...*

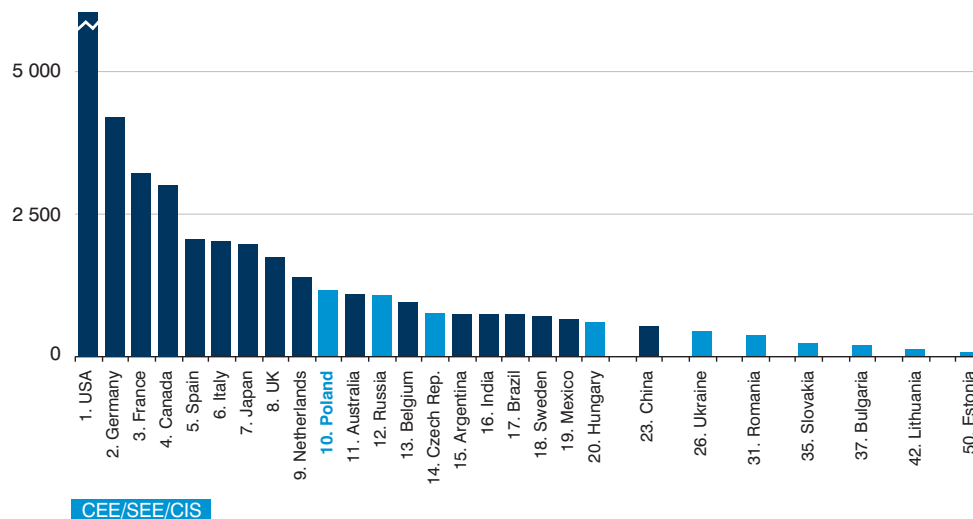
Country trends in participation in clinical trials – 2008

Rank	Country	Number of sites	Share by sites (%)	Growth (%)	Site density (no. of sites per 1 m population)
1	USA	36,281	48.7	-6.5	117.4
2	Germany	4,214	5.7	11.7	51.5
3	France	3,226	4.3	-4.0	49.3
4	Canada	3,032	4.1	-12.0	89.0
5	Spain	2,076	2.8	14.9	45.1
6	Italy	2,039	2.7	8.1	33.9
7	Japan	2,002	2.7	10.3	15.7
8	UK	1,753	2.4	-9.9	28.3
9	Netherlands	1,394	1.9	2.1	84.0
<b>10</b>	<b>Poland</b>	<b>1,176</b>	<b>1.6</b>	<b>17.2</b>	<b>30.8</b>
11	Australia	1,131	1.5	8.1	50.9
12	Russia	1,084	1.5	33.0	7.6
13	Belgium	986	1.3	-9.4	91.1
14	Czech Rep	799	1.1	24.6	76.0
15	Argentina	757	1.0	26.9	18.9
16	India	757	1.0	19.6	0.6
17	Brazil	754	1.0	16.0	3.9
18	Sweden	739	1.0	-8.6	79.1
19	Mexico	683	0.9	22.1	6.1
20	Hungary	622	0.8	22.2	62.1
23	China	533	0.7	47.0	0.4
26	Ukraine	440	0.6	31.0	9.6
31	Romania	354	0.5	19.4	15.9
35	Slovakia	246	0.3	27.7	45.7
37	Bulgaria	215	0.3	12.7	28.4
42	Lithuania	146	0.2	30.2	43.7
50	Estonia	83	0.1	34.6	61.9

Note: Trial density is the number of recruiting sites divided by country population in millions.  
Source: Datamonitor

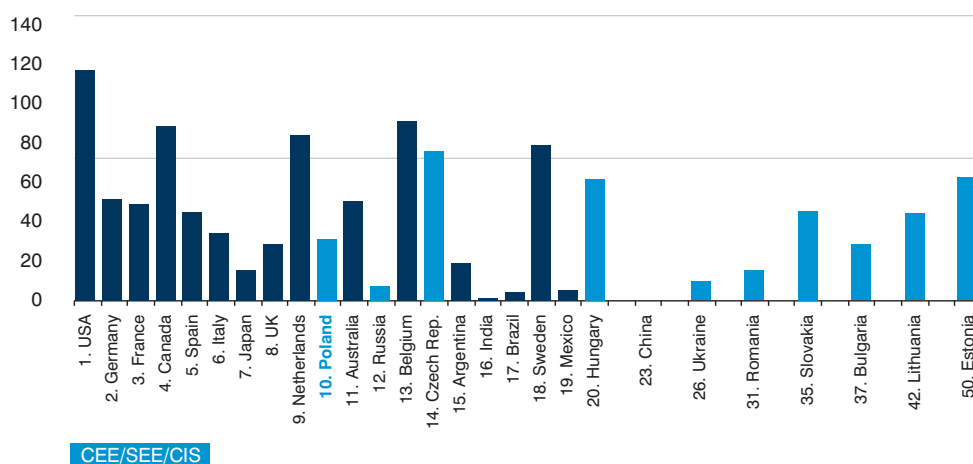
CEE/SEE/CIS

Number of clinical trial sites



...however the Czech Republic and Hungary, although smaller, are not far behind due to higher density of sites

Clinical trial sites density (per 1 m population)



Note: Ranking according to the absolute number of sites; Trial density is the number of recruiting sites divided by country population in millions.

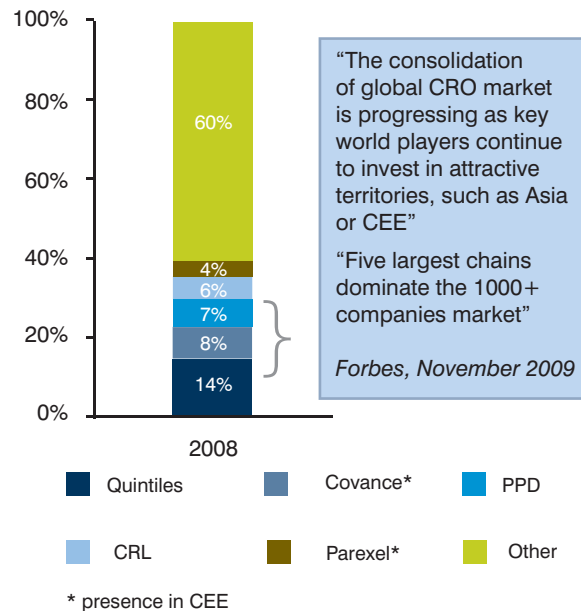
Source: Datamonitor, ClinicalTrials.gov

Although the market is consolidating around big internationals, the high growth pace appears to provide significant upside, which is also a potential for independent CROs

Recent M&A track confirms consolidation trend by large international players and entry into CEE/SEE markets

### Consolidation around big CROs

#### Global CRO market shares (by revenue, 2008)



Source: Business Insights, Press articles, PwC Analysis

### M&A activity in CROs – since 2007

<b>August 2009</b>	Millipore Corporation acquires BioAnaLab, an UK based CRO
<b>February 2009</b>	PPD acquires AbCRO, Bulgarian based CRO with operations in Romania and other SEE countries
<b>June 2008</b>	Parexel acquires ClinPhone, UK based clinical technology organization providing clinical trials services)
<b>April 2009</b>	Siro Clinpharm acquires Omega Mediation, Germany based CRO
<b>February 2008</b>	Worldwide Clinical Trials acquires MediQuest, Serbia based CRO with operations in SEE
<b>September 2007</b>	United BioSource Corporation acquires ClinResearch, Germany based CRO

Note: Major M&A deals since 2007 have been considered  
 Source: Mergermarket



## Section 3

# Clinical trials in Poland: Key characteristics



**Clinical trials in Poland: Key characteristics**

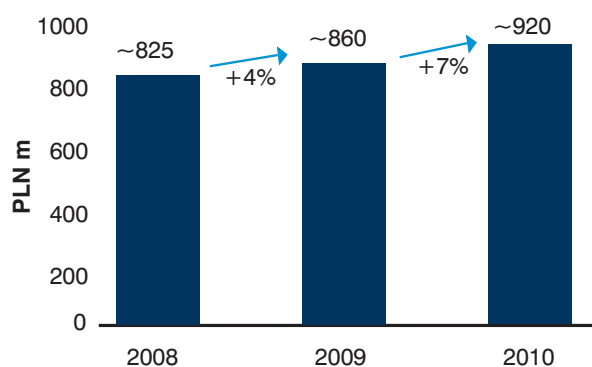
- *Poland remains the largest clinical trials market in CEE/CIS and stands for roughly 20% in terms of clinical trials number in Eastern Europe. However, both patient participation and site penetration rates indicate a potential for growth.*
- *It is also one of the most important markets – in more than half companies that operate on Polish market over 80% of new drugs introduced to the market were subject to clinical trials in Poland.*
- *The key drivers of the clinical trials market in Poland are the population size, efficient patient recruitment and high quality of execution. As of key advantages – patient recruitment and quality of medical staff are perceived as the most significant.*

## Market size and growth – Key market metrics

- Analysis based on PwC Survey data allows us to estimate total clinical trials market size\* at c. PLN 860m in 2009, with c. 7% growth prospects in 2010.
- However, one should bear in mind that the presented value of the market does not include the cost of drugs used during the course of the clinical research projects as this cost is difficult to capture in market terms.
  - While the cost of newly tested drugs is rather virtual, the interview feedback may suggest that cost of standard pharmaceutical treatment has potential to increase the total market size by 50%-60%.

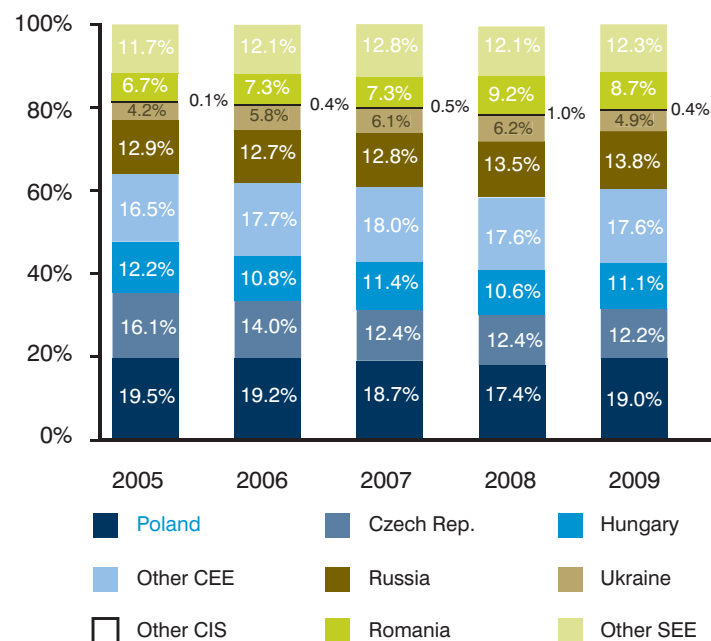
*The clinical market in Poland is worth c. PLN 860m – it has experienced moderate single-digit growth*

### Estimated clinical trials market size, Poland



Note: \*Market size is defined as total expenditure on clinical trials execution  
Source: PwC Survey, PwC Analysis

### Central East Europe, Number of clinical trials registered



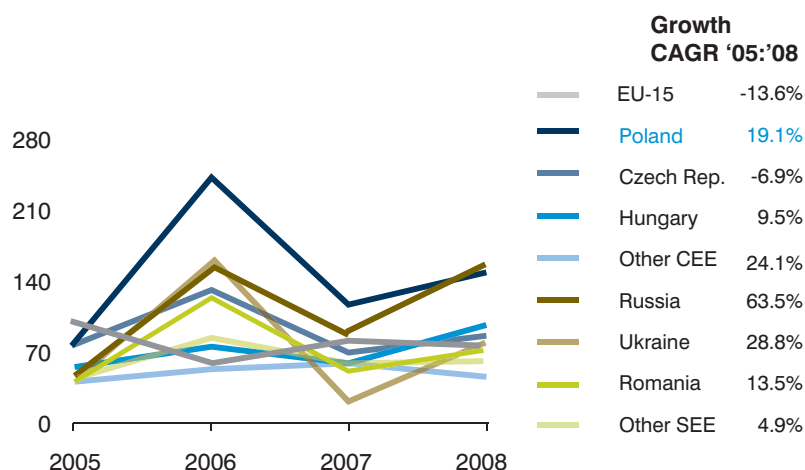
*Due to its population size, Poland remains the largest clinical trials market in CEE/SEE/CIS*

Note: CEE = Poland, the Czech Republic, Hungary, Estonia, Latvia, Lithuania, Slovakia; CIS = Russia, Ukraine, Belarus, Kazakhstan; SEE = Romania, Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Macedonia, Serbia, Slovenia.  
Source: WHO (WHO ICTRP collects data from 10 clinical trials registries, including ClinicalTrials.gov – USA, DRKS – Germany, NTR – the Netherlands and ANZCTR – Australia)

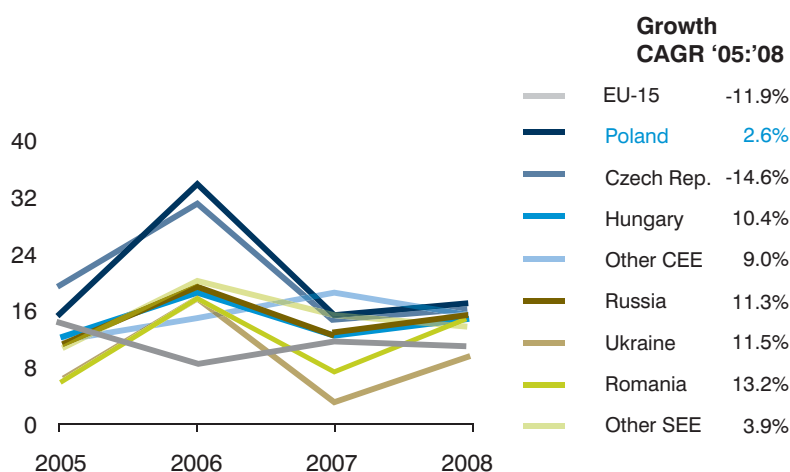
*Poland still exhibits one of the largest number of patients engaged in one trial. However, this differential versus other countries in the region has recently decreased*

- Based on WHO International Clinical Trials Registry Platform data, Poland retained the largest share in number of clinical trials in CEE/SEE/CIS for the last couple of years. This primarily appears to be due to large absolute market size.
- However, smaller CEE geographies, such as the Czech Republic and Hungary, appear to have attracted more trials in relative terms (e.g., per population).
- SEE's share grew from 18.4% in 2005 to 21.0% in 2009. CIS countries have been gradually gaining share from 17.2% in 2005 to 19.1% in 2009. Russia and Ukraine are the key markets in this region.
- Due to its relative size, Poland maintains its leading position in terms of number of patients engaged in one trial. However, this share declined since 2006, according to EMEA data on pivotal clinical trials. It is also true for patient density per site.
- All major CEE/SEE/CIS markets appear to be converging towards EU-15 levels in terms of patient density.
- The highest growth rates are exhibited by Russia and Ukraine, where overall clinical research market has grown dynamically.

#### Patients per clinical trial (pivotal trials submitted in MAAs to the EMA)



#### Patients per site (pivotal trials submitted in MAAs to the EMA)



Note: \*Data for pivotal trials submitted in MAAs to the EMA. Pivotal trials are those clinical studies that provide the significant evidence that is the basis for the approval decision; therefore, largely of phase III;

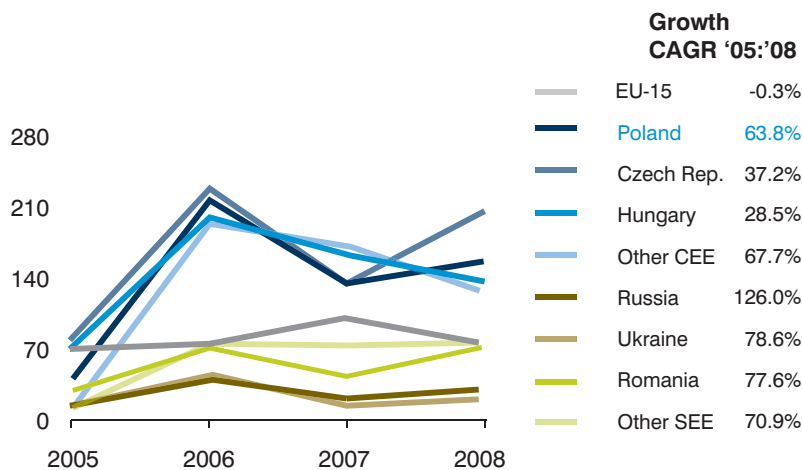
CAGR – Compound annual growth rate

Source: EMA

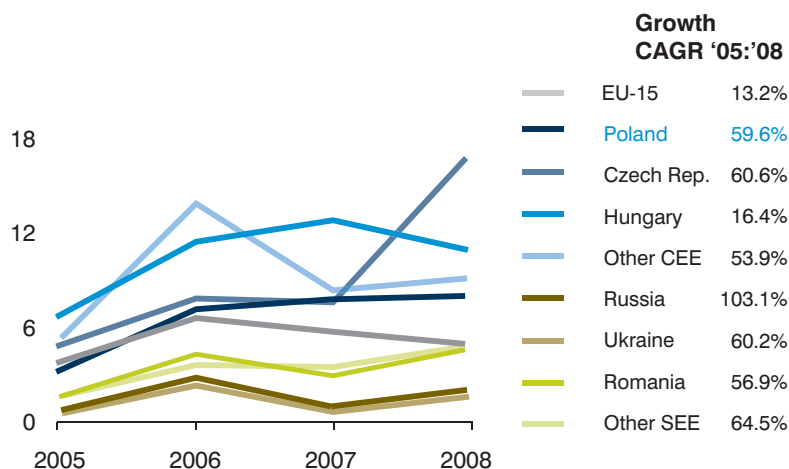
- Although in absolute terms Poland contributed 4.4% patients for pivotal clinical trials in Europe – second after Germany (6.3%) – in 2005-2008, number of participants per population in Poland declined since 2006 despite growth in pivotal clinical trials (321 in 2008 versus 250 in 2006).
  - The example of EU-15 shows that participation rates may decline along with economic development, unless new incentives are identified.
- There is a potential for more sites to be engaged in pivotal trials in Poland, compared to the penetration that the Czech Republic and Hungary show (both countries exhibit higher per capita number of sites).
- Russia and Ukraine have relatively high growth rates primarily due to low values at the beginning of the period.

*Both patient participation and site penetration rates in Poland are lower than those in the Czech Republic and Hungary, which indicate a potential for growth*

### Patients per 1 million population (pivotal trials submitted in MAAs to the EMA)



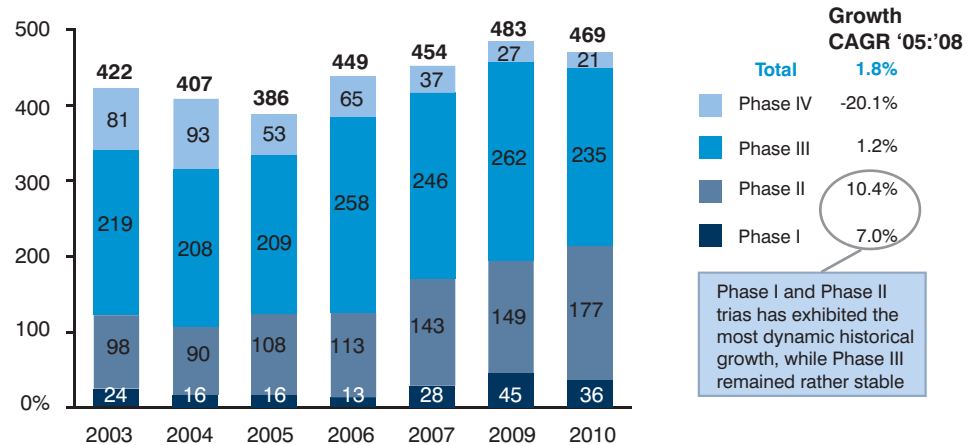
### Sites per 1 million population (pivotal trials submitted in MAAs to the EMA)



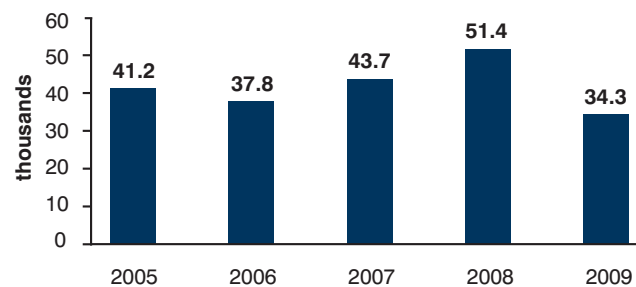
Note: \*Data for pivotal trials submitted in MAAs to the EMA; CAGR – Compound annual growth rate  
Source: EMA

*In 2009, there were 469 new clinical trials registered in Poland. This number has grown at c. 1.8% since 2003 (CAGR '03:'09)*

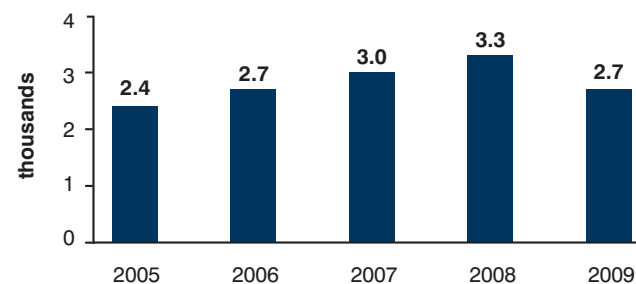
Number of new clinical trial registrations in Poland, by phase



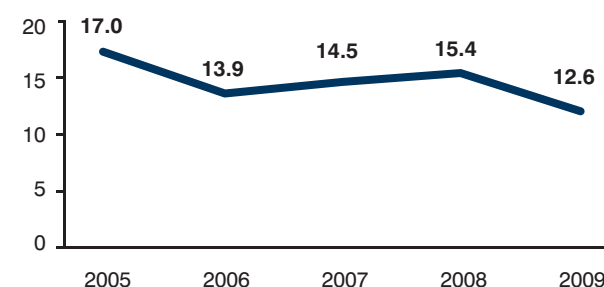
No. of clinical trial participants in Poland



No. of lead researchers in Poland



Average no. of participants per researcher in Poland



The average number of recruited patients per researchers has fallen in recent years;

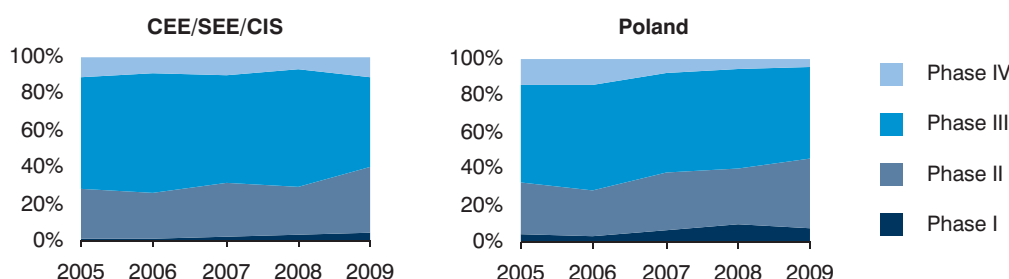
This may suggest recruitment gets more competitive as there are more sites and more lead researchers engaged in clinical trials

*It appears that the market underperformed in 2009, primarily due to the economic slowdown and the repatriation of a number of trials to WE/US*

Note: CAGR – Compound annual growth rate  
Source: CEBK, PwC Analysis



## Number of clinical trials registered by phase



Source: CEE/CIS: ClinicalTrials.gov; Poland: CEBK

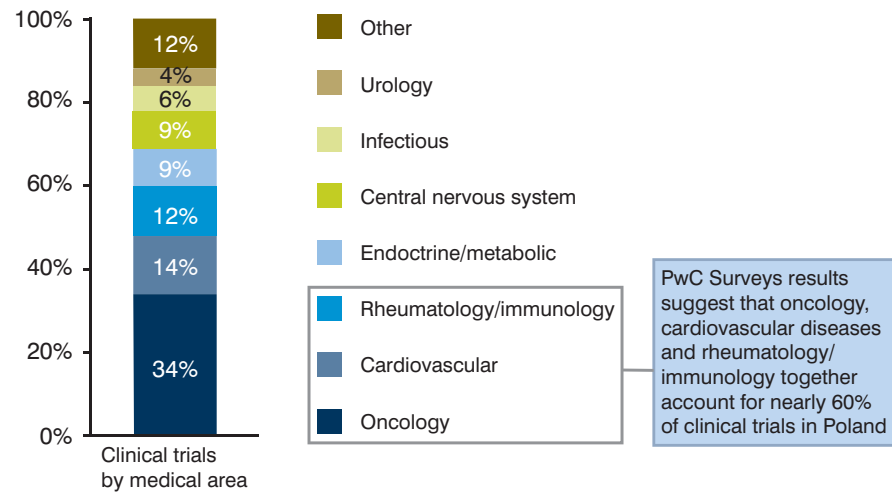
- Market insiders believe that Phase III will remain dominant in Poland and CEE/SEE/CIS, with a moderately increasing share of Phase II in the mid-term.
  - They also note that Phase IV is expected to be increasingly relocated from more mature markets to the CEE region, longer term. However so far, the number of Phase IV trials has exhibited the most significant decline, historically.
- However, early phases are still viewed as being rather underpenetrated in Poland. Despite large population and efficient recruitment, drawbacks such as administrative inefficiencies and delays deter sponsors from engaging in this type of trials at a larger scale.
  - “Early phase clinical trials can be seen as more risky from the sponsors’ investment perspective, as they require experienced sites and access to pool of patients. For such projects, locations where predictability of regulatory process and timing are more likely to be selected.”  
*CRO, Poland*
- PwC Survey results show that although early phase clinical trials are rather rare in Poland, they are expected to gain on significance. This shift is also because of low base for growth.
  - Over 60% of respondents believe that Phase I and Phase II trials will grow in Poland, but so will early phase projects in other CEE countries as well as globally.
  - The Polish market is expected to be dominated by Phase III, as 90% of respondents believe that one should rather expect a stable trend in share of this phase.
- The growth of early phase trials has been confirmed by CEBK data. Historically, the number of Phase I and Phase II trials has increased at the most dynamic rate.

*The majority of projects conducted in CEE/SEE/CIS and Poland are Phase III clinical trials. Per annum volumes of Phase III have been rather stable, while the volumes for Phase II have been growing*

*Questionnaire respondents believe that early phase trials will experience continued positive growth – phase III trial level is expected to be rather stable*

*Oncology and cardiology are the most often tested areas in clinical trials in Poland, according to PwC Survey respondents*

**Clinical trials in Poland, by medical area, 2009**

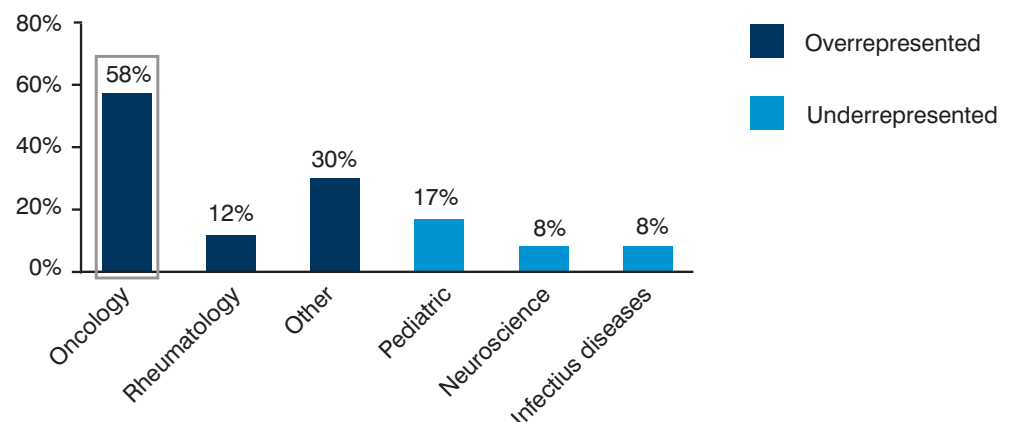


Note: Structure based on data collected via questionnaire  
Source: PwC Survey

- While respondents believe that oncology is rather over-represented in Poland vis-à-vis western markets (i.e. more oncology related trials are conducted in Poland as compared to average trial mix in WE), the majority of them (57%) claims that there are no significant changes in clinical trials mix by medical area between Poland and other CEE countries.
  - “Oncology indeed is a popular discipline in clinical trials executed in Poland as here sponsors can rather easily find a sample of patients in the late stage of diseases. This is not always the case in WE.”  
*Researcher, Warsaw*

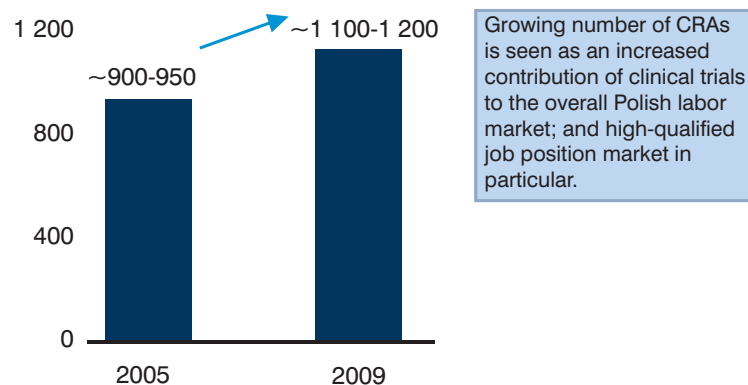
*Compared to WE, Poland is particularly seen as an attractive location for oncology clinical trials*

**PwC Survey: “Which medical areas are overrepresented/ underrepresented in clinical trials in Poland vs. WE?”**



Source: PwC Survey

## Estimated number of CRAs in Poland



Source: PwC Survey

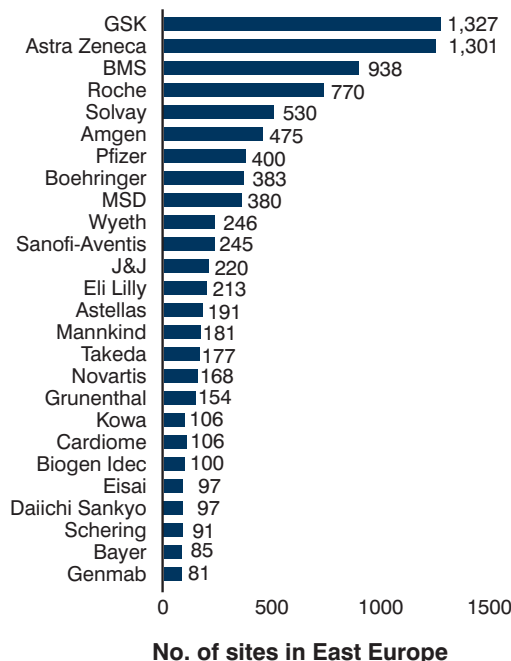
- Although the official statistics on the number of CRAs are unavailable, PwC Survey results may suggest that there are c. 1,200 CRAs in Poland.
  - “On average three full-time CRA workers are engaged per one clinical trial conducted in Poland.”  
*Pharmaceutical company, Poland*
- Of the respondents, 85% believe the number of CRAs has exhibited moderate but consistent growth in the last five-year period.
  - “Even though the number of trials has rather not grown significantly in recent years, the increased complexity of some trials may have indeed driven the increase in number of CRA jobs in Poland.”  
*CRO, Poland*
  - Increased complexity of trials is viewed to be the case in Poland and globally. Market insiders claim that Poland has good reputation and performance (i.e., high quality of researchers’ work) in hosting difficult projects, but they also point out that global clinical trials have become more complicated as goals outlined for the world of medicine to develop efficient drugs get more challenging.

*PwC Survey results suggest that there may be c. 1.2k CRAs in Poland, and this figure has grown in the last years*

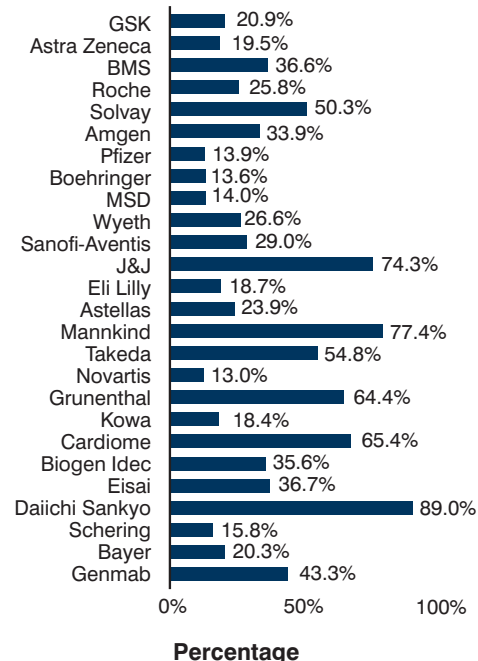
*Increasing complexity of clinical trials is viewed as positively impacting the number of CRAs in Poland and globally*

*GSK, AstraZeneca, BMS, and Roche appear to be the most significant sponsors in East Europe as they cooperate with the largest number of sites there*

Sponsors active in East Europe\*



East Europe sites as % of total Continental Europe sites



Note: 18-month observation from May 2006 to November 2007 is used for the analysis;

\*In this analysis East Europe includes: Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, Turkey and Ukraine

Source: Clinical Trial Magnifier Vol. 1:1 (2008)

*However, the largest sponsors' share of sites located in the region is rather minor*

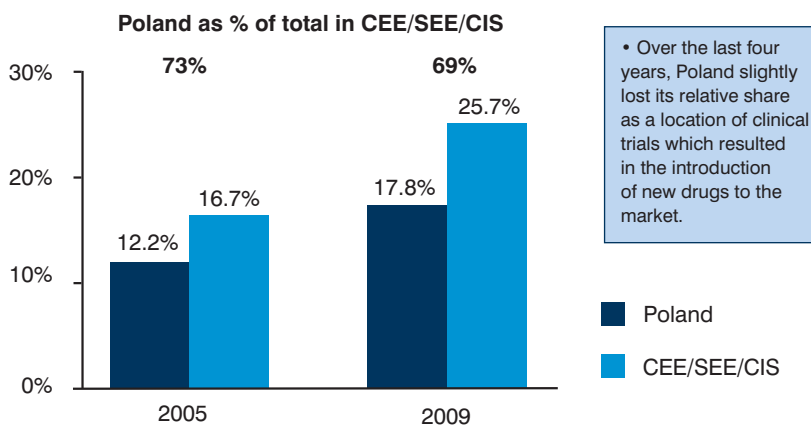
- A number of internationally well established players have firmly penetrated the CEE/CIS region in terms of number of sites they cooperate with (GSK, Astra-Zeneca, Bristol-Meyers Squibb).
- At the same time, there is a group of companies that put larger focus on this region rather than other continental Europe territories (J&J, Mannkind, Grunenthal).
  - “Decision on to what extent focus on locations in emerging regions is usually up to the specific company’s strategic approach. Although this has definitely risen in CEE/CIS in the last decade, sponsors will never want to lose relationships with sites in WE/US.”

*Pharmaceutical company, Poland*

## Poland as an attractive clinical trials market

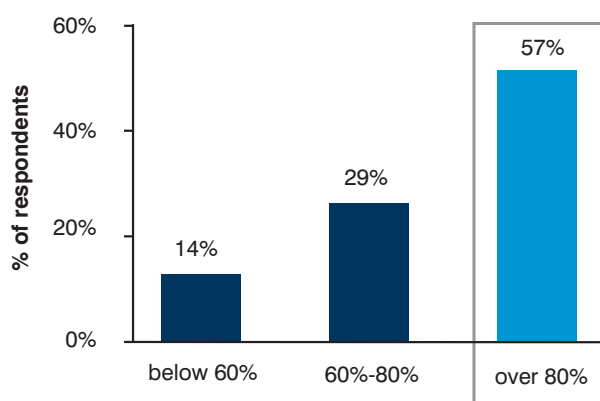
- There is an overall increasing trend in the number of finally approved drugs that have been tested in Poland and in CEE/CIS in general. However, Poland's share of these trials in the region's total slightly declined in the last couple of years.

### Percentage of successfully registered drugs tested in Poland and CEE/SEE/CIS



Note: \*Drugs approved include original New Drug Approvals (NDAs and BLAs), as reported by FDA; Clinical trials conducted in Poland and any CEE/SEE/CIS territory have been included, regardless of phase  
Source: ClinicalTrials.gov, FDA, PwC Analysis

### PwC Survey: "What percentage of new drugs introduced by your company having market authorisation in last 5 years (globally) were subject to clinical trials in Poland?"



Source: PwC Survey

*An increasing number of successfully registered drugs are being tested in Poland and CEE/SEE/CIS...*

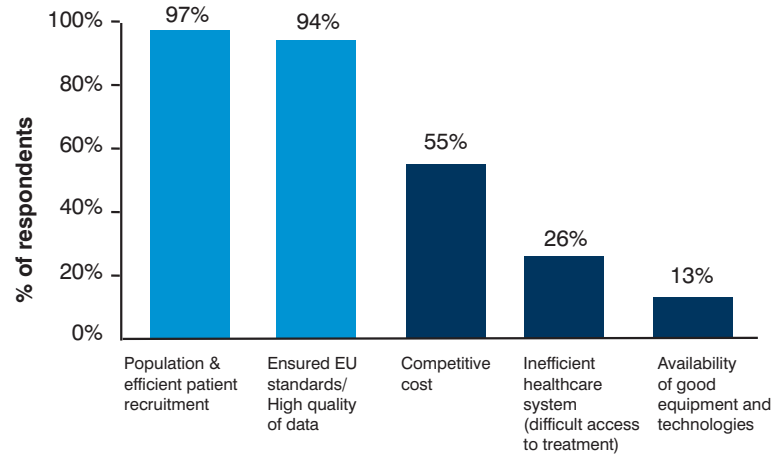
*...what may suggest that Poland and other geographies in this region are attractive clinical research markets*

*PwC Survey results show that population size, efficient patient recruitment and high quality of execution are key market drivers of the Polish clinical trials industry. Lower cost is not a key driver*

*Poland appears to be a more effective country, compared to other CEE/SEE geographies which do not possess such recruitment capacity potential. However, it is expected to be facing increased competition from CIS countries, longer term*

### Population

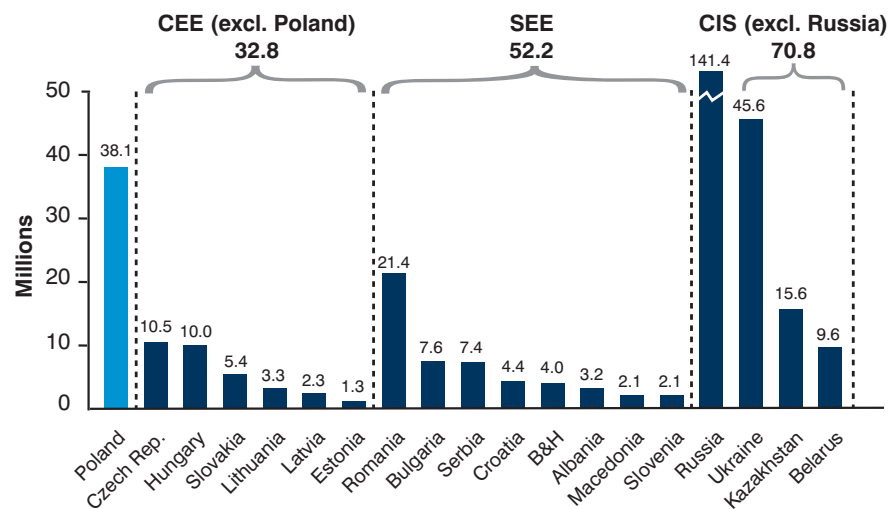
#### PwC Survey: "What are the key drivers of the clinical trials market in Poland?"



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

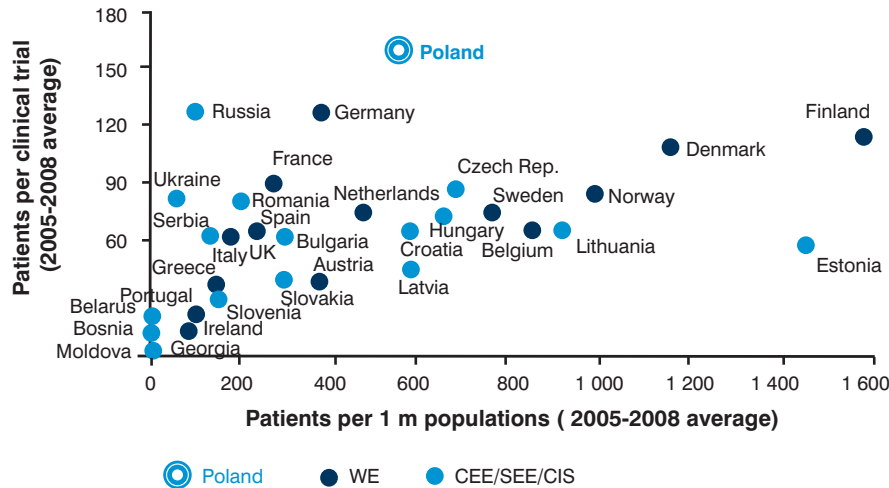
- Traditionally, one of the key attraction factors of Poland as a clinical trials destination has been the population size. With over 38m citizens, Poland is the most populated country in CEE/SEE, which gives it strong potential for increased access to patients.
- However, it appears that this factor should only have a medium-term effect, as in the long-term perspective, countries like Ukraine, Russia, or Turkey can benefit from a large population as well.
- Additionally, sometimes regulatory bodies, such as FDA, may require to conduct a trial in a given number of countries; therefore, running a whole recruitment in Poland is still impossible.

### Population by country



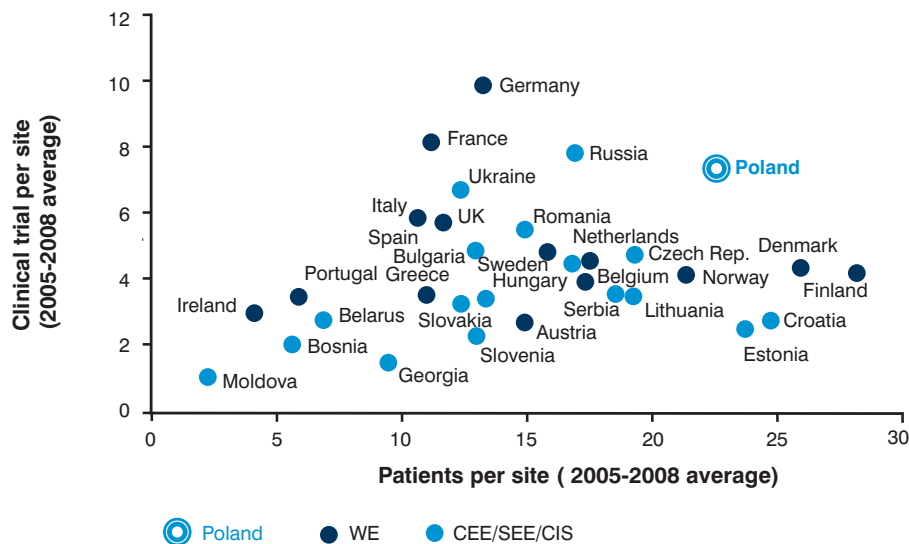
Source: IMF

**Average clinical trial size vs. participation rates**  
(pivotal clinical trials submitted in MAAs to the EMA)



*Poland attracts large clinical trials which engage a significant number of patients. The country participation rate is close to the cross-European median*

**Average site size (pivotal clinical trials submitted in MAAs to the EMA)**



*The penetration of patients within the site is also high relative to other countries in the region, which may suggest that clinical trials in Poland are concentrated in relatively large investigating sites*

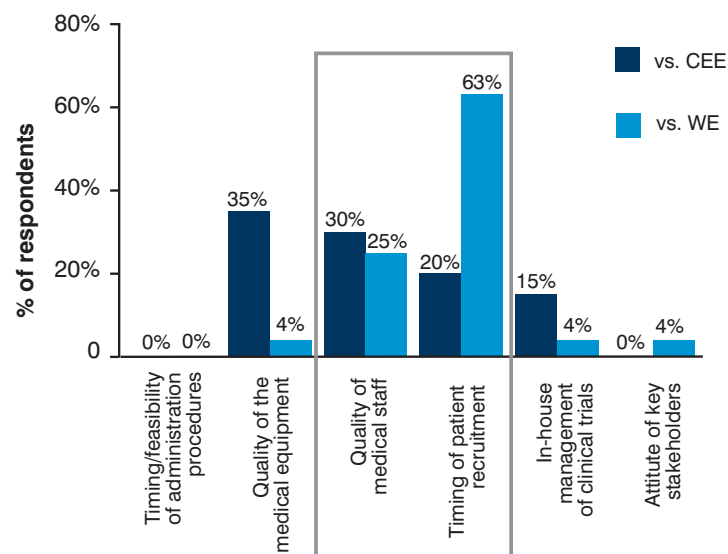
Note: \*Data for pivotal trials submitted in MAAs to the EMA  
Source: EMA

*Respondents perceive efficient patient recruitment as the most significant advantage of the Polish market versus WE*

#### Efficient patient recruitment

- Patient recruitment is generally viewed as efficient in Poland. This is believed to be primarily due to:
  - The previously mentioned population factor, especially vis-à-vis other CEE/SEE/CIS countries;
  - Greater incentive for a patient to participate in clinical trial, especially vis-à-vis more mature markets. This derives from better access to service under clinical research projects versus standard healthcare provisions.
- Regarding the latter factor, patients appear to be more incentivized in Poland, where healthcare services' intensity is perceived to be lower than in WE.
  - Participation in clinical trials, especially in case of in-patient testing, very often provides a better quality of service, faster access to treatment (as waiting lists do not apply), the availability of expensive drugs at lower/no cost, etc. This issue is discussed in further detail later in this report.
- Some interviewees pointed out that recruitment in Poland may be additionally facilitated versus WE, as general health condition of Poles would be poorer than in more developed societies.

#### PwC Survey: "What are the key advantages of the Polish market vs. CEE and WE ?"



Source: PwC Survey

- A majority of PwC Survey respondents believe that efficient patient recruitment is the key advantage of the Polish market vis-à-vis WE.
  - It appears though that this trend is expected to decline as long as Poland converges to more mature markets, in the medium-/long-term.



#### Ensured EU standards

- Poland's accession to the EU in May 2004 eventually imposed on Poland, as well as on other countries of the Community, all duties of a full Member State, including certain quality requirements of legislative framework, as well as general state administration.
- This accession is believed to have significant impact on the perception of Poland as a territory to conduct clinical trial.
  - “We have seen that sponsors would choose Poland rather than Ukraine as general legislative framework is more friendly than in territories, where EU standards do not apply.”  
*CRO, Poland*
- Additionally, Poland is expected to adopt and implement all legal requirements deriving from any amendments in the EU Directives.
  - However, some commentators believe that the implementation of some EU regulatory framework elements could still be faster. This would primarily be the adoption of guidelines related to harmonized documentation in the approval process, which is discussed later in the report.
- In alignment with this, Poland has well established, and incorporated into the clinical trials practice, ICH-GCP rules.

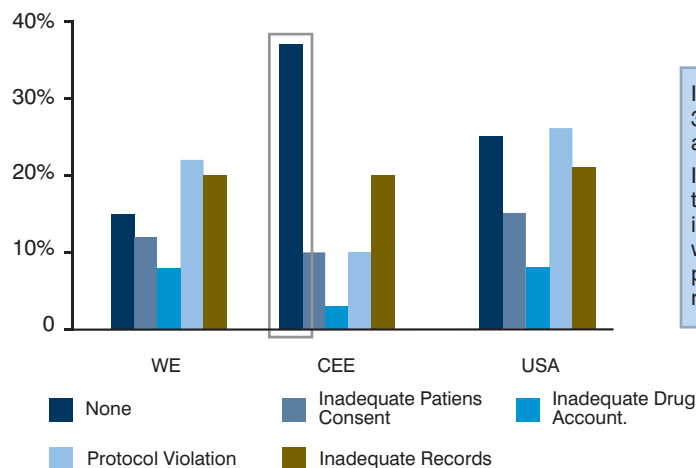
#### Established know-how

- Industry feedback suggests that Poland is a respected clinical trials destination with qualified and experienced researchers and supportive medical staff.
  - “Indeed Poland managed to build a perception of strong know-how in clinical trials over the last 20 years. International sponsors are attracted by quality of work conducted by medical staff in Poland.”  
*Pharmaceutical company, Poland*
  - “We are not aware of any Polish researcher who would be present on the FDA ‘black list’.”  
*Pharmaceutical company, Poland*
- Interviewees list factors such as the quality of data collection and processing, as well as mid-term and final reporting, as those that are arranged with proper diligence in Poland, which may not always be the case in lower-cost markets.
- FDA inspections show that CEE-based operators of clinical trials obtain higher results in terms of procedural transparency check than CROs in US and WE.

*Being subject to the EU legislative “umbrella”, Poland is perceived as a country with high procedural standards*

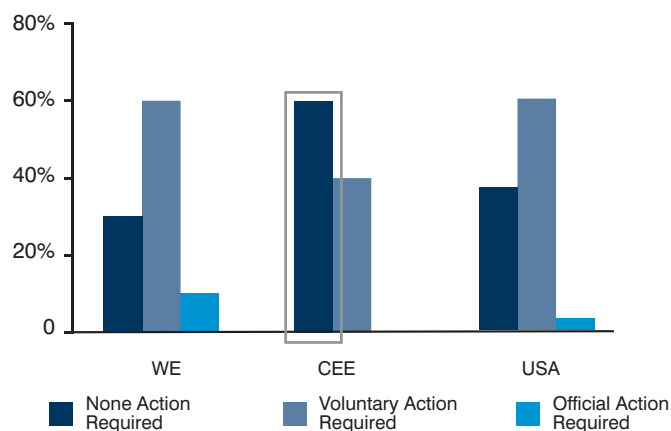
*The standards of clinical trial procedures in CEE are perceived as high. Cheaper markets may appear to underperform in this respect, which drives the demand for trials in CEE*

Findings of Food and Drug Administration Inspections (2007)



In Poland, FDA launched 3 inspections in 2007 and 6 in 2008;  
In the period 1997-2008, there were 38 inspections in Poland overall, out of which over 23 (or c. 60%) provided "no action required" outcomes

Proceedings of Food and Drug Administration Inspections (2007)



Source: FDA

*This may also provide opportunities for researchers to focus on scientific work*

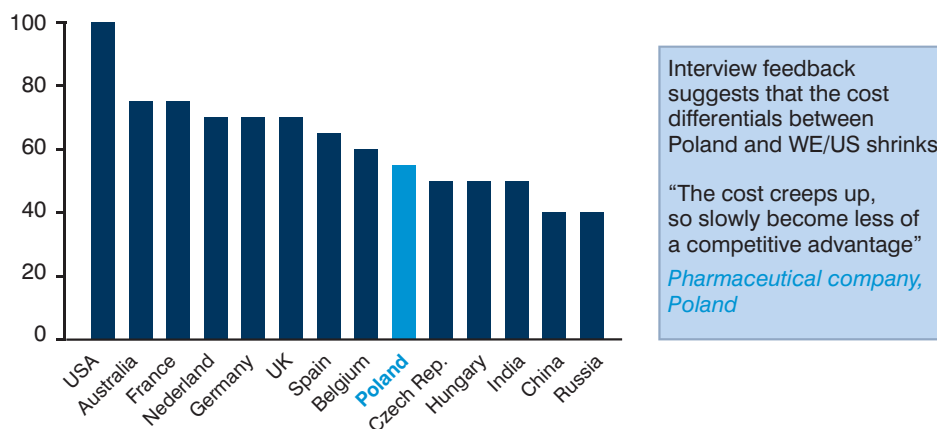
- Apart from purely economic incentives, engaging in clinical trial projects may also facilitate a professional career development for investigators, as they are given the opportunity to research on new areas of medicine, test modern standards of treatment, exchange information with foreign medical experts, and publish their findings in respected international journals.

### Cost advantage

- In the past, cost differentials between CEE and WE were more significant than they are nowadays, both in terms of fees and operational costs. In line with overall economic development, the cost of clinical trials in CEE/SEE/CIS has been converging to WE levels; however, the cost still remains competitive.
  - “Our view is that cost in Poland can be still up to 20-30% lower than in WE, but it is not always a decisive factor when you take into account timing, predictability and general smoothness of the process.”  
*Pharma company, Poland*
- Interviewers also point out that if cost was the most important criterion, sponsors will massively move trials from traditional markets to the emerging regions (e.g., CIS, South America, Asia, etc.). However, this shift is not as rapid as initially anticipated.
- As a confirmation to this factor it is worth noticing that despite a high relative cost, USA remains the largest clinical market in the world.

*Although still lower than in WE, cost in CEE no longer appears to be the key selection criterion*

### Average cost of clinical trials – international benchmarks (USA=100)



Source: PwC Analysis

# Section 4

## Benefits and risks of clinical trials



**Benefits and risk of clinical trials**

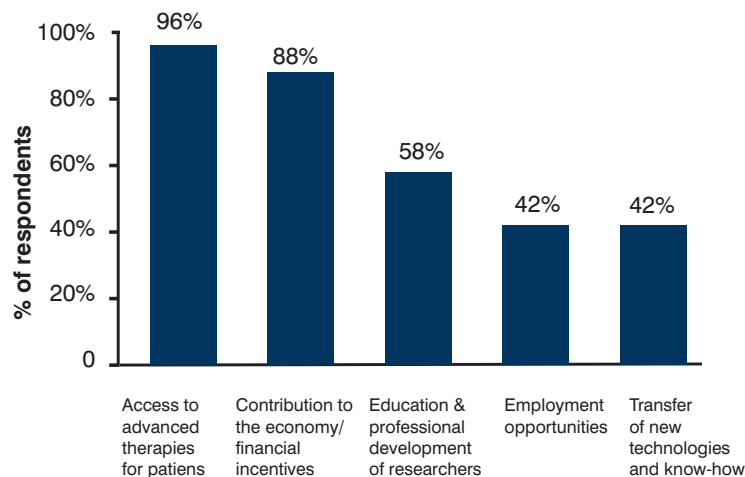
- *Among the key benefits is access to advanced therapies for patients as well as the contribution to the Polish economy. It is also of great importance that clinical trials can contribute to human capital growth in terms of know-how sharing as well as stands for professional development opportunities for researchers.*
- *Clinical trials can also provide alternative cost savings that can relieve the public healthcare system. Basing on a case study in oncology, alternative cost savings amount in 2009 to PLN 130m. However taking into consideration the higher standards of treatment the amount of savings may increase even up to c. PLN 0.5bn.*

*Clinical trials imply a number of tangible and intangible benefits to the host economy*

## Economic impact

- Clinical trials have an evident impact on the rest of the economy and are believed to provide a number of benefits to several stakeholder groups. One may divide the most important effects into purely material (tangible) and nonmaterial ones (intangible). The aim of this section is to outline the key issues behind them.
- **Tangible effects**
  - Contribution to the state budget;
  - Alternative cost savings;
  - Additional researchers' remuneration;
  - Employment opportunities/economic stimulus for other supportive businesses.
- **Intangible effects**
  - Facilitated access to better standards of treatment for patients;
  - Know-how spillover/transfer of new technologies;
  - Opportunities for researchers and young doctors.
- PwC Survey respondents believe that the access to advanced therapies for patients, as well as the contribution to the economy are the key benefits of the clinical research industry in Poland.

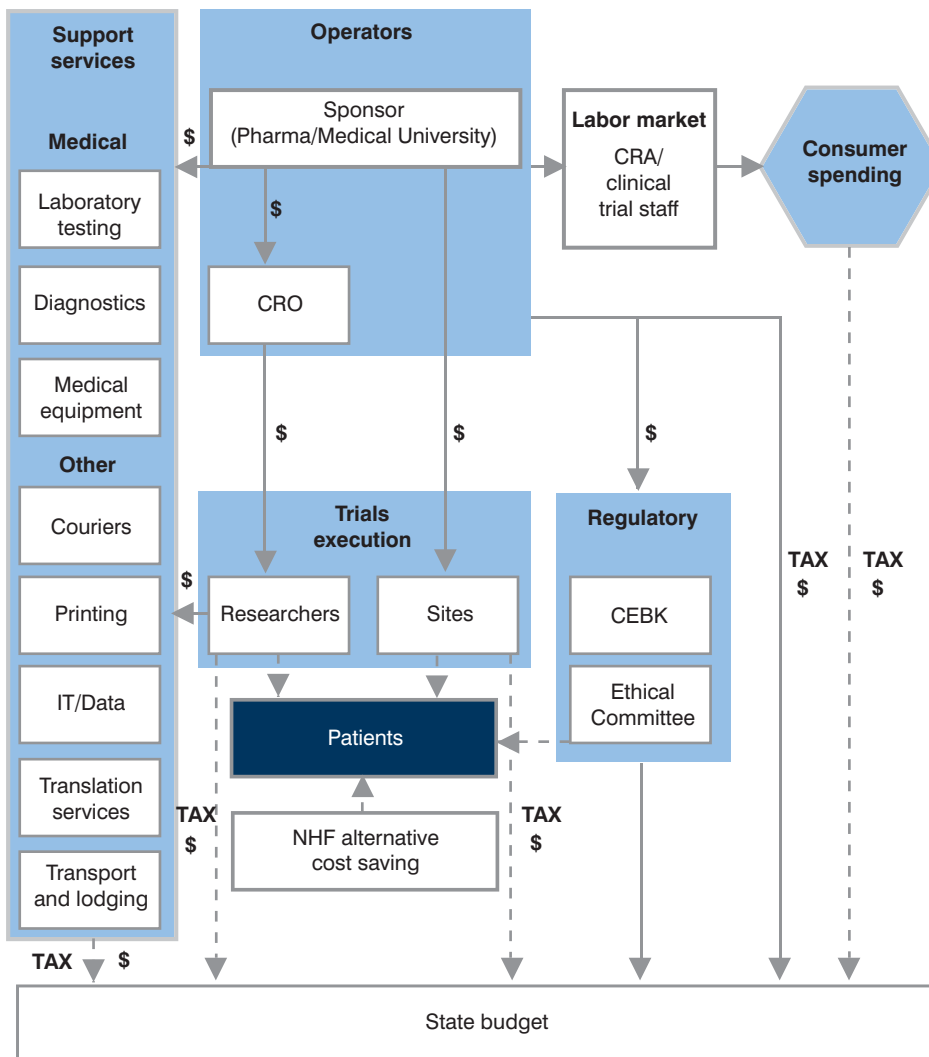
### PwC Survey: "What are the key benefits of clinical trials?"



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

- Clinical trials contribute to the general development of medicine, as by means of research projects, expectedly more advanced and more effective drugs become available to the human population in the long term.
- However, clinical trials can have more short-term impacts on the local economy (and patients) in the country of destination. These key impacts are summarized below.

*Clinical research market impacts a number of stakeholders and many of them benefit from clinical trials as an additional source of cash flow*

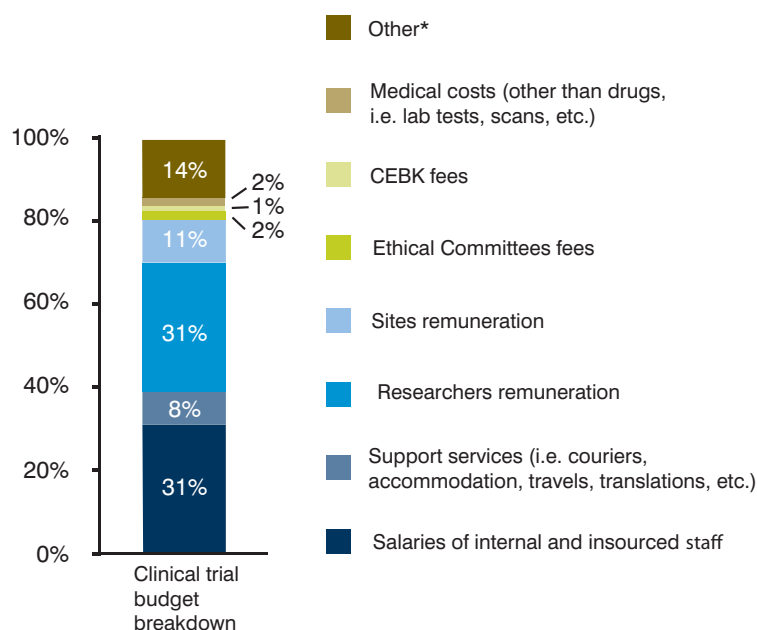


Note: \$ is a symbol of a cash flow

*High-level analysis of clinical trials' budget breakdown shows that researchers, clinical trials staff, as well as sites are the top direct beneficiaries of the market spillover effect*

- Clinical trials impact other parts of the economy. This includes other areas of the healthcare sector, contribution to the state budget, as well as a number of other industries that are interrelated with the clinical research market.
- As sponsors are very often large international companies, the launch of clinical trials in Poland contributes to the inward foreign capital investment.
- While an appropriate in-depth economic analysis is beyond the content presented, the data collected through questionnaire provides some insight on spillover effects.

#### Estimated clinical trial budget breakdown



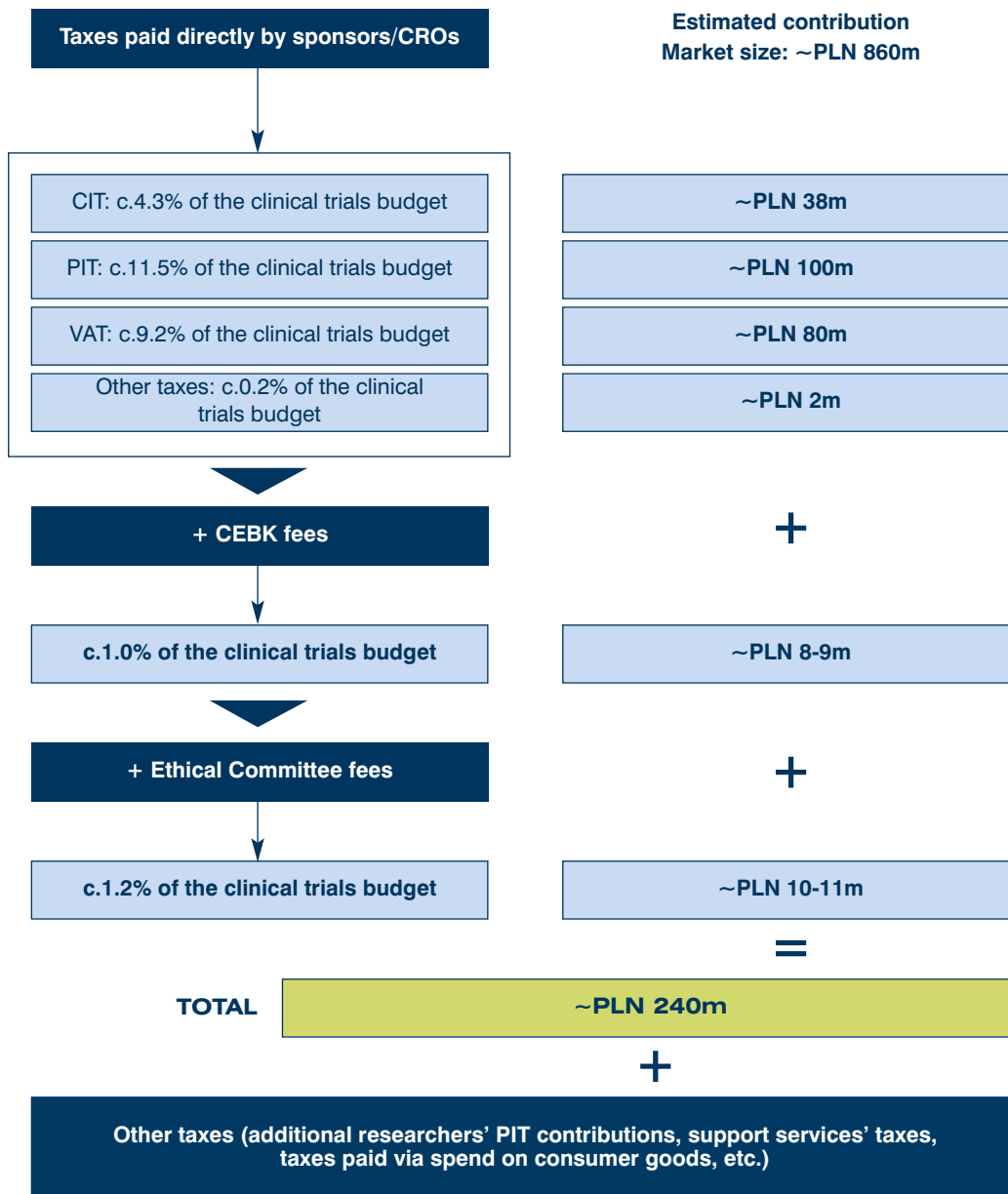
Note: \*Other involves any miscellaneous category as indicated by survey respondents  
Source: PwC Survey

*More than one-fourth of revenue earned on clinical trials by sponsors ends up as a directly paid tax contribution to the state budget*

#### Contribution to the state budget

- Our estimation, based on data from market participants, shows that c. 25% of revenue earned on clinical trials is contributed to the state budgets.
- We estimated the market value at c. PLN 860m; however, this can sum up to c. PLN 220m of direct contribution to the budget per annum and contains taxes directly paid by sponsors and CROs (via Corporate Income Tax (CIT), Personal Income Tax (PIT), Value Added Tax (VAT) and other taxes).
  - Additionally, the state budget indirectly benefits from CEBK and Ethical Committee fees (additional c. PLN 20m), as well as any additional taxes paid by other stakeholder groups (e.g., additional researchers' PIT contributions, support services' taxes, taxes paid via spend on consumer goods, etc.).





Note: Analysis based on PwC Survey data  
Source: PwC Survey, PwC Analysis

*Interviewed researchers confirm that clinical trials provide financial incentives for them, but very often emphasize that this is expected to be less attractive in the future*

*Clinical trials can provide alternative cost savings that can relieve the public healthcare system*

#### Researchers' fees

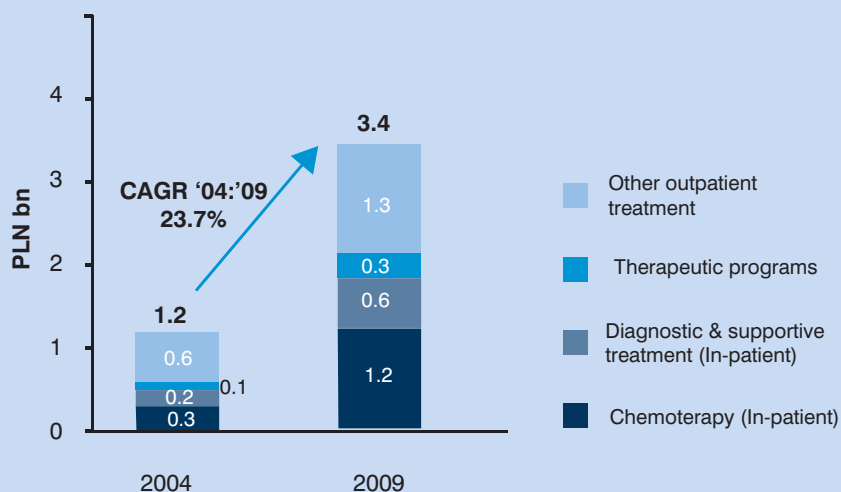
- As mentioned previously, research teams can also be incentivized to lead clinical trials, primarily due to the economic factor, as well as have the opportunity to be involved in modern medicine/scientific projects. The former topic has been widely discussed in the media over the last year.
  - As exact amounts are not always publicly available, market insight suggest that doctors can earn significantly more when leading clinical research projects, compared to the standard base salary offered in the public sector.
  - “There is a risk that tripartite contracting might put more pressure of sponsors to lower fees to be paid to researchers.”  
*Researcher, Warsaw*
  - The fact that researchers' remuneration from clinical trials is perceived as rather attractive provides an incentive for both experienced and young doctors to continue their career in the healthcare segment and remain in Poland, as foreign migration has proved to be subject to hot debate in the society in recent years.

#### Alternative cost savings

- It can be concurred that a certain portion of the public healthcare cost can be saved, thanks to financing from sponsors of clinical trials. Sponsors very often tend to bear the cost of comprehensive participant's treatment, including a number of supportive procedures that can be a part of publicly financed healthcare.
- Moreover, to maintain uniformity of clinical trial execution, very often sponsors tend to provide more intense care and access to upgraded therapy standards; therefore, the actual value of this therapy goes beyond the NHF reimbursement schemes.
  - “When I took part in a clinical trial, I felt like I was treated with more intensity, e.g. I had better access to more frequent diagnostics. It is understandable, as during the trial a participant needs to be monitored according to internationally acquired rules.”  
*Patient Association, Warsaw*
- However, market insiders claim that these savings may be underestimated or disregarded by healthcare policymakers.
- Although the extent of those alternative cost savings will certainly vary, depending on medical areas, the specifics of a particular clinical trial, as well as the accessibility of public service (i.e., awaiting lists and the availability of specific therapy methodology), we believe that examples of oncology and cardiology may serve as an indication for the importance of this phenomenon.

**Case study example: Oncology**

- The analysis based on questionnaire feedback shows that c. 4% patients suffering from any kind of oncology-related disease take part in clinical trials.
- Thus, their treatment is significantly financed by sponsors rather than the NHF, when assuming that the total NHF spend on oncology in 2009 provides the range of c. PLN 130m of direct alternative cost savings, excluding the value of the upgraded quality of medical service.
  - In this context, one has to bear in mind that public oncology spend has grown significantly during the last five years.
- However, we believe that this calculation methodology is rather conservative, as the advancement of therapies provided in the course of clinical trials is typically much higher than of standard therapies financed by the NHF.

**NHF expenditure on oncology, incl. medical treatment and drugs, 2004-2009**

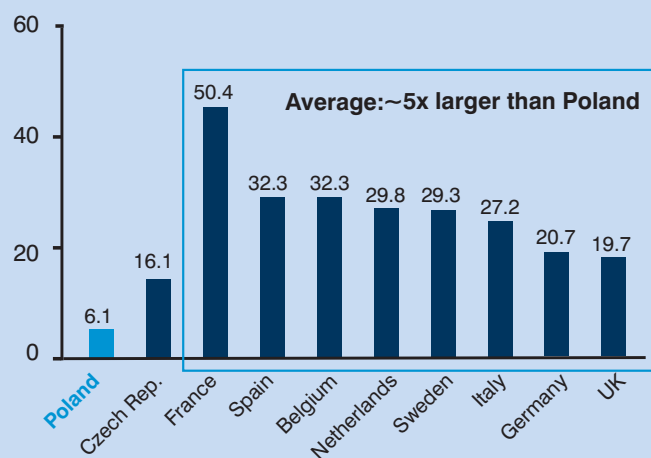
Note: Figures exclude neoplasm treatment of patients in wards other than oncology, e.g. lungs diseases, surgery, neurosurgery, etc.; CAGR – Compound Annual Growth Rate  
 Source: NHF, Ministry of Health, PwC Analysis

*The oncology example shows that the treatment of c.4% patients in this medical area is financed in the course of clinical trials, which may correspond to up to PLN 130m alternative cost savings...*

...however  
as the quality  
of treatment under  
clinical trial is usually  
higher than of standard  
available therapy,  
the actual value of such  
treatment can be  
c. four times larger  
– accounting for c.15%  
of the NHF spend  
on oncology

- If we were to include the oncology drugs spend per capita in countries with more developed healthcare systems, this may serve as a proxy for the quality of treatment differential between standard therapies (normally reimbursed by the NHF) and more advanced therapies provided by clinical trials' sponsors.
  - International benchmarks analysis shows that the real value of treatment under clinical trials therapies may be much higher than the already mentioned PLN 130m.

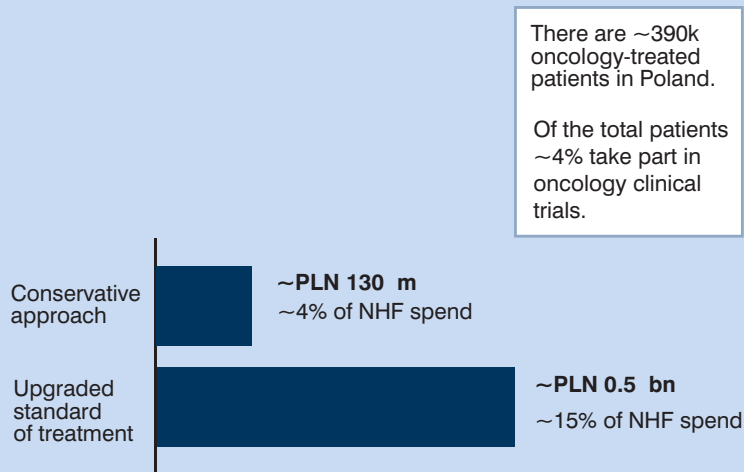
Est. annual spend on cancer drugs (per 100k population, PLN m)



Source: Karolinska Institute, 2009, PwC Analysis

- Our analysis shows that the actual value of treatment may amount even up to PLN 0.5 bn when this difference in the quality of therapies is taken into account.
- This amount constitutes c.15% of the NHF spend on oncology.
  - It is the value of treatment, if upgraded therapies were applied in all patient cases.

### Estimated NHF alternative cost savings in oncology



Source: Instytut Onkologii, Karolinska Institute, PwC Survey, PwC Analysis

- Feedback from interviews shows, for example, that in the field of oncology industry insiders estimate that c.20% of the Warsaw Institute of Oncology in-patient tumor treatment cost (direct) can be actually financed via clinical research projects, depending on the location of center.
  - “Poland has quite well developed network of oncology centers in all major cities. My view is that these sites are finely penetrated in terms of clinical trial participation what is certainly linked to the cost.”  
*Patient association, Warsaw*
- However, oncology is a specific example, as clinical trials’ penetration is relatively high in this therapeutic area – approximately one-third of patients involved in clinical trials in Poland participates in oncology-related projects.
  - One should also bear in mind that the majority of clinical trials overall in Poland refers to out-patient, “pill-based” projects.
- Nevertheless, the argument of alternative cost savings shall remain valid, provided clear rules on co-financing between the sponsor and the NHF (medical insurance funds) are introduced.

*Participants can benefit from a facilitated access to advanced standards of treatment and an increased general intensity of service*

*Given the R&D nature of the process, clinical trials can contribute to human capital growth in other healthcare areas*

*Economic incentives are perceived to have additionally stimulated diligence efforts during investigators' work. This effect can lower significance in the future, though*

## Intangible effects

### Access to better standards of treatment

- Different parties engaged in the healthcare sector admit that Poland still lags behind more mature markets in terms of intensity and the quality of service. The discrepancy in treatment methods of particular diseases between Poland and WE derives from the fact that the healthcare system in Poland remains continuously underfinanced. Participation in clinical trial is seen to provide better access to this service and an increased availability of medically advanced drugs for free.
  - Interviewees agree that treatment which is rather standard in WE can turn out to be very costly or even unavailable in Poland during standard treatment procedures. Participation in clinical trial would make it accessible.
  - In particular, this factor, to a greater extent, will be applicable to inpatient treatment in therapeutic areas where the availability of effective drugs is limited at this stage of medicine development (e.g., oncology, post-transplant treatment, etc).
- The vast majority of PwC Survey respondents indicated the above-mentioned factor as the key benefit of clinical trials (see the PwC Survey results on page 44).

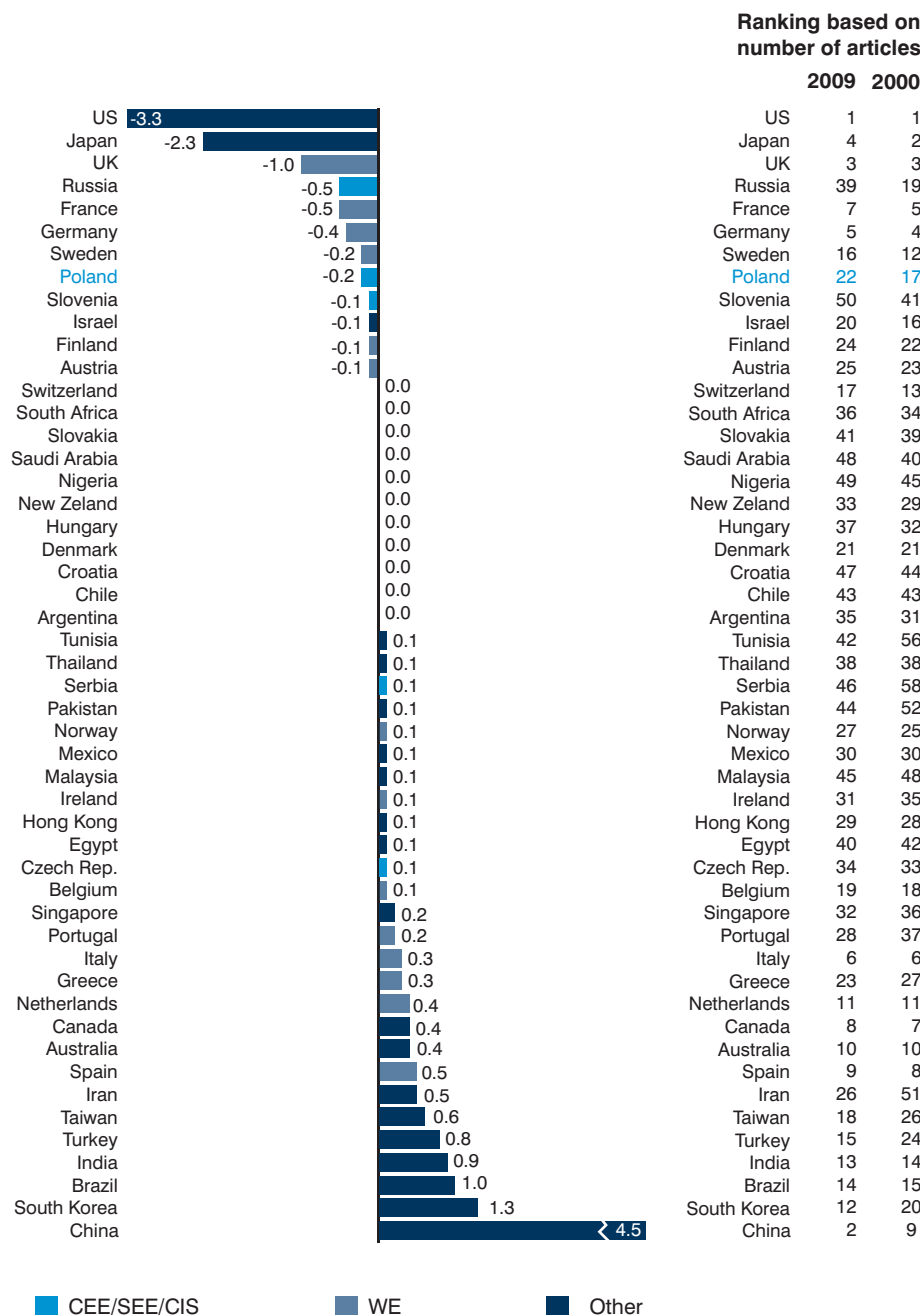
### Know-how sharing

- Clinical research projects assume a uniform and standardized methodology of clinical investigation and data collection and reporting. In this way, local medical staff and the healthcare system in general can benefit from skills earned during the research process.
  - “One needs to bear in mind that this refers not only to doctors, but also their assistants, all supporting staff and nurses as well. This knowledge increase can have positive spillover effects on other areas of healthcare.”  
*Industry commentator*
  - In order to coordinate research projects between different territories, clinical trial operators very often provide diagnosis-decision support systems for doctors. However, interview feedback suggests that not all medical staff believe that this is a significant asset.
    - > “Treatment standardization or so-called ‘cookbook medicine’ has its supporters and critics. While the former appreciate its uniformity, the latter oppose the lack of the field for individual doctor interpretation.”  
*Industry commentator*

### Opportunities for researchers

- Researchers in Poland appear to be more willing to participate in clinical trials investigation compared to more mature markets, given the significant remuneration for such work relative to their base salary in the Polish healthcare sector.
- Participation in clinical trials facilitates scientific work for doctors, as they have the opportunity to publish articles in international medical journals, and at the same time, obtain financing from sponsors. However, recently this factor appears to have lost its significance.
  - “Deteriorating climate over clinical trials in Poland appears to have lower incentives for doctors to take part in the projects. The atmosphere of a ‘witch-hunt’ makes incentives for doctors less evident.”  
*Pharmaceutical company, Poland*
- However, a recent analysis of trends in medical publications in respected specialist journals indicates a decline in the number of articles published by Polish researchers. Asian countries, particularly China, exhibit the strongest historical growth in this regard.

## Growth in the proportion (ppt) of all articles 2000-2009



*China, South Korea, Brazil, and India are the top four gainers in the proportion of articles published between 2000 and 2009*

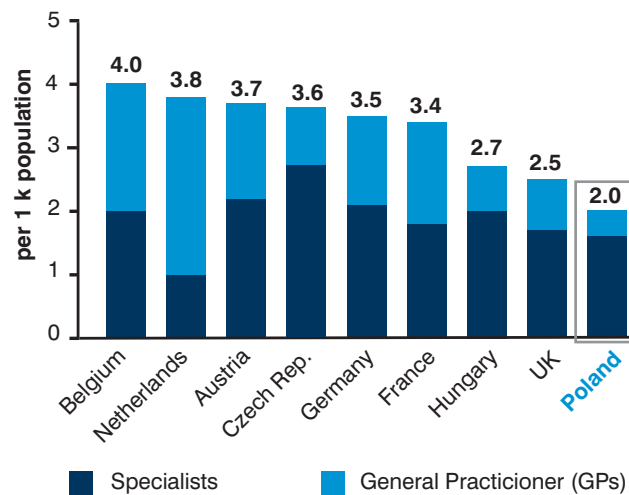
*In CEE/SEE/CIS, the Czech Republic and Serbia maintained positive growth in the proportion of articles published between 2000 and 2009, while Poland's input decreased by 0.2 ppt.*

Note: Articles accessible through PubMed database were taken into consideration  
Source: Clinical Trial Magnifier Vol. 2:12 (2009)

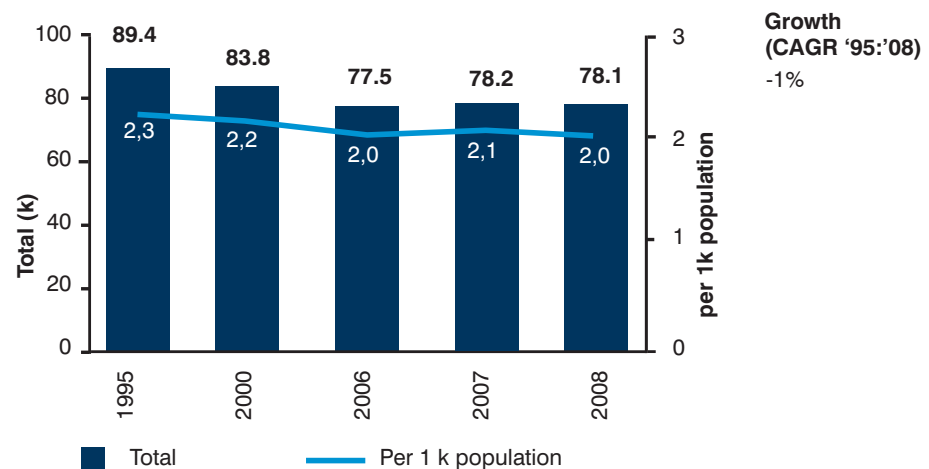
*Poland appears to be underpenetrated in terms of the per capita number of doctors – participation in clinical research projects may provide access to professional development for medical staff, both experienced and young*

- As the overall number of medicine graduates and doctors has fallen in Poland in recent years, the clinical trials market may appear to be an attraction for young people to become doctors. Participation in a clinical research project may provide a number of incentives, both financial and non-financial.
  - The latter ones could be: continuous professional and academic development, gaining additional experience during project execution, and networking with international medical staff.
  - “Clinical trials may provide opportunity to upgrade the quality standards of day-to-day work of doctors that are still at the beginning of their career. This can be for the benefit of the whole system – recent edition of Health Consumer Index in mid-2010 showed the Polish healthcare service is ranked on 24th place only in the EU.”  
*Researcher, Mazowieckie*

**Doctors per 1k population: general physicians and specialists, 2008**



**Doctors in Poland: total and per 1k population**



Note: CAGR – Compound annual growth rate  
Source: OECD, GUS



# Section 5

## Barriers to market development



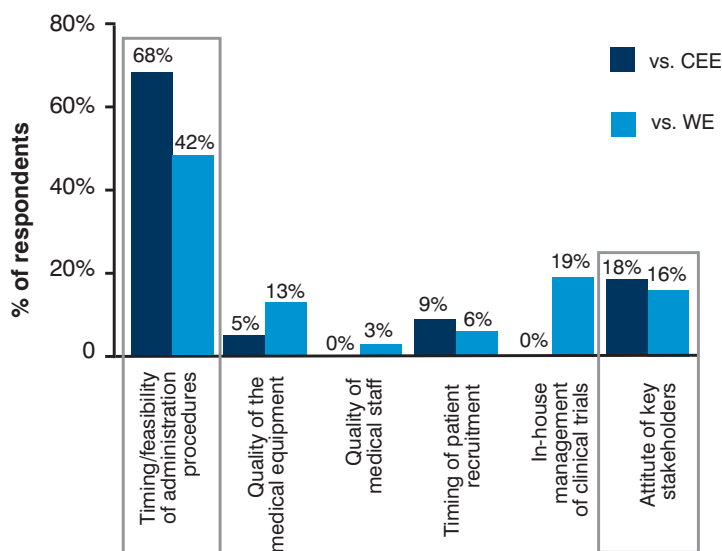
**Barriers to market development**

- *Key challenges to the Polish market comparing to CEE and WE countries include timing/feasibility of administration procedures and attitude of key stakeholders, which – when resolved – may result with c. PLN 45m-65m additional income to the state budget.*
- *Further development of clinical trials market can be accelerated by enhancement of clarity and transparency of rules and regulations as well as legislative improvements and simplification of CEBK registration process.*
- *Establishing administrative processes in terms of cooperation between sponsors and sites, e.g. dedicating an officer/unit in charge of clinical researches and developing efficient standards in contract negotiations, may also be a positive factor for the market growth.*
- *Good communication practices, e.g. information sharing, developing awareness and positive attitude of general public increase Poland's attractiveness as a clinical trials market.*

## Barriers to market development

- As already mentioned, due to its size and efficient patient enrollment, Poland is ranked at the top of the CEE clinical research markets. However, other smaller countries in the region have a higher density of trials and smoother operational processes.
- A number of drawbacks in the system has slowed down the market in Poland recently. This section is aimed at identifying these barriers to development, as well as presenting views of different stakeholders over any possible actions going forward.

### PwC Survey: What are the key disadvantages of the Polish market vs. CEE and WE



Note: Respondents were asked to indicate two key advantages and two key disadvantages

Source: PwC Survey

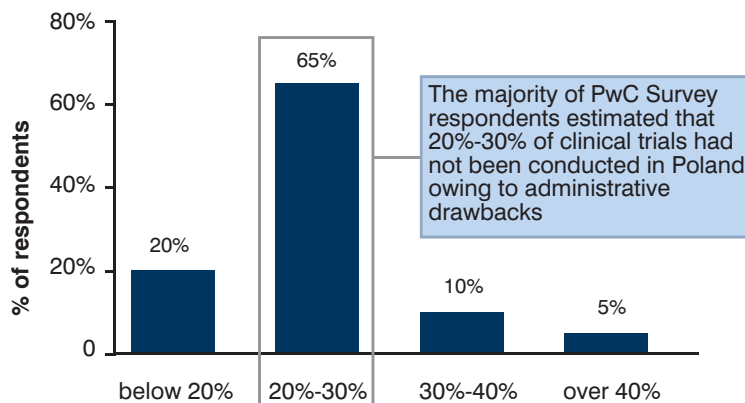
- Questionnaire feedback suggests that up to c.20-30% of clinical trials have not been conducted in Poland, but directed elsewhere (primarily to other CEE countries).
  - 84% of PwC Survey respondents indicated that the long approval/registration process is the most important reason behind the clinical trials not being conducted in Poland, but directed elsewhere.
  - 64% of PwC Survey respondents stated that this trend has gained significance in the last couple of years i.e., the share of “lost” trials have increased.
- Therefore, Poland may appear to attract proportionally more trials if administrative drawbacks are eliminated. Resolving those issues is expected to result in c.PLN 45m-65m of quick-win cash flow for the state budget.
  - “If registration time were shorter or at least just predictable, more clinical trials would be executed in Poland and more cash flow to the budget would be obtained.”

*Although Poland is generally perceived as an attractive clinical trials destination, there are a number of factors that jeopardize further market growth*

*Long and unpredictable registration procedures and excessive bureaucracy are the most significant growth barriers*

*The gain to the budget could be up to 20%- 30% higher, provided administrative drawbacks are resolved*

**PwC Survey: How many trials were not executed in Poland as a result of administrative drawbacks?**

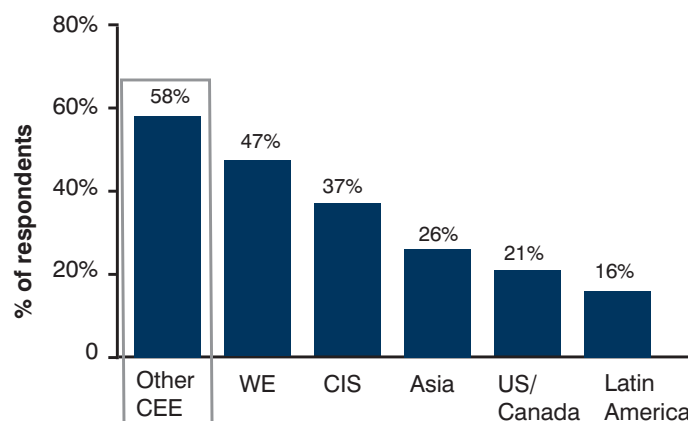


Source: PwC Survey

- The PwC Survey results indicate that mostly other CEE/SEE countries benefit from this fact and host the clinical trials, which have not been launched in Poland.
- The Regulatory Office admits that a shorter registration period would have the potential to increase the number of trials executed in Poland, once it is introduced by policymakers.

*The majority of respondents admit that mostly other CEE/SEE countries hosted those clinical trials, which were not executed in Poland*

**PwC Survey: “Which countries benefited mostly from this situation?”**



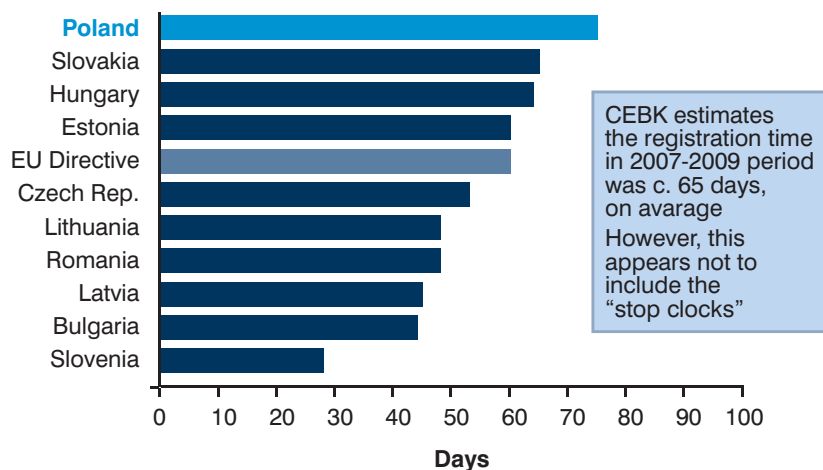
Note: Multiple answers available – results do not sum up to 100%  
Source: PwC Survey

### Long registration period

- Industry players point out that a long registration time is the most significant barrier to clinical trials development, as Poland exhibits one of the longest average period for trial registration in Europe.
  - It is particularly important as patient recruitment may be competitive between the territories. In such cases, due to long registration period a trial is registered after the recruitment stage is closed – what implies that the whole application process does not result in actual project execution.
- As outlined in the Directive, EU Member States are bound to follow maximum 60-day periods. However, actual registration time in Poland exceeds 75 days on an average, according to interview feedback.
  - “The reason for that is primarily linked to so called ‘stop clocks’. When the regulatory office issues comments of enquiries to our application file, it assumes the process is suspended until reply is provided.”  
*Pharmaceutical company, Poland*
- Market players mention that perhaps even more important, rather than long registration itself, is lack of procedural standardization.
  - “Lack of predictable approval data is an important inefficiency and this is particularly crucial for projects where the trial has to be launched simultaneously in a number of geographies.”  
*CRO, Poland*
- During the interview, the Regulatory Office representatives admitted that a shorter time period may attract more trials to Poland. However, they also pointed out that the 60-day deadline can sometimes be exceeded primarily because some applications are incomplete.

*As mentioned previously, PwC Survey results indicate that 20%-30% of clinical trials have not been conducted in Poland due to administrative drawbacks, mainly a long registration period*

### Average clinical trial registration period



Source: GCPpl days

*It is widely agreed that more clarity and transparency in law enforcement is necessary...*

- Market observers admit that a number of clinical trials that had initially been planned to be located in Poland were transferred to other territories due to a long cycle time.
  - In particular, Poland appears to be almost entirely excluded from the so called “critical path” trials, where time is the key territory selection criterion.
  - “In such cases, sponsors tend to locate execution of a trial in other CEE/SEE and CIS markets, where patient recruitment is still fast, but registration period shorter.”  
*CRO, Poland*

#### Increase in CEBK fees

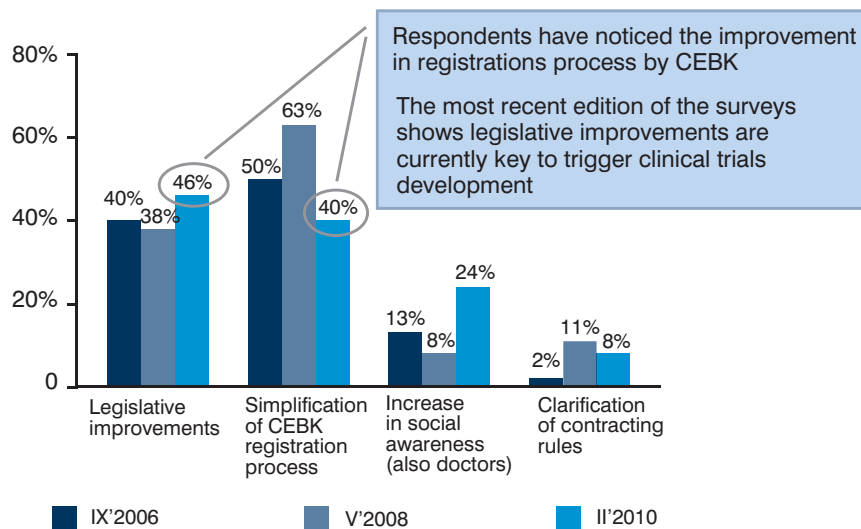
- Survey respondents jointly commented that a rumored increase in registration fees required by CEBK should not have a negative impact on the number of trials, provided it is combined with better quality of service.
  - Over 90% of questionnaire respondents admit that they are willing to pay CEBK more for better service.
  - “I don’t expect that any reasonable increase in fees for authorities will scare sponsors out from Poland. What is very important however, that sponsors would be willing to pay more, provided better quality of service, incl. lower registration periods, is guaranteed.”  
*Pharmaceutical company, Poland*

#### Insufficient transparency of rules / Administrative process drawbacks

- Industry players stress the need for transparency in the enhancement of legal rules related to clinical trials and their enforcement.
- Interviewees particularly emphasize on the slowly progressing implementation of the EU Directive, e.g., with regard to maximum clinical trial registration time.
- This also refers to issues of clear competency split. Industry players are of the opinion that different regulatory/approval bodies deal with areas that are not subject to their core mission.
  - While by definition it is Ethical Committee’s duty to provide opinion on content-related specifics of the trial. Obtained feedback suggests that often this is done by CEBK. According to the EU Directive, CEBK should solely focus on administrative issues. Therefore, industry players believe that there should be more clarity in terms of who provides opinions on what.
- Recent turmoil regarding clinical trials has given rise to a hot debate on the financing of research projects in Poland. Market insiders note that there is some misunderstanding between the sponsors and NHF on who should bear the cost of patient treatment.
  - This particularly refers to supportive procedures during the trial and remains a jeopardizing factor in clinical trials market development.
  - Market commentators point out that a threat of making the whole cost of patient’s treatment to be born by a sponsors might result in a decline of clinical trials conducted in Poland.
- On the other hand however, general feedback suggests there has been evident improvement in terms of mutual cooperation between industry players and regulatory bodies – and this improvement also derives from softening of procedural requirements.
  - “Ability to submit unsigned draft of contract between sponsor and site positively impacted clinical trial registration process and shortened the cycle time.”  
*CRO, Poland*

### External survey results

#### – Key factors that could trigger development of clinical trials in Poland



Note: Survey samples: 2006 – 82, 2008 – 64, 2010 – 63; Max 3 answers per respondent  
Source: PMR

- The Office for Registration representatives admit that gaining more operational independence for the Office has potential to slightly improve the organization. This independence is expected to be achieved in the future, following examples of other countries, mainly in WE. No timeframe for this issue has been agreed upon by policymakers yet.

### Slow implementation of the EU initiatives

- In 2007, the EU Heads of Medicines Agencies (HMA) founded Clinical Trials Facilitation Group (CTFG), the mandate of which is to ensure the protection of participants and the scientific value of clinical trials.
- This is expected to be primarily achieved by harmonization of National Competent Authorities' processes and practices relating to the clinical trials executed in more than one EU Member State. In this way, Voluntary Harmonization Procedure (VHP) has been established in order to assure joint assessment of clinical trials applications.
- VHP assures standardized and regular information sharing between the NCAs – this has been launched for the first time in January 2009. While most of the EU Member States took part in the initiative (at least in some parts of the framework), only the Netherlands and Poland entirely refused to join the process during the first wave of application process.
  - “We perceive this refusal as rather bad from the sponsor’s perspective, particularly because VHP – although a new mechanism – has already proved to assure predictable registration periods that are below 60 days in total.”  
*Pharma company, Poland*
- It appears however that there is potential for this decision to be revised
  - “We have received feedback from the URPLW MiPB representatives that the Office is considering participation in VHP since 2011. We are not familiar with any further arrangement in this regard though.”  
*Pharma company, Poland*

*...however some progress in excessive bureaucracy has been achieved*

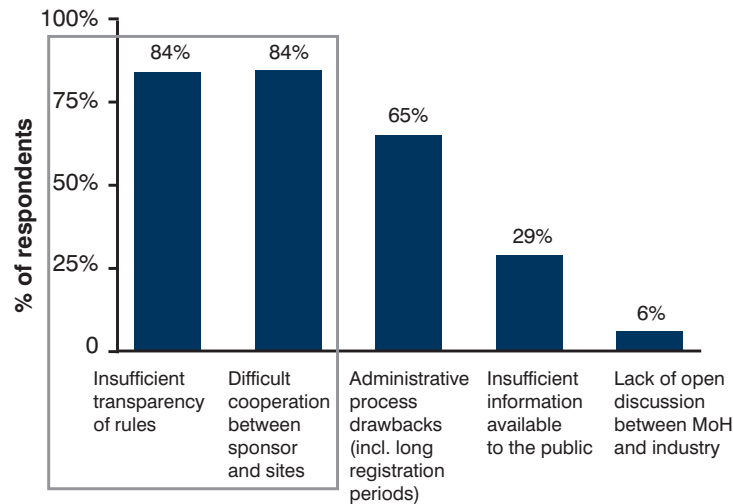
*In addition, Poland refused to participate in the first wave of CTFG/VHP mechanism, which proved to assure predictable registration time length. There are prospects however that this decision will be revised in the near future*



Cooperation between sponsors, sites, and researchers may lack facilitating administrative solutions, e.g., in terms of contracting

#### Sites management

PwC Survey: "What are the key obstacles for execution of clinical trials in Poland?"



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

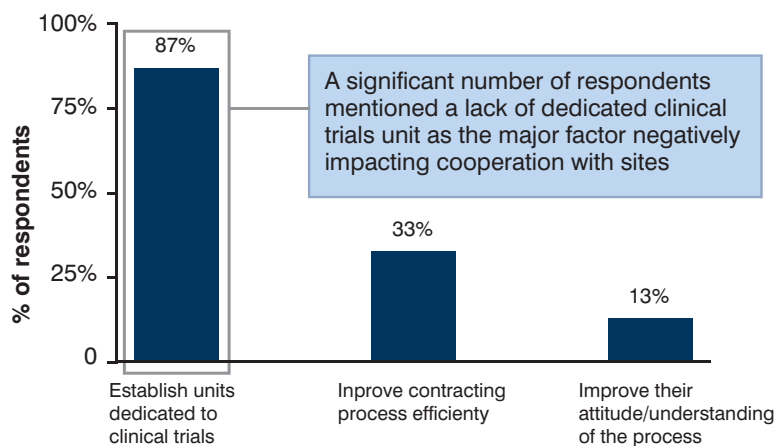
- Although sites in Poland are generally perceived to have a high quality of know-how and researchers' qualifications, only a minority appear to have established administrative processes to deal with clinical trials.
  - Both sides of the relationship (sponsors and hospitals) admit that mutual cooperation is facilitated, once dedicated officer/unit is in charge of clinical research projects within the site structures.
  - While there are examples of locations where this procedure has already been implemented and is believed to have brought plausible effect, many hospitals have put aside such an initiative. This is primarily due to financial difficulties and lack of common practice in this regard.
  - "Some part of medical society is rather conservative and less willing to become more open to relations with sponsors."

*Pharmaceutical company, Poland*
- Sponsors admit that the completion of administrative issues is generally faster in case of cooperation with private healthcare institutions i.e., non-public healthcare facility (NZOZ). The focus on such partners is expected to increase in the future.
  - However, as the in-patient healthcare in Poland is still largely public, public hospitals are expected to remain the main partners, especially where in-patient therapy is applied.
  - It appears that a part of public sites may benefit from such a commercial relationship to a great extent, provided the "best practices" schemes are developed.



- Difficulties in contracting with sites are seen as an important obstacle.
  - “Negotiating a contract is slow and cumbersome. This is primarily due to legislative framework drawbacks and deterioration of clinical trials image in the press. The report, recently issued by the Supreme Chamber of Control, appears to have even deepened this problem.”  
*Pharma company, Poland*
- Interview feedback suggests that lack of efficient standards in contract negotiations between sponsor, site, and researchers can result in delays in the whole process. This is particularly important when time requirements are key, which is typically the case.
  - Tripartite contracting sounds generally positive, provided it does not significantly delay negotiations.
  - “At the beginning there may be difficulties in transition period, however in longer perspective it may have positive impact, as it will involve site management into the study conduct.”  
*CRO, Poland*
- “The key conclusion is that financing of clinical trials needs to be dealt with properly. Indeed clinical trials are definitely an opportunity for a patient to access advanced treatment methods, but in the same time financing issue is yet to be clarified as it has to assure the hospital’s financial interest.”  
*Jacek Jezierski, President of Supreme Chamber of Control, Gazeta Wyborcza, 23/07/2010*

### PwC Survey: “In your opinion, how could sites improve their approach to clinical trials?”



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

*PwC Survey respondents note that establishing within a site a unit dedicated to clinical trials should significantly improve mutual cooperation*

*Accessibility to information on clinical trials can be seen as constraint by some stakeholder groups*

*Historically, the clinical research market in Poland has faced significant taxation-related challenges...*

*...primarily due to unclear tax regulations or its restrictive interpretation by tax authorities*

#### Insufficient information sharing

- The level of information that is widely available on clinical trials generally appears limited.
    - Market insiders indicate that sites and researchers may compete for clinical trials; therefore, they are less willing to share information on the project to be launched.
    - Feedback from patients suggest that this can result in limited access to trials from potential participant viewpoint.
  - Additionally, a number of interviewees pointed out the negative attitude adopted by some sections of the media, which deteriorates the perception of clinical trials by the public.
    - “Perhaps scandalizing articles are more interesting for an average paper reader, but we believe there should be much more reliability and objectivity generally in the media.”
- CRO, Poland*

#### Taxation issues

- The tax environment may block or stimulate the flow of investments and innovation. As stated earlier, the clinical trials industry contributes a significant amount of tax and other public contributions estimated at c. PLN 260m to the state budget. In this context, the clinical trials industry in Poland was facing significant challenges mostly due to unclear tax regulations or its restrictive interpretation by tax authorities. The market insiders highlight the following factors as tax barriers for market development:

#### Historical tax issues affecting the clinical market in Poland since 2004

- VAT on expertise clinical trials monitoring services increasing the costs of trials in Poland by 22%. The tax authorities' position changed in 2009 after four years of disputes and intervention of European Commission.
- Lack of customs exemption for clinical trials samples imported to Poland, which were partly waived in 2007 after three years dispute with customs authorities. The administration of that exemption is still problematic; therefore, many sponsors moved the flow of import of samples to other EU countries.

#### Pending tax issues requiring immediate change of tax legislation

- Unclear VAT treatment of services provided for sponsors by sites/hospitals engaged in performance of clinical trials – significant tax risk for hospitals (recently questioned by NIK, the Supreme Chamber of Control) that affects the process of entering into new clinical trials projects.
- Lack of clear PIT exemption for patients covering costs of participation in the trial, eliminating potential doubts or discussions with tax authorities on patients' side, which may negatively impact the patient recruiting process, as well as provide for tax risk on both patients' and sponsors' side.
- Lack of PIT exemption for free medicinal product provided to patients by sponsors/foundations after the end of clinical trial project. This issue is still unseen by tax authorities as a significant problem for sponsors and patients participating in trials.

#### Perspectives from other markets

- Other market perspective shows that taxes may attract the inflow of investments in innovation, including R&D funds related to clinical trials (the global spending for clinical research amounts to c. USD 50-80bn).
- Several countries try to apply multiple instruments attracting direct R&D investments from various industries. In case of clinical trials markets' decision about the distribution of R&D funds, apart from administrative effectiveness (which we discuss in other sections of the report), may be driven by available tax incentives in a particular country.

Type of R&D tax incentives	Nature of incentive	Country
Deductions and allowances for R&D	Taxpayer can deduct from tax basis defined multiple of his expenditures into R&D	Austria, Belgium, Czech Republic, France, Ireland, UK, Australia, Brazil, Canada, China, India, and Turkey
Tax credit for R&D	Taxpayer can reduce the amount of tax paid	Austria, Hungary, Italy, Spain, and USA
Collaborative R&D incentives promoting academic research or collaboration with universities	Collaboration with university under defined conditions is subject to tax incentive (tax credit or deduction up to certain limit)	Belgium, Denmark, Hungary, Italy, Spain, Japan, and Chile
PIT/Social security exemption for R&D	Incentive reducing the burden of PIT or social security contributions for scientist / researchers or companies hiring such professionals for R&D projects	The Netherlands

Source: Report "Design and Evaluation of Tax Incentives for Business Research and Development" prepared for European Commission, Directorate General – Research, (Nov 2009), PwC analysis

*It appears that Poland can learn from other geographies where tax requirements were softened to attract R&D investment*

- Properly designed system of R&D incentives may combine both goals i.e., growth in investments in clinical trials phase I to phase IV with other goals such as:
  - Academic research projects;
  - Investigators' driven clinical studies;
  - Collaboration between universities and business and further commercialization of scientific ideas;
  - Utilization of local R&D infrastructure (laboratories, universities, and sites);
  - Location of R&D results (registration of patents, location of R&D centers etc. );
  - Support of business angels investing their capital in high risk R&D startup projects.
- Lessons from other markets show that such R&D incentives system should be developed in close cooperation with the industry to avoid a situation where the system would be unattractive for business or its administration, and compliance or some formal restrictions would eliminate its effective usage.

*Industry players judge long and unpredictable registration period, lack of transparency of rules, and administrative drawbacks are the most significant barriers*

*Clinical trials operators would expect significant procedural improvements to be the key driver of growth in the future*

#### Industry (Pharmaceutical companies & CROs)

##### Key barriers

- Clinical trials operators believe that a long and unpredictable registration period is the most important obstacle to market growth.
  - “It appears that both startup time as well as overall cycle period are among the longest in Europe, up to 1.5-2 times longer than in other countries.”  
*Pharmaceutical company, Poland*
  - Interviewees estimate suggest that c.20%-30% of clinical trials in Poland can be lost at the very beginning due to the long cycle time.
- Although the clinical trials operators see an improvement in the cooperation with registry office and other regulatory institutions, some drawbacks in this regard are persistent. These drawbacks are primarily a reference to the lack of transparency and problems with standardized law enforcement.
- As patient recruitment is competitive between countries, delayed registration disables Poland from being the location for some trials – even though recruitment is perceived as efficient in Poland.

##### Possible actions

- The key action point for industry insiders is to improve efficiency of registration office work, which is expected to make start-up process quicker and overall outcome more predictable.
- While quality of work within the sites is generally perceived to be high, the key problem lies with administrative side of relations with the sites.
  - Sponsors generally see tripartite contracting as desirable, as it is expected to facilitate negotiation process. However, some of them claim that there is a risk of significant delays in the negotiation process due to increased discussion over remuneration for researchers and sites.
  - “The process of contract negotiation with hospital was on average longer in 2009 than in previous years. It would be seen as very plausible if sites set up a unit or just one person responsible for clinical trials. Some have already done so and we see this as very positive.”  
*Pharmaceutical company, Poland*

### Authorities (Regulatory Office & Ethical Committees)

#### Key barriers

- The feedback from interview with the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products (the Registration Office) suggests that some organizational aspects of clinical trials administration have potential to be addressed more efficiently, along with the development of more integrated and centralized EU approach.
- Although the Office representatives admit that a shorter registration period could indeed increase the number of clinical trials conducted in Poland (as examples of Belgium, Austria, or the Baltics show). It also strongly emphasizes the role of requirement of quality in application review, which can be time consuming.
- The interviewees representing Ethical Committees believe more transparency in competency split should be outlined in upcoming new legal act. Issues related to patient access to information and insurance were also raised.
  - “We believe that a full insurance of patients participating in the trial is of a great importance. This issue should be stressed out significantly in the nearest future.”  
*Ethical Committee, Pomorskie*

*Although regulatory bodies emphasize their watchdog rather than commentary role, they agree that certain organizational areas can be improved*

#### Possible actions

- It appears that increased independence of the Office in the future sounds plausible to the regulatory officers. Evolution from the current organizational structure – being directly attached to the Ministry of Health – and becoming a more independent body (‘central office’ or ‘governmental agency’) could improve operational efficiency, as examples from WE countries show (e.g., NICE in the UK).
- For increase in transparency, interviewees from Ethical Committees often pointed out a requirement of better implementation of the EU Directive or successful examples of other countries.
  - “The EU outlined clear rules of how the Committees should function. What we need to do in Poland is put more effort in process enhancement. The level of understanding of what the Committee can and cannot do varies across between the units.”  
*Ethical Committee, Lodzkie*
  - “We need more information that is publicly available to patients. Furthermore, in the US researchers file their annual conflict of interest declarations. Perhaps implementing such idea in Poland would result in better climate around clinical trials?”  
*Ethical Committee, Mazowieckie*

*These areas would primarily be greater independence of the Office for Registration, as well as clearer operational model of Ethical Committees*

*The site managers see lack of precise legal requirements standard to everyone as the key obstacle to development of clinical trials*

*They see the introduction of mandatory tripartite contracts, hospital specific guidelines, as well as better administration of clinical trials within the hospital as key actions to improve the current state*

#### Sites (Site management)

##### Key barriers

- Interview feedback suggests that hospital managers consider the fees obtained by hospital through clinical trials to be too small. Hospital managers are of the view that sites receive disproportionate reimbursement rates for cost borne during clinical trials.
- Additionally, some interviewees believe that as a result of Supreme Chamber of Control intervention, managers have greater awareness of being potentially accused of accepting uneconomical contracts so they may be more reluctant to approve new trial launches.
- Additionally, some interviewees point out that sponsors are expected to be more flexible when negotiating a contract with the site.
  - “I understand sponsors pay for the project and are the ones who bear the risk, so they expect everything will go as they want. But they also need to bear in mind that site is key in the project as it is the place where patients are actually being recruited.”  
*Public hospital, Slaskie*

##### Possible actions

- Tripartite contracting appears to be perceived as a positive phenomenon. This has been confirmed by interviewees who have used this solution in their hospitals and who believe such contracting assures full transparency and general consent of all sides.
- There is general anticipation that the new legislative framework is expected to bring more plausible rules for site managements than currently operating laws. At the same time, many hospitals issued their own clinical trial guidelines.
  - “As a result of recent controversies, we have set up specific guidelines to be respected by all operating stakeholders, incl. sponsors and researchers. Calculation of fees for the hospital is also there.”  
*Public hospital, Slaskie*
- Clear allocation of responsibility for clinical trials within the site sounds favorable as well.
  - “I must admit that not always it was clear who is responsible for trials, but this has been changing. We have clearly allocated responsibility for clinical trials to exact officer. In our hospital this would be one of the deputy directors.”  
*Public hospital, Slaskie*

## Researchers (Doctors)

## Key barriers

- During the interviews, researchers agreed that excessive administrative requirements negatively impact the clinical trials registration and execution process.
- Attractive remuneration is perceived as an important incentive for doctors to engage in clinical trials; however, it may be expected that fees will decline as a result of new policymaker intervention.
- Only recently, some difficulties in recruitment of patients have been observed.
  - “The extreme and sometimes exaggerated stories that can be read in the press can scare away patients to participate in clinical trial. Any reliable and widely accessible source of information is rather difficult to find.”

*Researcher, Warsaw*

*Doctors are aware that incentives to take part in clinical research projects may get weaker, both for researchers and patients, medium term*

## Possible actions

- As it is the case in WE, there should be more emphasis on cooperation between pharmaceutical companies and R&D centers or medical institutes.
  - “We believe that increased importance of R&D centers in the clinical trials process will result in focusing on more valuable projects, that have potential to contribute more to global medical development.”
- A more precise definition of competency split is also important. Interview feedback confirms that law on Ethical Committees is rather unclear.
  - “Ethical Committee should judge on medical aspects and CEBK should take care of administrative issues – it’s all messed up now.”
- Tripartite contracting per se sounds plausible to doctors, as it is expected to make the negotiations transparent. On the other hand, some interviewees are rather cautious in this regard, as they foresee that such a requirement may make engagement in research projects less attractive for doctors.

*Researcher, Wrocław*

*They also believe that additional emphasis should be placed on preselection of trials to be launched*

*Patient associations believe more emphasis should be put on education and enhancing patient awareness*

#### Patients (Patient associations)

##### Key barriers

- Feedback from patient associations suggests that the level of information available to patients is insufficient. Additionally, there is a need for education and building of awareness.
  - Interviewees particularly stressed that it is essential to learn about the benefits and risk of clinical trials for the patient, as well as technical aspects, such as informed consent, insurance options.
  - “An educated patient can be more aware participant of clinical trial and can be recruited faster, what is also for the benefit of researcher and sponsor.”  
*Patient association, Warsaw*
- Anecdotal evidence shows that sometimes a patients’ access to clinical trials may be constrained, primarily due to lack of information exchange between the clinical trials investigators.
  - “It sometimes appears that sites or researchers are competing for clinical trials, so the information on pending projects is not widespread and thus unavailable for the patient.”  
*Patient association, Warsaw*

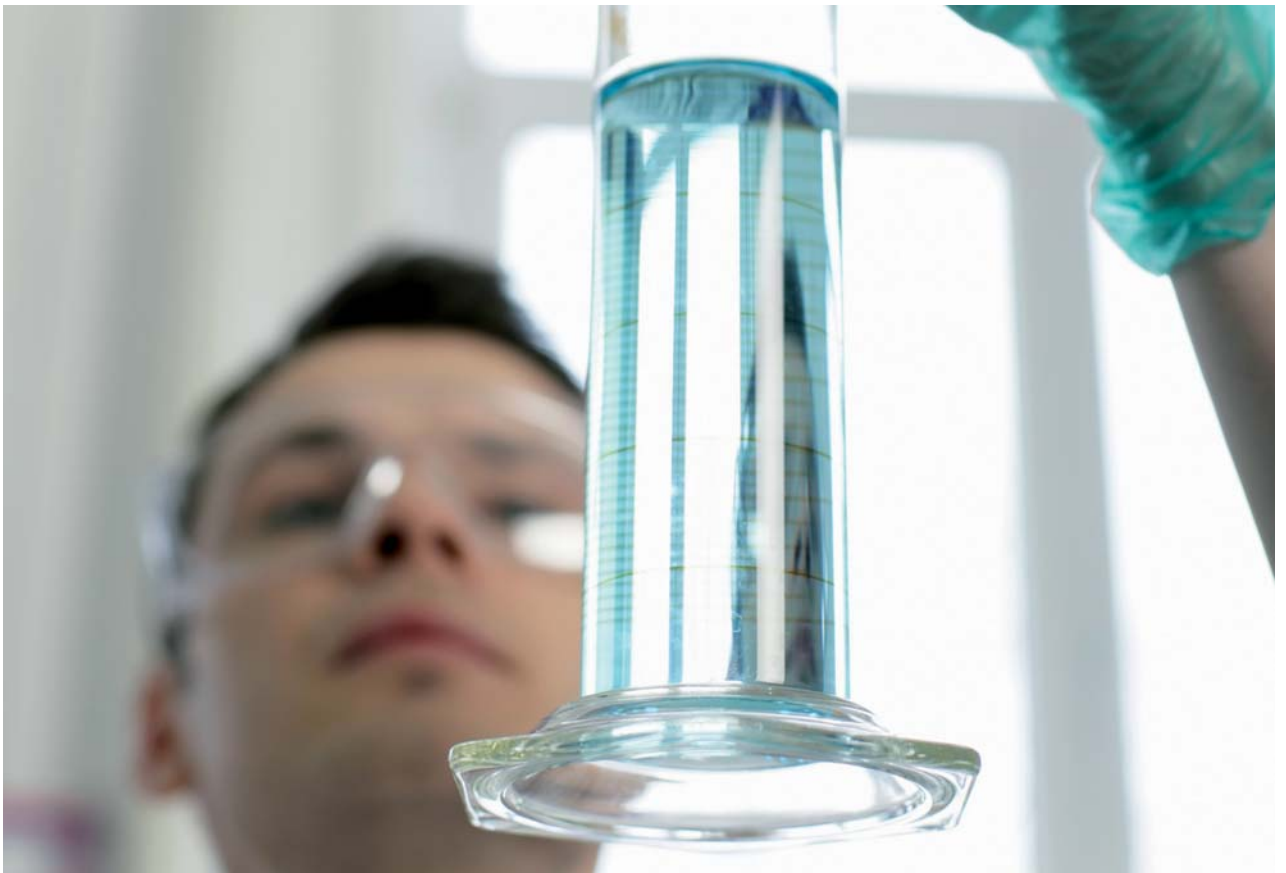
##### Possible actions

- Patient society believes that recently launched Community initiatives are expected to have plausible effects.
  - The EU launched the CORDIS FP7 project, which is supposed to be finalized in late 2010 and is primarily focused on the promotion of patients’ voice in clinical research, as the EU adopted a very ‘pro-patient’ approach, according to the respondents. Already mentioned CTFG/VHP is also aimed at protection of participants.
  - There is a general belief that this will have a systematic rather than ad hoc effect; however, a number of interviewees also admitted that the outcome of such initiatives is rather uncertain at this point.
- However, it also emphasizes the importance of bottom-up actions.
  - “We issue bulletins, try to be present and active in this awareness building. After all, we – as patient associations – are the ones who need to make the first step. But support from other stakeholders is essential here as well.”  
*Patient association, Poznań*



# Section 6

## Conclusions



### Conclusions

- *Poland remains the largest clinical trials market in CEE/CIS with a potential for growth.*
- *Clinical trials imply a number of benefits to Poland, including contribution to the health and wealth of society as well as to the economy and country development.*
- *In order to maintain competitive growth rates, Poland needs to launch a number of initiatives, including improvement of administrative drawbacks and introduction of other operational incentives.*
- *Accelerating the market growth and maximize the potential benefits to the economy is possible providing that administrative problems are to be resolved, transparency of processes enhanced and operational and regulatory rationalized.*

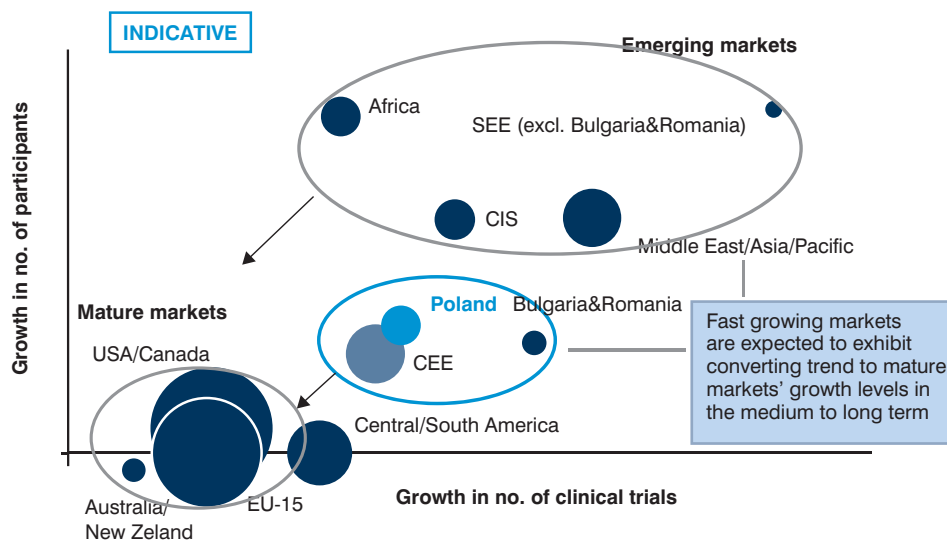
## Conclusions

### Uncertain future

- As the global market for clinical trials shifts eastwards to emerging geographies, where cost is lower and patient recruitment is easier, it can be expected that market growth rates of Poland/CEE converge to USA/Canada and WE growth level in the medium term along with market maturation.
- Currently, the key high growth regions are Asia, CIS, and Middle East. However, it appears only moderately sustainable in the long term, as sponsors may seek countries where clinical trials operational environment is more developed (e.g., patent protection rules are stricter and legislative framework friendlier and assured).
- As participation incentives become weak, to maintain positive growth and to continue to operate trials at home, mature markets have implemented several reforms, such as facilitation of administrative procedures, shorter registration times, and transparent contracting standards. Poland/CEE countries are expected to launch such facilitating initiatives if they want to compete with faster growing markets.

*In order to maintain competitive growth rates, Poland needs to launch a number of initiatives, following the example of more mature markets*

### Pivotal clinical trials submitted in MAAs registered at EMA

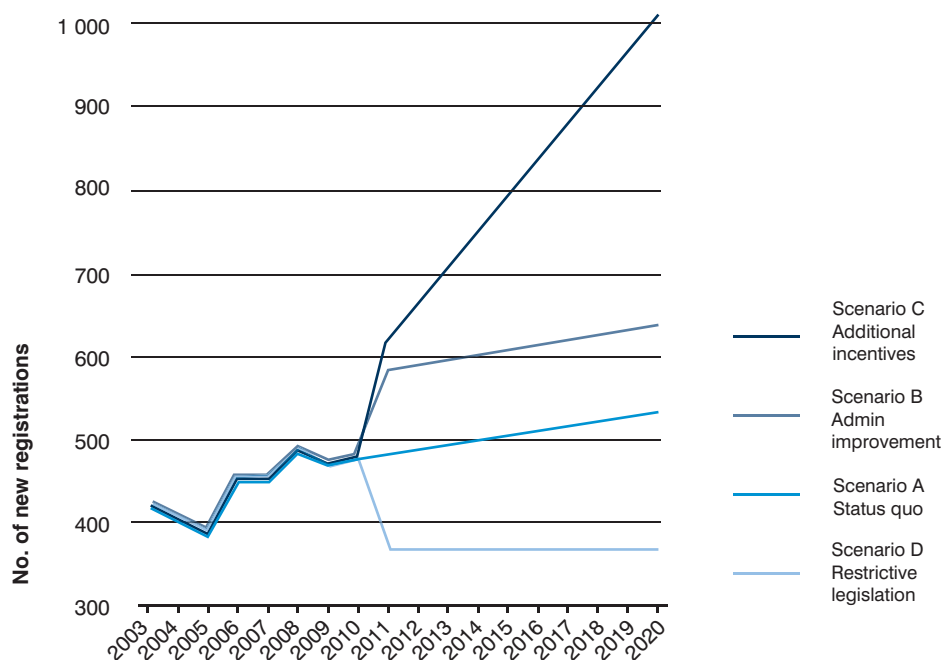


Note: Indicative; Analysis based on a sample of clinical trials, i.e. pivotal clinical trials submitted in MAAs registered at EMA; Bubble size indicates average per annum number of participants in 2005-2008  
Source: EMA

*Improvement of administrative drawbacks and introduction of other operational incentives appear to be the key to maintain significant growth in clinical trials in Poland...*

- Based on the assumptions deriving from CEBK data and PwC Survey, we have build up four scenarios that we believe can show direction of potential clinical trials development in Poland.
- It appears that only significant improvement in administrative processes as well as regulatory framework can trigger growth significant enough to outweigh the convergence trend towards WE/US and also competition from rapidly developing clinical research locations.

**Clinical trials in Poland – potential development**



*Note: Simulation is indicative and excludes potential global/macro trend changes (e.g., the impact of drug development path shortening or decline in R&D spend)*  
 Source: CEBK, EMA, PwC Survey, PwC Analysis

Major trend	Nature of incentive
<b>Scenario A: Status Quo</b>	<ul style="list-style-type: none"> <li>• No major changes in the clinical trials legislation environment</li> <li>• Poland's growth rate converges to WE/US rate in next 10 years – historic growth (c. 2% CAGR '03:'09) is gradually declining to reach moderate WE/US levels</li> </ul>
<b>Scenario B: Admin improvement</b>	<ul style="list-style-type: none"> <li>• The assumed increase primarily derives from shortening of time required to launch a clinical trial (including registration period, contracting, Ethical Committees' approval)</li> <li>• Significant administrative improvements resulting in 20% upward shift (effective in 2011 as assumed)</li> <li>• Shift is broadly achievable as registration timing has proved to be key for market players. Execution of 'critical path' trials expected to come to Poland (PwC Survey)</li> </ul>
<b>Scenario C: Additional incentives</b>	<ul style="list-style-type: none"> <li>• Incentives are expected to emphasize current competitiveness of the Polish market characteristics as well as adopt best practices from WE/US</li> <li>• Poland can effectively compete with both mature markets (based on recruitment and cost) and emerging markets (based on quality of execution and assured legislative/business standards)</li> <li>• We believe introduction of additional incentives is expected to result in accelerating the historic growth value. The level of the growth rate depends on portfolio of incentives</li> </ul>
<b>Scenario D: Restrictive legislation</b>	<ul style="list-style-type: none"> <li>• Potential introduction of excessively restrictive legislation is expected to negatively impact number of clinical trials in Poland, resulting in a downward shift</li> <li>• This scenario assumes that significant number of clinical trials are expected to be moved to other geographies with more favorable legislative environment</li> <li>• Judgmentally, we assumed 30% downward shift, however the real impact is hard to estimate and depends on the extent of restrictions – the growth rate has been assumed to remain flat throughout the period</li> </ul>

*...and this growth is expected to favor all stakeholders engaged in this industry*

*Increased contribution to the state budget appears to be a straightforward win for the economy*

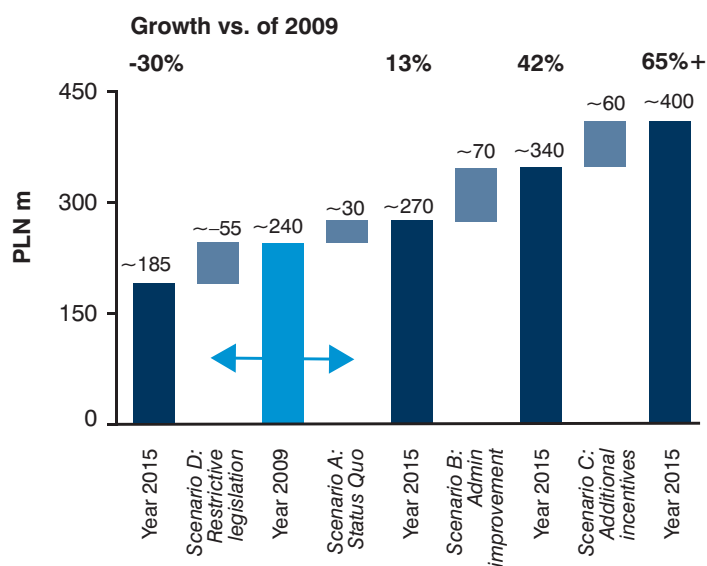
#### Benefits of growth

- Assuming the contribution levels of clinical research industry presented earlier in the report and the potential projections of the number of clinical trials under four scenarios, it appears that a number of stakeholders can significantly benefit from the clinical trials, once plausible interventions are made and more clinical research projects are attracted to Poland.

#### Contribution to the state budget

- Introduction of relevant incentives for sponsors has potential to result in a significant increase in contribution to the state budget, according to the projections (or decrease if the negative Scenario D does materialize).
- In five-year horizon, this benefit can increase by PLN 160m, provided administrative improvement as well as additional initiatives, such as transparency enhancement, are launched.
  - We believe this is a conservative approach as exact gain will depend on the exact portfolio of incentives to be introduced.

#### Potential contribution of the clinical trials market to the state budget (growth 2015 vs. 2009)



Source: PwC Analysis

### Alternative cost savings

- We have employed an example of oncology to roughly estimate the alternative cost savings for the public healthcare system. The results suggest that c.4% of patients are financed during the course of clinical trials, which amounts to c.PLN 130m alternative cost savings for the NHF.
- However, given that typically participants of clinical trials receive better standards of treatment, it can be concluded that the value of this upgraded treatment reaches up to c.PLN 0.5bn, which constitutes c.15% of NHF spend on oncology.
- Depending on the future development of public spend, the share of alternative costs in total public spend is expected to evolve. However, as the clinical trial volumes are expected to grow, the larger absolute value of treatment cost is expected to be co-financed in the course of clinical research projects. Consequently, large number of patients will be subject to financing from sponsors rather than purely from the NHF.
- However, if the excessively restrictive legislation will be introduced in the near future, it would imply lower number of clinical trials and therefore is expected to negatively impact alternative cost savings. In the example of oncology, this can be estimated at c.PLN 30m decline in direct savings for NHF.
- One should bear in mind that this mechanism is applicable to a number of other medical areas as well. Alternative cost savings jointly have significant potential to provide relief to the underfinanced healthcare system in Poland, provided clear regulations on co-financing between the sponsors and the NHF are introduced.

### Incentives and opportunities for researchers

- Participation in clinical research projects generally provides two types of incentives for researchers, financial as well as associated with professional development. The long-term validity of the incentives appears plausible also for other stakeholder groups.
- First, attractive remuneration levels appear to be an effective factor influencing medical staff's foreign migration decisions and have potential to retain the best specialists domestically. Broader career development opportunities also contribute to this phenomenon.
- Second, increased networking and experience gained through international cooperation are already positively impacting young doctors' "in-practice" learning. Intensifying this trend in the future is expected to integrate Poland into global medicine developments to a greater extent.

### Facilitated access to better standards of treatment

- Poland appears to be still lagging behind more mature healthcare systems in terms of accessibility to modern therapeutic methods. However, it appears that as clinical research project tend to imply employment of the most advanced, and costly, therapies globally available even more developed systems struggle to bear the financing of some of them.
- It can be concluded that the clinical trials are rather expected to provide greater intensity of healthcare services, also for longer term, when Poland will be converging towards more mature geographies.

### Know-how sharing

- Clinical trials contribute to the general knowhow upgrade within the medical society that retains an evident track in the general healthcare system development path.
- In future, this knowhow is expected to be the key, together with proper financing schemes, from the patient satisfaction viewpoint. Increased number of clinical research projects thus has the potential to trigger spillover effect deriving from education upgrade to materialize faster for the benefit of healthcare system endusers.

*Increased alternative cost savings have potential to provide greater relief for the underfinanced healthcare system in Poland. This should be combined with transparent regulations on co-financing*

*Medical staff is expected to be incentivized both financially as well as in terms of professional development opportunities*

*Last but not least, it appears that the core stakeholder in the healthcare system, a patient, is expected to benefit from the increased no. of clinical trials in Poland*

*Clinical trials in Poland require some operational rationalization. However, this shall not lead to excessive regulation, which may constrain future development and exploiting of the benefits*

#### Possible actions

- Having identified the benefits of a growing clinical research industry to the economy, one should point out some directions that would lead to the materialization of those benefits.

#### Legislative framework improvement – Rationalization rather than overregulation

- **Wise introduction of any new legislative rules:** It appears that current legislative solutions may require some improvement in terms of friendliness to clinical trial operators. However, policymakers should tailor any systematic changes in a confident yet wise way. Regulatory requirements are expected to improve and rationalize general operation of clinical trials, however, they shall not act as unnecessary obstacles.
  - For that, all the pros and cons, as well as the consequences of any new legal acts should be cautiously analyzed before requirements are implemented.
  - For the benefit of all stakeholder groups, such discussion should be arranged jointly with contribution from sponsors, CROs, site managers, researchers and patients' voice as well. It can be viewed that current public consultation mechanisms have potential to be more efficient and bring more adequate results.
  - In addition, the principle of de-bureaucratization should be the aim of the policymakers, and an introduction of complaint box perhaps is a worthwhile idea as well.
- **Access to information:** Information should be public and widely accessible, but only within the areas, which are key to the effectiveness of market operation.
  - It appears that introduction of publicly available platform for exchange of information would be favorable for several stakeholder groups:
    - > Sponsors, as it may outweigh the negative PR that sometimes puts a shade over the reliable information on clinical trials;
    - > Researchers and sites, as it may improve co-operation between them; and
    - > Patients, as it may facilitate access to recruitment and make potential participants fully aware of benefits and any risks of such participation.
  - In particular, it is important that the information on the area and aim of clinical trial is publicly available. This should also include investigators and sites engaged in the project, patient recruitment arrangements, and reliable information on benefits and risks of participation.



### Resolve administrative obstacles

- There are a number of administrative drawbacks, the facilitation of which is expected to have a significant positive impact on the future of clinical trials in Poland.
- **Shortening of registration time:** Market feedback clearly states that introduction of shorter registration periods will have immediate impact on the number of projects applied for in Poland.
  - Currently, Poland is almost entirely excluded from the so called ‘critical path’ trials where the length of a project is an absolute determinant. Resolving this issue has the potential to result in 20%-30% more trials, as market participants estimate.
  - Although in theory, according to the EU Directive, the maximum registration period is limited to 60 days, the actual average process turns out to be longer. This longer period is primarily due to the “stop clocks” applied by the Regulatory Office, that is suspension of the time count until reply to specific remarks is provided by the applicant.
- **Improvement of operational effectiveness:** Although sponsors and CROs believe that the co-operation with regulatory bodies has noticeably improved during the last decade, they still believe more emphasis should be placed on the standardization of administrative work.
  - Predictability is as key as the length of the process. A number of interviewees complained about uncertainty of the terms of application review process: its time horizon, the uniformity and rigorousness level of potential remarks as well as whether the nature of any comments is in line with the competencies of the relevant institution.
- **Higher fee for better service:** Interviewees jointly agree that increase in CEBK and Ethical Committee fees would not have much of a diverse effect on the number of executed trials, provided it assures better quality of service.
  - Introduction of fast track payment sounds plausible to the vast majority of market participants; and
  - This payment mode may also provide funds for financing operational effectiveness (e.g., increasing the number of staff and install better data processing systems), for the benefit of all stakeholder groups, including increased contribution to the state budget.
- **Faster implementation of the EU Directive:** Although generally Poland is perceived as a territory of high and ensured procedural standards, market insiders admit there are some elements in the community frameworks that could be implemented in Poland more thoroughly.
  - For example, as of now Poland is only one of the two countries in the EU, which has refused to participate in CTFG VHP initiative aimed at assuring a standardized and regular information sharing between the NCAs. There is potential however that this decision will be revised and Poland will join VHP in 2011 or shortly afterwards.

*In addition to that, the key issues to be resolved refer to the administrative drawbacks...*

*...and transparency improvement***Transparency enhancement**

- It appears that one of the most important areas that require improvement is transparency of the operational environment in the clinical trials. The transparency could be primarily achieved by establishing a clear set of rules governing the operational environment.
- **Clear competency split:** In terms of regulatory process, one of the key problems is lack of a clear competency split between different bodies, e.g., the Regulatory Office and Ethical Committee.
  - The objectives of CEBK and Ethical Committee appear to overlap.
  - A clear communication from the policymakers on the step-by-step guidelines is expected to provide clarification where competency split is not transparent enough. This communication is expected to be subject to joint discussions with the industry players (other stakeholder groups).
  - This is also linked to the already mentioned issue of standardization and uniformity of CEBK's duties and attitude to each particular application. It appears that introduction of a comprehensive set of rules would benefit sponsors, as it is expected to facilitate co-operation with the regulatory body, as well as CEBK itself, as it would provide support for the officers' work.
- **Relationship between operator, investigator, and site:** The co-operation of all three stakeholder groups is a pre-requisite for a clinical trial to be executed efficiently and according to the required procedures. Tripartite contracting appears to be a good solution in this regard.
  - Generally, the majority of interviewees welcomed the idea of tripartite contract introduction as it would effectively eliminate any conflict of interest, especially for the researcher. However, some of them indicated the risk that this may put some pressure of process timing as more time can be devoted to negotiations between all the parties involved.
- **Site management:** Sites which established dedicated units responsible for clinical trial affairs have already gained recognition from industry players. Managers of such hospitals admit that this significantly improved the information flow between directors, researchers, and sponsors.
  - The majority of oncology centers, including the one in Warsaw, have established specific organizational unit for the purpose of clinical trial management.
  - Establishing a dedicated unit may, among others, indicate a specific contact person, facilitate and standardize co-operation with local legal advisor, and make the whole process efficient.
  - Better organization of clinical trials within the site may attract large number of sites to take part in new projects in the future. One should bear in mind that Poland exhibits rather low penetration rates in this regard compared to other, smaller CEE countries (the Czech Republic and Hungary).
- **Clear rules on co-financing of patient treatment:** Several stakeholder groups emphasize the need for introduction of transparent rules regarding co-financing between a sponsor and the NHF.
  - Currently, the difference between costs of standard and non-standard therapy is not always clear. Introduction of clear regulation is expected to result in more efficient co-operation between the sponsor (the operator) and the site.










## Lessons from other countries

Country	Intervention / Characteristic	Effect	Impact on market
Several EU Member States	• Adoption of Voluntary Harmonization Procedure (VHP). As of 2010, Poland refused to join the program	• Ability to opinion on clinical trial application jointly between the countries	●
UK	• Establishing National Institute for Health Research as a platform for best practice exchange in clinical trials	• Enhanced access to information for all parties • Faster recruitment	●
UK	• Introduction of standardized template for contracts between the sites, researchers and sponsors	• Shorter and smoother negotiation process	●
UK / Belgium	• Increased cooperation between sponsors and R&D centers (conferences, joint debates, etc.)	• Improved perception of clinical trials in the public debate	●
UK / Belgium / Austria	• Regulatory office shortens maximum registration time to 30 days	• Shorter start-up period and attraction of larger no. of trials	●
Bulgaria / Malta	• Easier access to patient data in hospitals (stats on epidemiology – related indicators made available)	• Faster recruitment	●
Romania	• Increased quick responsiveness of authorities	• Smoother bureaucratic process	●
Baltic States	• Regulatory office shortens maximum registration time	• Shorter start-up period and attraction of larger no. of trials	●
Estonia	• All relevant clinical trials related information published in both Estonian and English	• Easier access to information for foreign parties	●
Canada	• Fiscal incentives for companies performing clinical trials	• More clinical trials attracted (vs. USA)	●

Positive ● ● ● Negative

*Some international benchmark view on lessons from other countries can serve as best practices guidebook for the benefit of potential evolution of the Polish market*

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Country	Intervention / Characteristic	Effect	Impact on market
USA	<ul style="list-style-type: none"> <li>• Introduction of annual researchers' conflict of interest declaration</li> </ul>	<ul style="list-style-type: none"> <li>• More transparency in researchers environment / better perception of trials by the public</li> </ul>	
Hungary	<ul style="list-style-type: none"> <li>• Cooperation between the Regulatory office and Investment Agency on promotion of clinical trials (brochures, presentations)</li> </ul>	<ul style="list-style-type: none"> <li>• Information sharing / Promotion of Hungary as a clinical research destination</li> </ul>	
Czech Republic	<ul style="list-style-type: none"> <li>• Regulatory agency adopting more customer-friendly approach</li> </ul>	<ul style="list-style-type: none"> <li>• Shorter start-up period</li> </ul>	
UK / Belgium	<ul style="list-style-type: none"> <li>• Facilitation of administrative procedures in response to increasing competition from emerging CEE markets</li> </ul>	<ul style="list-style-type: none"> <li>• Part of clinical trials retained domestically</li> </ul>	
Russia	<ul style="list-style-type: none"> <li>• Regulatory office introduces additional certificates for investigators, issued centrally</li> </ul>	<ul style="list-style-type: none"> <li>• Increased bureaucracy and limited access for investigators from distant locations</li> </ul>	
Russia	<ul style="list-style-type: none"> <li>• Mandatory translation of all clinical trials related documentation into Russian</li> </ul>	<ul style="list-style-type: none"> <li>• Slowdown of the application and monitoring process</li> </ul>	
Russia	<ul style="list-style-type: none"> <li>• Export of blood samples made forbidden (one month long)</li> </ul>	<ul style="list-style-type: none"> <li>• Lack of trust against regulatory body</li> </ul>	
Croatia	<ul style="list-style-type: none"> <li>• Introduction of requirement on CRA qualifications (2 years experience and Croatian nationality)</li> </ul>	<ul style="list-style-type: none"> <li>• Paralyzed the market due to lack of resources</li> </ul>	
Turkey	<ul style="list-style-type: none"> <li>• Contracts can be signed only with site management, excluding investigators</li> </ul>	<ul style="list-style-type: none"> <li>• Significant decrease in recruitment levels</li> </ul>	

Positive    Negative

# Appendix 1

## Glossary



## Glossary of terms and abbreviations

Term	Definition
ANZCTR	Australian New Zealand Clinical Trials Registry
BLA	Biologic license application
bn	Billion
c.	Circa
CAGR	Compound annual growth rate
CDER	Centrum for Drug Evaluation and Research
CEBK	Central Clinical Trial Registry
CEE	Central and Eastern Europe. In this report this includes: Czech Republic, Hungary, Estonia, Latvia, Lithuania, Poland, Slovakia
CIM	Confidence in Mechanism
CIS <sup>1</sup>	Former Commonwealth of Independent States. In this report this includes: Russia, Ukraine, Belarus, Kazakhstan
CIS <sup>2</sup>	Confidence in Safety
CIT	Corporate income tax
CORDIS	Community Research and Development Information Service
CRA	Clinical research associate
CRL	Clinical reference laboratory
CRO	Clinical research organization
CTA	Clinical trial application
CTFG	Clinical Trial Facilitation Group
DRKS	German Clinical Trials Register
EMA	European Medicines Agency
Est.	Estimated
EU	European Union
FDA	Food and drug administration
GUS	Central Statistical Office
HMA	Heads of Medicines Agencies
ICH	International Conference on Harmonization
ICTRP WHO	International Clinical Trials Registry Platform
IMF	International Monetary Fund
Incl.	Including

Term	Definition
IND	Investigational New Drug
IT	Information technology
k	Thousands
m	Millions
MAA	Marketing Authorization Application
M&A	Mergers and acquisition
NCA	National Competent Authority
NDA	New Drug Application
NHF	National Health Fund
NICE	National Institute for Health and Clinical Excellence
NIK	Supreme Chamber of Control
NME	New Molecular Entity
no.	Number of
NTR	Netherlands Trials Registry
NZOZ	Non-public health care facility
OECD	Organization for Economic Cooperation and Development
p.a.	Per annum
PhRMA	Pharmaceutical Research and Manufacturers Association
PIT	Personal income tax
PLN	Polish zloty
PMR	PMR Consulting
ppt	Percentage points
R&D	Research and development
SEE	Southern and Eastern Europe. In this reports this includes: Romania, Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Macedonia, Serbia and Slovenia
UK	United Kingdom
URPLWMIpB	Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products
USA/US	United States of America
USD	United States dollar
VAT	Value added tax
VHP	Voluntary Harmonization Procedure
WE	Western Europe
WHO	World Health Organization

# PwC Pharma & Life Sciences



**Mariusz Ignatowicz, Partner**

[mariusz.ignatowicz@pl.pwc.com](mailto:mariusz.ignatowicz@pl.pwc.com)

Telephone: +48 22 523 48 12

Mariusz is a PwC Pharma & Life Sciences CEE leader. He has 15 years of experience in serving exclusively clients from pharmaceutical and healthcare services sector. Currently he is responsible for over 25 industry clients operating in Poland, advising them on financing subject to local statutory pricing control mechanisms, tax optimization, structuring of clinical trials monitoring services and many other topics.



**Tomasz Jędorowicz, Senior Manager**

[tomasz.jedorowicz@pl.pwc.com](mailto:tomasz.jedorowicz@pl.pwc.com)

Telephone: +48 22 523 48 54

Tomasz has 11 years experience of working for clients from broad pharmaceutical and healthcare industry, focusing on key business issues such as: marketing policy, advertising, clinical research, reimbursement, statutory pricing, management of regulatory risk as well as cooperation between the private and public sector.



**Jacek Ostrowski, Senior Manager**

[jacek.ostrowski@pl.pwc.com](mailto:jacek.ostrowski@pl.pwc.com)

Telephone: +48 22 523 41 84

Jacek works at the PwC Strategy Group CEE. During nine years of consulting work, he gained strong experience in market reviews, commercial due diligence, strategic advice and business planning, particularly in pharmaceutical and healthcare sector in the CEE region, working primarily for private equity clients.



**Bartosz Wiśniewski, Senior Associate**

[bartosz.wisniewski@pl.pwc.com](mailto:bartosz.wisniewski@pl.pwc.com)

Telephone: +48 22 523 48 95

Bartosz works at the PwC Strategy Group CEE. He has three years' experience of working on market reviews, research and commercial due diligence with particular emphasis on pharmaceutical and healthcare industry. He has a BA from Bocconi University, Milan, Italy and MSc from Erasmus University Rotterdam, the Netherlands.





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