

Resource for Multisite Studies and Emerging Markets – Poland

Following European Union accession on 1 May 2004, Poland has implemented EU directives 2001/20 and 2005/28 and established a friendly environment for clinical trials. Having 38 million citizens and a post-communistic centralised healthcare system makes it a very attractive country in which to conduct clinical studies, thus it is not a surprise that ClinicalTrials.gov shows 647 ongoing/starting studies in the country.¹ Nevertheless the clinical site density in Poland per million population is only 30.8, compared to 76 Czech, 62 in Hungary and approximately 50 in Germany/France/Spain.²

According to a PwC (previously PricewaterhouseCooper) survey from November 2010, the clinical trials market in Poland is worth about 900 million Polish zloty (approx. 200 million euro) and continues to be the largest one in Central and Eastern Europe (CEE). Each year there are over 450 new clinical trials registered in Poland's Regulatory Affair office. This number does not reflect observational studies, as those do not undergo RA submission. Another PwC survey confirms that the reasons for successful clinical trials growth in Poland are the accessible population allowing for efficient patient recruitment with the assurance of EU standards and high data quality. Sixty per cent of all studies in Poland are in the following therapeutic areas: oncology, rheumatology/immunology and cardiovascular trials.²

Healthcare System Characteristics:

The centralised healthcare system is obligatory and covers almost all citizens. It is paid and supervised by National Health Fund (NHF, Narodowy Fundusz Zdrowia³). The majority of patient treatment still occurs in public healthcare units. Official government data shows 995 public and 1260 non-public hospitals, whereas ambulatory units are about 4k in public sector and 20.5k private units.⁴ Of course, not all of these hospitals are suitable for conducting clinical trials. There has been a significant tendency seen to move clinical trials from public hospital facilities to private clinics in order to get a faster study start and a better financial ratio. 38% of clinical sites that Premier Research worked with in 2010 were private institutions.

The Polish healthcare system is characterised by poor accessibility of a patient to be seen by a medical specialist. A typical wait to meet with a neurologist, gastroenterologist or allergist can range from three months to one year. Clinical trials participation gives patients much quicker medical care access. Furthermore, Poland, similar to other developing European countries, has problems in assuring wide accessibility for the new medical therapies. These therapies are mostly grouped in special NHF programmes, not always accessible for every patient. For that reason clinical trials are often the only option for the patient to get new medical therapy access. Conversely, Polish healthcare units are unusually well equipped; they are able to perform CT or MRI assessments. The summation of these factors has led to excellent patient recruitment rates.

Regulatory Background:

Polish law is a bit complicated for the inexperienced person as there are four main medical legal acts related to clinical trials conduct:

1. The first, the Medical Profession Act (Dz.U. 1997 Nr 28 poz. 152), describes clinical studies as medical and scientific experiments.
2. The second, the Polish Pharmaceutical Law (Dz.U. 2001 Nr 126 poz. 1381), is applicable for clinical trials with medicinal products and is the main act of law in Poland covering clinical research.
3. The third is the Act on Medical Devices (Dz.U. 2010 Nr 107 poz. 679).
4. The fourth defines responsibilities of Polish Regulatory Affair Agency (Dz. U. 2011 Nr 82, poz. 451).

There are also several law orders including one that covers Good Clinical Practice (GCP) and Good Manufacturing Process (GMP). For these reasons, in 2009 the Ministry of Health started working on a separate Law Act on Clinical Trials; however the final launch is not expected before 2012. A pretty important aspect of the new Polish law is the requirement for investigator and sponsor compulsory third party liability insurance (not a 'patient insurance') for all interventional studies. These liability insurance values have been announced in a special decree, and depend on the amount of participants.

Regulatory Submissions:

Considering the various law regulations, it is extremely important to have great regulatory know-how to guide sponsors through all these legal acts, which is in fact not so difficult. Currently, it takes approximately five to six months for the proper approvals in Poland.

Following the implementation of EU directives 2001/20 and 2005/28 into Polish Law, a parallel approval for studies with medicinal products from one central regulatory authority (RA) and one central ethics committee (EC) is required. For medical devices studies, EC approval must be obtained prior to regulatory submission. Observational studies (Phase IV and others), both interventional and non-interventional and with or without medical products, mostly require only one central EC approval. In May 2011, the Ministry of Health moved pharmaceutical registration responsibility to the Office for Registration Medical Products, Medical Devices and Bioacidal Products, and they became the only central regulatory affair body in Poland.⁵ This change should improve the regulatory submission process in the short term.

For the moment in Poland, an applicant needs 60 days in order to obtain RA approval; unfortunately the Polish Agency does not allow the Clinical Trial Application (CTA) to be submitted with the Voluntary Harmonisation Procedure (VHP). The Polish CTA application must support EudraCT. There is no need to translate the whole protocol into the

local language, and there are no meeting dates or submission windows, thus the dossier may be submitted any working day. Prior to the agency starting the submission process, the agency will verify that the submitted documents are complete. It is extremely important to have suitable knowledge and submit a correct dossier, otherwise the agency may return in 30-40 days, noting that the submission was incomplete and that the submission process was not started. It is extremely important that the final executed contracts between sites/PIs be submitted before the submission timeline reaches day 60. Additionally, it is widely known that the submission process may be withdrawn at any time without any negative impact on the study in other participating countries. However, not widely known is the fact that the process may also be put on hold, without any negative impact, to provide missing signed contracts.

As mentioned previously, the EC approval process for medicinal product studies can be obtained in parallel with RA approval. It is important to note that there are different types of ECs in Poland. There are about 22 ECs located in regional medical chambers applicable for non-institute/non-university sites.⁶ Medical universities utilise their own ECs for university clinics, and other ECs are affiliated with most large clinical institutes.

Due to a change in the pharmaceutical law in 2004, the applicant must choose one of the PIs to take the role of the study country coordinator and use their associated EC to become the central EC voting on all sites participating in the clinical trial. This step is an important one, as the CEC also requires signed study contracts, thus the CEC selection must be connected with fast PI-coordinator contract execution. Although the CEC votes on the study on its own, it is obligated to contact regional ECs proper for other (than coordinator) sites in order to obtain information, for example if the site is eligible to participate in the multicentre clinical study. The applicant is not involved in this process, although the majority of local ECs will charge the applicant per each site's assessment.

Contracting Issues - Facts and Myths about Poland:

All individuals involved in clinical trial conduct in Poland have heard about issues connected to clinical trial agreements and the submission process. The fact is the signed clinical trial agreement must be executed prior to receiving EC and RA approval, and those bodies must receive an original or certified copy of the agreement. The myth is that this is 'mission impossible'. The problem is that CROs and sponsors often use contract templates for hospital negotiations that often contradict Polish and sometimes even EU legislation. In Poland, the sponsor and investigator hold the biggest responsibility for study conduct. The hospital mostly provides facilities and allows the investigator to run the clinical study. Secondly, personal data protection is very strict in Poland. Thus having a 30-page hospital contract makes 'mission impossible'. The Polish GCP association, together with the INFARMA association, have worked out a tripartite agreement template, which reflects all Polish and EU legal aspects and has all parties' rights properly protected.^{7,8} Current contract execution problems are also caused by a control performed in 2009 and 2010 by the Supreme Audit Office in Polish clinical hospitals.⁹ It showed several

unintentional mistakes in hospitals connected with drug order procedure and clinical trials cost/benefit ratio procedure. These inadvertencies were not connected to clinical trial quality - most (if not all) hospitals have implemented suitable corrective actions and now the process is better. Still the best approach for contracting in Poland is working with someone that has experience with this area.

Patient Population:

Although the start-up period in Poland is longer than other countries, the sites are able to achieve patient recruitment quickly. Assuming that it is not a very short study, Polish sites are well suited to contribute to patient enrolment. The success is mainly due to a relatively inefficient public healthcare system coupled with strong patient-physicians relationships. These trusted relationships, similar to other CEE countries, equate to higher patient retention and increased adherence in protocol procedures. The PwC Clinical Trials Report presents that oncology studies account for 34% of the overall clinical trial market in Poland, followed by 14% for cardiovascular and 12% for rheumatology. Endocrine/metabolic, CNS, infectious disease, urology, and some miscellaneous indications round out the remaining trials.² Over-expression of oncology trials in Poland is due to the prior mentioned problematic accessibility for new medical therapies. Nevertheless, success in each study, regardless of the indication and complexity, is connected with proper feasibility data collection. Polish clinical trial units are mostly fluent in English and respond to feasibility questionnaires properly, although timelines must not be tight for proper response.

Costs:

Conduct of a clinical study in Poland still costs roughly 20-30% less than countries in Western Europe (WE), although investigators' fees are mostly similar to WE. Costs of medical procedures are now also similar to the west.

The RA application for clinical trials with medicinal products costs only 4,000 to 8,000 Polish zloty (approximately 1,000-2,000 Euro), and there is no amendment fee for medicinal products clinical studies. Regulatory fees have not changed for the past three years, thus it is probable that there will be an adjustment in the near future. EC costs have become more expensive due mostly to local EC assessment costs. CEC approval costs about 6,000 to 12,000 Polish zloty (1,500-5,000 Euro) per central application, plus 1,500 Polish zloty (approximately 380 Euro) per each local site assessment. An amendment fee is usually between 1,000 and 2,000 Polish zloty (260-520 Euro).

Due to often large distances for patients to travel to the sites, sponsors must take higher travel reimbursement costs into consideration. The best way to reimburse costs is to work with an external local company, as the tax and data protection law is very unclear in this area.

Quality:

As mentioned earlier, Polish investigators are mostly fluent in English, and this reflects in proper communication and good study conduct.

Reviewing FDA data from 1994 to 2006, CEE countries had on average 0.85 findings per inspection versus 1.77 in

WE. There was only one administrative FDA sanction for CEE against 18 in WE.¹⁰ From 1997 to 2008, 38 FDA inspections were held in Poland and 23 (60 %) provided no action required. Premier Research Poland has also participated in two FDA inspections, both in 2010, auditing two hematology units in Poland. Both showed excellent site performance with no action required for either the site or Premier Research. Recent calculations have shown that about 1,200 CRAs in Poland work for more than 50 CRO and pharmaceutical companies.² The number of studies in Poland has been relatively stable over the last two to three years. It is also worth mentioning that almost all big pharma companies are present in Poland, with some having big clinical trial management centres located in Warsaw. Sponsors often give the role of the international principal investigator to Polish investigators.

IMP/Laboratory Logistic Procedures:

Poland has been an EU member since May 2004, and in December 2008 Poland also joined the Schengen Agreement, which affords even better logistic and communication schemes. There is no import license requirement for EU-released IMPs. Also, other medical equipment needed for study conduct does not need import licenses, and export licenses for biological samples are not required. However, special requirements are in place for control substances and radiology active delivery.

Summary: Why to Run Studies in Poland?

1. Clinical trials have been conducted in Poland for more than 20 years. Thus, Polish investigators are highly experienced in clinical study procedures and are mostly fluent in English. The majority of physicians have undergone several GCP trainings.
2. While the regulatory approval process is not as short as in other EU countries, it is unified with the EU legislation and timelines are clear and predictable. Although contracting is a tough part of the submission process, it can be easily accomplished by thorough preparation using correct agreement templates. Furthermore there are huge efforts currently underway by the GCPpl and INFARMA associations in order to make the clinical trials business more transparent. They have worked out Rules for Conducting Clinical Trials in Poland, which intend to self-regulate the pharma and CRO industries in order to have the highest ethical standards in the clinical trials area.⁶ The key point is to work on better patient education (regarding rights, data protection, IMP characteristics and PI activities) when study-related documents are produced (for example informed consent forms) or study team trainings performed. The other important point of this transparency is principles related to financing (i.e. linking investigators' remuneration with tasks, excluding double financing study procedures by both the sponsor and NHF, and having the clinical site study budget described only via the tripartite contracts in Poland).
3. IMP management and logistics is simple and does not vary from other EU countries. There are no import/export licenses needed for IMPs and laboratory samples sent from/to EU countries. Only controlled substances that are delivered via specialised pharmaceutical wholesalers need

an import license.

4. Private clinics, SMOs and private hospitals are a growing part of the Polish healthcare system. These units provide an excellent environment for clinical trial conduct and give suitable competition for the public units. Nevertheless, each new study conduct must be considered carefully. A proper feasibility process must be in place, especially in highly developed areas like oncology, rheumatology and/or cardiology. Often it is worth utilising a less experienced site and making the effort to train them properly and providing greater attention during early enrolment to obtain higher recruitment figures.
5. The best recruitment results are obtained when the recruitment period is no shorter than nine months; shorter recruitment periods should be planned carefully. February to May and September to November are the most efficient recruiting months in Poland.
6. The main disadvantage is still the long regulatory timeline typically averaging closer to 90 days instead of the 60 days specified in the EU directive. Poland has yet to join the VHP registration procedure, but this should be positively solved in 2012. The biggest negative is still the administrative procedures connected to contract negotiations, and this is not only with regard to hospitals. Often CROs' and sponsors' procedures require several internal contract revisions, and this makes the contracting process longer. This is a result of the growing awareness of clinical trials risks and benefits, but this is a positive trend and should hopefully be improved by all parties in the short term.

References:

1. www.clinicaltrials.gov
2. *Clinical Trials in Poland – Key Challenges*, report by PwC, Nov 2010; <http://www.pwc.pl/pl/pl/biuro-prasowe/Clinical2010XI.pdf>
3. www.nfz.gov.pl/new/index.php
4. www.rejestrzoz.gov.pl, data as of 05 Nov 2011
5. *Urzęd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych*, www.urpl.gov.pl
6. www.infarma.pl/uploads/media/Rules_for_conducting_clinical_trials.pdf
7. www.gcppl.org.pl
8. *infarma.pl - Employers' Union of Innovative Pharmaceutical Companies INFARMA*
9. *Supreme Chamber of Control, results of clinical trials control (Polish version only)* <http://www.nik.gov.pl/plik/id,1862,vp,2203.pdf>
10. *Palaveev, R. European Pharmaceutical Contractor, Autumn 2007*



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