Clinical Trials in Central & Eastern Europe: Keeping Up with Global Competition

A great number of willing patients, highly experienced researchers and EMA-compliant legislation make the CEE region an attractive research site destination. CEE is also the region with the lowest percentage of inspections that required official or voluntary action. The data at large suggest that the high productivity of CEE sites is accompanied by regulatory compliance and data quality standards that are not inferior to those in Western regions. Six countries from CEE (Hungary, Czech Republic, Estonia, Bulgaria, Slovakia and Latvia) rank among the top 10 countries globally in terms of accessibility of industry R&D clinical trials to patients. However, the clinical trials landscape is shifting rapidly and with the increasing competition from the South-East Asian region, the global industry is expecting further improvement of the business and regulatory environment in the CEE region. This article gives an overview of the key challenges and opportunities the region presents, and analyses the latest regulatory initiatives that are aimed at creating even more favourable conditions for conducting clinical trials in the region.

Size and Maturity of the Market

With a combined population of just over 104 million, and commitment to adhere to EMA's guidelines, CEE-EU countries like Hungary, Poland, Czech Republic, Romania, etc., have established themselves as a global powerhouse of clinical research. According to data compiled from EU Clinical Trials Register 2016, non-communicable diseases, represented mainly by cancer and heart conditions, are becoming increasingly significant healthcare issues in multiple CEE countries, which reflects the number of clinical trials conducted in each of the fields. Within the therapeutic areas of all trials, oncology indications are dominating in Hungary and Poland (25-27%), but even presented a significant share (on average 22.2%) of all trials ongoing within CEE countries.[1] Other fields where the industry sees the most frequently registered studies are rheumatology, allergology and neurology.

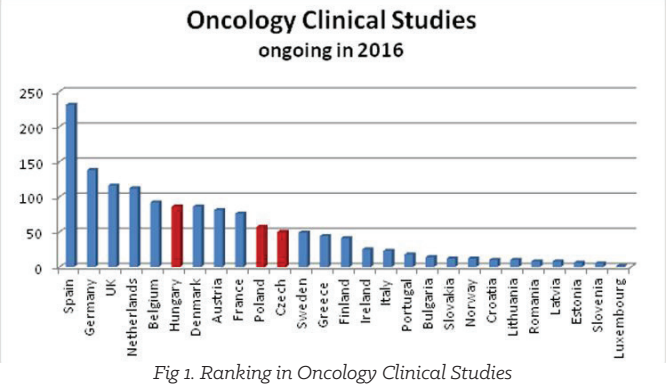

Fig 1. Ranking in Oncology Clinical Studies (trials ongoing in EU Clinical Trials Register, 2016)

What Makes a Region Attractive?

Large patient enrolment with efficient recruitment. Despite the existence of the national health insurance system, the present reimbursement programmes do not cover some of the advanced treatments, which creates an incentive for patients to enroll on trials that allow them to gain access to the advanced therapies that are otherwise not available. Willingness of patients to participate in clinical trials manifests itself in fast patient recruitment, that is positively noted by the sponsors and the CROs.

Another contributing factor, adding to the region's attractiveness, is the centralised healthcare system that allows easier access to patient data and makes available the stats on epidemiology related indicators.

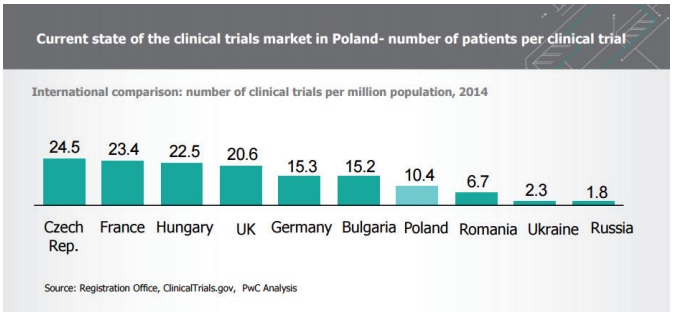

Fig. 2. International comparison: number of clinical trials per million population, 2014

Recognised Quality

According to the industry data, CEE was one the regions with the lowest percentage of inspections that required official or voluntary action. The data at large suggests that the high productivity of CEE sites is accompanied by regulatory compliance and data quality standards that are not inferior to those in Western regions.

Table 1. FDA[2] Site Inspection Findings (10/2008 –09/2015)

Region	No Action Indicated	Voluntary Action Indicated	Official Action Indicated	Count of Inspections (n)
Developed Markets	49%	46%	5%	14,580
Emerging Markets	43%	53%	5%	1962
CEE	59%	39%	2%	264
Poland	64%	34%	3%	80

Access to experienced, highly motivated and compliant investigators, who are highly driven to participate in multinational clinical trials as they see clinical projects as an opportunity to interact with the international medical community and to advance knowledge on the new methodologies and therapies, was also well noted by the sponsors.

Value for money: Dr Vladimir Misik, Founder & Managing Partner of LongTaal (former Head of CEE & MENA at Quintiles) argues that the advantage is not low cost, but rather "excellent value for money". The perks include what was earlier mentioned; predictable and high patient recruitment (driven by a centralised healthcare system), motivated investigators (income from clinical trials is a source of revenues to participating physicians in underfunded healthcare institutions), low patient drop-out rates (driven by historically very high trust of patients in their treating physicians). All that is coupled with an established high-quality track record (CEE has been ranking consistently among the very best across a range of quality indicators, ranging from inspection findings, to query rates, to clinical compliance).

Is the Landscape Shifting?

After the growth in 2012 and 2013, a decrease in newly registered studies has been noticeable since 2014. According to the data collected by the AIFP working group on clinical trials in the Czech Republic (this data is also highlighted in Longtaal analytics), the majority of studies are Phase III (56%) and Phase II (26%) and the percentage of Phase I studies is far below the European average (5%).

Shifting landscape…

Relative Market Growth – Active Sites

Region	2009-10 vs. 2011-12	2011-12 vs 2013	2013 vs 2014	2014 vs 2015
Developed Markets	-1.5%	-0.7%	-0.1%	0.5%
Australia/New Zealand	3.6%	6.6%	2.3%	0.5%
Israel	5.2%	7.1%	6.9%	5.1%
Japan	16.2%	-1.3%	-2.4%	2.4%
North America	-3.3%	-2.6%	-1.6%	0.2%
Western Europe	-1.6%	1.5%	2.0%	0.4%
Emerging Markets	4.8%	2.1%	0.4%	-1.3%
Asia (excl. Japan)	4.4%	3.8%	-0.6%	-3.1%
MENA	0.1%	-6.9%	0.0%	-0.6%
Latin America	0.2%	-0.1%	-1.5%	-1.6%
Sub-Saharan Africa	-5.0%	-3.1%	-0.2%	-6.9%
Turkey	5.9%	19.2%	12.6%	7.9%
CEE+CIS	7.6%	2.0%	1.2%	-0.5%
CEE	7.9%	1.8%	2.3%	-0.2%
Bulgaria	12.3%	11.8%	7.0%	2.1%
Croatia	11.7%	-4.0%	-15.0%	4.0%
Czech Republic	5.3%	4.6%	7.4%	0.6%
Estonia	4.6%	-10.3%	-2.8%	-1.0%
Hungary	11.5%	3.0%	1.6%	1.4%
Latvia	7.4%	-1.2%	-7.4%	-1.7%
Lithuania	1.6%	-8.0%	-6.6%	-5.4%
Poland	3.9%	3.0%	4.1%	-0.3%
Romania	12.8%	-2.2%	-1.1%	-2.6%
Serbia	23.9%	-2.9%	-4.9%	6.1%
Slovakia	4.6%	-5.5%	0.6%	-5.9%

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Fig. 3. Relative Market Growth – Active Sites (Longtaal analytics, 2015)

Could a gradual decline in the number of clinical trials conducted in all CEE-EU countries be attributed to the increasing pressure from East Asian and South Asian regions, especially South Korea, China and Japan? Gjon Mirdita, Regional Head CEE & MENA at QuintilesIMS, who delivered a talk at the Adam Smith Conferences' CEE Clinical Trails Forum in 2016, believes that the negative trend is a call for action that comes from the global industry expecting further improvement of the business and regulatory environment in the CEE region.

The industry participants also believe that the CEE-EU countries would benefit from keeping to the stricter deadlines for assessment of clinical trial applications, limiting the time between development of protocol and clinical trial registration, as well as from ensuring that ethics committees adhere to the set timelines. The necessity to find the most effective approach to shorten a lengthy process of negotiating contracts with hospitals, which are part of the submission package to clinical trial approval, is another business-related issue that the companies active in the region would need to resolve.

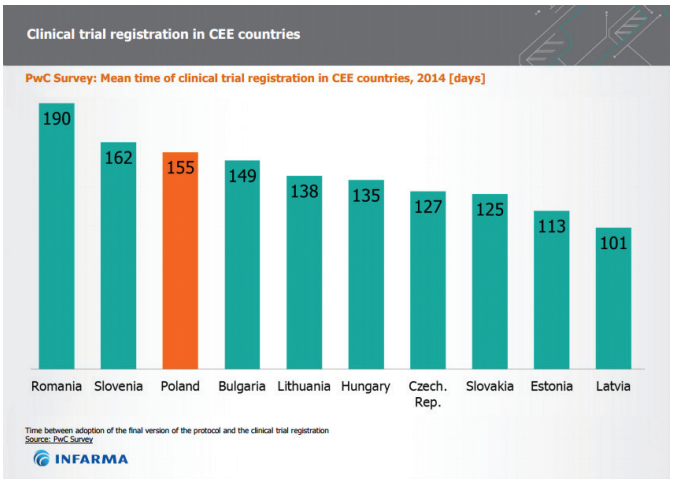

Fig. 4. PwC Survey: Clinical trial registration in CEE countries

Regulatory overview

The adoption of the Clinical Trial Regulation EU No. 536/2014, expected to come into operation in October 2018, is certainly one of the most important regulatory developments for the CEE-EU countries. This Regulation harmonises the assessment and supervision processes for clinical trials throughout the EU, via an EU portal and database. The goal of Clinical Trial Regulation EU No. 536/2014 is to create an environment that is favourable to conducting clinical trials in the EU, with the highest standards of safety for participants and increased transparency of trial information. The Regulation will require: 1) consistent rules for conducting clinical trials throughout the EU; 2) information on the authorisation, conduct and results of each clinical trial carried out in the EU to be publicly available.

General expectations are that this Regulation will simplify and accelerate the study start-up, and will be beneficial to all industry players from patients to CROs and sponsors. However, within CEE-EU countries, the sentiment is mixed and sometimes cautious. At the Clinical Trials in CEE Forum, organised by Adam Smith Conferences in April 2016, Dr Teresa Brodniewicz MSc., PhD., President GCPpl, has expressed the collective concern that the launch of 536/2014 should be accompanied by removal of the key barriers and should introduce incentives and instruments beneficial to CT stakeholders.

Three key Polish associations, including INFARMA, GCPpl and POLCRO, in 2014 commissioned PWC to prepare a summary of recommendations that concluded that the launch of 536/2014 without any adoptive actions could make Poland a less attractive country as a CT destination. For the region's key stakeholders, the implementation of the new legislation is a perfect chance to analyse and improve the functioning of clinical trials in Poland, removing the main obstacle – the submission of all signed contracts. They argue that Poland should introduce access to drugs after the clinical trial and compassionate use (the measure has already been implemented in Germany, France and Italy). Among other measures that would benefit the industry and patients, Dr Brodniewicz also highlighted the introduction of remuneration for patients and healthy volunteers (Phase I and BE) and tax exemption for compensation of expenses related to the participation in CT.

The calls for monetary incentives were also echoed by Dr Vladimir Misik, who believes that in order to ensure ongoing healthy CT-related revenue stream, governments across CEE countries will need to consider a range of monetary incentives (such as R&D tax breaks) already introduced in other countries.

Although CEE-EU countries are compliant with EMA's regulation, there is a certain discrepancy and flexibility for the states within. Among the countries with proactive government is certainly Hungary, which has already combined regulatory and ethical ("single-route") submission, which resulted in a much more predictable 55-60-day timeline and simplified approval procedures. At present, the Hungarian Ministry of Health Care (together with leading associations) are developing new operational guidance for the state hospitals. The document will contain guidance on the study site standard operating procedures (SOPs), with detailed recommendations on feasibility, contracting procedures, study conduct and internal monitoring. It will also contain examples of the detailed guidance and expectations for the contract templates, helping to establish a unified approach and standardise quality across state hospital sites. Dr Laszlo Veres, President of the Hungarian Clinical Trial Management Society, believes that such initiatives, although non-compulsory but "strongly recommended", will increase the efficiency of the clinical trials conducted in Hungary.

A number of the regional clinical experts are concerned with the lack of a unified standard among the CEE sites. Given the increasing complexity of clinical trial design and logistics, as well as growing reliance of many sponsors on remote oversights of clinical trials, this is a great issue. Sites equipped with professional clinical trial departments and/or professional study coordinators are able to operate successfully in increasingly complex environments, while the majority of sites in CEE are lacking the required professional clinical trial infrastructure. Building such a professional CT infrastructure, using a portion of CT revenues available to sites and investigators, will be key to the continuing success of sites in CEE, believes Dr Misik.

Technology is the key

The region could further improve its attractiveness by offering access to de-identified electronic medical records (EMR) data, which would allow the assessment of patient recruitment potential of medical institutions located within the region. This would enable significant shortening of the site identification process whilst increasing predictability of sites successfully reaching recruitment targets within defined timelines (a major obstacle in a majority of global clinical trials). In addition, providing access to such data can be monetised, thus providing a source of additional clinical trial revenues for governments/medical institutions located in the region.

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