

The Heart of New Europe

Adrian Iancu at Global Clinical Trials looks at the growth and benefits of clinical research in Romania

With over 470 million inhabitants, the countries of central and eastern Europe have regularly been included in multinational trials over the last decade. The resulting incentives for pharmaceutical and biotechnology companies in the area have led to a steady increase in clinical research across the region. This increase in clinical R&D has had a pronounced effect on the local healthcare system, as the most advanced therapies and medical treatments are becoming increasingly available, and this region is quickly becoming one of the foremost areas of growth for clinical trials.

POPULATION

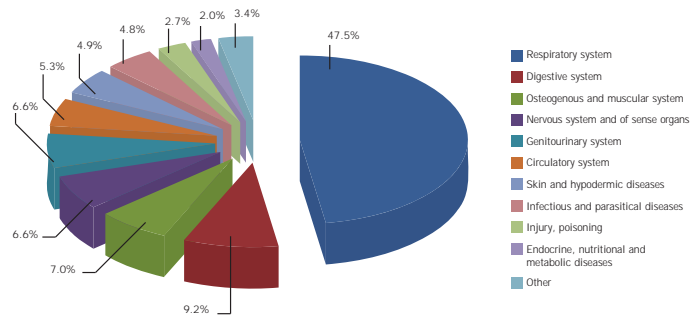
Romania is the fourth most populated eastern European country and a relatively new member of the EU. More than 55 per cent of its 21.4 million people are located in urban areas, which is a significant advantage for site placement and patient recruitment. The major concentrations are in the cities of Bucharest, Iasi, Timisoara, Constanta, Cluj-Napoca and Craiova. The key new disease cases, as reported by family doctors, belong to the respiratory, digestive, osteogenous, muscular and nervous systems, while the leading causes of death are circulatory system diseases, neoplasm, digestive system diseases and injuries, poisoning and other external causes (1).

HEALTH SYSTEM

Romania has approximately 142,034 hospital beds (6.6 beds per 1,000 people) and about 46,936 physicians (21.7 physicians for 10,000 people) (1). The system is funded by the National Healthcare Insurance Fund, to which the workforce makes mandatory contributions. Funds are also allocated from state and local budgets as well as external credits. Private health insurance is developing slowly and about 36 per cent of the population's healthcare spending is out-of-pocket because of low public funding.

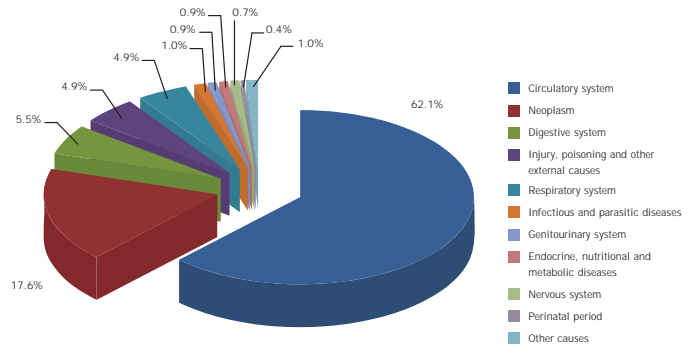
The Romanian healthcare system is generally below average by European standards. Currently, Romania sits in 32nd position in a table of 33 European countries. In 2008, Romania was in 27th position in a group of 31 countries in the European Healthcare Index. Unfortunately, the budget allocated for the Romanian Health Department for 2009 – the lowest budget since 2000 – dropped almost 20 per cent against the previous year, to the effect of 3.2 per cent of the GDP (2). Due to limited resources, access to modern medicines and diagnostic methods are not available to all patients, and some rural areas have only limited access to pre-existing resources. Patients are frequently drug naïve, and in much later stages of serious diseases than patients recruited in other western European sites. Patient recruitment is aided by the high incidence of many of the diseases commonly targeted by the pharmaceutical industry. Romanian patients tend to have exceptionally high

Figure 1: Top 10 new cases of illness, by disease classes, declared by family physicians



Source: National Institute of Statistics – Statistical Yearbook 2007

Figure 2: Top 10 causes of death



Source: National Institute of Statistics – Statistical Yearbook 2007

compliance, explained in part by the culture's trust of the family physician. Accompanied by a very high literacy rate of 98 per cent, Romanian subjects are easily accepted into clinical trials, and are sought after.

LEGISLATION AND COMPETENT AUTHORITIES

Even before its EU accession, Romania made significant efforts to align its legislative and regulatory framework to EU directives. In 1997, one year after the adoption of ICH-GCP guidance as the unified standard for the EU, US and Japan, the GCP norms became law in Romania. The full implementation of the Clinical Trials Directive (Directive 2001/20/EC) in 2004 streamlined and harmonised the procedure of conducting clinical trials and the corresponding administrative

| Population statistics (population: 21,584,365) | | | |
|--|--------------------|-------------------|---------------------------|
| Age structure | Sex ratio | Urban-rural ratio | Life expectancy at birth |
| • 0-14 years: 18% | • 0.95 male/female | • Urban – 55.2% | • Population: 72.18 years |
| • 15-64 years: 68% | | • Rural – 44.8% | • Male: 68.69 years |
| • 65 years and above: 14% | | | • Female: 75.89 years |

Source: National Institute of Statistics – Statistical Yearbook 2007

The main documents required for CTA

- Confirmation of EudraCT number
- EU Application – xml file
- Clinical Trial Protocol plus Amendments
- Medication Labels and instructions
- IB
- IMPD
- GMP certificate
- Insurance for research subjects
- Delegation of authority letter for CRO, as the CTA must be submitted only by a local representative

Documents required to be translated into Romanian

- Patient Information and Informed Consent form
- Medication Labels and instructions
- Scales and questionnaires intended for patient use
- Advertisements used for patient recruitment
- Documents used for patient recruitment

requirements. Romania promoted its ability to promise accurate and valid clinical research, which reassured sponsors and research organisations that data collected there would be acceptable by the standards of both the US FDA and the EMEA. The EU accession in 2007 has further created new opportunities for strengthening public health services and for upscaling investments in the health sector. Each of these developments has contributed to the view that Romania offers several distinct advantages to the pharmaceutical industry.

In terms of regulating authorities, the National Medicine Agency (NMA) is an organisation that is responsible for approving clinical trials for pharmaceuticals and biologics. The Ministry of Health, meanwhile, is responsible for approving clinical trials with devices. The time from submission to approval is no more than 60 days, with the potential for delay in clinical trials with advanced therapies such as: genetic therapy; somatic-cell therapy; a combination of these genetic and somatic therapies; and therapies with medicines containing genetically modified organisms (GMOs). The NMA provides centralised opinion from the National Ethics Committee (NEC) for multinational, multicentre clinical trials. The Clinical Trial Application (CTA) can be submitted in parallel to NMA and NEC approval. The application file can be submitted in the local language or English. The trial protocol is usually accepted in English – it is standard to have the CRF in English as most investigators are comfortable working in this language.

CLINICAL TRIALS IN ROMANIA

As a developing market, Romania has attracted many pharmaceutical and biotechnology companies. More than 100 pharmaceutical companies have opened offices in Romania, and, according to the market research data released by the Cegedim Research Company, the local pharmaceutical market reported a turnover of €960 million in 2004, €1.7 billion in 2007, €1.95 billion in 2008 and little over €2 billion in 2009 (3). The market average annual growth rate is 10 to 15 per cent, depending on the budget allocations. The medicines with the biggest sales in 2008

were those for the cardiovascular system, digestive system, nervous system and infectious diseases. It is estimated that the structure of drug consumption will change, with those designed to affect the nervous system becoming more prevalent as the overall pathology in Romania resembles more and more the pathology in the EU.

Multinational pharmaceutical and biotechnology companies appreciate the advantages of quicker start-up times and lower costs and have grown accustomed to including Romanian sites in their international trials. Driven by the growing interest in Romania's clinical research potential, more than 20 CROs have opened offices or are presently performing clinical trials there.

A large number of investigators have received GCP training thanks to their participation in international clinical trials, and an awareness of ICH-GCP principles is steadily increasing among the medical profession.

The trend observed over the last decade indicates that the number of CTAs received by the competent authorities has almost doubled every four years, rising from 76 applications in 2000, to 140 applications in 2004, to 266 in 2008 (4).

The two following figures illustrate the growth in the number of CTAs in Romania during the 2004 to 2008 period, both in absolute numbers and by development phase.

Figure 3: Number of CTAs Received by NMA

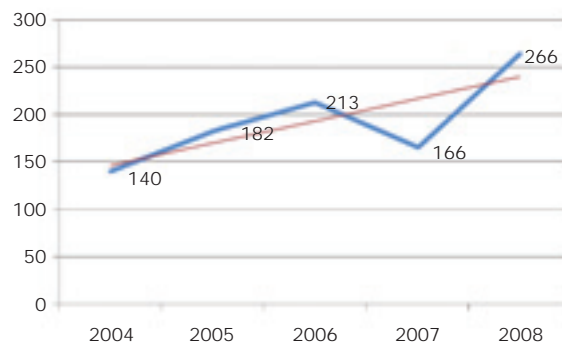
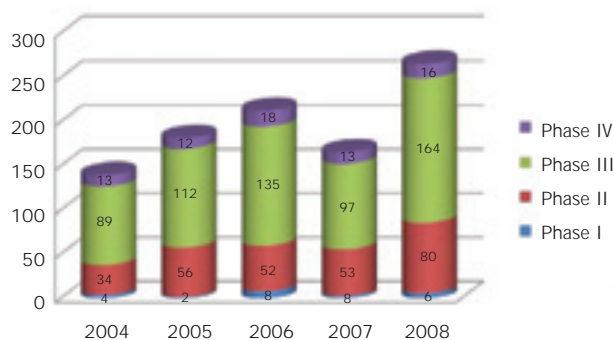


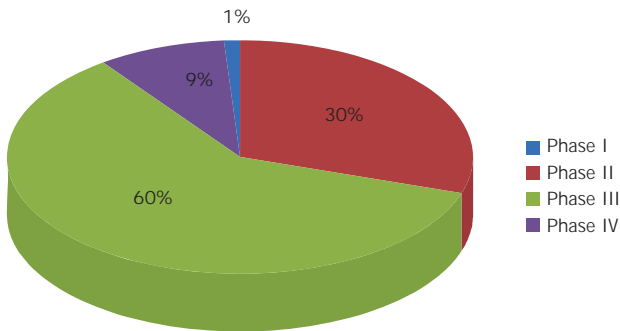
Figure 4: Clinical Trial Applications received by the National Medicine Agency from 2004 to 2008, by study phase



Source: National Medicine Agency – Informative Bulletins

When considering the breakdown of trials by clinical development phase, Phase III trials represent about 60 per cent of the applications, and Phase II trials around 30 per cent. These proportions are also valid for the approved trials, as confirmed by the US Government website, clinicaltrials.gov. According to this site, 718 clinical trials were listed for Romania in January 2010. Of those, 683 were investigational and 35 observational trials, while 206 were active (opened or enrolling).

Figure 5: Clinical trials listed for Romania on www.clinicaltrials.gov, by trial phase

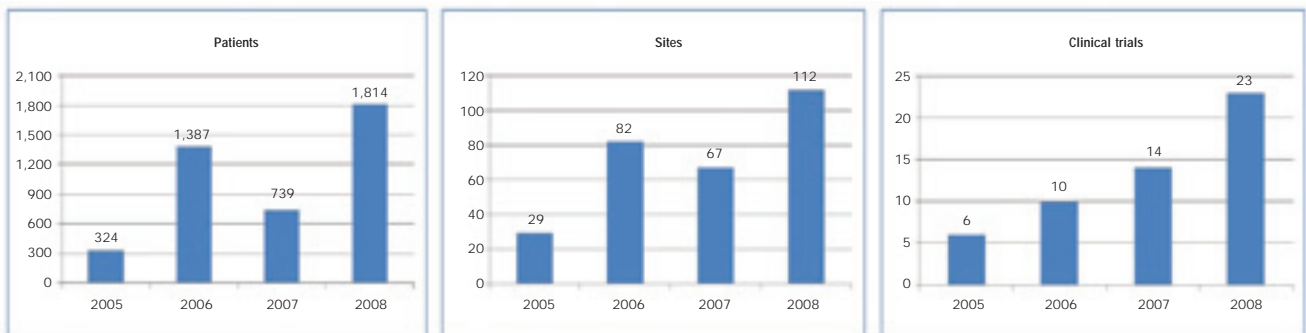


The significant and constant increase in the number of CTAs has been sustained by the reported high patient recruitment rate and excellent data quality from these trials.

Over time, the results from clinical trials performed in Romania will become part of the Marketing Authorisation Applications submitted to the EMEA. This is a confirmation not only of the quality of the data obtained, but also speaks of the excellent training and professionalism of Romanian investigators. During the period of 2005-2008, there were a total of 308 applications to the EMEA (new applications, line extensions and type two variations). Romania contributed to these applications with data from 4,266 patients recruited in 53 pivotal clinical trials (an average of 80.5 patients recruited per trial).

Within the same period, only four routine GCP inspections were performed by the EMEA, one in 2007 and three in 2008, all with excellent outcomes. No triggered inspections were performed during this period (5).

Figure 6: Distribution of the number of patients, investigator sites and pivotal clinical trials contributed by Romania and included in MAA submitted to the EMEA during 2005 to 2008 period



KEY STRENGTHS

The drivers of the Romanian clinical research market appear to be varied. In particular, Romania has:

- The fourth largest population in eastern Europe
- A decentralised healthcare system and a sound medical infrastructure
- Highly qualified and experienced investigators trained in GCP-ICH guidelines
- Logistical activities facilitated by the fact that Romania is an EU Member State
- Lower start-up, project management and monitoring costs
- A well structured and reliable regulatory process with short timelines
- Legislation aligned to international quality standards
- A high percentage of treatment-naïve subjects
- A motivated and educated subject pool
- A large, diverse, compliant and literate patient population
- High and fast recruitment rate
- A medically qualified interface between sponsors and investigators (most CRAs are medical doctors), which ensures good communication, understanding and adherence to trial protocol
- Excellent data quality

These points highlight Romania as a site of choice for clinical research, and pharmaceutical companies value these benefits, continuing to invest in the development of clinical research in Romania. Undoubtedly, providing access for its citizens to the most advanced medical treatments and clinical practices also helps. The National Institute of Pneumology, for example, signed a strategic partnership with ASCENT Clinical Research Solutions for exploratory clinical research in 2009. This collaboration facilitated the Institute's access to the newest generation of clinical pharmacology equipment used in the research of the most advanced therapies and provided specialised training programmes to the Institute's research team (6). GlaxoSmithKline, a major player in the global pharmaceutical market that owns a production capacity in Brasov County, has invested €3 million in Romanian clinical research over the last three years. As predicted by a market research publication, GSK will double its investments in clinical studies, and will be investing over €6 million in the next two to three years in medical research in Romania (7).

CONCLUSION

Romania has no shortage of patients looking for alternative forms of medication or willing to participate in clinical trials. However, Romania is still an emerging market for conducting clinical trials, compared to other CEE countries, such as the Czech Republic and Poland. With efficient patient recruitment, and with patient literacy rates comparable to the US, compliance is not a primary concern. Taking into account the aforementioned factors – excellent patient attributes, rapid study enrolment, reduced fees and hourly rates, a higher percentage of drug naïve patients, and a reliable regulatory process – Romania has transformed itself into an extremely productive clinical trial environment. The bottom line is that Romania offers sites with many years of research experience, local CROs practiced in GCP-ICH, and a history of generating quality clinical data in a scientific atmosphere conducive to successful research.

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About the author



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