Going Further East in CEE

Many countries in the former Soviet Union have untapped potential for clinical research. Anna Anokhina and Dmitry Meshkov of MB Quest Inc examine recent developments in Eastern Europe

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Driven by the search for patients for clinical trials, skilled investigators and increasing budget pressures, clinical research expanded rapidly in Central and Eastern Europe (CEE) in the mid 1990s. Pharmaceutical sponsors found these emerging markets enrolled patients quickly and were often more compliant than those in the US and Western Europe.

As the number of and interest in trials in CEE grew, sponsors began to investigate the potential for research in countries of the former Soviet Union including Russia, Ukraine, Belarus and Georgia. Initially the focus of this region was as supplemental enrolment for studies where the recruitment of patients was lower than expected. The quality of data in these studies was high and verified by corporate audits and FDA inspections (1).

While CEE still holds significant advantages for research, the region's popularity continues to grow – increasing the number of competing studies. Finding the required number of patients that fit the inclusion criteria can be challenging for many sponsors, especially for larger Phase III studies. Looking further East to countries of the former Soviet Union can give sponsors advantages in patient recruitment and retention.

This article describes the existing status of clinical studies in CEE and assesses the mechanisms and perspectives supporting further development of clinical studies by reviewing the demographics, availability of experienced investigators capable of conducting industry-sponsored clinical research, the history of trials, and regulatory procedures.

Comparative data on patient populations indicates that the largest countries involved in clinical research in the territory of former Soviet Union (that is, Russia, Ukraine, Kazakhstan, Belarus and Georgia) have a combined population of more than 220 million people – more than Western Europe and comparable with the US (see Table 1). The area spreads across 11 time zones from the Pacific Ocean in the East to the Baltic Sea in the West. The vast territory does not significantly affect the population's access to clinical sites because the majority of people live in highly concentrated urban areas.

Initially, clinical research in Russia was based in Moscow – the most highly populated city in Europe, with a metro area population of 13.4 million. Moscow's population density is also the highest in Russia, estimated at 6,232 people per km^2 (compared to that of New York, at 1,081 people per km^2) (2). It is supported by a large public transportation system that includes: five airports, nine rail terminals and the world's busiest metro subway system (3). Together with Russia's second largest city, St Petersburg (5.3 million), the patient pool nears almost 20 million people in only two cities.

Table 1: Comparative data on population in selected countries participating in clinical trials

Country	Population (million)	Cities with over one million people
US	301	25
Russia	**143**	**13**
Germany	83	3
UK	60	2
Ukraine	**46**	**5**
Poland	38	1
Kazakhstan	**15**	**1**
Czech Republic	10	1
Belarus	**10**	**1**
Georgia	**4.6**	**1**

Novosibirsk, located in southern central Russia, is the country's third-largest city and has the largest railway station along the trans-Siberian route. Other cities connected by rail within 300km of Novosibirsk include Omsk, Tomsk, Kemerovo and Novokuznetsk, contributing to a combined patient pool of nearly 10 million inhabitants living a short distance from centralised hospitals and outpatient clinics offering research opportunities across several therapeutic areas.

Russia's centralised healthcare system contains a large database of patients with diagnosed conditions, and newly-diagnosed patients are updated on a regular basis. Russia has 700 large, state-approved clinical trial sites and hospitalisation costs are generally provided by the state or personal insurance and are not added to trial expenses. All of these factors allow target recruitment goals to be reached faster and with fewer sites – creating additional cost savings for sponsors.

Other nations in the former Soviet Union also have concentrated populations, centralised healthcare systems and large therapeutic hospitals, but on a smaller scale than in Russia. In Belarus, for example, most clinical centres are located in the capital of Minsk with 1.8 million people in its urban centre. Studies are also conducted in Gomel, Vitebsk, Mogilev, Brest and Grodno, where more than 2 million citizens are concentrated. In the Ukraine, clinical research is more evenly distributed across the country. Traditionally, most clinical centres are located in Kiev (with a population of 2.6 million) and Kharkov (1.5 million).

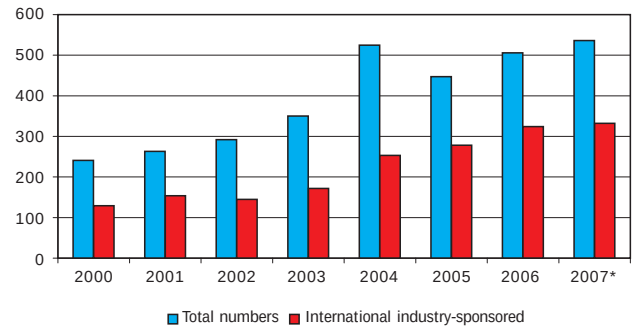
Georgia is a relatively small country compared to Russia, with 4.6 million people. Nevertheless, it is very attractive for clinical research due to high standards of medical care and the government's policy of prompt regulatory and ethical reviews, allowing clinical studies to start within restricted timeframes. Centralised clinical centres, capable of working with most therapeutic areas, are located in Tbilisi (1.1 million), the nation's capital, which contains about 20 per cent of Georgia's total population. These centres refer patients from most of the country, but additional sites are available in other cities.

Kazakhstan is a relatively new participant in the arena of clinical trials; however, continued growth is expected because the area offers opportunities for multi-ethnic studies – over half the population is composed of a variety of Asian ethic groups. The most attractive cities for clinical research are Almaty, with nearly 2 million citizens, and Astana, Chimkent, Pavlodar, Ust-Kamenogorsk and Taraz, each with more than 300,000 inhabitants.

GROWTH OF STUDY ACTIVITY

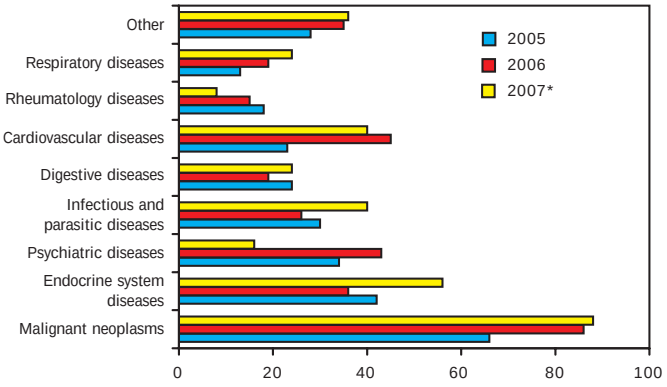
Russian regulations provide regular web-based reports containing data about approved clinical studies (4). The number of industry-sponsored clinical trials in Russia has doubled since

Figure 1: Number of trials approved by Russian regulatory authorities



** Based on estimates of studies approved in Q1 2007*

Figure 2: Therapeutic areas for international trials in Russia in 2005-2007



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2000 (see Figure 1). This growth has been relatively steady, without significant fluctuation. It slowed somewhat in 2002-2003 because of extended approval timelines which reached five to seven months. The extension was caused by a sequential review process, with an increased number of applications by specialised committees and the Central Ethics Committee before the Ministry of Health could provide final approval. The procedures soon improved after the review process became parallel, allowing the average timelines not to exceed four to six weeks, which led to rapid growth in 2004.

Russia's neighbours are also actively involved in research. Based on estimates from their respective local regulatory authorities, there were 158 international studies and 150 locally-sponsored studies in the Ukraine alone in 2006. In Belarus, industry-sponsored trials started in 2004 and by April 2007 a total of 16 studies were successfully completed. Since April 2007, regulatory authorities in Georgia have approved 28 international clinical studies. In Kazakhstan, only a few studies are underway; however, the number is expected to increase in the near future because of rapid economic development due to foreign investment.

TYPES OF STUDIES CONDUCTED

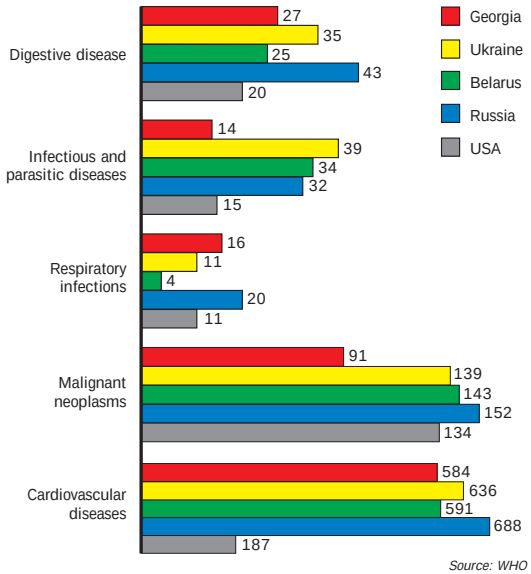
Comparison data of therapeutic research areas are available for Russia (see Figure 2), but the percentage of studies by area are comparable for Belarus, Georgia and Ukraine because their medical care systems, infrastructure and healthcare problems are alike. The data for Russia reveals a recent increase in oncology trials based on recent development of new chemotherapy agents and the spread of malignant neoplasms among the population (see Figure 3). Other major areas of research have a significant number of active studies as a result of new drug development, including: cardiology, endocrinology, gastroenterology and rheumatology.

In 2006, there was a significant increase in studies in Russia and the Ukraine focused on drugs using monoclonal antibodies for the treatment of different diseases. Accurate elimination of inflammation mediators or blocking of cell receptors is widely studied for treatment in oncology, gastroenterology (Crohn's disease and non-specific ulcerative colitis), rheumatology (rheumatoid arthritis and systemic lupus eruthematosys) and endocrinology (type 2 diabetes).

While the World Health Organization (WHO) mortality figures do not correlate directly with actual incidence because of healthcare affordability, they do show that the region has significant healthcare problems across a variety of therapeutic areas. Many patients in these areas cannot afford high quality healthcare, and might benefit from the free treatment that clinical trials provide.

All phases of industry-sponsored clinical studies can be successfully conducted in Eastern Europe. In Russia, the respective proportion of Phase I-IV studies has been stable between 2005 and 2007. Most of the studies in this period were Phase III (55-61 per cent), Phase II studies contained 29-36 per cent and Phase I and Phase IV were 4-5 per cent each. Pharmaceutical companies have recently expressed increased interest in Phase I studies in Russia. Initially, Phase I studies were mostly performed at internationally recognised, specialised medical institutions, such as the Russian Research

Figure 3: Age-standardised death rate per 100,000



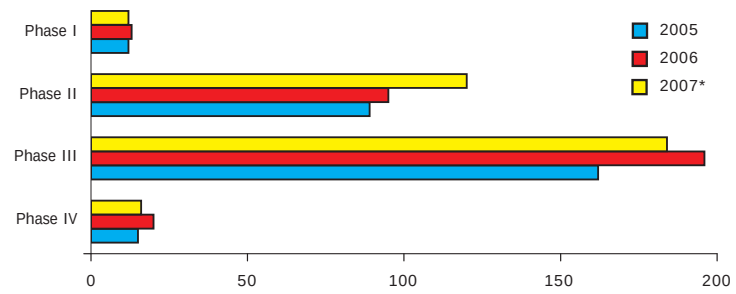
Source: WHO 2002

The process of regulatory and ethical reviews is crucial in order to assure patient safety and data quality. In Russia, regulatory and ethics approval now averages 15 weeks in duration, and includes toxicology, pharmacology, ethical, legal, administrative and other expertise reviews as standard. The process is the same in the Ukraine, and the requirements regarding clinical studies are included in state law (6,7).

Oncology Center and Endocrinology Research Center in Moscow. Recently, however, several GCP-compliant Phase I units were established in Moscow, many of which have facilities for overnight stays. In Georgia, three of the last 28 studies (11 per cent) were Phase I, some of which were initiated because of sponsor's previous positive experience with patient recruitment and quality data from later phase studies.

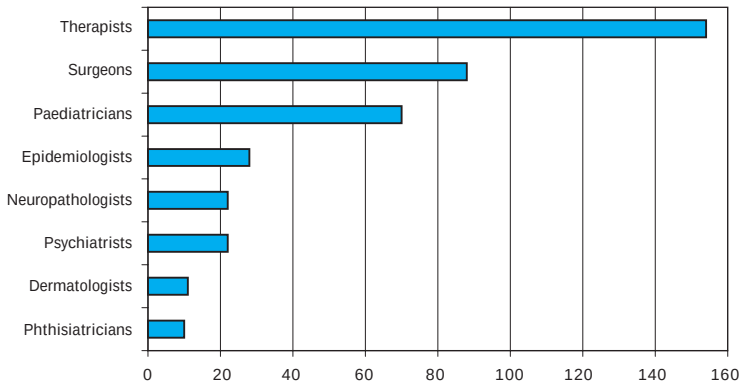
This growth, both in the number of studies and quality of data, was achieved due to the high numbers of qualified medical specialists and staff. Figure 5 represents the number of qualified specialists in Russia. In total, Russia has 679,800 doctors in 11,100 hospitals and 21,100 out-patient clinics. In Ukraine there are 223,000 medical specialists including 143, 202 physicians and 369,755 nurses. Belarus has 1,918 hospitals with 45,000 physicians and medical specialists and 115,000 nurses. Georgia has about 20,000 physicians and 17,000 nurses. Kazakhstan has 1,200 hospitals, 54,800 physicians, and 117,000 nurses (5).

Figure 4: Number of phases of trials in Russia in 2005-2007



** Based on estimates of studies approved in Q1 2007*

Figure 5: Number of qualified specialists in Russia (thousands)



REGULATORY AND ETHICS

Previously, reviews for Russia were conducted sequentially, which caused significant delays in the process. Through the cooperation of the Association of Independent Pharmaceutical Manufactures (AIPM), CRO representatives, investigators, social organisations and Russian regulatory authorities, the procedures allowed a parallel process to be established that maintained a high quality review, while limiting its duration. The final version of the Federal Drug Law of 22nd June 1998, along with several amendments, including those of 22nd August and 29th December 2004, finalised certain state requirements regarding international clinical studies in Russia. This law also validated the translation of ICH GCP of 1996 as a mandatory regulatory document for implementation in all clinical trials in the territory of the Russian Federation, which extends to Belarus, Georgia, Kazakhstan and the Ukraine.

The process of regulatory and ethical reviews is crucial in order to assure patient safety and data quality. In Russia, regulatory and ethics approval now averages 15 weeks in duration, and includes toxicology, pharmacology, ethical, legal, administrative and other expertise reviews as standard. The process is the same in the Ukraine, and the requirements regarding clinical studies are included in state law (6,7). A similar approach is used in the laws of Kazakhstan (8) and Georgia, yet Georgia's review process differs greatly from the other former Soviet countries in that it takes only five to six weeks, making it very attractive for rescue studies. In Belarus, regulatory study approval averages 18 weeks, yet there is a pending revision of clinical trial regulations. The revision's purpose is to establish more convenient procedures for review and control of multi-centre international clinical studies (9).

Significant delays can occur with ethical reviews during the summer months in Russia and the Ukraine because most members of their Central Ethics Committees take extended vacations. These vacations – spanning July and August – need not cause disruption with proper planning. Georgia's warmer weather means that the effect of summer vacations is negligible.

A very important consideration for sponsors interested in conducting trials in this region is the selection of investigational sites. In each country the site must have a license or alternative document which authorises study participation. To obtain this license, or to be included in the list of approved sites by regulatory authorities, the site must prove its compliance to GCP standards and the availability of relevant resources. By working with an experienced local partner, sponsors will be able to verify this site requirement. In addition, during recent years the regulatory authorities of the afore-mentioned countries established procedures of inspections similar to the FDA and EMEA. For example, in Russia in 2005, representatives of Russian regulatory performed 27 inspections at sites participating in clinical studies.

CONCLUSION

This assessment indicates that these CEE countries have proven research and patient recruitment potential, whether they are considered as developed (Russia and Ukraine) or developing (Georgia, Belarus and Kazakhstan). Their history of successful trials provides evidence of steady growth and support from their government's health authorities. Each has appropriate population sizes, suitable infrastructures and transport systems, centralised medical care for referring patients to specific centres and experienced specialists working to international standards. All of these factors, combined with their untapped potential for additional studies, make the Eastern European former-Soviet region an increasingly attractive one in which to conduct research. ◆

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References

1. **Borfitz D, Expanding Opportunities in Central and Eastern Europe, *CenterWatch Monthly*, Vol 11, 4, p5, April 2004**
2. **United Nations World Urbanization Prospects: 2005 Revision**
3. **http://mosmetro.ru/pages**
4. **http://www.roszdravnadzor.ru**
5. **http://www.astanazdorovie.iteca.kz/ru/2007/kazakhstan**
6. **http://www.moz.gov.ua**
7. **http://www.who.int/patientsafety/events/05/apsd/04_Ukrainarus.pdf**
8. **http://www.dari.kz**
9. **http://www.government.by**