

FOCUS ON EUROPE

CLINICAL TRIALS LOCATIONS

Discover Russia

for Conducting Clinical Research

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Russia boasts a modern medical system, GCP-compliant investigators, and an abundance of compliant subjects.

Considerable time has passed since the first GCP-style multinational clinical trial was successfully conducted in the former Soviet Union in 1989. To understand where Russia is now, it seems reasonable to stop running, glance back retrospectively to see the traversed road, and reflect. What was in place 12 years ago? What kind of clinical trials environment lay beyond the Iron Curtain?

Certainly, no good clinical practice (GCP) rules were accepted by regulators, or by the medical research community. The Clinical Pharmacological Research Institute (CPR) first translated good clinical practice guidance in 1989, because it was a part of a study protocol. Several years later, CPR and PSI Pharma Support Inc. jointly translated the official text of the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice. It was published in 1999.¹ In the same year, the Russian-language version of GCP became a part of national regulations under the name of OST-42-511-99.²

It took that long because regulators did not want to accept the international rules. They wanted instead to create their own national GCP guideline in support of Russian drug companies, which had no resources to conduct well-designed clinical studies. Finally, a new generation of Russian officials agreed that it is not wise to have a double standard—one for big, rich, Western pharmaceutical companies, and one for poor domestic drug manufacturers—and the battle was over.

Besides the lack of GCP standards, clinical trials were not gov-

erned by any regulations at all. Anyone could do anything. Of course, there was the Constitution of the USSR, which protected patients' rights, but that was it. Not a word about informed consent, no ethics committees, nothing. The time needed to obtain study approvals from the State Pharmacological Committee was unpredictable and took up to two months—depending on nobody knows what. No customs regulations were in place—any drug could be imported. It was up to each customs house officer to decide what could cross the border.

The situation was even worse in the field of communications. Faxes and copy machines were prohibited by law. There were no automatic phone connections. To make an international phone call one had to call the operator well in advance (from two hours to two days) and schedule time for a communication session. No private foreign economic activity, no hard currency transfers from abroad, no money exchange points existed. Foreign pharmaceutical companies had no offices in Russia. Contract research organizations did not even consider setting foot in the country.

That was the very beginning. Then came years of hard work, political turmoil, financial instability—years of change. Where are we now? What is the clinical trials situation in modern Russia?

Currently, more than a hundred foreign pharmaceutical companies are accredited in Russia, most located in Moscow. The largest ones have several hundred employees and modern offices in prestigious locations; some of them even have manufacturing facilities. Most are generic drug

companies. Only about two dozen are large, international, innovative drug companies that not only sell medicines, but also conduct clinical trials. In addition, about a dozen foreign pharmaceutical and biotech companies, who have no representatives in Russia, nevertheless conduct clinical studies there.

Regulators

The structure and function of Russian regulatory authorities with reference to clinical trials is quite transparent. The primary body is the Russian Federation Ministry of Health Department for Control of Quality, Effectiveness, and Safety of Medicinal Products and Medical Devices—Federal Drug Agency for short. The agency has within its structure the State Pharmacological Committee (SPC), which is responsible for the pharmacological (scientific) expertise of the study, and the National Ethics Committee (NEC), responsible for ethical expertise.

The NEC is constituted in strict accordance with the ICH guideline. The submission file must include the protocol in both the original and Russian language, the investigator's brochure, the case report form, the insurance policy, and so on. The insurance policy should be issued by a local insurance company; a global policy does not work in Russia. This local insurance is medical insurance for subjects enrolled in the clinical trial. Its cost depends on the phase of the study—the earlier the phase, the higher the cost. Cost also varies from company to company.

The sponsor submits the study file to the Federal Drug Agency, which simultaneously sends two copies to

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Implications of Russian Drug Law

Below are practical implications of the Federal Drug Law important to those conducting clinical trials.

- Only one government body now approves clinical trials—the Federal Drug Agency of the Ministry of Health.
- The agency requires that experts of the National Ethics Committee grant approval.
- Insurance requirement is for health insurance for subjects, acquired locally—not liability insurance for sponsor.
- Nonregistered drugs for clinical trials may be imported to Russia, but each shipment needs a separate import license, issued by the Ministry of Health.
- Only drugs manufactured in Russia can be exported (consider the unused clinical trial materials).
- Drugs for clinical trials must be clearly marked—for example, labeled “For clinical trial.”
- No subject may be involved in a study without written informed consent.
- Clinical studies may not be conducted on orphan minors, pregnant women, military personnel, or prison inmates.
- Any adverse event (AE) must be reported to the authorities. When, how, and by whom the AE should be reported is not transparently specified in the law. It is also not quite clear who should be notified.
- Only medical institutions licensed and approved by the Federal Drug Agency may participate in clinical trials.

Essential Documents

In addition to the Federal Drug Law, the following documents regulate clinical trials.

- Ministry of Health Order No103 from 24 March 2000, which regulates the study approval process.⁴
- Ministry of Health Order No16 from 24 January 2000, which constitutes the license commission.⁵
- Regulations on the National Ethics Committee.⁶
- State standard OST-42-511-99 (national GCP rules, which are at most a translation of ICH GCP).
- Letter of the Federal Drug Agency No291-22/91 of 26 July 20017 on adverse drug reactions notification.

both the SPC and NEC for approval. Once approved by those bodies, the files go back to the agency to be signed by its chairman. Altogether, the approval procedure takes about two months. The bureaucrats of the new wave are quite reasonable and educated people, communicating actively with regulators in America, Europe, and Asia. They talk extensively with clinical trials professionals in Russia and abroad, participate in international meetings, and do a great deal to make the image of Russia more attractive in the eyes of possible clinical trial sponsors. And during the last two years they have had great success.

The Federal Drug Law

The Federal Drug Law (N° 86-FZ)³ was signed by the president of the Russian Federation on 22 June 1998. When published, the law caused a series of discussions in the press and among professionals. Despite all its pros and cons, the law established a legal basis for drug development and clinical trials; in general it was a step forward. The law

- defines the authority of the Federal Drug Agency in drug development (Part III, Articles 10–12).
- introduces the notion of ethical expertise and ethics committees (Part III, Article 8).
- describes conditions for the manu-

facturing (Part IV, Article 13), labeling (Part IV, Article 16), and registration of medicinal products (Part V).

- regulates importation and exportation of drugs to and from the Russian Federation, including clinical trials supplies (Part VI, Articles 20-6 and 21-3). According to the Drug Law, the Federal Agency issues an import license for each specific shipment of the study drug. Export of any drug, including those for clinical trials, is permitted only for drug manufacturers. Part IX is specifically dedicated to drug development—preclinical and clinical studies. This part describes the
 - clinical trial approval (Article 37).
 - content of the clinical study agreement and financial issues (Article 38).
 - obligations of the investigator and investigational site (Article 39).
 - subjects’ rights—voluntary participation in a clinical study and content of the written informed consent—and lists the categories of subjects who are vulnerable (Article 40).
 - obligations for reporting adverse events (Article 41).

Practical implications of the Federal Drug Law are outlined in the accompanying Implications box.

The Essential Documents box lists documents important to Russia’s regulatory process. We may argue how much these documents comply with international regulations, with common sense, or with the wishes of the drug companies, investigators and patients, but the researchers must work according to these regulations and respect them.

Conducting trials in Russia

Recruitment. There are several reasons to conduct trials in Russia. One is that subject recruitment rates in Russia are high—much higher than in the United States and Western Europe. For some diseases and therapies, it is almost impossible to enroll enough subjects in the developed countries. Enrollment for drug treatment of stable angina, for example, is difficult when most patients in the West

undergo revascularization as soon as the diagnosis is established.

Russia also has a huge number of treatment-naïve patients, mainly in oncology, HIV, and hepatitis. Marketing is also an issue. Clinical trials provide pharmaceutical companies with access to regulators, opinion leaders, and practicing physicians.

Cost of conducting studies. Cost considerations also claim attention. It is often implied that the cost of clinical studies in Russia is much lower than in the United States or Western Europe. In fact, however, they are not a great deal lower. The sponsor may save about 20% on investigator's fees, but the local insurance requirement, the higher cost of courier services, telephone, and Internet communications, and the imposition of customs duties—including a 20% value-added tax (VAT) will even out the differences. If you add the cost of installing additional equipment at study sites (which may be required to perform some tests) and the cost of concomitant treatment that should be provided to the subjects, the overall study cost may be even higher than in more developed countries.

Then why go to Russia? The best answer lies with the overall time of the study completion. In most cases, time costs more than money.

Two other issues that arise, however, are ethics and data quality. Both issues were quite negatively addressed in well-known articles in the *Washington Post*^{8,9} which alleged human rights violations, fraud, negligence, and other problems in Eastern Europe. A Letter to the Editor published in *Applied Clinical Trials* disputed that article, stating that *Washington Post* reporters exaggerated the situation.¹⁰ To our knowledge, sponsors have conducted hundreds of audits that revealed neither substantial deviations from study protocols, nor violation of GCP. Ethics committees in Russia are constituted in strict accordance with the ICH guideline, and some of them were also positively audited. Data quality can be judged to be good. Cases of fraud are, in general, much less frequent than in the United States.

During the past two years, the pharmaceutical companies most active in conducting clinical trials in Russia have been ASTA Medica AG; AstraZeneca; Bristol-Myers Squibb; Eli Lilly; Janssen; Merck, Sharp & Dohme; Pharmacia; Servier; and Yamanouchi. Each of these world-renowned firms conducts up to eight trials at a time in Russia. It is hard to imagine that any of them would continue to recruit subjects for multiple studies if the data they obtained was not good enough to satisfy European or American regulatory authorities. A complete list of the 50 pharmaceutical companies currently conducting clinical studies in Russia is too long to be present here, but some recent entries to the Russian clinical trials arena are Abbot, Pfizer, and Procter & Gamble.

CROs

When clinical trials came to Russia 12 years ago, foreign pharmaceutical companies had no representatives in this country. Thus, they started to work through local groups of researchers. The first group was based in the Research Institute of Cardiology in St. Petersburg, and later became the CPR Institute. During the next couple of years, the first CROs were established in Russia: Clinical Pharmacological Research (CPR) Institute and PSI Pharma Support Inc. in St. Petersburg, and Innopharm in Smolensk. The role of these three oldest CROs cannot be overestimated. They translated GCP guidelines and introduced them to

the regulators, medical professionals, and community; implemented the most reliable communication technologies; established data management systems; and implemented modern methods of statistical analysis. They created comprehensive standard operating procedures (SOPs) and invented effective project management technology. And they have been quite successful in conducting clinical trials in Russia.

Of course, there were European professionals who stood behind these inventions and achievements—people who believed in Russia, trusted Russian physicians, and spent a lot of time and enthusiasm teaching the Russians how to do things, and do them properly. In those early years, there was no competition—each CRO worked in its own niche. The second half of the 1990s was marked with rapid development of local CROs as well as the invasion of international ones. Currently, about 10 international and domestic CROs are conducting clinical trials in Russia, including those first three CROs, which successfully continue to do business in Russia.

The main difference between Russian CROs (including the Russian offices of international CROs) and CROs in other countries is that in Russia all clinical research associates (CRAs) are medical doctors. The CRO may pay much higher wages than government-owned medical institutions, and can then select the best, most highly experienced profes-

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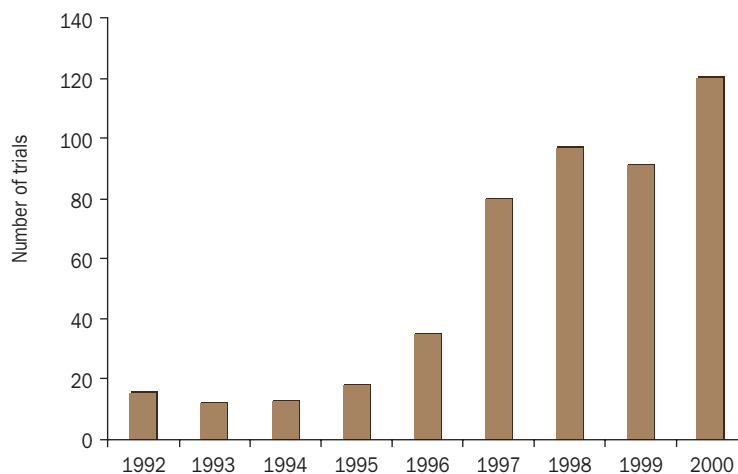


Figure 1. International clinical trials approved in Russia since 1992.

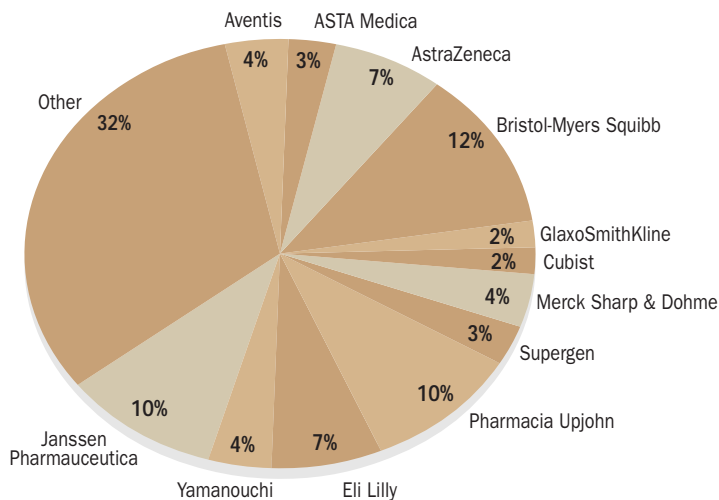


Figure 2. Sponsors of clinical trials in Russia during 2000–2001.

Russian CRAs are trained in GCP, and many are also members of international professional organizations such as DIA and ACRP.

sionals. Many CRAs speak fluent English, which helps a great deal in communication between investigators and sponsors, in monitoring, in reporting, and so on. Russian CRAs are trained in GCP, and many are also members of international professional organizations such as DIA and ACRP. Russian CROs provide the full spectrum of services, including regulatory submissions, medical monitoring, project management, handling clinical trial supplies, data management, statistics, reporting, medical writing, and so forth.

Investigators and sites

Investigators. Russian investigators are, of course, medical doctors, but their medical education differs from that in the United States. A high school student who wishes to be a doctor must pass a series of difficult exams. The student then spends six years at medical school, learning basic biosciences during the first three years, and medicine (internal medicine, surgery, and obstetrics-gynecology) for three more years. After receiving a diploma, the student spends two or three years in practice (residency) in a specific field, and finally is issued a license. This license should be renewed every five years. Russian doctors are highly qualified—many speak English fluently, attend international conferences, and are members of European and American professional societies.

When selecting an investigator,

sponsors generally have two choices: a well-known physician, a policy maker who is often a full professor, a head of the chair, or director of a hospital; or a less prominent but more enthusiastic person, usually a department head or an assistant professor. Very rarely a prominent person who also exhibits great enthusiasm.

The first approach is commonly more expensive, because the policy maker expects higher fees. Furthermore, policy makers probably will not do the work themselves, but will hire a couple of co-investigators, who also require salaries. Another problem with policy makers is that they conduct multiple clinical trials simultaneously—sometimes competitive ones—so they have less time to devote to each study, and lower motivation. These people are employed mostly when the sponsor’s priority is marketing goals. If the main goals are high recruitment rate and logistical simplicity, the sponsor might prefer a less prominent but more effective person, who will select subjects personally, complete forms on time, attend all meetings, promptly answer phone calls, and work closely with the study monitor. Each particular project requires a trade-off between the advantages of the two approaches to decide which one to implement. Our experience says that a good mixture of both approaches is the most effective way to conduct a study in Russia.

Institutions. The medical system of

the country is quite centralized—a heritage of the Soviet past. Each area of medicine has a “chief specialist”—a “lord high fixer.” This is also true for geographical areas: chief cardiologist of Moscow, chief oncologist of Northwest Russia, and so on, and this system is still very much Moscow-centric. To make it simple, two categories of medical institutions are of interest.

- Huge specialized institutions in each field of medicine. Normally, each will also be a teaching and research hospital, with outpatient facilities (for example, Institute of Oncology, Center for Cardiology).
- Huge multipurpose regional hospitals—each also with an outpatient facility—which cover almost all medical specialties in a certain geographical area. Usually, it will have the name of a saint or a number, for example, Saint-Elizabeth Hospital, Hospital #32.

Both types of institutions generally have between 500 and 1500 beds, and process tens of thousands of inpatients and hundreds of thousands of outpatients annually. The hospitals are well equipped, have more-or-less modern diagnostic and treatment capabilities, and are staffed with highly trained personnel. The major differences from the Western model are that

- nurses are much less involved in the process of medical care, and are hardly ever involved in clinical trials—they may do the study procedures, such as injections or blood draw, but they neither deal with subject consent nor complete the study forms.
- in most cases, the study drug is kept at the investigator’s office—not in the hospital’s pharmacy—and pharmacists are usually not involved in the clinical trial at all.
- the hospital administration should not only be notified about the clinical trial, but also be a contractual party in the study agreement.

In general, the Russian medical system perfectly suits the needs of clinical trials, providing the sponsor with huge centralized medical facilities, heavy patient traffic, and highly motivated investigators.

Unlike Americans, Russian patients usually spend their whole lives in the place they were born—which is good for research and follow-up purposes.

Subjects

What surprises everyone who starts a clinical trial in Russia is the unbelievably high subject compliance. Russian subjects don't miss appointments, they take all the required pills, they fill in the questionnaires and diaries, and only very rarely do they withdraw their consent. The dropout rate is low, and subjects lost-to-follow-up barely exist. Russian subjects do what their doctors tell them to do. What a phenomenon!

Two possible explanations are generally offered. One is that Russian patients still consider the doctor a boss—probably a remnant of the Soviet—or even pre-Soviet—past, when doctors were the richest and most educated part of the population, and most patients were poor and illiterate. Russian patients may also be motivated to participate clinical trials because trials give them access to the best medical facilities, best diagnostic methods, best physicians, and potentially the best medications (if it is not a placebo)—free. The only cost is to be compliant, which they consider not too much to ask.

Also surprising is the low rate of adverse events. Perhaps Russians, who spent most of their lives in less-than-ideal conditions, just pay little attention themselves, and do not want to bother their doctors with a complaint like a running nose, a headache, or a dry mouth.

Unlike Americans, Russian patients hardly ever move from place to place. They usually spend their whole lives in the place they were born. That is good for research and follow-up purposes. On the other hand, what is bad for research purposes is that many patients in Russia have no primary physician. They have the right to visit any specialist with no referral, so they simply do not need a gatekeeper.

Communication among different health care providers is not as good as we would like. This may lead to a situation in which the only source of information about a subject is not a medical source. For instance, if someone is hospitalized during the follow-up period in a hospital not participat-

ing in the clinical trial, the investigator may not learn about it unless informed directly by the subject or a subject's family member.

Two more cultural differences should be kept in mind: Russian patients, much more often than their American counterparts, use alternative medicine, particularly physical therapy, herbs, acupuncture, and massage; and Russian doctors use autopsy several times more frequently than in the West.

A new era

Thus, by the beginning of the 21st century, the clinical research environment in Russia is formed. Several facts have emerged.

- Russia has regulatory authorities and national regulations that are compliant with the international GCP guideline.
- Many pharmaceutical companies have their offices in Russia and currently conduct clinical trials in this country.
- Local and international contract research organizations are actively operating in Russia, monitoring dozens of clinical studies.
- Investigators at hundreds of Russian sites recruit thousands of subjects and provide s with data of highest possible quality.
- Clinical trials in Russia are CGP-compliant, and performed in strict accordance with international scientific and ethical standards.
- Russian investigators are highly motivated.
- Russian subjects are extremely compliant.
- Patients with rare diseases and treatment-naïve patients are available.

These factors make Russia a very promising location for future clinical studies.

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