ThermoFisher SCIENTIFIC

UKRAINE & RUSSIA:

OPPORTUNITIES & CHALLENGES FOR CLINICAL RESEARCH

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Abstract

Ukraine and Russia share a great deal more than a common border, including a host of characteristics that have made these neighboring countries among the world's most desirable locations for clinical trials. Despite political tensions in the region, the opportunities for conducting trials in Ukraine and Russia far outweigh the challenges, and interest in bringing studies to these sprawling countries remains high.

This E-book examines why Ukraine and Russia are among top choices for clinical development, discusses the opportunities and challenges they pose, and provides recommendations for overcoming hurdles to deliver successful trials.

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Introduction

Ukraine and Russia share a great deal more than a common border, including a host of characteristics that have made these neighboring countries among the world's most desirable locations for clinical trials.

In 2019 there were 1,200 active or recruiting trials in Russia and 503 in Ukraine, according to clinical trials.gov[1], the registry of clinical trials. Meanwhile, CenterWatch indicated that hundreds of new trials were recruiting in both countries.[2]

There are many reasons why these two nations are so popular among biopharmaceutical companies developing new products. Both boast years of clinical trial experience, centralized medical infrastructures and large populations, including deep pools of modern, treatment-naive patients eager to participate in clinical research in a wide range of therapeutic areas. This translates to rapid patient recruitment and enrollment, coupled with excellent compliance and retention. Today, Russia and the Ukraine rank # 2 and #8, respectively, in total enrolled clinical trial participants.[3]

Well-trained medical and site personnel uphold international research practices and standards, enabling them to generate high-quality clinical data at costs significantly lower than those of Western Europe and the United States. For Ukraine, the procedure for obtaining permits authorizing import of clinical study materials was significantly simplified and the tax rates applicable to the import of medicines and medical devices intended for clinical studies were significantly reduced in 2015.[4]

It goes without saying that there are challenges to conducting clinical trials in Russia and Ukraine, the most obvious of which is ongoing political unrest. Other hurdles include the sprawling countries' respective sizes, some infrastructure issues and extreme weather. None of these issues is insurmountable given careful planning, the support of experienced partners and a commitment to knowing and fully complying with regulatory requirements. Use of a depot or other local facility providing feet on the ground can help alleviate these concerns.

All things considered, sponsors long ago concluded that the benefits of conducting trials in Russia and Ukraine far outweigh the challenges. In fact, 70% of new drugs registered in Europe in 2015 were tested in phase II-III clinical trials in Russia.5

This E-book examines why Ukraine and Russia are among top choices for clinical development, discusses the opportunities and challenges they pose and provides recommendations for overcoming hurdles to deliver successful trials.

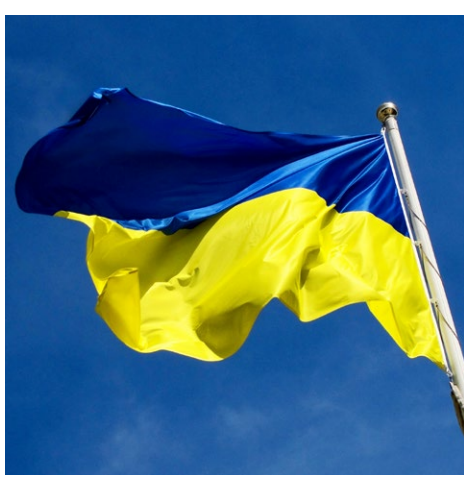
Ukraine: A clinical research veteran

From the standpoint of international clinical trials, Ukraine is a seasoned veteran. This Eastern European nation has more than 20 years of experience overseeing and conducting trials, a decade more than neighboring Russia.

Astute sponsors who turned to globalization about two decades ago discovered that Ukraine was especially well-suited for clinical trials. Aside from a large population and well-developed infrastructure, the country has harmonized its clinical trials legislation with respective European Union (EU) Directives and Guidelines. In addition, Ukraine has a cadre of educated, qualified and motivated investigators, as well as the infrastructure, systems and capabilities necessary to produce high-quality study data.

A well-defined contracting process and low cost structure for trials are other reasons for Ukraine's popularity among sponsors. Grants to principal investigators are on par with Belarus, Georgia and Russia.

Oncology is the country's top therapeutic area, followed by Cardiology/ Vascular Diseases, Psychiatry/Psychology, Respiratory diseases, Immunology and Rheumatology.



Snapshot: Ukraine's profile/infrastructure

Ukraine, the second largest country in Europe by size, is slightly smaller than the U.S. state of Texas and its population of 44.8 million is roughly equal to that of Argentina.

The capital city of Kiev is home to 2.8 million people. Nearly 70 percent of Ukrainians live in urban centers, among them Kharkiv, Dnipropetrovsk, Odessa and Donetsk, all of which have 1 to 1.5 million residents.

Good quality highways connect Ukrainian cities, making road freight the best means of delivering drug supplies to clinical sites. The use of a depot or local facility ensures that supplies can reach all Ukrainian cities in as little as one to two working days.

This rapid turnaround offers notable advantages for clinical trials, including quick resupply of drugs to sites, as well as reduced risk of temperature excursion thanks to short transit times.

Russia: A global trial leader

Russia emerged about a decade ago as a top choice for clinical trials and retains that position today. Aside from being the world's largest country, Russia is the seventh largest pharmaceutical market in the world and the ninth most populated nation.

Biopharmaceutical companies have flocked to Russia for a trio of reasons: relatively low trial costs, high quality clinical data and speedy patient recruitment. Russians enthusiastically participate in the hundreds of new clinical trials that are approved each year by the Ministry of Health (MoH).

Russia's top therapeutic area is Oncology, Neurology, and Infectious Diseases. Other popular areas include Gastroenterology, Cardiology, and Immunology.[6]

Snapshot: Russia's profile/infrastructure

Russia occupies the east of Europe, stretching as far as northern Asia, and occupying more than 11 percent of the earth's land mass. Due to its size, it borders more countries than any other nation. Its neighbors include 14 countries from Norway all the way to China.

Russia has a population of 142 million, more than 12 million of whom live in the capital city of Moscow. St. Petersburg follows with 5 million residents. A dozen other Russian cities have populations that exceed one million. Several are emerging as important clinical trial destinations, including Kazan, Yekaterinburg and Novosibirsk.

As one might imagine, the vast majority of clinical sites are located in major cities, which makes delivering supplies relatively straightforward. Despite Russia's vastness, a depot or facility in Moscow can make next-day delivery of drug supplies in that region possible. Delivery to more remote locations takes two to three working days, due to the still relatively limited transportation infrastructure.

6. "Clinical Trials in Russia 2018" The Synergy Orange Paper. srgcro.com

Similarities outweigh differences

In addition to sharing a border, many similarities between Ukraine and Russia make them ideally suited for clinical trials.

Decades of collective global clinical trial experience

Together, Ukraine and Russia have three decades of clinical trial experience. Ukraine, which leads with 20 years of trial experience under its belt, hosted more than 200 studies in 2014 and was recruiting for more than 75 new studies in late 2015. Russia has been a highly-ranked site for clinical trials for a decade and shows no signs of slowing down. In 2014, the Russian Ministry of Health approved the start of about 750 new studies sponsored by companies in 35 countries, including the United States, United Kingdom, Switzerland, Germany, France and India.

Large populations and pools of naïve patients

Ukraine and Russia have a combined population of about 190 million people. Furthermore, patients in both countries—many of whom are modern, treatment-naïve—eagerly participate in clinical trials as a means of obtaining faster and potentially superior treatment. As a result, Ukraine and Russia enjoy rapid patient recruitment and enrollment, accompanied by excellent compliance and retention.

Benefits of centralized medical infrastructures

A major benefit of government-funded centralized healthcare systems includes large databases of patients with diagnosed conditions, such as cancer, heart disease and respiratory conditions. These patient databases enable trial recruitment.

Desirable therapeutic areas

The top therapeutic areas in Ukraine and Russia reflect leading drug development targets, enhancing these countries' value for sponsors. For example, cancer, which dominates clinical trials as the number-one therapeutic area, is also the top therapeutic area in both Ukraine and Russia.

Well-trained site personnel

Staff at investigator sites in both countries have training in Good Clinical Practices (GCP) and adhere to European Union (EU) values and international standards, enabling them to produce high quality data.

Relatively low trial costs

Costs to conduct trials in Russia and Ukraine are significantly lower than those in the United States and Europe. This is attributable to the typical grant size for principal investigators and high concentration of patients in cities, where most trials take place.

Management of extreme weather

This region experiences steamy summers (up to 40 degrees Celsius or 104 degrees Fahrenheit) and frigid winters (lows of -20˚ Celsius or -4˚ Fahrenheit) with frequent heavy snowfall. Fortunately, both countries are well prepared for this type of weather and snow is cleared efficiently from main roads. An experienced supply partner protects shipments with special insulated shippers and works closely with couriers to assess risks and communicate potential delays to sponsors.

Ukraine: Trials continue as requirements ease

Given continuing media coverage of political unrest in the region, it is no surprise that some clinical trial professionals are wondering if Ukraine continues to be a viable choice for clinical trials.

The answer is yes. To date, trials underway in Ukraine have been largely unaffected by ongoing tensions with Russia. Hundreds of studies continue uninterrupted as new trials get underway. In 2014, when the unrest reached a crescendo, Ukraine was hosting more than 200 trials. The following year, recruiting was underway for another 75 new studies.

There are changes to note, however. Because Crimea was annexed by Russia, studies taking place in this region can no longer be supplied from Ukraine. Sponsors have had to decide whether to continue trials underway at Crimean sites or transfer subjects at those sites to Russian offices for monitoring.

In addition, supply shipments to two territories in eastern Ukraine—Luhansk and Donetsk—are not recommended at this time due to active and ongoing unrest in the area.

These territories represent just 7 percent of all clinical sites in Ukraine.

Ukraine's new rules

In order to align with EU standards and reduce the complexity of the import process, Ukrainian officials passed sweeping regulatory changes and reduced duty charges on drug shipments in December 2014.

- Study sponsors are no longer required to obtain an umbrella license before a study can commence, nor is an import permit required for every drug shipment. In addition to time savings gained due to these regulatory changes, sponsors are reaping the benefits of sharply lowered duty charges. Officials cut the import tax on drug shipments from a high 20% in 2015 to just 7% from 1 January 2016. Collectively, these changes have made it easier, faster and more affordable to bring clinical trials to this nation.
- Now, Ministry of Health (MoH) approval of the clinical trial, which is granted in 60 calendar days, automatically permits the importation of clinical trial drugs. The distributor need only receive the green light from the Importer of Record (IoR) before shipping a new order of supplies.
- Shipping now requires a copy of the MoH approval, certificates of analysis for every drug batch, a proforma invoice for each shipment that facilitates customs clearance at the destination airport and an apostilled Power of Attorney when an external party, such as a depot, is acting as IoR on the sponsor's behalf. In addition, the sponsor is no longer required to prepare drug calculations or request import license extensions.

A certificate of compliance is required only if vital information—such as the manufacturer's name and address, batch number and/or expiration dates—is missing from the certificate of analysis.

As a result of these changes, it now takes only two weeks for a first shipment of investigational drug to reach Ukraine, assuming an experienced partner is managing distribution and importation.

Comparator drug importation requirements are the same as those for investigational drugs. However, a special import license is required for medical devices such as EKG machines. Obtaining the license is costly and can take time. Here again, planning ahead and partnering with an experienced IoR is recommended.

After the IoR ensures that drug shipments enter the country, the distribution partner handles planning for smooth delivery to investigator sites. In some cases, the IoR and the distribution partner are one and the same. Since many building blocks in Ukraine bear the same address, it can be tricky for couriers to locate the right building or building entrance. This can also be the case in Russia.

A knowledgeable distribution partner will ensure that the courier's paperwork contains as many specific details as possible about the destination—e.g. the floor level as well as the address, directions about using the north or south entrance, and noteworthy landmarks—thus guiding the courier to the right location and thereby preventing delays.

Russia: reduced duty charges balance complexity

After a decade as a top-ranked clinical trial location, there are indications that Russia has begun provoking some concerns on the part of clinical trial professionals. In a 2014 survey conducted by the Fisher Clinical Services team, for example, respondents named Russia as among the most difficult places to conduct clinical research.

These concerns appear to be based upon a combination of recent delays in regulatory approval for trials and the continuing complexity of Russia's import license application process.

Recently, it has been taking somewhat longer than usual—as many as 95 calendar days—to obtain regulatory approval to conduct trials in Russia. According to the timelines set by Russian authorities, regulatory approval is typically granted in 57 calendar days, so these delays may be easing.

However, most of the concern is driven by Russia's import license application process, which is more complex than that of other countries. Importing clinical supplies into Russia requires an umbrella license that stipulates the total quality of supplies that may be shipped into the country, based upon the size and duration of the trial. It takes two to three weeks for the license to be granted.

In order to obtain the license, the sponsor must submit a lengthy list of documents, including:

- A copy of the Russian MoH approval for the clinical trial
- A Russian translation of the protocol
- Power of Attorney (PoA), assuming that the sponsor is using an external IoR. Having a depot assume IoR duties can take pressure off a sponsor's shoulders.
- A customs calculation document reflecting the quantity of supplies to be imported based upon the number of subjects, dosing requirements and study duration. It is important to note that no overage may be added to the calculated quantity. Therefore, damage to or loss of supplies may result in the need for the sponsor to obtain an additional license, a process that can take five weeks for approval.
- Certificates of Analysis for the drug batches to be shipped
- Scans, copies or photos of the labels
- A proforma invoice for each shipment

Once the umbrella license is in place, it takes about two weeks to complete the delivery of supplies, assuming an experienced partner is managing distribution and importation on the sponsor's behalf.

Importing comparator drug also requires the IoR to obtain an import license from the MoH. This process is identical to that for obtaining an umbrella license, including submission of the same documents. Comparators and clinical trial drugs are frequently listed on the same umbrella license. Prior to importation, comparators must be labeled with clinical trial information. Certain clinical devices may also require an import license.

Russia's reduced duty charges

Like Ukraine, Russia also made it more affordable to conduct trials in the world's largest country. In September 2014, Russia reduced the duty on supplies of drugs imported for clinical trials. Duty charges dropped to 5.3 percent from 7.7 percent for chemically synthesized drugs, and this dropped further in 2016; the customs duty is now set at 3% which is on par with the duty fees for biological drugs. The Duty Paid Value of 10 percent must be paid in addition to the landed costs.[3]

Establishing a local presence: The role of a depot

A local presence in Ukraine and Russia can be invaluable in reducing the pressures of conducting clinical trials. Given these nations' respective sizes, infrastructures and weather, a key to ensuring timely supplies to investigator sites is the use of a depot.

A depot is a warehouse where large quantities of drug supplies can be sent and stored under highly secure, temperature-controlled conditions. Depots contain refrigerators for storing cold drugs, as well as capacity for such items as temperature monitors and shipment boxes. Dispatch areas provide a location for staff to process and pack site orders for pick-up by couriers. Because they speak the local language as well as English, the depot staff are on hand to manage cultural nuances and any issues that arise with respect to drug supplies.

A depot can act as IoR, permitting it to complete required tasks on behalf of the sponsor, such as:

- Obtaining import permits and license applications
- Making tax and duty payments
- Coordinating the dispatch of supply shipments
- Facilitating customs clearance
- Monitoring shipments to maintain the integrity of temperature-controlled GxP supplies

Selecting a depot

The decision to use a depot or other local facility in Ukraine or Russia comes with an obligation to review candidates before signing an agreement. Here is a checklist of recommendations:

Demand high standards

- Audit the depot to ensure that the facility maintains high professional standards, and confirm that the facility has a track record of excellence.
- Carry out due diligence to confirm the depot/facility's financial stability.
- Verify the oral and written communication skills of the staff in the local language and English.

Look for solid IoR capabilities

- Choose a depot with experience in fulfilling the role of IoR, and that they have an established network of contacts with trusted brokers and customs officials.
- Confirm that the facility has ample funds to cover costs such as customs clearance.

Confirm security of drug supplies

- To ensure drug supplies are well protected while in storage at the depot or in transit, make sure the depot can source quality approved shippers—insulated boxes that keep drug within an appropriate temperature range—as well as temperature monitors.
- Evaluate the couriers used by the depot. Good couriers should be proficient in handling clinical supplies; they will monitor the weather closely and make timely recommendations with respect to risks. Couriers should also have excellent track-and-trace capabilities so the location of supplies in transit can be known at all times.

Train and communicate

- Before entrusting a depot with drug supplies, train staff and communicate your expectations. Conveying your storage and shipping requirements will minimize errors, facilitate smooth processes and provide peace of mind.

Case study: Triumphing over the Russian Winter

Weather extremes of freezing winters and steamy summers are hurdles to supplying and conducting clinical trials in Ukraine and Russia. Like both of these countries, however, a competent distribution partner is accustomed to challenging weather conditions and prepared to deal with them.

A best-in-class partner will plan carefully and use high-quality insulated shippers to protect drug supplies from temperatures that routinely dip to -20˚ Celsius or -4˚ Fahrenheit during winter months. But special packaging is only one part of the solution; another is working closely with experienced local couriers to assess the risks of transporting drugs and potential delays and communicate these risks to the sponsor.

December 25th, 2014: Moscow

In this capital city, where Russian Orthodox Christmas is celebrated on January 7th, it was business as usual for the employees of the Thermo Fisher Scientific clinical trial supply distribution facility—that is, until snow began falling heavily. Soon, fleets of government snowplows were deployed to clear the busiest highways in and around Moscow, as others tackled snowfall on the streets where locals lived and worked. Meanwhile, flights were being delayed.

As the snow continued to fall, it was all hands on deck, with staff working furiously to ensure that supply shipments, packed for travel in special shippers, would dispatch as scheduled. Soon, it was clear that extraordinary measures would be necessary to permit couriers to reach the facility and pick up the shipments. Depot staff pitched in to face down the storm, clearing the ground around the dispatch area and connecting roads twice.

As the day wore on, shipments were picked up and, thanks to the tireless work of depot staff and couriers, all deliveries reached their destinations safely with no major delays.

When it was time for the Fisher Clinical Services team to make their way home, some colleagues had to leave their snowed-in cars behind and take trains. Although their trips home took a couple of hours, everyone arrived safely. One intrepid colleague who decided to drive home spent five hours in traffic that evening, although his trip normally takes 20 minutes.

The following day, some colleagues were slightly delayed in arriving at work, where their first task was digging out their cars. Work quickly resumed, and all shipments scheduled for that day were dispatched without a problem. Everyone drove home that evening on clear roads.

Tangled traffic

Gridlocked Moscow roads on Dec. 25th as commuters make their way home. Most of our employees opt to leave their snowed-in cars behind and take trains.

Digging out

Snowplows clear Moscow streets of heavily falling snow during the Dec. 25th storm as our employees work furiously to dispatch supplies.

Seven best practices: Bringing a clinical trial to Ukraine or Russia

These practices are based upon 20 years of experience in conducting clinical trials in Ukraine and Russia.

1. Begin planning well before regulatory approval is expected.

Timelines can be difficult to predict, so it is important to accomplish as much as possible in advance of a regulatory green light. For example, do not wait for regulatory approval before starting to prepare the documentation that is required to ship supplies into these countries.

2. Do your homework before choosing a depot.

All depots are not equal, so be sure the one you choose has a track record of excellence and is secure and financially stable. Verify the oral and written communication skills of personnel, both in the native language and English. Establish a communication plan early to help plan your project and manage it through completion.

3. Ensure the integrity of supplies.

Ukraine and Russia are huge countries of weather extremes, so ensure the integrity of temperature-controlled supplies by using appropriate shippers, choosing couriers based on performance metrics, and training depot staff about appropriate handling.

4. Work with trusted partners who have excellent track records.

Having a depot or local facility act as IoR can ease a sponsor's pressure and ensure timely shipments. In choosing an IoR, look for experience, financial solvency and a solid network of contacts with brokers and customs officials. Keep in mind that a seasoned IoR is also the best means for remaining up-to-date on frequent regulatory changes in Ukraine and Russia.

5. Be clear on importation timelines and manage stakeholder expectations.

Knowing importation timelines permits you to communicate these to those who need to know, manage expectations around drug delivery, and ensure that first-patient-in dates are achievable.

6. Know and meet document requirements.

Avoid delays by being aware of document requirements and meeting them. While this is always good advice, it is particularly important in Ukraine, whose import requirements recently changed, and Russia, where the import license application process is complex.

7. Plan for unforeseen delays.

Contingency planning is not an option. It is a must, for it mitigates risk from the beginning to the end of a trial. Think a massive snowstorm, a railway strike, an active volcano spewing ash and shutting down air travel and, yes, political unrest. To quote Franz Kafka, a Czech writer who clearly understood the need for contingency planning: "Better to have, and not need, than to need, and not have."

"Better to have, and not need, than to need, and not have."

Franz Kafka, 20th Century writer

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Published 09/21

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