



Approaching Clinical Trials in Central & Eastern Europe: The Promise of Access to New Patient Populations

Highlights:

- In the past 3 decades, medical product discovery, development and distribution have become increasingly globalized.
- 80% of applications for drugs and biologics now contain data from outside the US (OIG).
- As of July 2019, Clinicaltrials.gov indicated that 34% of its registered studies were US only; 49% were non-US only; 5% were both US and non-US; and 12% were not specified.

Globalization Advantages

Over the past two decades, trials have shifted from being conducted primarily in North America and Western Europe to other locations to help sponsors find more patients with therapeutically relevant disease profiles as quickly as possible. According to the Office of the Inspector General (OIG), over half of all clinical trials sites are now outside the US and the percentage of non-US investigators conducting trials under INDs doubled over the decade from 2000 to 2010. In addition, the number of non-US FDA regulated investigators increased by 50% between 2000 and 2014. There is a clear trend towards conducting trials in Central and Eastern Europe (CEE) because there are several advantages to doing so.

Heightened recruitment and retention

Incidence and prevalence of certain diseases in these other areas add to recruitment capabilities sponsors have available to them. Often these patients are highly motivated. Patients and their doctors, especially in countries where clinical research is less common, may perceive clinical trials as offering new or otherwise unavailable treatments and they may be more interested in participating, making recruitment both easier and faster. This can also increase patient retention as the trial may provide the patient's only access to care and to free treatment.

There may also be greater access to treatment naive patients, who have participated in no previous studies. Therefore, it may be easier to assess the true effect of a single experimental drug because there is less concern about previous treatments impacting the results of the drug being tested.

Cost reduction and shortened timelines

The costs for conducting trials in CEE is less than that of the US or Western Europe, by up to as much as 50 percent, according to ClinicalTrials.gov. Both start-up and initial regulatory approval could potentially take less time as well, further reducing the cost burden. With universal healthcare being the norm in many countries, there are often highly-trained medical staff at large hospitals, interested in learning about new techniques and opportunities.

For seasonal illnesses, or those impacted by climate or air quality, being able to conduct trials in different countries gives sponsors the ability to hold them year-round. This continual trial conduction shortens duration of the total trial timeline, and may speed the time to close and submission.

A kick-start to marketing and commercialization

Global studies provide physicians in those countries where the trials are conducted early experience working with the investigational product in their patients, often setting the groundwork for regulatory approval and easier acceptance or promotion of the drug once it has gained approval. It is important to note that regulatory approval may require the participation of that particular patient population within the country or region where you wish to market the drug. So, if your plans include global marketing, it's important to ascertain if studies must be conducted in each of the countries where you plan to introduce the drug, device or biologic.

Critical Considerations

Feasibility

Conducting feasibility studies is always a critical consideration and one well worth its cost. Research of multiple factors are important:

- Current status of the disease incidence and prevalence by country
- Competitive trials already being conducted in the country
- Past trial enrollment information
- Country regulatory assessment
- Clinical and medical review of the protocol, study plan or synopsis in light of each country's concerns
- Potential logistical or operational challenges
- Identification of sites and, if possible, conduction of site surveys for further site feedback on the proposed study and enrollment targets
- Standard of care that is current for the given indication

Learn from the experience of your CRO, which may have conducted multiple other studies in these countries. International CROs are familiar with the accepted protocols, regulatory issues and patient population cultural mores.

Regulatory perspective

Ensuring both EMA compliance and internal country standards may present a challenge in some cases due to the diversity of rules and expectations. EMA-adhering countries offer a transparent regulatory process with predictable start-up timelines. Examples of EMA-adhering countries in CEE include:

- Czech Republic
- Hungary
- Poland
- Romania
- Bulgaria

While other CEE countries may follow their own internal standards and require more in-depth knowledge from local qualified staff, they may also offer large, willing patient populations seeking access to advanced therapies due to competitive centralized healthcare systems. Countries in Central and Eastern Europe that follow their own standards include:

- Russia
- Ukraine
- Serbia
- Turkey

Start-up factors

Start-up requires local, well-trained staff with extensive knowledge of country-specific procedures. CROs with local start-up teams serve as catalysts to getting sites up and running quickly, helping to accelerate enrollment in adherence to study timelines.

Site and investigator selections serve as some of the greatest challenges in clinical trial execution, so it is imperative to be mindful of quality when evaluating the following:

- Investigator and staff experience with proven results
- Site equipment
- Patient access and historical enrollment data
- Geographic location with regards to the therapeutic indication
- Risk of study timelines

Build and maintain site and CRO relationships throughout the trials to stay on top of both advantages offered and challenges presented, and to keep your trials on time and within budget.

Challenges to Anticipate

Legal requirements

Differing legal standards for site contracts, including insurance requirements and legal documentation, are not unusual. In addition, these standards could change over time, as they are not always static and established. Changing standards could affect study start-up timelines, which could then differ according to country, and may require changes in protocol requirements and/or study population.

For example, including pediatric patients will require a Pediatric Investigation Plan (PIP), potentially increasing start-up time and regulatory complexity if it is not anticipated as the protocols are developed. In some countries, use of placebo may be questioned, so it is important to know that ahead of time.

CROs must provide guidance and support to sponsors so that the process of running a global trial can be navigated in the most efficient and timely manner possible.

Country standards of care

Standards of care include both customary medical attention provided to patients with the disease being studied, which is not always easy to assess, and also standard of care during the study, in addition to protocol adherence.

Although all the countries may be on the same continent, they do not necessarily offer the same homogeneity as you might find when working within a single country. Therefore standards must be taken into account to achieve accurate analysis and interpretation of results.

Drug approval authorities may also want to see that the drug works effectively even with different scenarios of background treatment, because such variety will inevitably occur in actual practice once it is on the market.

Customization

More customization may be required based on cultural differences and/or norms. For example, some types of recruitment practices common in one country may be viewed as intrusive in other countries with greater privacy concerns.

Remember to stay focused on the goal of conducting well-run studies with patient rights protected, protocol adherence and quality data. Study staff must be trained on strict ethical standards, ensuring appropriate patients are selected, fully informed, properly consented and treated per protocol, with full protection of rights and following industry standards of Good Clinical Practice.

Some cultural norms may be simpler to anticipate. For example, learn the country's holidays and vacation months in advance.

Language differences

Although English is increasingly the language of business, recognize that not everyone speaks English, especially among the patients you are hoping to recruit. Therefore, documents and consent forms must be translated into the native language of the country, or into one in which the patient is fluent.

Even among English-speakers, there are fluency differences among physicians and research staff. These fluency levels must be identified during site assessment and selection. They are also a consideration during investigator meetings and throughout staff training.

All language issues can be readily addressed – there are many translation firms that are well-versed in medical and clinical trial jargon – but costs and time considerations must be built into the study plan.

Best Ways to Gain Efficiencies

Communications

After feasibility studies, an important next step prior to protocol finalization is to solicit feedback from thought leaders and operational staff in each country where you wish to conduct trials. This will help to cut costs of translation and significant changes to protocols, rather than having to do it after supposed finalization.

Early study planning cannot be stressed enough. Sponsors and CROs both need sufficient time for planning and gaining regulatory feedback and answers to questions. A little extra time spent up front will be well worth it by the submission process.

Training

Site training opportunities must be maximized. During investigator pre-planning meetings, sponsor and CRO should focus on most critical components of study success, not every little detail, which can be addressed later. Getting the overview is important and it's critical to recognize how much people can absorb in initial meetings.

Initiation visits should include a presentation that reiterates key points to ensure all sites are trained to the same standards.

Caveats

When a study is conducted outside the US under an IND, that study still must comport with all relevant FDA regulations as if it were being conducted within the United States. It is important to assess and ensure compliance to protocols, clinical trial requirements and GCP.

Since 1975, provisions that permit submission of foreign clinical trials data not conducted under an IND were codified in 21CFR312.120. Essentially, the FDA accepts foreign clinical data from studies not conducted under an IND if the following conditions are met:

- Study was conducted in accordance with Good Clinical Practice
- FDA is able to validate the data from the study through an onsite inspection

For additional information, see:

- Guidance from the FDA: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions (March 2012)
<https://www.fda.gov/media/83209/download>

- Clinical Trials FDA guidance docs: overview
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trials-guidance-documents>

Conclusion

When it comes to conducting clinical trials in Central and Eastern Europe, numerous opportunities exist. It is important to work with a CRO that stays current on regulatory changes, guidance and policies in each of the countries where you plan to conduct trials – and to be sure that CRO knows how to translate this into timelines, budget and operational conduct of the trials.

Synteract, with offices in both the US and Europe, has feet on the ground and established relationships with international monitors, vendors and investigators, as well as regulatory strength in multiple countries. Our cross-functional project teams work closely with sponsors and sites to accomplish whatever needs arise.

Ultimately, for our management and the people that work for us, it is all about improving the quality of human lives: it's why we are all in this industry. To us, "Bringing Clinical Trials to Life," is both descriptive and aspirational because we bring your drug concepts and innovative ideas to life through clinical trials, and we assist in bringing better medicines to market internationally to aid the quality of life for patients who need them – because patients are waiting.

For more information, see our [country-by-country breakdown](#) of advantages and challenges on conducting clinical trials in CEE and contact Kate Mullis at kate.mullis@synteract.com to discuss how we might help you with your upcoming clinical trials.

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