



Clinical Trials in Emerging Markets:

Goldmines or Landmines?

Over the past decade, biopharmaceutical companies have increasingly turned to emerging markets as a way to reduce clinical trial costs and timelines. Areas such as Eastern Europe, India, and Latin America—with their ready population of treatment naïve patients—can be an answer to the intense competition for patients seen in developed markets. Many of the countries within these regions may now be considered as “emerged” countries but yet, conducting trials in these regions does require some special attention and expertise. Before deciding to conduct studies in these areas, companies should have a full appreciation for the ethical, medical, regulatory, legal, and operational hurdles that must be surmounted for success. Here we highlight a number of those issues and offer our recommendations for how sponsor companies can deal with them effectively.

The Allure of Emerging Markets

Sponsors’ interest in emerging markets as loci for clinical trials has been mounting for at least a decade. (See Figure 1A and 1B.) In 2011, this phenomenon reached a tipping point: for the first time, more data were submitted to the European Medicines Agency in marketing-authorization applications on patients from outside of Europe and North American than from within those areas. While the “Rest of the World” designation includes some mature markets such as Australia and Japan, there is, nonetheless, a clear takeaway: emerging markets have become a hot bed of trial activity.

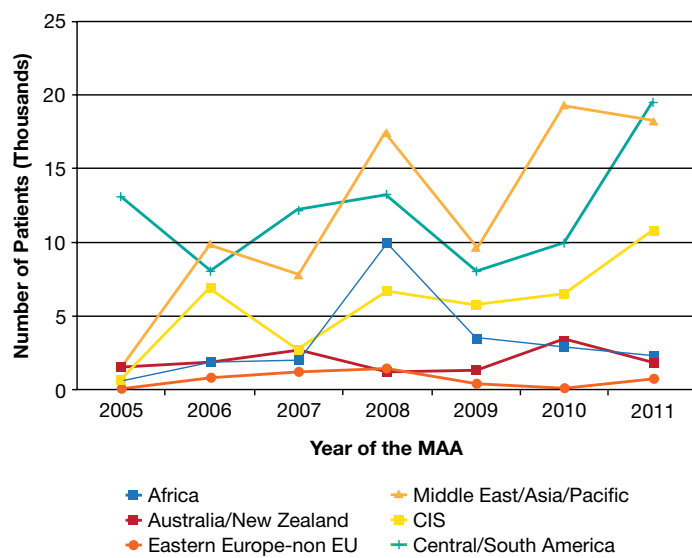


Figure 1A

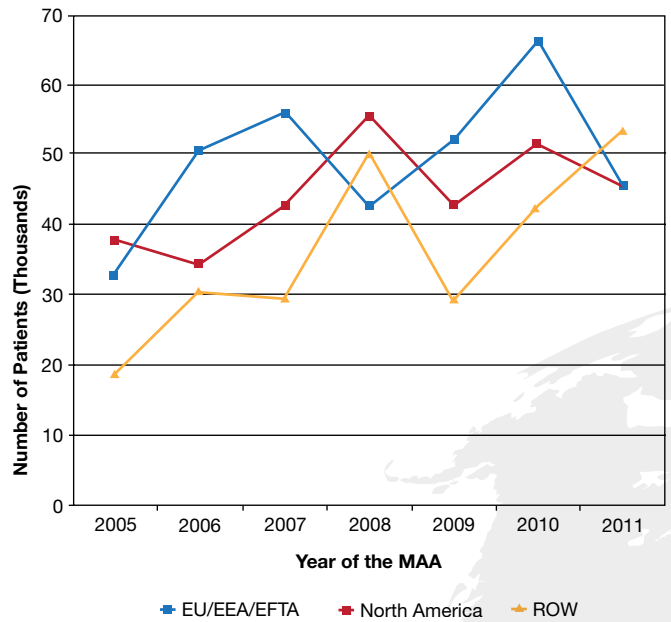


Figure 1B

The need to improve trial efficiency is a driving force behind the trend; however, commercial interests are also at work. An informal poll of Pharm-Olam clients conducted recently shows that respondents’ motivation to run trials in emerging markets is fairly evenly divided between the need to reduce study timelines (30%), the need to cut trial costs (27%), and the desire to create awareness for the product in trial countries (27%). In some countries, running local trials is a prerequisite for gaining marketing approval. However, even in countries where that is not the case, sponsors are finding that conducting local clinical trials raises product awareness in what are often substantial future markets.

Much has been written about the benefits of conducting research in emerging regions. For those companies that are still new to the prospects offered by Eastern Europe, India, and Latin America as trial sites, it is well worth reviewing some of the realities that are often glossed over. By discussing the types of considerations that must be taken into account, our goal is to help sponsors make informed decisions when developing their trial strategies; with foreknowledge and proper planning, companies can, indeed, realize the promise of these unsaturated trial markets.

The following material pertains generally across regions rather than to specific countries, as the level of clinical trial experience varies by country. Some countries in Eastern Europe, for instance, are considered as “emerged” (e.g., Poland, Czech Republic, Hungary etc.), while others are still emerging (e.g., Kazakhstan).

Can Enrollment Be Too Easy?

One of the primary reasons that sponsors have sought to conduct research in emerging markets is their need to improve patient recruitment rates. In general, these markets provide easy access to patients who are either treatment naïve or modern-treatment naïve. Fewer sites are needed because patients all flow through centralized healthcare systems with strong referral networks. And participating in trials gives patients in these countries access to the latest therapies and, often, closer medical supervision, more advanced diagnostic equipment, and more extensive follow-up care than they would otherwise receive. It follows, then, that patients in emerging markets are, as a rule, very willing to take part and very motivated to remain compliant with their treatment regimen.

That is all to the good, but the flip side of this benefit is that in many cases, patients cannot afford, or do not have access to, effective treatment outside of the trial. In this situation, when patients give their informed consent to participate in a trial, does it really constitute free involvement on their part? Bioethicist Dr. Arthur Caplan has asked, "...can you really follow Western ethical rules in very poor nations or among very poor populations

An Ethical Stance

A number of sponsors have issued Public Policy documents to address some of the ethical concerns mentioned in this article. Samples may be found at:

<http://www.gsk.com/content/dam/gsk/globals/documents/pdf/GSK-on-clinical-trials-in-the-developing-world.pdf>

http://www.merck.com/about/views-and-positions/clinical_trial_ethics_march2012.pdf

https://www.pfizer.com/files/research/nejm_paper_globalization_of_trials.pdf

¹ Miller, Talea, "Explosive Growth in Foreign Drug Testing Raises Ethical Questions," The RunDown PBS NewsHour, Aug. 2011. <http://www.pbs.org/newshour/run-down/sending-us-drug-research-overseas/>

in other countries? Meaning, are they really giving you informed consent or will they sign up for anything that you show up with because they are desperate and have an overwhelming faith in anybody in a white coat?"¹

Patients' eagerness to participate (because they have no treatment alternative or because they seek closer medical supervision) can translate into an eagerness to please the Principal Investigator (PI), which may impact Patient Reported Outcome measures. It is important that the study site teams are well trained on the study and that they are coached on how to explain the study to patients. Patients should be informed that an experiment is being conducted and they may or may not feel better as a result. In all cases, it is of utmost importance that the patient reports true and accurate symptoms—not what he or she assumes will make the PI happy.

Another ethical consideration relates to how the patient is treated after the conclusion of the study. If a patient is responding well to a therapy, is it ethical to withdraw treatment at the end of the study if there is no alternative treatment available in the country? (Some countries, such as Brazil, do allow PIs to request continuation of treatment from the sponsor.)

Recommendations

- Ensure that PIs are well trained in explaining the trial to patients and gaining their informed consent. In particular, PIs may need to be coached on how to review the study details with patients who have poor literacy skills. Role-play exercises with PIs can be very helpful in preparing PIs for patient interactions.
- Deliver patient materials in a variety of media. DVDs and online videos are often very helpful and well received.
- Stress to both sites and patients that the study should capture information on side effects and adverse events—and that any ailment the patient suffers during the course of the study should be reported. The study coordinator must see that patients are encouraged to make such reports and reminded that by doing so, they will be complying with the researchers' goals.

Are Study Participants Representative of Target Patients?

In some cases, sponsors may seek marketing approval primarily in developed markets for the very drugs they studied in emerging markets. Indeed, the new medication may not become available to patients in emerging markets for several years—possibly until it is available as a generic. This conflicts with the position of the Council for International Organizations of Medical Sciences that, “Clinical Research should be responsive to the health needs and priorities of the communities in which the research is conducted and any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”²

It also means that drugs are being investigated within a population that could be quite different from the target population, a situation that runs counter to the FDA’s recommendation, “It is very important to ensure, to the extent possible, that the population included in the clinical development program is representative of the target patient population.”³ When such differences exist, they can manifest themselves in:

- A different incidence of disease that could make it more difficult, not less, to find the right patients in a given country.
- Different life expectancies, which must be taken into consideration when evaluating outcomes data. For example, an overall survival of two years may be considered very good in one country, but only fair in another.
- Questions about the extrapolation of study findings to a different population. For example, it may be possible to study a biologic compound in a treatment naïve population in an emerging market. However, once the compound is marketed, most of the target patients will not be treatment naïve. How can we be sure that adding a new agent will be beneficial to patients who are already receiving multiple effective therapies—given that the agent was tested against a placebo in a treatment-naïve population?”⁴

Or, alternately, the study population may be exposed to a variety of homeopathic therapies that were not excluded by the protocol and that would not be common in the target population. Again, how might this affect its efficacy?

Similarly, the standard of care is likely different in the study population than in the target population—that is, in fact, part of what makes recruiting in emerging markets so much easier. However, that disparity could pose challenges in ensuring that the protocol can be executed properly. Consider the case, for example, in which the standard of care for asthma rescue therapy is not available in a study country. How would this be handled to both protect patients and ensure the integrity of the data?

Recommendations

- Perform a thorough feasibility study in advance of selecting study countries. This should explore the incidence of disease and the standard of care in each trial country.
- Specify the required standard of care in the protocol; sponsors should make no assumptions about the availability of medications, diagnostics, and procedures in study countries.
- Target patients for research on the basis of the intended geographic reach of the product, similar to FDA and NIH policies for target enrollment of special populations. This will require performing a detailed feasibility analysis in the emerging region before the protocol is finalized to ascertain if the trial can and should be conducted in the region.

² “International Ethical Guidelines for Biomedical Research Involving Human Subjects,” Council for International Organization of Medical Sciences, 2002.

³ “Guidance for Industry: E7 Studies in Support of Special Populations,” U.S. Food and Drug Administration, Feb. 2012.

⁴ Glickman, Seth W. MD, MBA, et al, “Ethical and Scientific Implications of the Globalization of Clinical Research,” *The New England Journal of Medicines*, 360; 8, Feb. 19, 2009.

Is It Permitted?

In some countries within emerging regions, only entities that are registered locally are permitted to conduct clinical research. Thus, sponsors must work with vendors that are established and licensed to operate in the study country.

In some instances, the process of contracting with sites can be complex and protracted due to special provisions and requirements, as well as the fact that many hospitals now have their own legal departments. It can take two to three months to get a clinical research contract negotiated and finalized. Sponsors are well advised to ascertain:

- Do contracts with sites have to be submitted to regulatory authorities for approval?
- Do sites require that research contracts be reviewed and approved by the Institutional Review Board or Local Ethics Committee?
- Does the contract template need to be included with the clinical trial application?
- Are sponsors required to contract with all individuals conducting research (not only the PI, but co-investigators, study nurses, local laboratories, and pharmacies)?
- Do the documents have to be notarized and/or apostilled?

Recommendations

- Give the legal department early notification of the study countries of potential interest. This will give the attorneys time to examine the local laws and prepare a compliance strategy.
- Work with local vendors who are not only licensed in the country, but who also understand all the local requirements and practices.
- Be flexible in drafting contract terms and conditions. If using a CRO, provide your CRO with a list of mandatory requirements vs. what is negotiable. When “fallback” language is agreed upon in advance between the sponsor and the CRO, the CRO is able to negotiate with sites without having to come back to the sponsor to discuss every small change.
- Plan for ample negotiation time. Know that some countries will be ready before others, accommodating a staggered study start up.
- Ensure that all contracts conform to the provisions of the U.S. Foreign Corrupt Practices Act.
- Work from common contract templates wherever possible. (TransCelerate BioPharma, Inc. is in the process of harmonizing contract documents.)

What Other Unusual Situations Could Arise?

Sponsors familiar with running global trials will, of course, be familiar with the detailed planning needed to orchestrate a trial across many countries. However, emerging markets often present additional logistical challenges, above and beyond those ordinarily to be expected from a large trial footprint. These include:

- **Resourcing.** It is quite possible that demand for the treatment provided through the trial will create an influx of patients that overloads sites. And, when large study teams are involved, extra monitoring may be required to ensure that they follow the protocol consistently.
- **Comparator Product Availability.** In some countries, the active comparator may also be a fairly new drug that is not available and has to be imported. If the comparator product is not licensed for use in that country, both the comparator and the study drug will have to be treated as investigational.
- **Equipment Availability.** In some cases, the diagnostic equipment needed will not be available. And simply furnishing hospitals with the necessary equipment is not always the answer; in some cases personnel must be trained and have years of experience in using the equipment before they are fully qualified to operate it in a study.
- **Supply Chain Logistics.** Emerging markets can pose difficulties in obtaining import/export licenses, charging high customs duties, getting supplies through customs, transporting supplies to remote areas, maintaining a cold chain for temperature-sensitive products, and allowing for public holidays.
- **Collecting Patient-Reported Outcomes.** Preparing to collect patient-reported outcomes can be time-consuming because the questions or scales involved may not be validated in the local language, a process that can take as much as three months and cost additional money. These tools must also be culturally relevant.

Recommendations

- Again, conduct a thorough feasibility study to include finding out if the comparator product will be available and whether patient diaries/questionnaires have already been validated in the local language.
- Take extra care in training site staff and in providing materials to help them discuss the study with patients. (Be aware that in some countries, it is common for other family members to be part of study visits, and so they, too, will need to be kept informed.)
- For fast-enrolling studies: once the first patient at a site has enrolled, temporarily halt further recruitment at that site until after a site-monitoring visit. The monitor will then determine if everything is in order for recruitment to proceed.
- Ensure that ample training resources are available, both for initial training and follow-up training as needed to ensure that the protocol will be followed.
- Work with local partners who have the necessary network to ensure the timely release of the product and other trial supplies through customs.
- Be prepared to have agreements with multiple couriers; no single courier seems to be best across these regions.

Is It Really Less Expensive?

The ease of recruiting patients in emerging markets translates directly into cost savings for sponsors. And, investigator fees in these regions are much less than in the U.S.

Yet, sponsors have often found that in working with some of the large, bureaucratic institutions, they are hit with unexpected charges. These can include everything from re-consenting fees, Institutional Review Board fees, and archiving fees to charges for dry ice and processing serious adverse events.

So, one question worth answering is, “Does the discount in investigator fees (which average less than half of those in the U.S.) and speed of enrolling patients more than make up for the additional site charges and operational costs of conducting trials in emerging markets?” It is true that conducting trials in these markets may require more complex operational processes. However, if you are familiar with the trial landscape and the requirements, then the benefits—both in terms of time and cost—can be very significant. The fact that so much patient data is now originating from the emerging or the recently-emerged markets shows that the benefits far outweigh any risks. In fact, so much so that we are continually in search for the next emerging market.

Recommendations

- The aim, of course, is to have no surprise fees crop up that weren't outlined in the clinical trial agreement. The best assurance against this is to work with a CRO having on-the-ground experience in the target country.
- Budget for some contingencies, even though they will be minimized with careful planning.

Proper Planning is Key

Perhaps the single most important activity in ensuring that trials in emerging markets are successful is to conduct a feasibility study before the protocol is finalized. By the same token, the feasibility study should not be conducted too early; the ideal timing is within three months of trial start up to minimize the chance of country conditions changing in the interim.

The feasibility study should:

- Gather input from local affiliates and CROs on local requirements, procedures, and conditions. This includes confirming that the regimen as proposed will be allowed in the country and discovering any logistical issues that need to be taken into consideration.
- Include feedback from sites on a blinded synopsis of the protocol to ensure that it will be workable for them.

On the basis of the information gathered during the feasibility study, sponsors should be able to finalize their development plans with a sound understanding of what to expect. Even so, it is prudent to have contingency plans in place and to “expect the unexpected.”

Conclusion

Undoubtedly, emerging markets have much to offer study sponsors. They can be a rich source of treatment-naïve patients who are motivated to participate in clinical trials. And, they offer potential savings from faster enrollment and lower PI fees. To realize these benefits fully, sponsors contemplating using emerging markets as trial sites must plan carefully, factoring in ethical, medical, regulatory, legal, and operational issues that differ from those encountered in developed markets. None of these are insurmountable. By working closely with the right study partner who has local experience in emerging markets, sponsor companies can avoid, or at least mitigate, the challenges and maximize the rewards of selecting these markets as trial locations. Choosing the right partner to conduct the study is a sponsor's single most important decision in guaranteeing successful trials in emerging markets.

About Pharm-Olam International

Pharm-Olam International is a global contract research company with a presence in over 40 countries, offering a wide range of comprehensive, clinical research services to the pharmaceutical, biotechnology, and medical device industries. From Phase I to Phase IV, Pharm-Olam focuses on delivering the highest quality data, achieving targeted enrollment, and meeting projected timelines.

**We are experts in running trials
in emerging markets.**

For more information on planning successful trials within Emerging Markets, contact info@pharm-olam.com.



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