CHAPTER 16

Design of Clinical Trials for Emerging Countries

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16.1. INTRODUCTION

The emerging world of clinical development comprises countries beyond the USA, Canada, Western Europe, and Japan that are well suited for global clinical trials. These regions and countries are Central and Eastern

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Europe, South Africa, Latin America, India, China, and South East Asia. Although there are numerous differences in the healthcare environment within this group of countries, they all have important similarities, namely, the potential for rapid subject recruitment and an opportunity for cost savings. However, these emerging countries have relatively nascent clinical trial environments characterized by evolving regulatory approvals processes, less robust systems for subject protection, and smaller, albeit fast growing, domestic pharmaceutical markets. They all present concerns to a varying extent about extrapolation of date accrued from their countries to the more developed regions of the world.

This chapter will examine the opportunities and challenges that emerging countries collectively present for international Phase II–III clinical trials and recommend an approach for the most effective utilization of these countries within global clinical development programs.

16.2. OPPORTUNITIES

The reason for the exponential increase in the utilization of emerging countries for international Phase II–III trials is the opportunity they present for swift, meticulous, and cost-effective clinical trial conduct. Access to patients, investigators, sites, and a cost-effective labor force are the fundamentals that support this.

16.2.1. Access to Patients

The increased complexity of clinical trials and the large pipeline of products in early clinical development have resulted in increased competition for clinical trial participants in North America and Western Europe. Competition is more fierce for patients with cancer, neurological, and cardiovascular diseases. Slow patient recruitment can delay product launch with revenue loss during the precious product patent life. Therefore, access to patients remains critical for the success of clinical development programs. Emerging countries offer this access, hence their inclusion within Phase II–III clinical trials is becoming standard practice.

Emerging countries have delivered the benefits of patient access and there are numerous success stories of patient recruitment rates being up to seven times faster than in North America and Western Europe. This is particularly true for oncology trials. Furthermore, the efficiency of clinical trial conduct is enhanced because the number of patients contributed per

site in an emerging country is many times greater than that of their counterparts in North America and Western Europe.

The reasons that emerging world countries are able to recruit clinical trial participants in such a rapid and efficacious manner are as follows.

First, most emerging countries have large numbers of patients with diseases of both the developing and industrialized world. In addition to widely prevalent infectious and tropical diseases, rapid and extensive urbanization in countries such as India, China, South Africa, and Brazil has resulted in disease prevalence similar to that found in North America and Western Europe. For example, India and China have the world's highest prevalence of metabolic syndrome, i.e. individuals with a combination of insulin resistance, hyperlipidemia, and obesity.

Second, the evolving urban centric healthcare systems of emerging countries require patients to travel to centralized hospitals for their healthcare needs. The resulting convergence of large patient numbers at centralized facilities is conducive for swift, efficient, and hence cost-effective patient recruitment.

Third, huge unmet medical need exists in the emerging world. Healthcare provision is a mixture of private and inadequate state-subsidized care. There is low health insurance coverage. Therefore, for a large proportion of the population, participation in clinical trials remains a way to access high-quality healthcare. This is true also in the USA and parts of Europe; however, given larger populations and deficiencies within state healthcare systems, the pool of patients with unmet medical need willing to participate in clinical trials is substantially larger in emerging countries. Furthermore, the authority position of physicians and the respect that patients have for them make patients more likely to participate in a clinical trial if this was recommended by their physician. Strong relationships between patients and their physicians also result in better study retention with lower dropout rates.

16.2.2. Access to Investigators

Emerging world countries have well-trained, motivated physicians well suited to be investigators for global clinical trials. Medical education is often delivered in English and is based on a system similar to that in North America and Western Europe.

Physicians at academic centers are well trained, fluent in English, and computer literate. Many specialists have received postgraduate medical

training in North America or Western Europe. The number of good clinical practice (GCP)-trained physicians is increasing.

The motivation for physicians to participate in international clinical trials is more than financial. It is also a means to participate in international clinical research, keep abreast with developments in their field, and access state-of-the-art treatments for their patients. Hence, physicians are motivated to participate in clinical trials and are willing to adhere meticulously to study protocols. As in the USA and Western Europe, not all physicians are well suited to being clinical investigators, so access to the right physicians is necessary.

16.2.3. Access to High-Performing Clinical Trial Sites

The centralized, hospital-based, healthcare delivery systems typical of emerging countries mean that patients travel to relatively few, central, urban hospitals for their healthcare needs. These hospitals that cater to large numbers of patients are usually well equipped with state-of-the-art diagnostic and therapeutic facilities. Furthermore, they are staffed with physicians and academic staff who are well suited to be investigators. This set-up provides for clinical trial sites with the potential to be highly productive. However, site support in terms of staff, processes, and systems is essential for these sites to deliver their full clinical research potential.

16.2.4. Potential for Cost Savings

Clinical trial conduct in emerging countries can be up to 50 percent cheaper than in North America and Western Europe. These cost savings result from lower trial budgets and lower operational costs.

Investigator and site fees are a fraction of those in North America and Western Europe. The lower investigator fees are due to relatively lower physician earnings, a keenness to attract global clinical trials, and comparatively few trials. As the clinical development sector matures, the investigator fees will increase, as has already occurred in Eastern Europe; however, in most emerging countries there will remain a differential before they approach the levels in the USA. Treatment costs are half those in the USA, with lower costs for medication, diagnostic services, and hospitalization. Thus, although there is an expectation for the trial sponsor to cover the costs of hospitalization, comparator, and supplementary treatments and investigations, the amounts involved are never high by US standards.

There is an opportunity to save up to 50 percent of clinical trial execution costs compared to North America and Western Europe. This is because of relatively reduced labor costs for clinical operations personnel such as project managers, monitors, data managers, medical writers, and biostatisticians. Because patient enrollment is concentrated at few sites, more patients are covered per site visit and there is less required travel. This reduced travel requirement, along with relatively cheap domestic travel fares, results in much reduced study-related travel costs. Lower costs of support services such as handling of clinical trial supplies, printing, translation, and local courier services further contribute to cost savings.

16.2.5. Global Social Responsibility

The inclusion of emerging countries in global clinical trials is not a form of exploitation as it is often misrepresented to be, but a way of contributing to the development of their evolving healthcare systems. Hence, the governments, medical institutions, and physicians within emerging countries strive to attract international clinical trials and attempt to ensure that they have the requisite regulatory and ethical frameworks.

The key benefits to the patients and healthcare systems of emerging countries are that trial participants have the opportunity to access cutting-edge, often life saving treatments.

Participation in clinical trials, irrespective of being enrolled in the placebo or treatment arm, is known to improve health outcomes, and this is all the more true for the patient group with otherwise limited access to healthcare. Investigator and site fees are partially utilized for the purchase of equipment and facilities, with benefit to all users. Participation in international clinical research enhances the practice of evidence-based medicine, thorough record-keeping, and better patient communication, and thus contributes to the overall improvement of healthcare standards [1].

16.3. CHALLENGES

The key challenges of conducting international clinical trials in emerging countries are navigating the regulatory approval process in a timely fashion and ensuring that the accrued clinical trial data meet international standards of data quality, scientific acceptability, and ethical integrity. Understanding and addressing these challenges at an early stage of study planning is critical for success.

16.3.1. Regulatory Approval Process

The prolonged and uncertain regulatory approval processes that remain a feature of many emerging countries can delay study start-up and could negate the speed advantage of rapid patient enrollment. However, as the clinical development environment in emerging countries is evolving, the regulatory processes are becoming more streamlined with an improvement in both the speed and predictability of obtaining clinical trial approval. China has the most prolonged regulatory approval process, requiring an average of nine months to navigate a path through six regulatory approval bodies. Latin America continues to be uncertain, with numerous instances of unexpected delays, whereas India has made some progress following implementation of the "fast track" stream, whereby, in situations where US Food and Drug Administration (FDA) investigational new drug (IND) or European Medicines Agency (EMA) clinical trial approval is available, the regulatory approval process is abbreviated and streamlined. Following regulatory approval, there is a process for obtaining the import license for clinical trial supplies as well as one for obtaining ethics committee approval. Processes, documentation, and timelines vary among emerging countries, so local and up-to-date knowledge is essential.

16.3.2. Uncertain Data Quality

There are concerns about the data quality standards in emerging countries which are considered to be relative newcomers to the global clinical development sector as it is perceived that investigators, sites, and clinical operations personnel have limited experience. Furthermore, the number of GCP-trained physicians is limited, though growing. It is also recognized that the constrained healthcare resources require investigators to juggle the demands of patient care and clinical research, limiting their focus on clinical trial conduct [2].

In recognition of these concerns, stakeholders within the clinical trial environment of emerging countries have undertaken numerous initiatives to improve their data quality standards. Clinical research training is being delivered in a number of ways that include study start-up activities, and GCP training of investigators and site personnel.

Local contract research organizations (CROs) and emerging country affiliates of global CROs are fully cognizant of the importance of training and continue to make substantial investment is this area. Accredited training

institutes have been set up in countries such as India to meet the demand for trained clinical research personnel, and as a result there are currently 10,000 GCP-trained clinical research professionals and 1500 GCP-trained investigative sites in India.

Furthermore, to ensure a high standard of data quality, CROs and pharmaceutical sponsors well versed with working in emerging countries provide additional site support in the form of site management staff and relatively intensive monitoring schedules. Investigators are often supported by clinical research fellows and nurses, which does not adversely affect study budgets because of lower labor costs. Furthermore, the leading service providers within emerging countries have invested in setting up quality assurance programs with regular site audits.

Governments of emerging countries recognize the importance of data quality and GCP compliance as the foundation for a thriving clinical development industry. Hence, they have encouraged their regulatory authorities and national medical research councils to establish initiatives to ensure that international standards for clinical data quality are attained.

However, the most important validation of clinical data quality is its acceptability by international regulatory authorities. Both the FDA and EMA have accepted emerging world clinical data from pivotal Phase II and Phase III trials for over a decade. Reassuringly, FDA audits in emerging world countries have recorded findings similar to those in North America and Western Europe. There have been 14 FDA inspections in India since 2005 with no "Official Action Indicated" verdicts. Thus, from the international regulatory perspective the quality of data from emerging countries is not a concern.

Sponsors could have concerns that clinical data obtained from emerging countries may not be universally applicable because of the perceived differences in diets, lifestyle, attitudes to pain, concomitant usage of alternative medicines, and genetic differences.

A sound understanding of the characteristics of patient populations in different emerging countries is essential to overcome these concerns. For example, it is worth considering whether the widespread use of traditional Chinese medicine will affect the interpretation of the data from China.

16.3.3. Ethical Standards

There are concerns that the ethical standards in emerging countries may be different from those in North America and Western Europe; all the more

so because in these countries there are clinical trial subject populations with unmet medical need, reverence for physicians who remain authority figures, and linguistic and cultural barriers for subjects to understand fully the implications of trial participation. The GCP guidelines for many emerging countries are based on the Declaration of Helsinki, World Health Organization (WHO), and International Conference on Harmonisation (ICH)-GCP. Notwithstanding this, ICH-GCP compliance in such an environment presents a challenge and there remain concerns about exploitative trial designs, weak informed consent, and inadequate post-trial access to study medication.

Stakeholders in the clinical research sector including government, industry, and academia have embraced the critical importance of compliance with the international ethical code and implemented numerous initiatives to do so. These include training, guidelines, legislation, and inspection processes. Informed consent given without any coercion is the cornerstone of GCP-compliant clinical research and arguably the inability to comply with this requirement should disqualify a country from participating in global clinical trials. Hence, meticulous attention to this tenet of clinical research is crucial, especially given the nascent clinical trial environment in emerging countries with large disparities in access to healthcare.

Access to biomedical innovation and free healthcare is an important motivator for clinical trial participation in all parts of the world. A survey of potential clinical trial participants in the USA revealed that about 50 percent of clinical trial participants claim that their primary motivation to participate in a clinical trial is to access free medication [3]. Thus, it is not surprising that within emerging countries with substantial inequity of healthcare resources access to free medication is an important motivator for clinical trial participation. This author submits that provided consent is free and informed, this remains wholly ethical and compliant with the principles of ICH-GCP.

16.3.4. Protection of Intellectual Property Rights

In the past, the legal system in countries such as India, Russia, Brazil, and China did not recognize intellectual property rights in accordance with international law. This has enabled their domestic generic pharmaceutical industry to flourish. From January 2005, as a full member of the World Trade Organization (WTO), India has been committed to recognizing and enforcing product patents in all fields of technology including pharmaceuticals.

Furthermore, as the economies of these countries have developed, their governments have realized the importance of sound intellectual property legislation to protect home-grown innovation. Hence, concerns that domestic generic pharmaceutical companies will be able to take inappropriate advantage from the conduct of innovator drug trials are not valid [4].

16.3.5. Low Commercial Potential

Although certain emerging world countries such as Brazil and China represent the fastest growing pharmaceutical markets in the world, the USA, Western Europe, and Japan continue to be the largest in revenue terms. The commercial potential of a country is important for country selection in a global clinical trial. Therefore, in terms of current market size, emerging world countries are commercially less attractive. However, they do represent future high-growth markets and offer the opportunity to shorten the clinical development timelines with earlier product launch in more lucrative markets.

16.4. RECOMMENDATIONS

Recognizing the opportunities and challenges listed above is essential for effectively designing and conducting clinical trials in emerging countries. Both trial design and conduct should be carried out so as to maximize the advantages and minimize the risks associated with emerging countries. Although the specifics of the trial will influence protocol design and trial planning, issues related to emerging country clinical trial conduct discussed below are universally applicable.

16.4.1. Regulatory Strategy

To fulfill the international regulatory requirements and meet the commercial imperatives, a proportion of the subjects in most global clinical trials should be enrolled from North America and/or Western Europe. The remainder could be recruited from one or more emerging countries to gain the advantages of expeditious and cost-effective clinical development that they so clearly offer. Given the above caveat, the best mix of countries should be selected on the basis of the product characteristics, country-specific regulatory approvals processes, and protocol-specific considerations.

The proportion of subjects to be recruited from emerging countries is dependent on the factors cited above as well as the trial objectives, commercial strategy for the product, and the scientific aspects of trial design. Unless there were compelling reasons, it would be unwise to recruit more than 80 percent of the total number of clinical trial participants from emerging countries. This is because the marketing authorization for the largest global markets is controlled by the FDA and the EMA. Further regulatory authorities in other countries continue to look to these more experienced regulatory agencies when making decisions about both marketing authorizations and clinical trial approvals for their own countries. Although neither the FDA nor the EMA has categorically stated its views on the proportion of evaluable subjects that may be enrolled from emerging countries, prevalent industry wisdom is that including a fair representation of subjects from the USA and Western Europe is essential so as to ensure a subject population that includes representation from their largest commercial markets. Given population flows around the world, it is possible to obtain a satisfactory racial mix by conducting trials only in the USA and Western Europe; however, the reverse may not be the case if the trial were to be conducted entirely in an emerging country. Ensuring that a proportion of subjects is white Caucasians is recommended.

Furthermore, it is currently perceived that some of the world's most experienced investigators and sites are in the USA and Western Europe. Hence, there is a concern, perhaps unfounded, that a pivotal clinical trial submission to the FDA or EMA with no developed world participation might signal inferior data quality or less than the best available expertise. It is likely that this perception will change, however, ensuring that representation of developed country sites and investigators does contribute to the data's credibility. In addition, the regulators of emerging countries take reassurance from the fact that the very same protocol has been approved by a more experienced regulator and is recruiting subjects in the USA and/or Western Europe. Given the sensitivity about the exploitation of emerging country populations, their regulators and ethics committees are suspicious of Phase II–III clinical trial applications that seek to recruit exclusively in their emerging country. Hence, unless there is a compelling scientific case to restrict recruitment to emerging countries, this is not recommended.

Given the similarities in the advantages of including emerging countries within Phase II–III clinical trials, arguably, a single well-selected emerging country could deliver the objectives of patient access, speedy recruitment, and cost savings. The risks of increasing the number of emerging countries

in a global trial are loss of focus and requirement for increased resources. The counter-balancing advantages are a mitigation of the risks, by "placing eggs in more than one basket". If there are concerns that one of the selected emerging countries might experience delays with regulatory or ethics approval or there might be issues with enrollment of suitable subjects, then there is a case for increasing the number of emerging countries with the expectation that one of the other selected emerging countries could "step up" and take over the patient recruitment allocation of its emerging country counterpart. Thus, by including more than one emerging country there is a contingency solution built in from the outset. Including an emerging country as a rescue should other countries experience difficulties is also a viable approach; however, this would involve delays when regulatory approvals are awaited. If a thorough feasibility assessment is performed that addresses medical, clinical, and regulatory issues, the risks of the selected country not performing are negligible, and therefore a strong case could be made for selecting, albeit carefully, only one emerging country.

Regulatory approval processes, documents, and timelines vary among emerging countries. It is essential to understand these for the selected emerging countries and to anticipate potential hurdles. Up-to-date knowledge and meticulous compliance with the study start-up regulations are essential to mitigate the risk of delayed study start. At the time of study design it is advisable to factor in the requisite study start-up timelines with the intention of compensating for these with swift patient enrollment. Ensuring that all study documentation and start-up procedures are completed in accordance with local regulatory requirements with necessary language translations is vital to minimize unexpected delays. For certain indications or product types it may be prudent to avoid certain emerging countries in anticipation of prolonged regulatory deliberations. It is also worth understanding the process, documentation, and timelines for ethics approval. Advice should be sought on potential ethics committee objections with thought given to ways of pre-empting these.

16.4.2. Ethical Integrity

It is critical to try to ensure that all emerging country trials are conducted with ethical integrity and subject protection to the highest international standards. Sponsors and CROs with experience of clinical trial conduct in emerging countries know that careful investigator and site selection is essential to ensure the ethical integrity and scientific validity of

the data. Investigators and site personnel play a vital role in ensuring that all clinical trial participants are provided with trial-related information in their own language with adequate provision for consultation with family and often community members. It is often required to have translations of patient-facing materials available in up to a dozen different local languages. In addition, sites provide counseling staff to discuss questions that participants and their families might have. Indeed, more experienced sponsors take the view that if there is any doubt over the investigators' ability to comply with a robust informed consent process it is best to exclude that site. Hence, the best in class investigators fully recognize the importance of informed consent, more so keeping in mind socioeconomic deprivation of their patients, and make every effort to comply. They do so not only for ethical reasons but also to ensure that clinical research in their country continues to flourish, recognizing that unethical practices will be the death knell of this nascent sector.

It must be acknowledged that the sociocultural approach to informed consent is different in certain countries. For example, it is not unusual for family members to give consent along with or on behalf of the subject. Access to subsidized healthcare is a strong motivator for patients to participate in clinical trials, and respect for physicians and their role as authority figures may make it difficult for subjects to refuse clinical trial participation. It is important for the sponsor and CRO to be aware of these factors and give particular attention to the informed consent process, endeavoring to ensure that subjects fully understand that they would be participating in a clinical experiment and appreciate the various consequences.

As yet, relatively few investigators, sites, or ethics committees within emerging countries insist that the sponsor provides post-trial access to their product. As the clinical trial environment in these countries matures, it is inevitable that investigators will demand post-trial product access for their patients, and sponsors should begin to plan for this. Most sponsors would not consider conducting a clinical trial in a country in which they have no intention of ever marketing a particular product. However, given the relatively lower commercial importance of emerging countries, product launch might be delayed, and so the timelag between trial completion and product launch could be considerable. Furthermore, there remains the thorny issue of subjects being unable to afford the medication. Post-trial and indeed post-launch access on a named patient basis will become an increasingly important consideration.

16.4.3. Feasibility Assessment

Protocol feasibility assessment from the medical, operational, and regulatory perspective is the first, crucial step for the successful clinical trial conduct in an emerging country.

Drawing on local experience, knowledge, and relationships, it is advisable to obtain an accurate feasibility assessment as early in the trial planning phase as possible.

It is important to ascertain the feasibility of the trial protocol within the emerging country's healthcare environment. This must include consideration of the standard of care for that particular disease state. Although increasingly there is a uniformity in healthcare standards across the world with a universal recognition for what is deemed to be best practice, in the underresourced healthcare environments of the emerging world there remain substantial differences in standard of care. This is perhaps most heightened in oncology, where there remains a discrepancy in the number and aggressiveness of the lines of treatment provided. Understanding these differences in standard of care not only prevents inappropriate protocol design but also could provide an opportunity to conduct certain trial designs that may no longer be possible in the USA or Western Europe.

There are relatively large numbers of treatment-naïve patients in emerging countries as a result of underresourced healthcare systems and differing clinical practices. Hence, it is possible to enroll steroid-naïve asthmatics or antiretroviral HIV patients in countries such as India or South Africa. This could be valuable for proof-of-concept clinical trials. In addition, differences in clinical practice may permit the inclusion of a placebo-controlled arm. For example, ethics committees in countries such as India may permit a placebo control arm in Alzheimer's disease trials because they could take the view that there is no available effective treatment. Understanding and taking advantage of such differences in healthcare standards could deliver much value to certain clinical trials.

Owing to ethnicity, diet, or cultural practices, disease profiles may be different from those seen in the Western world. Furthermore, differing standards of healthcare could result in the diagnosis of certain conditions being made at a later disease stage.

Seasonal differences between the countries in the northern and southern hemisphere enable year-round patient recruitment for disorders with a seasonal variation in incidence. Appreciating differences in disease profiles and accommodating for these is an important component of feasibility assessment.

A number of factors such as diet, alcohol intake, coprevalent disease, use of supplementary non-allopathic medications, and pain threshold modify disease behavior and responses to pharmaceutical intervention. The impact of these factors, if any, needs to be ascertained when selecting an emerging country. It is possible to identify and compensate for the effect of any such factors by minor modifications in the protocol such as additional baseline investigations or alterations to the inclusion–exclusion criteria. Clearly, there are substantial benefits to doing so early in the study planning process.

Quality of life questionnaires to be used in emerging countries need to be modified to accommodate country- and culture-specific differences. Attitudes to pain can be markedly different in subjects from emerging countries compared to their Western counterparts. This modification is above and beyond accurate translations into regional languages.

It is also essential to ensure access to prescribed diagnostic and therapeutic interventions with respect to the requirements of the trial protocol. It may be necessary to import comparator treatments or additional diagnostic kits, and ascertaining this at an early stage is good practice.

Certain trial protocols require long-term follow-up, but the socioeconomic situation in emerging countries may not be conducive to this. In such situations either special arrangements to ensure effective subject follow-up must be made or a decision taken not to use that particular emerging country. Similarly, if successful trial conduct requires access to comprehensive patient registries or databases and quality medical records, a number of emerging countries would need to be disqualified.

Racial differences have a limited impact on pharmacokinetics. The most significant effect is related to body mass index. However, it is important to explore whether the racial mix of the population of the considered emerging country would have a marked pharmacokinetic influence. In certain situations it may be appropriate to consider the human leukocyte antigen (HLA) subtypes prevalent in the population and, if necessary, include HLA subtyping or other genetic tests as part of the baseline trial investigations. Ideally, the study population should have a racial mix close to the population in which the product is finally expected to be used. It is worth avoiding conducting the entire study in a single racial group by trying to achieve a mixed population. However, the vast majority of marketed drugs have been developed in the Caucasian population, often 70 kilogram white males, with select bridging studies. The opportunity for heterogeneous study populations presented by emerging countries is a valuable

one, provided the racial implications, if any, on pharmacokinetics and treatment outcomes are well understood.

Protocol feasibility assessment must address the above-mentioned medical and scientific issues and not focus only on estimating subject enrollment rates. If there are issues related to protocol feasibility, at an early planning stage an informed decision must be made about whether to modify the protocol so as to make it conducive for the selected emerging country. If such modifications could jeopardize the overall trial objectives, it would be best to abandon plans to conduct the trial in that emerging country. Such a timely decision could result in substantial time and resource savings.

16.4.4. Patient Recruitment Amongst Plenty

In spite of the fact that emerging countries have large numbers of potential clinical trial subjects, it is important to develop a customized patient recruitment strategy. Patient enrollment tools well suited for emerging countries include health camps where patients are offered free health check-ups and given general health education. During these visits they are also informed about ongoing trials in neighboring centers and, if they meet inclusion criteria, they are offered the opportunity to participate in the trial. Such an enrollment strategy is particularly effective for indications such as hypertension, obesity, lipid disorders, and undiagnosed diabetes mellitus. Patient referral from community clinics, general practitioners, and other specialists in the region is an important patient enrollment method and it is worth deploying local resources to affect this. Depending on local practices it may be necessary to arrange a reward system for referrals. Review of the institution's databases and medical records would be another useful way of identifying potential subjects. If advertising is used, it is essential that the medium and message are customized for the emerging country environment. Simply transferring advertising campaigns developed for the USA or Western Europe, perhaps with translations, is rarely effective. Compelling study design that carefully considers the participant's perspective remains one of the best ways to attract study participants, as is the case everywhere in the world.

Retention of subjects until study completion is important to ensure the study's statistical validity. In view of the less developed socioeconomic setting in emerging countries, close attention to facilitating patient follow-up and study continuation is necessary. Strong patient–physician relationships encourage high levels of patient retention as patients tend to be in awe

of the investigator and hence desirous of complying with their instructions. However, the challenges of their daily lives may make it difficult for them to adhere to visit schedules. Site personnel who are able to establish rapport with participants can effectively motivate them to comply with visit and follow-up schedules. It would also be worthwhile to consider providing a budget to the site for supporting subject retention. These discretionary funds are used for transport and compensation for daily loss of wages for both the subject and their carers. Study design plays an equally important role in retention. Studies with fewer blood draws and less frequent site visits often have better subject retention. Designing trial logistics that have been customized for the local setting can also be valuable.

16.4.5. Selection of Vendors

The options facing a sponsor seeking to utilize emerging countries for their clinical trial would be to engage their own clinical operations staff in that country or to engage a CRO. Large pharmaceutical companies are likely to have clinical operations resources in the key emerging countries of the world. In the absence of this, the sponsor could engage a global CRO, offering the advantages of a one-stop shop service and standard global processes. Increasingly, sponsors seek to engage a specialist regional CRO for the emerging country because such specialists offer deep local knowledge and relationships, usually operate to a high quality standard, and deliver more of the emerging country-derived cost savings to the sponsor compared to their global generalist counterparts. The specialist CRO would work alongside other CROs that operate in other countries. Irrespective of which option is selected, it is essential to ensure that there is access to the local knowledge, expertise, and relationships essential for successful emerging country clinical trial conduct. Notably, relationships with high-performing sites, investigators, and the regulator's office are important.

Apart from clinical operations resources, it would be necessary to select local vendors to provide ancillary services such as central laboratory, imaging, and electronic data capture (EDC). The evolving clinical trial landscape in these countries has resulted in numerous high-quality vendors, making it possible to select vendors best suited for the trial requirements. There is also a number of specialist service providers providing clinical trial supply management, translation, centralized electrocardiogram (ECG) monitoring, and interactive voice response system (IVRS) services.

16.4.6. Smart Application of Technology

In recent years, there has been an exponential growth in technology tools, systems, and processes that claim to support drug development. The suite of offerings is now mature; hence the savvy user should be able to select technologies and craft solutions able effectively to meet operational challenges. This means progression from slavish adoption of technology to crafting solutions to serve real needs and achieve critical endpoints. Given the robust information technology (IT) infrastructure and widespread IT skills within most emerging countries, along with freedom from legacy biases, there is an opportunity for the smart application of technology to overcome some of the data quality issues that may exist.

EDC should become standard practice with a halt to legacy paper-based systems. This, combined with the deployment of clinical trial management systems and electronic document management, would help to address concerns that may exist regarding the loss of control sponsors located in the West may experience when conducting trials in distant countries across time zones. Such application of technology would enable real-time access to clinical trial data, providing the opportunities for remote, centralized, monitoring, timely detection of issues with prompt escalation and early trend and signal detection.

Furthermore, given the widespread availability of mobile telephony and wireless networks within emerging countries, there are numerous opportunities to deploy this technology for patient-reported outcomes and to ensure subject compliance. The hurdles at the moment are related to local language translations and subsequent validation.

It would be remiss not to highlight the compelling case for conducting data management in India for global studies, i.e. not only studies conducted in India. Access to a large resource pool with IT and business process skills in a low-cost labor environment provides the basis for cost-effective data management services. Excellent English language skills, a large number of IT-literate biomedical graduates, and a motivated and flexible work ethic contribute to the attractiveness of this proposition [5].

16.4.7. Compensating for Relative Inexperience

The amount of global pharmaceutical research and development dollars spent in the emerging regions of Latin America, Asia Pacific, and Central–Eastern Europe has multiplied many times over the past decade [6].

However, the total expenditure in these three regions continues to be less than a few percent of the global spend, implying that although the emerging countries are enjoying a period of brisk growth, their global contribution to clinical development continues to be a small one. Furthermore, although international clinical trial activity is growing at a substantial rate within emerging countries, this growth is occurring from a very low denominator base. Therefore, when designing and executing clinical trials within emerging countries, it is critical to recognize the relative inexperience and limited clinical trial infrastructure that may exist in these countries. It must also be noted that present international clinical trial activity within emerging countries involves a tiny fraction of the subject, investigator, and site pool available in these countries, and there exists considerable scope for continued growth. Recognizing this, investment in developing emerging country clinical trial capabilities has much medium- to long-term value. Investing in building investigator relationships and clinical trial site capabilities remains essential for both sponsors and CROs who seek to continue to conduct clinical trials in emerging countries.

16.4.8. Building Investigator Relationships

In view of the relatively nascent clinical trial environment in emerging countries, investigators play a critical role in that they not only enable access to trial participants but also are custodians of the data's scientific and ethical integrity. It is ultimately the investigator and site staff who ensure that subjects are recruited, the protocol is adhered to, and data are collated in a GCP-compliant manner and in keeping with the project expectations. In a country with limited healthcare resources the sanctity of the informed consent process remains a concern for sponsors. As investigators play a critical role in ensuring that informed consent is correctly obtained, attention to their selection and management is even more important in these countries than is the case in the more experienced clinical trial locales of the world.

Investigator selection is the first and perhaps most important step towards building a pool of high-quality investigators. Emerging countries offer a pool of physicians from which clinical trial investigators may be recruited. However, the vastness of this potential pool and the variation in their training and suitability for clinical research do pose a challenge. Although many physicians are keen to participate in global clinical trials motivated by the prestige, financial gains, and opportunity to offer better medical care to their patients, only a few have the requisite mindset and capabilities. Until

recently, the experience that many of these physicians have had of clinical trial participation was restricted to domestic postmarketing studies usually conducted with limited resources and rigor. In view of the variability of available physician talent and their limited clinical research experience, it is imperative to circumvent the large numbers of enthusiastic ill-suited investigators and identify those with the necessary mindset, postgraduate qualifications, and patient access required for international clinical development.

As emerging countries contribute increasing amounts of pivotal clinical data for product registration studies, scientific and medical questions related to disease behavior, diagnostic tools, and genetic and environmental influence will become more important. Standard of care, availability and validity of rating scales, influence of HLA type on treatment outcome, impact of nutritional status, and sociocultural attitudes to management of terminal illness are examples of questions whose relevance will increase as the contribution of emerging countries to global clinical development accelerates. Determining the answers to these questions will be necessary for the correct interpretation of clinical trial data, appropriate protocol design, and correct subject selection. Experienced investigators within emerging countries are a valuable resource to provide guidance on these scientific and medical issues, and seeking their input on trial design and data interpretation will become increasingly important. Wise sponsors will be those who view emerging country investigators not just as reliable patient recruiters but as scientific and medical experts, and accordingly build long-term working relationships with them [7].

16.4.9. Developing Clinical Trial Sites

Clinical sites with a high potential to contribute subjects are those with heavy clinical workloads. Given centralized healthcare delivery in emerging countries, general hospitals located in urban areas that treat large numbers of patients have the potential to be highly productive clinical trial sites. However, these sites have to meet the huge demands of healthcare delivery with limited resources. In such a busy clinical environment dedicated resources to support clinical research are usually limited. As a result, sites often experience resource constraints and are hindered from delivering subject enrollment and the clinical data quality of which they could be capable. For such sites to deliver their clinical trial potential they must be supported by resources and staff clearly designated for clinical research.

High-potential sites need to be carefully selected, trained and supported. The necessary investment in capital, time, and resources curtails the number of sites that may be developed and requires discipline in rejecting sites unable to meet standards. Furthermore, sponsors and CROs need to make themselves attractive to their preferred sites. This approach would result in a move away from tactical feasibility assessments and initiation of large numbers of sites in numerous countries to a strategic and long-term relationship with select sites.

Contingency planning will minimize the risk of missed timelines and budget overspends. Within each of the selected countries, both developed and emerging, there should be contingency sites in case of unforeseen issues with the selected sites. While budgeting for emerging country utilization, managers often overlook the less obvious costs of conducting trials in emerging countries. Although there is much potential for cost savings, it is important to factor in costs associated with international travel, additional training, and extra audit visits which are often essential to provide emerging country sites with additional support.

The objective of site selection is to engage with only select investigators and clinical trial sites able and willing to meet international performance standards. Typically, these would be general and specialist hospitals with busy clinical workloads and a good standard of diagnostic, therapeutic, and infrastructure facilities. These institutions would need to be staffed with motivated physicians interested in and willing to be committed to clinical research; ideally, each site should have at least one lead investigator. The hospital would have a busy clinical workload with access to large numbers of patients, both those attending the hospital and referrals from satellite clinics. Ideally, the hospital should have its own ethics committee or institutional review board that is correctly constituted and meets regularly. If this was not the case, then easy access to a central ethics committee would be essential. Experience of participating in international clinical trials would be desirable; however, given the need to develop clinical trial sites within emerging countries, a lack of experience should not exclude a potential site if other criteria were met.

Although there is still relatively limited competitor trial activity in a number of emerging countries, this is rapidly changing at "first tier" sites that have developed experience and a track record. These sites are becoming increasingly busy with participation in numerous trials. To ensure that there will be sufficient capacity within emerging countries to accommodate the increasing numbers of clinical trials being earmarked for them, it is essential

for "second tier" clinical sites to develop capabilities. Often these sites are located within smaller cities, still large by most standards, with populations of around two million, with healthcare facilities that also serve populations from surrounding rural and semirural areas. Initiatives to train potential investigators based in these places, allocation of funds to build infrastructure and resources at these sites, and commitment to growing the network of investigative sites will contribute to the development of necessary site capabilities and future capacity.

Site support should include training, equipment and, importantly, staff whose role is to facilitate the conduct of all ongoing clinical trials at the site. In the emerging country setting, the division between site management and study monitoring could be artificial and wasteful. Better productivity, data quality, GCP compliance, and subject protection can be achieved by coordinated team working, supported by proactive quality assurance measures. Support at the site level by dedicated, trained resources employed either by the site or by a site management organization is recommended.

Sponsor engagement, ideally in the form of site visits, either at the stage of investigator selection or early in the study cycle, positively influences site performance and recruitment. Demonstration of a sponsor's interest in the environment in which subjects are recruited can substantially influence study performance. If geographical challenges make site visits difficult, investigator interaction via electronic, telephone, and written communication is essential.

There is value in ongoing site development, which should include training. Ongoing clinical research and GCP training for investigators and site staff would meet the needs of new joiners and provide refresher courses to existing staff. Trial- and protocol-specific training should be delivered before the study start. Additional site development activities are the setting up of processes, systems, and tools to support effective clinical trial conduct; providing advice on investing in additional equipment, if required, such as freezers, computers, and fax machines, and preparing and supporting the site through site audits and participation in the quality assurance cycle.

Investment in developing clinical trials sites in the emerging clinical trial environment provides for a long-term relationship with ensuing benefits. It is possible to make the site even more conducive to clinical research by facilitating the compilation of patient databases for the site and building relationships with satellite clinics able to refer patients. By fostering strong investigator relationships at the site, it would be possible to collate the investigator's recommendations and advice on study design and accurately

assess protocol feasibility and estimation of subject enrollment. Ease of addressing contractual issues and negotiation of study budgets would be the business benefits of a mutually beneficial long-term relationship.

An important source of clinical operations wastage is non-productive clinical trial sites. Apart from the waste of resources spent on initiating and monitoring these sites, non-productive sites have a detrimental effect on morale and arguably have poorer data quality because the investigator and site personnel have not developed any familiarity with the study protocol. Therefore, weeding out non-productive sites, by working predominantly, if not exclusively, with a relatively limited number of tried, tested, and trusted clinical trial sites would deliver value and prove to be worth the investment.

16.5. CONCLUSION

The inclusion of emerging countries in international clinical trials will continue to increase until a time in the not too distant future when the present separation of emerging and emerged countries will become unnecessary. Until then, attention must be paid to understanding how the medical, clinical, regulatory, and operational differences that exist within these emerging clinical trial countries may be effectively utilized to achieve the trial objectives. Addressing in advance potential hurdles that could arise from discrepancies between the product characteristics and protocol design and peculiarities of the emerging countries being considered will mitigate most of the risks associated with these regions. Therefore, access to local knowledge, relationships, and expertise will remain paramount.

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