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How should you safely outsource pharmacovigilance to an Indian contract research organization?

Brian Edwards

Within Europe and US, it is not unusual for a company to outsource part or sometimes much of its pharmacovigilance system. Reasons to do this include lack of experience and resource, especially with commercial pressures to get the product to market. Sometimes, all the necessary parts of the system cannot be implemented in time by a company as first-time marketing authorization holder. However, additional factors may drive outsourcing in India, such as neither a physical presence nor a cultural experience as well as reduced costs, so that even call centres acting for Western Europe may be placed in India. As regards development in general, it is hoped that the Indian research environment may help solve enrolment challenges on large multinational Phase III studies or indeed be a source of treatment-naive patients for Phase II or III. However, robust pharmacovigilance is critical to ensure quality and to protect the interests of patients whether this applies to investigational and marketed products. With the understandable surge of commercial interest in clinical research in India should we be overly concerned whether relevant parties really do understand what safety means? No one doubts the enthusiasm of investigators or the comparatively higher number of patients per site that can be enrolled. However, all clinical research, both observational and interventional, is governed by the internationally applicable Declaration of Helsinki. Similarly, if the results from Indian trials are to be used for regulatory submission in the West, then GCP compliance is essential. Before discussing how to outsource safely, I will discuss the current contract research and regulatory environment in India. This may indicate areas of concern which may require closer attention by a potential sponsor.

Different Contract Research Organization Business Models in India

The heterogeneous concept of a Contract Research Organization (CRO) in India is that, a CRO might refer to independent locally owned CROs, an affiliate of a multinational CRO, one owned by a larger non-healthcare companies (such as an IT company wanting to move into pharmaceuticals), one owned by a healthcare or pharmaceutical company or a hybrid of a CRO and a site management organization. In addition, there are significant differences in costs and capabilities. Only a small number have experience in multinational Phase II and III studies sponsored by US or EU companies. Costs for CRO services can vary by as much as fivefold. For instance, the cost per monitoring visit can vary between $400 and $2500 per visit. Employee turnover can be as high as 60% (a healthy number in a Western CRO might be approximately 10-20%); 95% or more of investigators meet recruitment goals. However, although for US studies query rate are typically 10-20%, the rate rarely exceeds 5%. Thus, there is no cohesive business strategy to develop the Indian pharmaceutical sector with enormous amount of variations in existing CROs.

Sponsors should be aware that high rates of staff attrition and turnover study monitors may well impact a CROs’ safety capability. Previously training in pharmacovigilance and GCP is a major issue with very few training courses in India, resulting in not enough GCP and pharmacovigilance trained personnel.[1] The consequence of these factors may lead to the more experienced sites becoming overloaded with projects and the better investigators conducting proportionately more trials. In addition, the more attractive sites for recruitment may indicate that medical investigators already have a high patient load for their normal clinical practice, squeezing time for research subjects. This point is critical because of the challenge of informed consent from illiterate patients as described in a BBC documentary.[2] Thus, it is critical the CRO industry rises to the Quality challenge by building quality as an integral part of all processes. This indicates that recognizing the costs of quality control and quality assurance checks are essential, not just an overhead.

Changing and Comparatively New Regulatory Environment for Pharmacovigilance

Although the Drugs and Cosmetics Act was passed in 1940 with the prime purpose of regulating the import, manufacture, distribution and sale of drugs, it was not until 2001 that GCP guidelines were produced in India. With the latest amendment (dated 20th Jan 2005) to the Schedule Y of Drugs and Cosmetic Act 1945, the reporting of adverse events from clinical trials has become clearer and consistent with ICH requirements for reporting serious adverse events. This permits the conduct of Phase II to IV clinical trials in India. A national pharmacovigilance
Clinical Issues Specific for an Indian Population

Any sponsor has to consider whether the prevalence of disease, standard of care and size of eligible population is comparable to elsewhere in a development programme. Ethnic and geographical differences have a significant impact. In the past, studies have been considered as high risk if there was a history of excess death in a population. The sponsor’s staff may require cultural sensitivity training to avoid misinterpretation. For instance, headshaking and nodding can mean different things to both sides. Therefore, seek understanding of local and global requirements, the reality is that some basic training of EC members and regulators in these emerging and evolving ethical issues should be balanced against sponsor demands for fast approval.

The challenges of implementing an effective system are obvious with these multiple responsibilities in the regulatory system with limited expertise and capacity for both regulatory evaluation and inspection. Neither processes nor understanding of ethical issues exist for the newer types of trial such as proof of concept, novel therapies such as live organisms (vaccines), plant based medicines and non-pharmaceutical products such as devices and radionuclides so that sponsors will have to give very clear guidance. In addition, the requirements of data confidentiality have not been defined because data privacy laws are still at an early stage. Thus, investigators in India find it difficult to compare trial remuneration to ensure that they are getting the “best deal” compared to Western countries.

In contrast to the European regulatory systems, which were allowed many years to develop and mature by the media, there is already a considerable and understandable impatience in the media focus on research and safety with accusations about guinea pig syndrome. There is heightened awareness and concern that informed consent is truly voluntary sensitive to the way the product is applied as well as other extraneous factors that may confound the efficacy or safety of the drug compared to other populations. For example, the widespread use of traditional medicines and likely use as a concomitant medication needs to be taken into account. Even when setting up a spontaneous reporting programme, different arrangements may be needed to follow up on adverse reactions of special interest with a low threshold signals in such a different healthcare environment.

How do you identify and choose CROs who are safe to conduct pharmacovigilance or indeed any other aspect of clinical research?

The principles of assessing and choosing a vendor are the same as elsewhere.

Although you ideally would like a CRO who understands local and global requirements, the reality is that some basic “top-up” training may well be required especially to ensure that both the sponsor and the vendor have common understanding about safety. The relationship will need to be actively managed so that the sponsor treats the CRO as a partner and not just a mere vendor. Open and honest communication is recommended. The sponsor’s staff may require cultural sensitivity training to avoid communication problems. Culturally, Indians are averse to conflict and will be very polite and say nothing. Thus, seek reverse feedback to make sure both parties understand what was said. For instance, headshaking and nodding can mean different things to both sides.

Wherever possible, align business processes and determine whose SOPs will be followed. There will need to be extra sensitivity and oversight to avoid inadvertent human rights infringements. The informed consent process will need to be thought through in depth. For instance, to capture the spirit of the Nuremberg code, for clinical trials in psychiatry it would be logical that the “family” is consented, as well as the patient. Investing time and money in the relationship, particularly when it comes to training, will pay off by ensuring that sponsor has explicitly communicated your expectations. Meeting frequently in person would be wise. This should all reassure EU and US authorities when it comes to submitting data. A recent survey of sponsor and vendors revealed that major causes for out of scope costs were an increase in scope that was not anticipated at project start and change in project assumptions during the course of the project. This is particularly applicable to pharmacovigilance as workload can increase unpredictably because you are dealing with the unexpected. Thus, scope creep and change need to be discussed in advance with an agreed smooth process for change orders. It is well worthwhile to schedule contract reviews at regular intervals during the project as in pharmacovigilance; the scope and nature of the work has invariably changed after at least 6 months. It is quite possible that, with training, the unit cost per case report might well be reduced, so budgets should be transparently presented so that efficiencies can be sought. Above all, a blame-free approach should be encouraged. When mistakes happen in good faith, and they will, the CRO should be allowed to follow due process to correct errors. However, an issue escalation process is needed so that senior executives within the sponsor can be promptly informed of serious safety issues which often go global in 24 to 48 h like it or not. Fraud or violation of ethics should be grounds for immediate termination of the relationship and these, hopefully rare circumstances, should be described in the contract.

Is there another way to assess safety?

I would encourage the Indian pharmaceutical sector not to repeat the mistakes made by the West and just adopt a “regulatory approach to safety”. After all the safety of a medicine is just as dependent on the safety of the organization which produces it or uses it within a clinical trial. Firstly,
I would strongly recommend that all stakeholders in the Indian pharmaceutical sector collaborate to develop Guiding Safety Principles. What they may look like has been described elsewhere.\[9\] I would strongly recommend that the Indian pharmaceutical sector take a more business-like approach and consider the concept of a safety case for evaluating a CRO. The safety case is a well-established mechanism whereby other safety-conscious industries outsource projects. Its application to a CRO has previously been discussed elsewhere.\[9\]

In a general sense, a safety case presents an argument that a system is safe to operate in a given context. To be safe is to be free from harm. The harm could be to an individual, a group of individuals or to society as a whole. In a wider context, harm could include impact on an ecosystem or the general environment. The argument needs to be evidence-based, rational and objective. The safety case has to be sufficiently robust to withstand scrutiny by stakeholders and, rarely, as evidence in a court of law. Thus in the context of clinical trials and marketed products, this would refer to how a CRO has organized itself to establish a system which protects the interest of patients.

I would suggest a safety case is a detailed document, prepared by the CRO that outlines the safety processes within a CRO, the results obtained from evaluating this processes and the management arrangements to provide an overall description of safety within a CRO. It must demonstrate to the satisfaction of the regulatory or supervisory authority, by its contents and supporting material that the CRO knows what technical and human activities occur to deliver safety, how they are to be managed and how safety will be assured in the event of an emergency. It must also identify methods to be used for monitoring and reviewing all activities in connection with the CRO, with a view to the continual improvement of the safety within a CRO. Once a safety case has been accepted, the regulatory authority continually reviews the safety performance of the operator, through analysis of reported episodes of non-compliance and on-site audits, to determine whether the applicable standards and arrangements are being followed.

A typical safety case consists of three main parts: a Facility Description (FD), a Formal Safety Assessment (FSA) and a Safety Management System (SMS). The FD describes the facility, the FSA describes the hazard and risk studies and the SMS describes the safety management systems. The three documents must be linked particularly to demonstrate that the FD and the SMS are consistent with the outcomes from the FSA. Typically, the SMS is a high-level document that serves as a “roadmap” to more detailed documents such as plans and procedures.

This approach leads to significant benefits to both CROs and their clients as it ensures that processes are well understood before implementation so that during bidding process sponsoring companies know whether they are comparing like with like. In particular, this approach ensures that the sponsor understands the risk implications of using a particular CRO and, if appropriate, help that CRO design and implement changes to reduce risk to patients. Development of the safety case ensures transparency and traceability of the safety argument. The safety case is a living document that is developed throughout the project life cycle. It forms a complete statement of acceptability at each stage. The safety case provides a base line against which audits and reviews may be conducted. Internal audits are conducted to provide assurance to senior management that the safety case has been implemented as intended. Equally, the regulator may undertake audits as part of their processes. The safety case approach provides a systematic means for identifying an appropriate level of preparedness in response to an emergency. This could include providing suitably trained personnel and crisis response and undertaking emergency exercises based on the scenarios developed in the safety case.

Conclusions

The commercial attraction of India must not detract sponsors from the realities of outsourcing safely whether this is just pharmacovigilance or an entire clinical trial. The current clinical trial and pharmacovigilance regulations and ethical guidelines are relatively new, experience of their application by all stakeholders and application of acceptable standards of GCP and pharmacovigilance still variable. In particular, the pharmacovigilance system is in its infancy and is hampered by many factors.\[10,11\] Thus, we cannot expect ethics committees and investigators to be handed guidelines and regulations and told to “get on with it” without adequate training programmes. Sponsors should understand the subtle differences between India’s GCP, ICH GCP and FDA’s GCP such as in the implementation of ICH E6. So, two-way communication is equally important so that both sides understand each other’s point of view. Thus, when I am in doubt how to set safety priorities I turn to the core documents which universally guides us regardless: The Nuremberg Code and the Declaration of Helsinki. The unequivocal emphasis given to informed consent given in these documents explains why the challenge of getting truly informed consent in the vulnerable patient has attracted significant media interest and skepticism from some authors. It is imperative that his critical safety process must be sensitively implemented with adequate training and monitoring in place to assess adequacy. The Declaration also places great emphasis on balancing benefit and risk, which is predominantly a training issue which will never be solved by regulations alone. Sponsors must communicate to better understand what the Indian patient wants from safety and what investigators and prescribers need in the way of safety training. Although India may well help accelerate drug development, if costs start to rise, quality and safety may suffer. We must not forget that a short-term attitude and a healthy approach to safety are often incompatible. One thing we have learnt in the West is that once trust is lost in the safety system, it is extremely hard to regain.

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