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Controlling Compliance Risk in Global Clinical Research Activities

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To say that globalization matters to pharmaceutical and medical device companies is an understatement. Labor, research, and payer coverage and reimbursement obstacles in North America and Europe, as well as increasing patent challenges, are forcing an intense focus on maximizing development activities and commercial opportunities around the world, including in jurisdictions that were barely on the radar screen in decades past. At the same time, speed to approval in developed markets remains critical, and a significant portion of the value proposition of research conducted in developing markets is often focused on support of approval applications in the US and EU, where the scrutiny of research and publication practices has steadily grown. Taken together, these trends require legal, regulatory, and compliance professionals to pay close attention to how clinical research activities are planned and executed.

Oversight of Clinical Trial Conduct

While many US companies have decades of experience setting up product distribution chains and other commercial support functions for finished, approved products (such as sales staff) in developing markets, fewer have extensive experience running multi-country clinical trials. At the same time, the logistical and regulatory challenges associated with conducting research around the world can be daunting. A common approach is to outsource some or all of the "day-to-day" research activities to contract research organizations (CROs). Often clinical operations teams will seek to achieve initial alignment with CRO partners on core trial-related elements, such as protocol compliance, milestone payments, recruitment goals, and other metrics, but fail to properly consider the full range of execution risks and compliance considerations. A common mistake is a failure to ensure a comprehensive approach to alignment on performance expectations and real time reporting needs. For example, without a clear agreement setting forth responsibilities for promptly collecting, recording, and reporting adverse product experiences, a CRO's interpretation of applicable regulations may be out of synch with those of the sponsor company, leading to difficulties in reporting appropriately detailed information in a timely fashion. European regulators, in particular, have scrutinized safety reporting functions and new requirements require companies with European applications to have a consistent approach to trial-related reporting, even when the study conduct occurs in a different jurisdiction.

Similarly, sponsors can run into challenges when clear quality metrics are not set forth in written agreements with or training of CRO partners. In the case of large CROs, the expert clinical trialists who appear in initial meetings and in a "relationship management" capacity may not necessarily be the staff responsible for day-to-day site management and monitoring responsibilities. This particularly a risk due

to the significant downsizing of clinical trial management and oversight staff within companies, presumably based on the rationale that the CRO is taking on responsibility for many activities required under applicable laws. Although legally correct in certain respects, as a practical matter the drug manufacturer/sponsor typically remains at primary risk of failure, and will suffer the consequences in terms of reputation, money and asset failure (e.g., delayed approval) if clinical trials are not properly managed to ensure compliance.

These oversight changes underscore the need for sponsors to ensure that the CRO and sponsor have a common understanding of applicable regulatory requirements and compliance policies up front, including appropriate training. Central to achieving success in such outsourced trials is an agreement and associated systems that mandate a constant flow of data from clinical sites – and use of analysis tools to probe that data. A best practice in this area is to tie success or milestone payments to a mix of factors – reported on an ongoing basis — associated with clinical research excellence and compliance with sponsor policies rather than solely speed of execution. This will increase the likelihood of consistent quality management, avoiding significant protocol deviations and data integrity issues that may result in useless data and regulatory sanctions.

Critical Role of Risk Analysis and Management

Another critical tool to ensuring compliance in global trials is ensuring the proper initial analysis of the key risks among and in trials, and allocating management, monitoring and auditing accordingly. This should begin at the earliest stages of a trial and continue to be used when evaluating a company's portfolio of research activities in order to allocating company and CRO resources. Such risk-based planning should include consideration of a wide range of properly weighted factors, including, but not limited to, the geographic distribution of investigators and subjects, the history of research compliance in the jurisdictions in the study, the local healthcare systems involved, the design and complexity of the trial, and the nature of the drug or device under study.

Managing Anti-Corruption, Transparency and Publication Practice Challenges

Beyond core good clinical practice compliance, as jurisdictions around the world increase their data and payment transparency initiatives, impose new requirements related to subject injury compensation, and enforce anti-bribery laws, policy compliance in such areas has become critical. Applicable diligence and compliance guidance should be comprehensive and clear in these areas, and an emphasis should be placed on issues such as consistency in the use of validated fair market value databases governing payments for study sites and procedures, close tracking and auditing of payments made to sites and investigators, particularly where government institutions are involved, and compliance with transparency reporting requirements.

Another important area for oversight is clinical study publication planning and execution. We have seen a major uptick in governmental scrutiny of publication practices in enforcement matters, starting in the U.S. and now frequently a focus in the EU and Japan. In addition to ensuring that publications are accurate and disseminated appropriately — and that publication processes are driven by research and medical functions rather than commercial personnel — careful attention should be paid to ensuring that international standards for publication are adhered to, such as the recommendations of the International Committee of Medical Journal Editors. These recommendations provide best practices for key issues such as authorship and conflict of interest disclosure.

Points to Consider

Based on our experience in this area, we offer the following non-exclusive set of considerations for legal and compliance functions involved in the planning and oversight of multijurisdictional clinical trials:

• What proportion of your research management and monitoring personnel are contracted parties or vendors? How essential to patient safety, data integrity, and legal compliance are the tasks that are being handled by these third parties, and are real time controls – and associated data flow mechanisms – in place to ensure quality and compliance?

• How much time has your organization taken to conduct due diligence on clinical research vendors and sites, to train these third parties on your company's policies and procedures, and to monitor and audit their conduct? Does that diligence extend to the site as a whole – including all-important clinical study coordinators – or just the "big name" investigator?

• Are there systems in place to ensure that problematical clinical investigators and sites – i.e., those with persistent GCP problems or other compliance issues – are either effectively retrained or precluded from participation in your research activities?

• Are you allocating your clinical research oversight efforts according to risk analysis and management standards, or does the level of oversight vary by business unit or vendors involved?

• Do your contracts with these parties responsible for oversight include certifications with anti-corruption laws and local regulatory requirements? Are systems for determining payments for sites and investigators sufficiently validated as based on fair market value, and are they used consistently across your vendors and trials?

• Do your contracts include the ability to withhold or "claw back" payments if there is a suspected breach of your company's policies or applicable laws? Are milestone payments consistent with incentivizing quality and not just speed?

• Do employees at your company responsible for managing research have sufficient experience to identify and address deal local compliance risks, or are you wholly reliant on assessments made by vendors?

• Is your legal, compliance, regulatory, and quality staff sufficiently “plugged in” to help clinical staff identify and resolve potential issues in a timely fashion?

• Does your company have consistent, written standards for planning for, and review and approval of, clinical data publications and communications in the various regions in which you operate? Do legal, regulatory, or compliance functions have insight into publication planning activities?

By emphasizing the above questions, and ensuring that the true risks of globalized clinical research are appreciated and managed, compliance and legal functions within pharmaceutical and medical device companies can protect their companies in an increasingly complex research environment. Most importantly, companies can and increase the chances that the goal of such research – bringing new and improved therapies to patients with unmet medical needs – is achieved.