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## Corruption Risks in International Clinical Trials: Navigating Between Anti-Bribery Laws and Local Circumstances



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**C**linical trials present a host of potential corruption risks. Traditional corruption risk areas—such as repeated interactions with foreign officials and the payment of large sums of money to state institutions—

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are exacerbated in the clinical trial setting. In most countries in which clinical trials are sited, hospitals are typically government-owned or controlled, and physicians are employees of these governmental or quasi-governmental entities. This means that any financial interactions with research sites and investigators can be regarded, in a legal sense, as interactions with government itself, and excess payments for services rendered can be construed as bribes or kickbacks to governmental officials. Further, prospective study sites' cost structures can be complex, involving a myriad of administrative costs that are often presented as non-negotiable. In certain markets, benchmark cost information for clinical trials (e.g., procedure costs) may be scarce. In addition, cultural and business norms can pose challenges: In some markets, physicians may rely upon income from above-market clinical trial payments to supplement low salaries; while in other markets, a culture of deference to physicians may complicate clinical trial budget negotiations.

Recent enforcement activity in developing markets suggests that clinical trials are ripe enforcement targets, including for non-U.S. regulators. For example, in 2012, India's top clinical trial oversight body was ac-

cused of corruption in connection with the approval of new drugs on the basis of clinical trials that did not meet the country's regulatory standards for new drug approval. More recently, in May 2015, Chinese prosecutors disclosed a bribery investigation implicating a former national health official responsible for supervising clinical trials as part of the country's anti-graft campaign.

Increased international enforcement against corruption in the clinical trial setting is foreseeable. For U.S. companies operating in high-risk markets, there is no guarantee of a level regulatory playing field or an impartial anti-corruption enforcement approach. In addition, U.S. companies must be prepared to defend to domestic regulators their budgeting and payment practices for clinical trials conducted in international markets.

This article discusses several proactive steps that clinical trial sponsors and clinical trial services providers may consider to mitigate corruption risk.

## Basic Framework

Most clinical trials are funded by private companies, whose in-house scientists typically plan and design the studies. The companies that fund clinical trials typically enter into contracts with hospitals and physicians, under which the hospitals and physicians are paid to conduct the trials. In this structure, the company funding the clinical trial is the "sponsor" of the research, and the hospital-employed physicians who conduct the research with patients/participants are the "investigators."

Often, clinical trial sponsors are required to make upfront payments to study sites to cover various administrative and startup costs, such as payments to hospital research ethics committees to review and approve the proposed study at each individual site. Although compensation structures can vary widely from study to study, subsequent payments to clinical trial sites frequently are milestone-driven (*i.e.*, based on the sites' completion of participant enrollment and their progress through the protocol-required tests and procedures) or time-based (*e.g.*, quarterly payments for the expected duration of the study).

Clinical trial sponsors—or individual study sites—regularly engage third-party vendors to assist with various aspects of a clinical trial, including assistance obtaining regulatory approvals to conduct the study (for which local knowledge and experience can be invaluable), site selection and contract negotiation, monitoring of sites' compliance with protocol requirements, biospecimen transport and storage, data analysis and preparation of end-of-trial regulatory submissions and publications.

## Demographic and Enforcement Trends Intensify Corruption Risks

As though the basic clinical trial framework was not sufficiently fraught with corruption risk, changing demographics and expanding regulatory regimes require that clinical trial sponsors and clinical trial services providers increasingly operate in high-risk markets. For example, with economic growth and increased access to health care, the populations of prospective end-users

for new drugs in Brazil, China and India have increased exponentially. Each country, in turn, has promulgated new regulations increasing its oversight and control over clinical research activities. Some countries—such as China, Japan and India—are considering or have adopted requirements that in order to qualify for marketing approval, a new drug must be tested in at least some trials within the country. And while they are key strategic markets, Brazil (69th), China (100th) and India (74th) all fared relatively poorly in Transparency International's 2014 Corruption Perceptions Index. Similar trends can be expected in other developing markets whose populations and health-care markets are poised to expand, such as Mexico and Nigeria. Given the rapidly evolving landscape, even the most seasoned U.S.-based compliance personnel may struggle to keep abreast of the latest regulatory developments in the markets for which they are responsible.

## Proactive Steps to Mitigate Corruption Risk

To remain a step ahead of a changing enforcement environment, clinical trial sponsors and clinical trial services providers must act proactively to mitigate corruption risk. Fortunately, there are several practical controls that can be implemented with minimal business disruption.

**Site and Investigator Selection.** Robust due diligence of prospective clinical trial sites and investigators is fundamental to minimizing corruption risk. Appropriately, site selection typically focuses upon scientific and logistical capability to perform the requirements of the study protocol. It is important, however, that study sponsors—and clinical trial services providers to which site selection has been delegated—perform thorough due diligence of prospective investigators and sub-investigators, particularly in situations in which due diligence review of the prospective site is impractical or unlikely to be fruitful.

In general, investigator selection for clinical trials should be based on experience, merit and ability to perform protocol-required services (including subject enrollment). However, because these criteria are not wholly objective, and therefore subject to second-guessing by an aggressive regulator, clinical trial sponsors should consider implementing procedures to track the use of individual investigators over time. Ideally, such procedures would track the use of individual physicians across the entire spectrum of possible engagements, including speaking engagements, consultancies, investigator-initiated research studies and traditional clinical trials. The repeated selection of certain high-prescribers, consultants, speakers or key opinion leaders as investigators may appear suspicious to regulators, and thereby result in added investigation or litigation costs, even if the selections were merited.

**Selection of Clinical Trial Services Providers.** For clinical trial sponsors, it is equally important to exercise caution—and to conduct appropriate due diligence—when selecting clinical trial services providers, including contract research organizations ("CROs"), laboratory services providers and others. Vendor selection and due diligence are especially critical in high-risk markets, as well as markets in which clinical trial sponsors rely upon local vendors to identify and negotiate

with prospective study sites, or even to negotiate with governmental authorities.

Clinical trial sponsors should seek to enter into formal, written agreements with all clinical trial services providers, and to the extent possible, such agreements should include anti-corruption and conflict-of-interest provisions. Sponsors also should be mindful that allowing study sites to select their own vendors may increase the risk of improper payments. For example, if an investigator is permitted to select the CRO that will provide clinical research coordinator services for his or her site, that investigator may have an incentive to seek a kickback arrangement, through which the CRO pays to the investigator a percentage of the fees that the CRO receives from the study sponsor.

**Payments to Clinical Trial Sites.** Once site selection is complete, clinical trial sponsors—and clinical trial services providers, if applicable—must ensure that the fees paid to study sites represent fair market value for clinical trial services actually rendered. Although conceptually basic, negotiating clinical trial agreements (“CTAs”) that approximate fair market value can be difficult in practice. In addition, due to the complexity of clinical trial cost structures, an appropriate, but poorly documented, payment structure may be nearly as difficult to defend after-the-fact as an actual excess payment.

First, in most cases, payments to clinical trial sites should be made to investigators’ institutions, and not directly to investigators. This requirement promotes traceability of payments and reduces the opportunity for a rogue employee to make an improper payment to an investigator.

Second, all payments made to clinical trial sites should be traceable to (1) the sites’ individual budgets and (2) an overall budget for the entire clinical trial. Without this basic framework, it would be difficult to defend any payment to a study site as representing fair market value for clinical trial services provided. As a guiding principle, clinical trial sponsors (and clinical trial services providers tasked with budget development) should retain sufficient documentation to allow an independent observer to recreate the budget development process at both the site and overall study levels.

Third, all fees paid to study sites—as well as the corresponding payment schedules—should be detailed in the sites’ CTAs. Ideally, payments to clinical trial sites should be milestone-based—i.e., based on sites’ successful completion of tests and procedures required by the protocol. Unless national laws require otherwise, the budgets should reimburse for tests and services required by the protocol that exceed the standard of care that otherwise would be provided to the participants and paid for from other public or private sources, such as a national health insurance program. In some markets, national governments may require that the sponsor pay for all clinical trial procedures and services. Even in that situation, however, sponsors should take steps to avoid paying for services that are also being billed to and paid by other sources, as such double payment might be perceived as exceeding fair market value or even as a kickback payment to the site and investigators.

Fourth, to the extent feasible, clinical trial sponsors and clinical trial services providers should encourage the use of a single-template CTA across the entire study. In addition to ensuring uniformity of terms and

obligations (and thereby reducing negotiation costs), use of a template CTA facilitates transparency in cost structure from site-to-site. Site-to-site cost transparency, in turn, furthers both business and compliance objectives. In addition to memorializing all fees in written CTAs, sponsors should consider requesting written representations of fees that are presented by sites as “non-negotiable,” such as fixed-percentage administrative or overhead costs. While written representations alone may not justify the payment of above-market, “non-negotiable” fees, at least such documentation will support that the fees were not determined and paid arbitrarily.

Fifth, for markets in which reliable clinical trial cost data are available, sponsors should consider the use of a third-party database to obtain benchmark cost information—aggregated from clinical trials conducted by multiple sponsors—for protocol-required tests and procedures, as well as other site-level costs. Where practical, use of a third-party database removes subjectivity from the budgeting process, thereby reducing negotiating costs and rendering the resulting budget more defensible.

Sixth, clinical trial sponsors and clinical trial services providers should perform regular monitoring of study sites to ensure that sites are actually performing the services for which they are being paid. Site monitoring activities are not limited to ensuring patient safety, protocol compliance and data quality; indeed, frequent and thorough monitoring visits are the only effective way to ensure that the sponsor’s compliance and business interests are protected.

Finally, clinical trial sponsors should be mindful that monetary transfers to study sites are not the only potential form of excess payments. Clinical trial sites frequently request equipment (e.g., investigational product storage freezers, laptops, fax machines)—or funds to purchase equipment—during CTA negotiations. The provision of such equipment (or funding) may represent excess payment to study sites to the extent that the equipment (1) is unrelated to the clinical trial for which it is provided; or (2) is not returned—or purchased by the site at depreciated value—upon conclusion of the study. To mitigate this risk, the provision of equipment (or funds for equipment) should be recited in sites’ CTAs and should include a detailed statement of the study-specific need for any equipment provided or purchased. In addition, sites’ CTAs should specify how study-related equipment will be treated at the conclusion of the trial (e.g., by the sponsor reclaiming the equipment or the site retaining the equipment and paying the depreciated value to the sponsor).

## Conclusion

Conducting or managing a clinical trial, particularly in a developing market, entails a high degree of corruption risk; however, clinical trials have not yet been the focus of significant U.S. enforcement activity. This trajectory is primed to change over the next several years, as U.S. and E.U.-based pharmaceutical and medical device manufacturers increasingly look overseas for new markets for their products and as foreign regulators ramp up scrutiny of clinical research activity. In the interim, clinical trial sponsors and clinical trial services providers would be well-served to review their existing policies and procedures related to site and vendor selec-

tion, budgeting and payments, to ensure that such protocols are respected by in-country management and are defensible.