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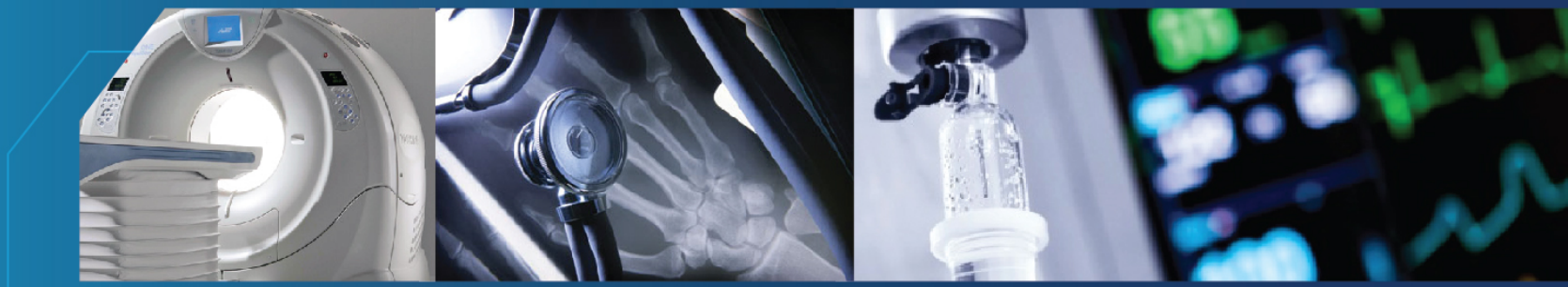
Bribery and Research Integrity in Foreign Clinical Trials: Practical Strategies for Reducing Your Company's Compliance Risks



Sue Sefarian
Health Care Compliance Officer
Johnson & Johnson

Johnson & Johnson HEALTH CARE COMPLIANCE & PRIVACY

John T. Bentivoglio

Skadden

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Topics for Discussion

- Context for Life Sciences Companies
- The Enforcement Environment
- Risk Areas for Foreign Clinical Trials
- Practical Strategies for Reducing Compliance Risks
- Questions & Answers

Business Context – Tremendous Need & Opportunity …

- The tremendous growth in research activities conducted in foreign countries is a result of a number of related factors:
  - General regulatory desire to see larger and longer term clinical trials as a pre-requisite for approval – in the US, EMEA and other markets.
  - Competition for clinical trial patients in more developed markets makes recruitment more difficult and more time-consuming than is often the case in Asia, Eastern Europe or South America.
  - Problems with finding treatment-naïve patients as study subjects; required for many investigations of novel compounds being investigated as a first line treatment – more success in finding these patients outside of North America or Western Europe.
  - Favorable costs of administration for trials, including recruitment and clinical monitoring, in Asia vs. North America or Western Europe.
  - Local regulators' interests in having compounds studied in populations with similar genetic characteristics/attributes as their citizens.

Business Context – … But Substantial Risks

Transparency Int'l – Corruption Index (2010)

Country	CPI Score	Rank
Denmark	9.3	1
US	7.1	22
Malaysia	4.4	56
Turkey	4.4	58
Brazil	3.7	69
China	3.5	78
India	3.3	87
Mexico	3.1	98
Russia	2.1	154

Enforcement Environment: OIG Report (2001)

Department of Health and Human Services

OFFICE OF
INSPECTOR GENERAL

The Globalization of Clinical Trials

A Growing Challenge in Protecting Human Subject

SEPTEMBER 2001
OEI-01-00-00190

FDA oversees significantly more foreign research than it did 10 years ago.

The number of foreign clinical investigators conducting drug research under Investigational New Drug Applications increased 16-fold in the past decade. In 1990, 271 of these foreign clinical investigators were in FDA's database. By 1999 the number grew to 4,458. FDA inspections of foreign clinical investigators conducting drug research have also increased dramatically, from just 22 in 1990 to 64 in 1999.

Sponsors have expanded research sites into many countries that appear to have limited experience in clinical trials.

The number of countries in which clinical investigators conduct drug research that is tracked by FDA increased from 28 in 1990 to 79 in 1999. Among the countries that have experienced the largest growth in clinical investigators are Russia and countries in Eastern Europe and Latin America. Sponsors explain this growth by pointing to readily accessible human subjects, potential new markets for approved drugs, and recent international agreements that ease FDA acceptance of foreign research data. Contract research organizations are also moving into these areas. FDA is also beginning to inspect investigators in areas where FDA-regulated research has not previously been conducted.

FDA cannot assure the same level of human subject protections in foreign trials as domestic ones.

FDA receives minimal information on the performance of foreign institutional review boards. It does not inspect these boards, nor does it tend to receive much information from the host countries of these boards. It cannot necessarily depend on foreign investigators signing attestations that they will uphold human subject protections. It has an inadequate database on the people and entities involved in foreign research.

Enforcement Environment: OIG Report (2007)

Department of Health and Human Services

OFFICE OF
INSPECTOR GENERAL

THE FOOD AND DRUG ADMINISTRATION'S OVERSIGHT OF CLINICAL TRIALS

September 2007
OEI-01-06-00160

Data limitations inhibit FDA's ability to effectively manage the BiMo program. Because FDA does not maintain a clinical trial registry, it is unable to identify all ongoing clinical trials and their associated trial sites. Further, because FDA does not maintain an IRB registry, it is unable to identify all IRBs. Even though FDA maintains six databases to track BiMo inspections, none includes complete information needed to track all such inspections. For example, ORA's database does not include complete information for inspection events that occur after it completes its inspection. The center databases do not consistently track inspection information.

Other factors hinder FDA's ability to effectively manage the BiMo program. Centers and ORA inconsistently classify OAI and NAI inspections. FDA relies on voluntary compliance to correct violations of regulatory significance. Uncertainty of timing and lack of coordination impede FDA's ability to conduct BiMo inspections. In addition, FDA guidance and regulations do not reflect current clinical trials practices.

We estimate that FDA inspected 1 percent of clinical trial sites during the fiscal year 2000–2005 period. FDA conducted 2,856 BiMo inspections that required a clinical trial site visit during the FY 2000–2005 period. Because FDA cannot identify the total number of clinical trial sites, we used the NIH clinical trial registry to estimate the proportion of clinical trial sites the BiMo inspections reached. The centers conduct more inspections that verify clinical trial data than inspections that focus on human subject protections. Seventy-five percent of the BiMo inspections during the FY 2000–2005 period were surveillance inspections, which generally target previously completed trials and often focus on verifying the quality of clinical trial data. Also, FDA inspected few IRBs, which offer considerable oversight of human subject protections.

Enforcement Environment: OIG Report – 2010

Department of Health and Human Services

OFFICE OF
INSPECTOR GENERAL

CHALLENGES TO FDA'S ABILITY TO MONITOR AND INSPECT FOREIGN CLINICAL TRIALS

June 2010
OEI-01-08-00510

FINDINGS

In FY 2008, sponsors relied heavily on data from foreign clinical trials to support their marketing applications for drugs and biologics. Eighty percent of approved marketing applications for drugs and biologics contained data from foreign clinical trials. Over half of clinical trial subjects and sites were located outside the United States. Western Europe accounted for most foreign clinical trial subjects and sites; however, Central and South America had the highest average number of subjects per site. Based on the increase in foreign clinical investigators conducting clinical trials under INDs over the last10 years and the observations of FDA reviewers, sponsors' reliance on foreign clinical trials for FDA-regulated drugs and biologics appears likely to grow.

FDA inspected clinical investigators at less than 1 percent of foreign sites. FDA inspected clinical investigators at only 1.2 percent of clinical trial sites for applications approved in FY 2008. FDA inspected 1.9 percent of domestic clinical trial sites and 0.7 percent of foreign clinical trial sites. The agency targeted domestic sites and original applications, although inspection files and interviews with medical reviewers indicated the main reason for inspecting a specific site was a large number of enrolled subjects.

OIG Report – 2010 (cont'd)

Department of Health and Human Services

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INSPECTOR GENERAL

CHALLENGES TO FDA'S ABILITY TO MONITOR AND INSPECT FOREIGN CLINICAL TRIALS

June 2010
OEI-01-08-00510

FDA should require standardized electronic clinical trial data and create an internal database. Requiring sponsors to submit their clinical trial data in a standardized electronic format would help ensure that reviewers had all necessary information from sponsors to effectively analyze the data, enable FDA to create an internal database to systematically cull clinical trial information, and enable FDA to more effectively select sites for inspection and meet its review timelines.

FDA should monitor trends in foreign clinical trials not conducted under INDs and, if necessary, take steps to encourage sponsors to file INDs. As sponsors submit future marketing applications with the results of foreign clinical trials that were not conducted under INDs, FDA should assess whether enrolled subjects were at additional risk and whether clinical trial data collected were both accurate and reliable. Should FDA determine that clinical trials not conducted under INDs compromised the rights, safety, and well-being of subjects or the integrity of the data submitted by sponsors, it should consider taking steps to encourage sponsors to voluntarily consult with FDA on their clinical trial protocols or submit INDs to the agency. FDA could also explore providing incentives to promote these, if it deems them appropriate.

OIG Report – 2010 (cont'd)

Department of Health and Human Services

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CHALLENGES TO FDA'S ABILITY TO MONITOR AND INSPECT FOREIGN CLINICAL TRIALS

FDA should continue to explore ways to expand its oversight of foreign clinical trials. To improve its oversight of foreign clinical trials, FDA could take the following additional actions:

Continue to develop inspectional agreements with foreign regulatory bodies. By sharing past inspection details as well as future plans, FDA would be better able to maximize its resources allocated to inspections of foreign clinical trial sites. FDA's recent agreement with the European Medicines Agency is a positive step for the agency to extend its oversight capability outside the United States.

Inspect clinical trials in more countries. FDA could target clinical trials in more countries, such as those in countries that the agency has not previously inspected or where Good Clinical Practice standards have only recently been adopted.

Look to new models of oversight. FDA could explore other oversight models, such as a quality risk management approach, to oversee clinical trials.

DOJ Enforcement Policy

DOJ Announces Industry-Wide Probe of Pharmaceutical Industry

"The depth of government involvement in foreign health systems, combined with fierce industry competition and the closed nature of many public formularies, creates, in our view, a significant risk that corrupt payments will infect the process. Our remarkable FCPA unit and our terrific health care fraud unit will be working together to investigate FCPA violations in the pharmaceutical industry in an effort to maximize our ability to effectively enforce the law in this high-risk area."

Lanny A. Breuer,
Assistant Attorney General
Criminal Division, DOJ
Nov. 12, 2009

DOJ Announcement (cont'd)

"Our focus and resolve in the FCPA area will not abate, and we will be intensely focused on rooting out foreign bribery in [the pharmaceutical] industry. That will mean investigation and, if warranted, prosecution of corporations to be sure, but also investigation and prosecution of senior executives. Effective deterrence requires no less.

"Indeed, we firmly believe that for our enforcement efforts to have real deterrent effect, culpable individuals must be prosecuted and go to jail where the facts and the law warrant."

Enforcement Environment : FCPA Generally

Enforcement units at DOJ, SEC and FBI

- Dozens of dedicated lawyers and agents
- SEC has reportedly dedicated 40+ lawyers to FCPA unit
- Collaboration between U.S. agencies and foreign governments

Use of law enforcement tools normally seen in “hard core” crimes

- Search warrants and sting operations
- Jan. 2010 –22 individuals charged in massive FBI sting
- Electronic surveillance
- Cooperators (*e.g.,* employees, competitors, other third parties)

2011: Cases Going to Trial

- Lindsey Manufacturing
- Shot Show Sting
- Terra Telecom

Risk Areas – Entities and Individuals

- Hospitals
- Investigators
- Charities
- Health authorities
- Inspectors
- IRBs
- Safety authorities
- Customs personnel (clinical supply chain)
- And, of course, CROs

Risk Areas – Activities

Payments to

- **Clinical trial investigators combined with:**
  - Wrongful influence over the integrity of data
  - GCP violations or subject protection issues
- **Government officials to influence approvals or obtain information**
  - 10/10 – Arrest of Chinese government official for taking bribes from pharmaceutical company in exchange for speeding market authorization for an investigational product (AGA Medical)
  - Payments for early access to information about safety, approvals, etc.
- **CROs to influence government action, or by CROs to influence such actions**
- **Investigators to bolster patient enrollment**

Risk Areas – Additional Issues

- Investigative site selection criteria
  - Why was a particular site selected?
  - Is there a justification for the need for the study?
- Payment Issues
  - Fair market value/overhead charges
  - Large up front payments without reconciliation
  - Documentation and record keeping
  - Cash payments to PIs or IRBs
- Consultants
  - Are government officials currently engaged as consultants, on the books for regular payments, etc.?

Clinical Trials Compliance: CROs

- Contract Research Organizations (CROs) perform a wide range of services across the research and development spectrum – not limited to well controlled, double-blind Phase II or III clinical trials:
  - Pre-clinical activities:
    - Animal studies
    - Tissue studies, blood work and analysis, etc.
  - Early stage clinical studies
    - Phase I –PK/PD; Healthy Volunteers
  - Phase IV – post-approval safety surveillance and other Phase IV commitments
  - Non-clinical studies – patient registries, outcomes studies, etc.
- Need to understand the needs of each study and the particular capabilities of the proposed research partner.

How to Select a Research Partner

- "Big" Global CROs may not necessarily have better qualified personnel or more impressive relationships with potential investigators or the regulatory authorities.
- Some smaller, in-country CROs can do stellar work; others may have lax practices or lots of turnover in personnel, etc.
- Global CROs may have a better reputation in the US or EMEA – what is the use you are making of the particular research? Primary or confirmatory study?
- "Qualification" and due diligence of the particular CRO should be a high priority – who is doing this? Your local country R&D organization? Your central clinical operations group? A country manager?
  - Consistent vetting on standard criteria applicable to the type of service is critical.

Selecting a Research Partner (cont'd)

- Great variability in CRO quality and efficiency
  - "Local" CROs are almost always cheaper than the large global organizations – this may or may not have any relation to the quality or experience of the CRO.
  - Companies may not share experiences (good or bad) with CROs - even among their own regional operations - due to perceived liability concerns. This is especially true in China.
  - Turnover of personnel may be high as CROs in key markets often are in bidding wars for qualified personnel.
  - You may find MDs working as a CTM or CRA - due to low government pay to physicians; alternatively you may find newly hired (and less experienced) personnel staffed on your trial due to high demand in the region.
- Many large multi-national companies have negotiated contracts with Global CROs – but often driven by procurement, may not be well versed regarding quality and compliance issues in local markets.
  - Contacts may not address significant practical issues, such as turnover rates in personnel; approval of permissible sub-contractors, etc.

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Bribery/Corruption and CROs

- Corruption is perceived as endemic in many countries - especially China and India - but not so much in other foreign markets (*e.g.,* Japan, Australia, Costa Rica).

- Policies governing payments often run into local limitations (especially “cash"). Cash payments are commonly forbidden by global policies.

- Corruption by physicians is exacerbated by policies in countries which require payments to be made to government hospitals where the physicians may not be adequately compensated (the corruption may exist at the hospital level with physicians underpaid) - a particular problem for Principal Investigators.

- Selection of PI and placement of trial locations may be subject to bribery in government owned facilities.

Bribery/Corruption and CROs

- Typical issues to address in due diligence/contracting with CROs – Compliance Considerations:
  - Do any of the principals of the CRO have close family ties or relationships with government officials, or are they co-owned by government officials?
  - What is the CRO's reputation for integrity in the market?
  - Have any media reports been issued calling the CRO's reputation into question?
  - Does the CRO have a compliance officer, compliance program, or compliance policies and training? If not, obligate them to comply with your company's program and get trained.
  - Does your contract include a clause that prohibits the CRO from making corrupt payments to investigators, government officials, customs agents, etc.?

Post-Engagement: Use of CROs

- Often a significant communications/coordination gap between “global trials" that are being managed by personnel in the US or Europe, and local or regional clinical and compliance/quality resources in specific regions/countries. Possible results:
  - Local knowledge of CRO capability or performance issues which are not shared with global/headquarters trial managers.
  - Variations in policy (global vs. local) regarding accepted handling of payments and accounting that cannot easily be explained re: “fair market value", "payments to HCPs" and payments to government officials (FCPA/UK Bribery Act issues).
  - Use of "unqualified" (no formal qualification or less formal than global standards) CROs by local trial managers.
  - Lack of controls over sub-contracting or use of temporary employees.

Clinical Trials: Data Integrity Issues

- Significant and real concern of companies and regulators
  - DOJ prosecutors have indicated this area is a priority.
  - Consistent with DOJ view that “patient safety” safety issues a key factor in decision making.

- Contracts that offer incentives for enrollment may lead to "phantom" trial participants:
  - Completely falsified data for participants that do not exist.
  - The inclusion of trial participants that should have been excluded by protocol - but whose medical records may be altered (forged) to allow enrollment.
  - The use of test samples (duplicates or partitioned) from legitimate patients to provide test results for a fabricated participant record.
  - “Pay for results" - this is the biggest concern for FDA - the possibility of false/fabricated data being used in submissions.

Data Integrity Issues – Compliance Strategies

- The type of compliance program you have in place should reflect the risks posed by the country, your contractor, the type of trial and your comfort with your company's controls.
  - Know your market, including the health system structure, role of relevant institutions and individuals, and cultural practices
  - Tailor your compliance practices as necessary
- Are you using the monitoring and auditing resources available to you internally? Internal Audit? Quality? Compliance Auditors? External resources?
- Have you conducted appropriate due diligence in qualifying your CROs? What are your CRO's procedures for assessing their sub-contractors or their selected PIs and sub-investigators?

Data Integrity Issues – Compliance Strategies

- What contractual rights do you have to ensure compliance, provide effective oversight, and take action if problems arise?
- What is your level of control and approval of items such as the Fair Market Value (FMV) of investigator payments, recruitment budgets, etc?
- How involved are the local country personnel? Are improper incentives posing a risk?
- How well is feedback on performance of CROs shared across your organization, including among local country organizations?

Questions?

Sue Sefarian
Health Care Compliance Officer
Johnson & Johnson
609.730.6601
sseferia@its.jnj.com

John T. Bentivoglio
Skadden Arps Slate Meagher & Flom LLP
202.371.7560
john.bentivoglio@skadden.com