Clinical Trials Abroad: Managing the Legal Risks
Navigating Regulatory and Privacy Challenges, Minimizing FCPA and Other Risks

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Today’s faculty features:
Maureen Bennett, Partner, Squire Sanders, Boston
Jan Murray, Of Counsel, Foley & Lardner, Boston

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Clinical Trials Abroad: Managing the Legal Risks

Jan E. Murray
Foley & Lardner LLP
Boston, MA
617-226-3132
jemurray@foley.com
Presentation Overview

- Growth in Global Clinical Trials
- International Regulatory Framework for Conduct of Clinical Trials
  - Support of Drug Marketing Authorizations
    - ICH/GCP
    - Academic International Research
- Good Clinical Practices
- Conducting Clinical Trials
  - Responsibilities of Sponsor
- Clinical Trial Agreements: Insurance/Indemnity
Growth in Global Clinical Trials

- From the US perspective, clinical trials in support of marketing authorizations have increasingly been conducted outside the US.
  - “Sources have estimated that between 40% and 65% of clinical trials investigating FDA-regulated products are conducted outside the US.” (OIG, “Challenges to FDA’s Ability to Monitor and Inspect Foreign Clinical Trials,” June 2010)
Growth in Global Clinical Trials

- From European perspective, growth in trials conducted outside the EU/EEA/EFTA is increasing:
  - According to a Reflection Paper published in April 2013 by the European Medicines Agency (EMA), of the total number of pivotal trials for drugs in the years 2005-2011 subject of EU authorisation applications, 27.8% were conducted in the ROW (outside EU/EEA/EFTA and US/Canada) for that period with the trend generally on an upward trajectory.
International Regulatory Framework
Clinical Trials Marketing Authorizations

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- ICH was organized in 1990 in response to concerns about new and increasingly fragmented regulation world-wide that was drastically slowing the process of securing authorizations to market new drugs even as pharmaceutical companies were increasingly global in operation
International Regulatory Framework
Clinical Trials Marketing Authorizations

- The ICH is a joint effort of industry and government authorities of the United States, Europe and Japan
  - Industry represented by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
  - US Food and Drug Administration (FDA), European Medicines Agency (EMA), Japan Ministry of Health, Labour and Welfare (JMHLW)
Conducting International Academic Biomedical Research

- For US academic institutions, Office for Human Research Protections (OHRP) oversees through the Federalwide Assurance (FWA) program international research conducted or supported by a federal agency
  - Must conform to the Common Rule, 45 CFR Part 46, in domestic and foreign institutions where research is conducted or supported by federal agency
Conducting International Biomedical Research

- In July 2011, OHRP released an Advanced Notice of Proposed Rule-making that discussed a proposal to significantly revamp the Common Rule (76 Red. Reg. 44512, 7/26/2011)

- The proposal would result in a risk-based approach to review of research to better calibrate the level and intensity of review to the risk and would “de-regulate” certain types of social and behavioral research
Conducting International Biomedical Research

- Foreign institutions that are the site of US conducted or supported research must complete an FWA for international sites.
- OHRP permits an agency to substitute an equivalent standard and cites several widely accepted international standards on international FWA but in notice stated that these were not intended as routine substitutes for Common Rule (71 Fed Reg 38645, 7/7/2006).
Other International Standards Biomedical Research

- World Medical Association
  - Declaration of Helsinki and progeny
- Council for International Organizations of Medical Sciences (CIOMS)
  - International Ethical Guidelines for Biomedical Research Involving Human Subjects
- World Health Organization
  - Handbook for Good Clinical Research Practices
International Regulatory Framework
Biomedical Research

- Clinical research conducted also subject to laws and regulation of the foreign jurisdiction
- Office for Human Research Protections (OHRP) of the US Department of Health and Human Services publishes an exhaustive compendium of standards, guidelines, laws and regulations world-wide that is regularly updated
  - “International Human Research Standards, 2012 Edition” is available on the OHRP website
International Research Issues—Academic

- Organisation for Economic Co-operation and Development (OECD), Global Science Forum published a paper outlining difficulties in conducting research internationally for non-commercial purposes.
  - Points to complexity and fragmentation of regulation by countries.
  - In EU alone, the number of applications for non-commercial trials fell by 25% between 2007-2011.
In February of this year, OECD recommended an approach to harmonizing regulation of non-commercial trials.

In 2012, OECD published recommendations regarding the “Governance of Clinical Trials” that proposes adopting a risk-based approach.
International Regulatory Framework

Definition of GCP:

- International ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects
- General principles incorporate concepts that are common to many other international standards
Good Clinical Practices

- Based on US Food and Drug Administration (FDA) regulations first developed in the 1970s that are a variant of the so-called “Common Rule”
  - See comparison of Common Rule versus FDA regulations posted on FDA website
  - Regulation of trials in support of marketing authorizations, 21 CFR 312; 21 CFR 812
  - Human Subjects Protections, 21 CFR Parts 50 and 56
Good Clinical Practices

- ICH/GCP adopted as guidance by FDA as are other ICH guidelines; posted on fda.gov (Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance 1996)

  - Ethical guidance/human subjects protection, see Directive 2001/20/EC

- Adopted in Japan by the Ministry of Health, Labor and Welfare and revised in 2008 to ease burden of conducting trials
Good Clinical Practices

- Adopted as guidance or regulation by many countries world-wide and is seen as the “gold standard” for clinical trials in support of marketing authorizations
Principles of GCPs

- Note: The principles that follow are based on US adopted guidance; each country regulates or formulates GCP guidance differently.

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
Principles of GCPs

- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.
- The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
Principles of GCPs

- The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

- The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

- Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
Principles of GCPs

- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
Principles of Good Clinical Practice

- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
- Systems with procedures that assure the quality of every aspect of the trial should be implemented.
Summary Outline of GCP Requirements

- **Note:** The following description is based on US adopted guidance; each country regulates or formulates GCP guidance differently.
- Identifies the Role of the IRB in protecting human subjects
- Specifies the Role of the Investigator
  - Qualifications
  - Adherence to protocol
  - Securing informed consent
  - Reporting responsibility
Summary Outline of GCP Requirements

- Clinical Trial Protocol Requirements
  - Trial Design
  - Trial Objectives and Purpose
  - Treatment of Subjects
  - Assessment of Efficacy
  - Assessment of Safety
  - Data Handling
  - Financing and Insurance
  - Publication Policy
Summary Outline of GCP Requirements

- Investigator Brochure
  - Essential information

- Essential documents for the conduct of the trial
GCP Requirements for Sponsors

- Responsible for Trial Design
  - Must use qualified experts for each stage from design to preparation of reports
- Quality Control
  - Implement and maintain quality assurance and quality control systems with written SOPs; sponsor must have direct access to all trial-related sites and source documents
  - Trial Management, Data Handling; Record-keeping; and Independent Data Monitoring Committee
GCP Requirements for Sponsors

- Selecting Investigators
  - Must select investigators qualified by education, training and experience to conduct the trial
  - Acquaint investigator with protocol; secure an agreement (Clinical Trial Agreement (CTA)) with investigator and institution to conduct trial in accord with protocol, GCPs and observe data collection auditing and record-keeping duties

- Compensation to Subjects and investigators
  - If required, sponsor should insure or indemnify investigator/institution against claims arising from the trial except for malpractice

- Financing the Trial
  - Should be documented in CTA
GCP Requirements for Sponsors

- Confirmation of Review by IRB
  - Secure documentation of IRB review and action from investigator and monitor subsequent reviews and action by IRB (should also be addressed in CTA)
- Provide Information on Investigational Product
- Notification of Regulatory Authorities
GCP Requirements for Sponsors

- Manufacturing, Packaging, Labeling and Coding

  - Investigational Product
    - Product and comparators properly labeled and manufactured in accordance with GMP and coded in a way that protects blinding
    - Provide information to enable investigator to properly store product
    - Permit rapid ID of blinded product in case of medical emergency
    - Provide notice and information in case or significant formulation changes
GCP Requirements for Sponsors

- Record Access—CTA should ensure that investigator/site provides direct access to documents
- Safety information—responsible for ongoing safety evaluation
- Adverse Drug Reactions—expedite required reporting
- Premature Termination or Suspension—promptly inform investigators and ensure that clinical trial reports are prepared and submitted
GCP Requirements for Sponsors

- Sponsors have extensive monitoring responsibilities
  - Through monitoring, sponsor has to ensure that the rights and well-being of human subjects are protected; reported data trial is accurate, complete and verifiable; and that the trial was conducted in accordance with GCPs
  - Sponsors must select and appoint qualified monitors
GCP Requirements for Sponsors

- Monitoring responsibilities, cont’d.
  - Sponsor has to ensure that the monitoring program is adequate for the nature and size of the trial
  - Monitors must verify that all aspects of trial—investigator qualifications; appropriate storage of product; compliance with protocol; securing informed consent; enrollment of appropriate subjects; maintenance of all source documents; accuracy and completion of CRFs; review adverse event, subject dropout, dose/therapy modifications; and communicating deviations from GCP, protocol other requirements; prepare monitoring report
GCP Requirement for Sponsors

- Sponsor must develop and implement auditing plan which should be governed by number of subjects, risk and regulatory importance; audit reports should not be routinely requested by regulators.
Sponsors and CROs: GCP Requirements

- Sponsor may transfer any or all of the sponsor’s trial-related functions to the CRO but ultimate responsibility rests with Sponsor.
- Any function transferred to CRO must be documented in writing; any not specifically transferred to the CRO are retained by the Sponsor.
- All references to the Sponsor in the guidance apply to CRO if it has assumed that responsibility.
Key Take-away(s) for Sponsors

- Must have adequate staff in both numbers and education, training and experience who are properly supported to conduct the trials.
- Any outsourced function has to be actively monitored and managed by the Sponsor.
- Trials should be adequately insured both in terms of sponsor and subject risks.
Clinical Trial Agreements/Allocation of Responsibility Among Key Players

- Insurance against Human Subject Injury: Some countries by regulation or by custom require a clinical trial sponsor to be insured against claims arising from injuries to human subjects (See e.g., guidelines of Association of the British Pharmaceutical Industry)

- Not usually required in US but US companies will purchase coverage (master product liability or human clinical trial liability policy)
Clinical Trial Agreements/Allocation of Responsibility Among Key Players

- Both sponsors and institutions should understand how these policies work in international trials and with indemnity clauses.
- If these master liability clauses are written to cover “Differences in Conditions” or “Differences in Limits” that arise from when nationally required policies fall short, company (and others) will be protected if for example lower limits of nationally required policy falls short (see Goudsmit, F., 9 JClinResBestPrac, February 2013).
AGENDA

- International Clinical Trial Agreements/Contractual Issues
- Informed Consent/Data Privacy
- Outsourcing and CRO/ARO Management
- Foreign Corrupt Practices/Anticorruption
- Risk Based Monitoring
- Clinical Data Transparency
- Other Emerging issues
Challenging Clinical Trial Agreement Issues

- Identity of the parties (e.g., is PI an employee of the institution?, is CRO a party)
- Payments to Institution/PI or both
- PI commitment to conduct trials in accord with ex-local laws
- Indemnification by Institution
- Institution Insurance
- Subject Injury/Sponsor Insurance
- Consistency with ICF
CTA Issues in Certain Jurisdictions

- Approved CTA templates (e.g., Australia, UK, The Netherlands)
- Tripartite Agreements including CROs (UK)
- Even where no approved templates, in some jurisdictions site templates required as a practical matter (Spain, Italy, France)
- Separate CTAs for site, PI and pharmacy (France) and CNOM approval of payments
- Some Institutions are not legal entities (e.g., Mexico)
- Some Institutions/PIs have affiliated entities (e.g., Brazil, Chile, Israel)
- Private Office (Colombia)
Increased Focus on Ethical Issues on Global Basis
Importance of Demonstrating Free Will in Consent
Protection of Subject Privacy
E.g., EU has issued series of Reflection Papers on Ethical Issues

Key Themes Developed include:

- Need for Capacity Building for ECs
- Need for GCP Inspections before marketing authorisation phase
- EMA to prioritize countries for enhanced scrutiny
- MA dossiers to include more details on:
  - Independent EC review
  - Fair compensation for injury
  - Justification for placebo
  - Justification for including vulnerable populations
  - Access to treatment post-trials
ETHICAL ISSUES
INFORMED CONSENT/DATA PRIVACY

- US High Profile Ethical Concerns:
- Pfizer/Trovan trial in Nigeria
- Public Citizen attention to foreign trials
- SuPPORT Trial
- Havasupai Native American
- US Government admits deliberately infecting Guatemalan citizens in 1940s with STDs
- High Profile product liability issues tied to alleged financial arrangements between companies and HCPs
US - In 2011, President Obama directs Presidential Commission for Study of Bioethical Issues to “determine if federal regulations and international standards adequately guard the health and well-being of participants in scientific studies supported by the Federal [US] government.”

Commission convened International Research Panel consisting of experts from Brazil, India, Russia, China, Argentina, Belgium, Guatemala, Uganda, Egypt and US.
KEY FINDINGS FROM COMMISSION:

- Community Engagement is important, but not a guaranty of ethical research
- Individual Consent always required, even in hierarchical/patriarchal communities
- Funders of research should support training of investigators and IRB/EC members
- Additional attention to harmonizing existing standards, rather than adopting new standards
- US should implement system/fund to compensate research subjects for research-related injuries
INFORMED CONSENT/DATA PRIVACY

- Translations
- Genetic Information
- Risks and Procedures
- Subject Injury
- Continuing Access
- Data Protection
INFORMED CONSENT/DATA PRIVACY

- HIPAA
- EU Privacy Directive
- Canada Personal Information Protection and Electronic Documents Act (PIPEDA)
- New Zealand Privacy Act
- Australian Health Privacy Guidelines
- Japan Personal Information Protection Law
- Argentina Health Privacy Law
- Other Countries
  - Chile, Mexico, Paraguay, Peru, Brazil
Managing CRO Relationships

- Differing/Expanding Roles of CROs/AROs/SMOs in global clinical contracting
- Used to be roles were limited to outsourcing of discrete tasks or to handle defined capacity shortfalls
- Today’s role is more oriented toward programmatic outsourcing/supporting both virtual companies and multinationals
OUTSOURCING AND CRO/ARO MANAGEMENT

- Defining Roles/SOWs
- Collaboration or Outsourcing?
- SOP Compliance/Which Party’s?
- MSA Coordination with CTAs
- Letters of Delegation/Powers of Attorney
- Assignment and Termination-CROs in play with private equity firms
- Non-Compete?
- Performance metrics/Shared Risk and Reward
OUTSOURCING AND CRO/ARO MANAGEMENT

- CRO as signator “on behalf of Sponsor” (does local law allow for third party beneficiary enforcement of rights?)
- CRO involvement in payments/budgets/CTAs
- Who communicates with Investigators?
- Legal Representative for EU Clinical Trial Directive or Data Privacy Directive
- CRO responsibility for Affiliates and Subcontractors
OUTSOURCING AND CRO/ARO MANAGEMENT

- CRO Compliance Systems-Verification and Auditing
- CRO Monitoring Plan for Study-Risk Assessments
- CRO Alignment with Risk Based Monitoring Guidance
- Co-Monitoring proposals
- FCPA/Anti-Corruption/GCP Training
OUTSOURCING AND CRO/ARO MANAGEMENT

- Attention to Site/Investigator performance and resources
- IRB/EC Assessment
- Clear contractual delineation of Sponsor, CRO, site, investigator duties
- Local ICF and data privacy compliance
- Implement Quality System Oversight
- Implement Risk Based Monitoring
- Consider new EMA inspection factors (vulnerable populations and high risk countries)
- SOP Compliance
Foreign Corrupt Practices Act

“Prohibits companies or their agents from using a payment or the promise of a payment of anything of value to a foreign official...directly or indirectly, to influence his or her official actions in violation of his or her duty, or to secure improper advantage or to induce the person to use his influence to affect official action.”
FOREIGN CORRUPT PRACTICES/ANTICORRUPTION

- Also prohibits use of intermediaries or subsidiaries to make corrupt payments
- Most HCPs in ex-US hospitals are foreign officials for FCPA purposes
- Pharmaceutical and health care industry are among the watch list of DOJ
US Foreign Corrupt Practices Act
- Prohibits bribery of non-US “foreign officials” by US people or companies
- Requires US issuers to maintain accurate books and records and reasonable accounting controls

UK Bribery Act
- Commercial bribery also prohibited
- No exception for facilitation payments
- Corporate offense for failure to prevent bribery
- Pharma/Med Device Trade Standards

Other Countries’ Anti-bribery Laws
Direct payments to investigators or entities controlled by them

Payments not transparent to the clinical trial site organization

Start-up fees

Equipment donations

Patient recruitment referrals or incentive payments

Associated consulting arrangements

Research collaboration arrangements

Clinical research organizations and other intermediaries

Travel and hospitality associated with clinical trial work
FOREIGN CORRUPT PRACTICES/ANTICORRUPTION

- Risk Minimization Strategies:
  - Adopt comprehensive policies, applicable to pre-marketing and post-marketing relationships with HCPs
  - Adherence to 2003 OIG Guidance, PhRMA Codes, Disclosure laws
  - Carefully document and audit all services rendered by HCPs, including level of effort, need for services and compensation for FMV
  - All contracts provide confirmation PI/HCP of compliance with applicable Institution/government funding agency COI rules
  - Ensure that CROs and other agents have policies in place; include language in contracts
Background

- FDA/EMA focus on quality systems of sponsors
- FDA 2010 New Guidance on Investigator Oversight
- FDA establishment of foreign offices
- FDA July 2010 Clinical Investigator Inspection Checklist focusing on international sites (including vulnerable populations and countries where site inspection has not been conducted)
- FDA/EMA- Joint Cooperation Initiative-General Trend on information/compliance coordination
FDA issued its guidance based on “increased variability in investigator experience, ethical oversight, site infrastructure, treatment choices, standards in health care and geographic dispersion.”

This guidance focuses on monitoring methods used by sponsors or delegated CROs to oversee conduct of and reporting of data from clinical investigations.

The primary focus is protecting human subjects and maintaining integrity of data.
Risk Based Monitoring

- Backdrop is Clinical Trial Transformation Initiative (multi-stakeholder public-private partnership to improve monitoring.
- Industry monitoring focus is on “periodic, frequent visits to each clinical investigator site”
- Academic and government rely more on centralized and alternative monitoring
- FDA says growing consensus that risk-based monitoring that focuses on most critical data elements are more likely to ensure subject protection and overall study quality.
- Recognition of increased role of technology in data collection/transmission
FDA to allow sponsors to submit monitoring plans for ‘feedback’

Transcelerate proposal for “model” RBM plans

The most important tool is “a well-designed and articulated protocol”, as poorly designed protocol or CRFs can render a trial unreliable despite rigorous monitoring

FDA discusses relative value and role of different onsite and centralized monitoring.
Onsite Monitoring-can identify data entry errors; provide assurance that study documentation exists and assess familiarity of study staff with protocol and staff attention to detail. Onsite monitoring best done early-on in trial, as findings can lead to opportunities for training.
- Centralized Monitoring - FDA encourages greater reliance on centralized monitoring
- Standard checks of range for consistency and completeness of data
- Statistical Analyses of data trends and aggregate analyses
- Verify source data remotely
- Assess Site characteristics and performance metrics (screen failures, eligibility violations)
In developing monitoring plan, sponsors should perform a risk assessment for each trial that considers types of data to be collected, activities required and range of potential safety and human subject protection issues.

Following data should be subject to more intensive monitoring: critical study endpoints, protocol required safety assessments; evaluation of adverse events; adherence to protocol eligibility criteria; procedures for maintaining the blind; verification that informed consent obtained properly; procedures for study drug accountability.
Factors to Consider in Developing Monitoring Plan:

- Complexity of study design
- Type of endpoints
- Clinical complexity of study population
- Geography
- Relative experience of PI and of PI and sponsor
- EDC use
- Safety of study drug
- Quantity of data
Monitoring Plan should clearly define roles, including CRO roles

Plan for managing non-compliance, including root-cause analyses

Perform Study Specific training, including CRO monitors and investigators

Alternative training may be appropriate—webinars, online training

FDA again states that sponsors remain ultimately responsible, even if duties transferred to CRO
In addition to financial transparency, issues arising regarding data transparency
- GSK announcement re: available patient level data
- EMA proposal regarding availability of CSRs
- Transcelerate initiatives
OTHER EMERGING ISSUES

- Adaptive Clinical Trials
- Crowdsourcing
- E-PRO increase
- Fraud/Data Manipulation

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