

Conducting Clinical Trials in the US and Abroad: Navigating the Rising Tide of Regulation and Risk¹

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I. Introduction: Legal Framework and Regulatory Guidance for the Conduct of Clinical Trials

This section overviews the legal framework for conducting clinical trials in the US and abroad for clinical trials involving Food and Drug Administration (FDA)-regulated trials and those that are launched by US entities such as academic medical centers (AMC) that are not subject to FDA regulation. Other laws that also affect certain aspects of the clinical trial implementation will also be considered. Also included in the overview is information about major regulatory guidelines set forth by international bodies such as the International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH).

A. Legal Framework for Conduct of Clinical Trials in the US and Abroad for FDA-regulated products

Clinical trials are conducted by US pharmaceutical and medical device companies in support of an application to the FDA for authorization to market a drug or device. Pharmaceuticals and biologics are regulated under a different set of laws and regulations than apply to medical devices but both are regulated by the FDA. This subsection will focus on Investigational New Drug applications (INDs) that must be completed to file a New Drug Application (NDA) because most clinical trials conducted by pharmaceutical and biotech companies are undertaken pursuant to an IND.

The level of regulation imposed on medical devices before and after their introduction into the market place depends upon the classification of the device. Medical device companies seeking to bring to market a Class I or Class II medical device must simply file a pre-market notification, known as 510(k), unless the device is exempted from this requirement. A Class III device, those that are subjected to the strictest

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regulation, must be tested in clinical trials that are conducted pursuant to an Investigational Drug Exemption (IDE) in support of a Pre-Market Approval application (PMA). Differences in the regulation of clinical trials conducted pursuant to IND and IDE regulations will be noted.

i. Applicable Federal Law and Regulation Governing Clinical Trials

The federal Food Drug and Cosmetic Act (FD&C) (21 U.S.C. §§ 301-392) was passed in 1938 after a tragedy involving a deadly sulfanilamide elixir; it required FDA testing for safety for the first time. In 1962, Congress passed significant amendments to the Act adding a requirement for proof of efficacy before marketing of drugs in response to the thalidomide tragedy. While the 1938 FD&C included devices, it was not until the passage of the Medical Device Amendments to the FD&C in 1976 that the classification of devices that provides the framework for FDA regulation of these devices was created.²

Section 505 of the FD&C (21 U.S.C. § 355) provides that no person may introduce a new drug into interstate commerce without first filing an application with the FDA. This section of the law specifies the general content of such an application. The FDA promulgated regulations implementing this section of the FD&C at 21 C.F.R. § 312. In 1991, the FDA and the Department of Health and Human Services (DHHS) adopted the so-called “Common Rule” intended to protect the rights of human subjects enrolled in clinical trials. This is codified at 45 C.F.R. Part 46 Subpart A for those clinical studies conducted by or with the support of federal agency or department and at 21 C.F.R. Parts 50 and 56 for those products subject to FDA regulation; the former are discussed in greater detail in a later section of this paper.

21 C.F.R. Part 312 describes the requirement for an IND before any clinical investigation of a new drug can take place. Generally, clinical trials in support of an NDA are divided into three phases that typically occur sequentially. An IND may apply to one or more of the clinical phases and must include detailed information about the design of the clinical investigation, the investigators who will conduct the trials and how the data will be gathered, maintained and analyzed. If a foreign clinical trial site is included in the IND, then the data gathered from that site is included in the NDA. Upon completion of the IND, if warranted, the sponsor will submit an NDA pursuant to 21 C.F.R. Part 314.

Medical devices subject to an IDE which will be tested in humans are regulated by 21 C.F.R. Part 812. An IDE is required for those devices that may not simply be introduced in the market by filing a 510(k) or pre-market notice and require a PMA. The manufacturer of the device must conduct trials to demonstrate the device’s safety and efficacy and these are conducted pursuant to Part 812.

² Other significant federal legislation has been passed in this decade that affects the way the regulatory framework is administered—i.e., the Medical Device User Fee and Modernization Act of 2002, P.L. 107-250, 116 Stat. 1588 (codified as amended in scattered sections of 21 U.S.C.), which permits the FDA to levee fees on applicants seeking product review. Also, the Pediatric Research Equity Act of 2003, P.L. 108-155, 117 Stat. 1936 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.) encourages drug companies to perform clinical trials. A discussion of these laws is beyond the scope of this paper.

All clinical trials conducted to secure FDA marketing authorization must adhere to 21 C.F.R. Parts 50 and 56 which are regulations designed to protect the rights of human subjects. Part 50 governs the requirement for securing informed consent from human subjects who participate in clinical trials. This requirement applies not only to drug trials but to any clinical investigation that involves other substances (e.g., food, additives) or medical devices.³ The general requirement for informed consent is set forth in 21 C.F.R. § 50.20:

[N]o investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Part 50 also includes requirements for documentation of consent and exceptions for the requirement, as well as special safeguards for children and other vulnerable populations. Further guidance on the FDA's view of informed consent is provided in its *Guide to Informed Consent*.⁴ The FDA has also adopted additional guidance in the form of the ICH *Good Clinical Practices* (GCP) which are discussed in greater detail below. FDA publishes guidance and information sheets to provide industry and researchers with more information about the agency's views on application of regulations among other topics.⁵ The guidance is not binding on the agency but is very helpful to those seeking to conform to the regulations.

21 C.F.R. Part 56 sets forth the legal obligation to secure review of any clinical investigation subject to FDA regulation by an independent body known as an Institutional Review Board (IRB).⁶ Under the requirements set forth in 21 C.F.R. Part 56, the IRB must not only approve the investigation before it can commence but also must monitor it and ensure that it is conducted in accordance with the approval given by the IRB. Part 56 also sets forth requirements for the composition and operation of the IRB. IRBs must meet these requirements to be qualified by the FDA. If the FDA determines that a registered IRB is not adhering to the regulations and that the lack of compliance may adversely affect the rights or safety of

³ 21 C.F.R. § 50.1

⁴ FDA, *Guide to Informed Consent*, April 30, 2009, <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm116333.htm>.

⁵ 21 C.F.R. § 10.115 describes the agency's guidance issuance practices.

⁶ 21 C.F.R. § 56.101. Under newly implemented regulations, IRBs that oversee research conducted involving FDA regulated products must now be registered with the FDA. 21 CFR §56.106.

human subjects, it may disqualify the IRB. In this case, the IRB may not oversee clinical investigations that support FDA marketing authorization or other action.⁷

21 C.F.R. § 56.105 permits waiver of the requirement for IRB review upon application by the sponsor to the FDA; a waiver may be granted by the FDA in circumstances where the agency determines that the rights of the human subjects can be protected by other mechanisms. These alternative mechanisms include review by an independent ethics committee operated under the regulatory framework of another country that adheres to international standards of clinical practice, which are described in the next section.

21 C.F.R. Part 54 requires certain disclosures regarding financial relationships between sponsors and investigators as a financial relationship may create a conflict of interest for an investigator that could adversely affect the trial outcome.

ii. Good Clinical Practices

Good Clinical Practice guidelines (GCPs) were formulated by the ICH, which was established in 1990 and is a partnership between government regulators and industry brought together to rationalize and harmonize regulation of pharmaceuticals. ICH founding members were industry and government representatives of the European Commission, the United States and Japan—these countries are the originators of most new drug development. In addition, others participate as observers—Canada, European Free Trade Area and the World Health Organization.⁸

The GCPs were prepared by the ICH's expert working group (EWG) on efficacy and were endorsed by the ICH Steering Committee in 1996. The EWGs have also developed other guidance pertinent to clinical trials and have contributed other important tools to the regulatory regime including MeDRA, the Medical Dictionary for Regulatory Activities, a compilation of medical terminology.

The GCPs reflect the US regulatory scheme codified at 21 C.F.R. Parts 312, 50 and 56 described above. The FDA has also adopted the GCPs as guidance.⁹ GCPs are:

a standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety and well-being of trials subjects are protected.¹⁰

⁷ 21 C.F.R. § 56.121

⁸ ICH.org, *Structure of ICH*, <http://www.ich.org>, (last visited September 14, 2009).

⁹ International Conference on Harmonisation; Good Clinical Practice: Consolidated Guideline, 62 Fed Reg. 25692 (May 9, 1997).

¹⁰ Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, 69 Fed Reg. 32469 (June 10, 2004).

While reflecting the US regulatory scheme, the GCPs provide greater detail on the roles, responsibilities and methodologies of designing, conducting and analyzing clinical trials. The GCPs incorporate many of the principles enunciated in the *Declaration of Helsinki*, a document that is one of the foundations of modern thinking on ethics in human experimentation.¹¹ The *Declaration of Helsinki* was adopted by the World Medical Association in 1964 and has since been amended several times, most recently in 2008.¹²

The general principles incorporated into the GCPs include:

Identifying and weighing the risks against anticipated benefits; the primacy of rights, safety and well-being of the individual over the interests of science and society; the necessity for a scientifically sound design reduced to writing in a clear detailed protocol; IRB or Ethics Committee review; use of qualified investigators to conduct the trial and qualified persons to provide medical care; the importance of freely given consent; accurate and verifiable recording and reporting of clinical trial information; preservation of subjects' confidentiality; observation of Good Manufacturing Practices in manufacturing,¹³ handling and storage of the drug and administration of the drug in accordance with the protocol.

The GCPs in several sections detail the roles and responsibilities of sponsors, investigators and requirements for data collection and analysis and record retention, among many other matters.

The GCPs have been widely adopted internationally and are the standard recognized by the legal authorities of many countries where clinical trials are conducted. The GCPs have been adopted as regulation or guidance in the founding ICH governments of the European Union, US and Japan, as well as other Commonwealth countries (e.g., Australia, Canada), Asia and South America.¹⁴

The Global Harmonization Task Force (GHTF) was founded in 1992 with a purpose similar to the ICH but for the medical device industry. The GHTF was founded by the regulatory authorities of 5 governments: European Union, Canada, Australia, United States and Japan.¹⁵ Its work groups have proposed the adoption of standards formulated by the ISO for certain aspects of clinical investigations. The FDA has sought public comment regarding these proposals in advance of further guidance in the area.¹⁶ However,

¹¹ World Medical Assoc., *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (as amended Oct. 2008), <http://www.wma.net/e/policy/pdf/17c.pdf>.

¹² There are other statements of ethical principles that have been adopted by world bodies (e.g., Counsel for International Organizations of Medical Sciences that has adopted the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*) or by national authorities such as the "Belmont Report," a product of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

¹³ Murray, J; "Legal Issues in the Conduct Of Multinational Clinical Trials by US Entities," in Steiner, J., ed., *Clinical Research Law and Compliance Handbook*, Jones and Bartlett Publishers, 2005

¹⁴ See, eg., the work of the Pan American Health Organization and the Association of Southeast Asian Nations that have used the GCPs to harmonize regulatory efforts among its neighbors.

¹⁵ <http://www.ghrf.org/>

¹⁶ 73 Fed Reg 39968, July 11, 2008

those conducting clinical trials to gather data on medical devices for regulatory purposes are subject to the regulations enshrined in 21 CFR Parts 812, 50, 54 and 56.

B. Legal Framework for Conduct of Clinical Trials in the US and Abroad by US Academic Medical Centers (AMCs) Not Subject to FDA Regulation

A regulatory regime is imposed on all persons and entities receiving federal funding for human subjects research through 45 C.F.R. Part 46; compliance with these regulations is overseen by the Health and Human Services Office for Human Research Protection (OHRP). 45 C.F.R. Part 46 includes subparts A through D; Subpart A is the heart of the Common Rule, while Subparts B through D address protections for special populations. Federal departments and agencies that fund or oversee research involving human subjects must adhere to the Common Rule even though the agencies may have different regulations or additional policies that reflect their mission but are still consistent with the Common Rule. As described earlier, the FDA's "Common Rule" regulations include requirements that relate to its mission to approve marketing of drugs and devices, but also see the National Science Foundation and National Institutes of Health (NIH) for additional policies and procedures related to research. It is critical to be aware of the requirements of the agency funding the research that will be performed outside the US.

Generally, all non-US sites conducting research that is funded or supported by a federal agency must meet the requirements of 45 C.F.R. Part 46. DHHS requires that all institutions that receive federal funding in support of research complete a Federal-wide Assurance (FWA) for approval by the OHRP that documents that the institution complies with the requirements of 45 C.F.R. Part 46, including identification of the IRB that meets the requirements.¹⁷ Any institution outside of the US that is engaged in federally conducted or funded research involving human subjects must complete an International FWA that indicates the human rights protection standards to which it adheres and that such standards comply with 45 C.F.R. Part 46.^{18,19} Engagement in research involving human subjects means that an institution will

¹⁷ IRBs must also be registered with OHRP and also with the FDA if overseeing research involving FDA-regulated products; see 21 CFR §56.106.

¹⁸ 71 Fed Reg 38646, July 7, 2006 wherein DHHS clarified that although several international standards are listed on the FWA for international sites, any such standard must still comply with 45 CFR Part 46.

¹⁹ The heads of agencies that fund human subjects research and are subject to the Common Rule may undertake the following: "When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy." See also discussion of OHRP's responsibility.

intervene or interact with living individuals for research purposes or obtain individually identifiable private information for research purposes.

NIH will also make some grants to foreign institutions typically as consortia members or subcontractors to US institutions. All grants that support research involving human subjects, wherever conducted, must adhere to the Common Rule, and foreign sites where research is conducted must have been the subject of an FWA filed with OHRP.

An international compilation of global national laws governing protection of human subjects is available on the Office of Human Research Protections (OHRP) website.²⁰

C. Other Laws Applicable to US Entities Conducting Research in the US and Abroad

i. In the US: State Law

State law shapes certain fundamental aspects of human rights protection for participants in clinical trials and may directly regulate the conduct of the trials. For example, state law defines who is legally capable of giving consent and may provide additional protections for clinical trial participants or special populations.²¹ State tort law also defines legal liabilities and limits that affect rights of compensation for clinical trial participants as well as the exposure of those conducting the trial. Some states are more actively regulating clinical trials to ensure accessibility by mandating insurance coverage of costs of trials by Medicaid programs or private insurers.²² While a review of all state laws are beyond the scope of this presentation, it is important for all entities conducting clinical trials to understand applicable state law. GCPs require that sponsors observe all applicable laws and the federal Common Rule does not preempt state regulation of clinical trials where it provides greater rights.²³

ii. Ex-US: Federal Law Applicable to International Activity by US Entities

Both AMCs and industry should be aware of certain federal law that applies to all US entities doing business internationally. Although commercial activity outside the US is governed by myriad laws and

²⁰ Office for Human Research Protections U.S. Department of Health and Human Services, International Compilation of Human Research Protections (Nov. 5, 2008), <http://www.hhs.gov/ohrp/international/HSPcompilation.pdf>.

²¹ See e.g., 12 V.S.A§ 7151 for a definition of Emancipated Minor; CA Health and Safety Code §24172 for California's Experimental Research Subjects' Bill of Rights.

²² See National Conference of State Legislatures, "Clinical Trials: What are States Doing," August 2009 Update found at <http://www.ncsl.org/default.aspx?tabid=14331> for a table of state laws mandating insurance coverage of clinical trials.

²³ 45 CFR §46.101(f)

treaties, this subsection highlights a few that may directly affect clinical trials and apply to both AMCs and industry. However, a thorough review of all applicable law should be undertaken before engaging in research outside the US. If the entity is relying on a third party, such as a contract research organization (CRO), it should be sure that the CRO makes appropriate assurance regarding compliance with these and other laws.

Federal law (Foreign Corrupt Practices Act, “FCPA”) prohibits the offering or payment of anything of value to a foreign official for the purpose of influencing that official in the exercise of non-ministerial duties.²⁴ The language of the law includes broad definitions for terms such as “foreign official” to include the employees of state-owned or controlled entities; these could include state-owned hospitals or medical clinics. Research sponsors should be wary of requests for payments to individuals such as principal investigators employed by public hospitals where those payments are requested to circumvent payment mechanisms in the contract with the hospital.

Export control laws are also applicable to international research and may govern certain research projects. Chief among these is the set of regulations known as the Export Administration Regulations that requires licensure of certain dual purpose items that may be exported including computers, software and biologics.²⁵ Civil and criminal penalties attach to violations.

Antiboycott laws and related legislation may govern the terms of agreements or arrangements with countries where research will be performed. The Export Administration Act Amendment bans agreements to refuse to do business with Israel and other countries and also agreements to discriminate against persons based on race, religion, sex or national origins and also to furnish information about the race, religion, sex or national origin of individuals. Exceptions exist to some of these prohibitions.²⁶

iii. The Laws of Other Countries Applicable to the Conduct of Clinical Trials by US Entities

Generally speaking all countries where clinical trials will be conducted have laws that govern the import of drugs or devices for investigational purposes; registration of clinical trials; oversight by regulatory agencies; requirements for indemnity and insurance; and subjects’ privacy and other rights to name a few. For example, the European Union has adopted a clinical trials directive that sets forth requirements for the conduct of clinical trials there and has published further guidance on aspects of the Directive.²⁷

²⁴ 15 U.S.C. § 78dd-1 et. seq.

²⁵ 15 C.F.R 730, 732, 742, 746 and 774

²⁶ 50 U.S.C. §2401 et.seq. See Department of Commerce website for further information, <http://www.bis.doc.gov/complianceandenforcement/antiboycottcompliance.htm#whatsprohibited>

²⁷ Directive 2001/20/EC

Each of the member states was required to pass national legislation conforming to the principles laid down in the Directive and each may have critically different details. Other countries require that the sponsor be a company incorporated in that country.²⁸ Any foreign entity planning to sponsor clinical trials in Brazil must first receive the approval of CONEP (National Commission on Research Ethics).²⁹ It is important to understand the law of the jurisdiction where the clinical investigation will take place.

²⁸ See regulations of the Therapeutics Goods Administration Australia

²⁹ Federal Law no. 6360, of Sept. 23, 1976 (DOU of Sept. 24, 1976)

Part II:

Special Considerations in Conducting Clinical Trials in Developing Regions of the Globe; Strategies for Securing Ethical Review and Special Informed Consent Issues; Risk/Liability Issues and Risk Minimization Strategies

I. Introduction

The conduct of clinical trials in emerging regions has been a growing trend over the past decade and is expected to continue going forward.

From 2002-2007, 41% of clinical investigation sites utilized by US companies were located outside the United States. During that same time period, the number of US sites decreased annually and the number of sites in Asia, Latin America and Central and Eastern Europe have increased, respectively, 29%, 13% and 16% annually.³⁰

Similarly, according to EMEA data, approximately one quarter of all subjects recruited for pivotal trials submitted in applications for marketing authorizations between 2005-2008, were recruited in Latin America, CIS, Asia and Africa.³¹

There are clear market forces driving the continued globalization trend, including larger numbers of “treatment naive” patients, large patient populations with diseases found in both the developed and developing world, increasing number of qualified investigators, faster recruitment, some lower cost structures and access to key global markets.

Despite these factors, the conduct of clinical trials in the emerging world present a number of challenges. For example, Africa, as a continent, is still very much in the early stages of developing regulatory and ethical guidelines, as well as basic healthcare infrastructure that can meet the needs of a population that is greatly in need of investigational and approved medications for the life-threatening diseases such as malaria, meningitis, HIV/AIDS, etc.³²

³⁰ Tufts Center for the Study of Drug Development, 2007 Report.

³¹ EMEA Strategy Paper: Acceptance of Clinical Trials Conducted in Third Countries for Evaluation in Marketing Authorisation Applications, December 5, 2008.

³² See, generally, Report of Research Ethics Policies on the African Region presented at World Health Organization Ministerial Conference on Research for Health in the African Region June 23-26, 2008; also, Developing Guidelines for Health Research in Africa dated November 2008, prepared by United Nations Economic Commission for Africa and African Union in collaboration with Good Clinical Practice-Europe.

Notwithstanding the challenges, global NGOs, pharmaceutical companies and individual governments are taking steps to encourage and promote the ethical conduct of clinical trials in Africa and other emerging regions.³³

This chapter examines some of the regulatory, ethical and contractual challenges that a life sciences company faces when conducting trials in the emerging regions of the globe and some potential risk management strategies.

II. Discussion

A. General Regulatory/ Litigation Risks

There are a number of regulatory issues that come into play when conducting trials on a global basis. Both US and European regulatory officials are stepping up their efforts to achieve further harmonization and to ensure that the integrity of data and protection of human subjects is assured, regardless of the location of the trial. For example, US FDA has recently amended its regulations regarding the conduct of clinical trials, not under an IND,³⁴ to require that such studies must comply with GCPs.³⁵

The EU is increasingly focused on clinical studies conducted in non-EU countries, with particular emphasis on the developing world. EU Directive 2001/85/EC, Recital 8 provides that “to be taken into account during the assessment of an application [for a marketing authorization], clinical trials conducted outside the European Community shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles which are equivalent to the provision of [the EU Clinical Trial Directive].”³⁶

The EMEA recently published a strategy paper on the evaluation of clinical trials conducted in such regions.³⁷ The paper notes that EMEA plans increased inspection of sites for compliance with GCP and ethical standards. “Two key factors in selecting sites and studies for routine inspection are the presence of vulnerable populations, including children, and investigator sites.”³⁸

³³ See, for e.g., <https://www.globalhealthprogress.org/>;
https://www.gavialliance.org/media_centre/press_releases/2009_06-12_AMC_lecee_kick_off.php.

³⁴ 21 CFR 312.3.

³⁵ 21 CFR 312.120.

³⁶ EU Directive 2001/20/EC.

³⁷ EMEA Strategy Paper: Acceptance of Clinical Trials Conducted in Third Countries for Evaluation in Marketing, Authorisation Applications; December 5, 2008.

³⁸ *Id.*, page 1.

Regarding “investigator sites,” it is worth mentioning that many US life sciences companies serve not only as official “sponsors” of trials in the developing world, but also may provide grant funding to independent investigators. Under United States regulation, such studies would be considered ones conducted by a so-called “sponsor-investigator.”³⁹

This concept is fairly well understood in the US to mean that the pharmaceutical company providing funding would not undertake any of the typical sponsor obligations. Outside the US, it may be the case that the party providing funding for a study would, nevertheless, be considered the sponsor under local law, regardless of whether the party(ies) who are recipients of the funding have by contract assumed sponsor and investigator like duties. In that case, particularly in emerging regions that may be lacking in well trained clinical trial teams, etc., a life sciences company may wish to perform additional due diligence or provide additional resource support for the trial.

On a broader level, the US life science community was awakened by the recent high-profile case (settled in part) in which the Second Circuit Court of Appeals held that a US sponsor could be sued in US court under the Alien Tort Statute, for alleged claims in connection with a clinical trial conducted in Nigeria.⁴⁰ This case underlines the need to ensure that a company conducting trials abroad remain on top of regulatory and ethical requirements and that it ensures compliance, even if those duties are being “handled” by third parties, such as a CRO. (See further discussion of CRO roles in Chapter 4.)

B. Ethics Review

It is widely accepted around the globe that research involving human research should be conducted only after an appropriate ethics review has occurred.⁴¹ In some regions, however, there is a lack of comprehensively functioning ethics committees.⁴²

A sponsor’s clinical trial agreement should contain provisions requiring the investigator to provide written evidence that a trial has been approved by a duly constituted ethics committee. A sponsor should consider including review of an ethics committee’s bona fides as part of its site and investigator selection

³⁹ 21 CFR 312.3(b).

⁴⁰ *Abdullahi v. Pfizer, Inc.*, 562 F.3d 163, 169 (2nd Cir. 2009). In that matter, reportedly settled in part for US\$75M (See, *Pfizer Reaches Settlement in Nigerian Drug Trial Case*, *The Washington Post* (April 4, 2009)), it was alleged that, among other things, ethics committee approvals were not received in advance of the trial from a proper ethics committee, proper informed consent was not obtained from children and/or their guardians, the risks of experimental treatment were not adequately explained, that consent documents were not provided in the appropriate native language and that the investigator was inexperienced.

⁴¹ National Bioethics Advisory Commission (NBAC), Volume I: Report and Recommendations of the National Bioethics Advisory Commission, Executive Summary 45 (2001) (“NBAC Report”), available at <http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf>.

⁴² See Footnote 3.

process. If there is a question as to the experience or qualifications of a local ethics committee or if there is a concern that a conflict of interest would exist based on the interest that the local ethics committee would have in approving the study, a prevailing recommendation by bioethics experts, and consistent with the approach taken by some multi-national pharmaceutical companies, would be to also obtain review from an independent ethics committee in another country or from a mixed committee including local representatives.⁴³

C. Informed Consent

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.⁴⁴ GCP requires, among other things, obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating a study.⁴⁵

Special issues regarding informed consent arise when conducting clinical trials in the developing world. Specifically, when subjects for a study may be considered part of a “vulnerable population”, additional measures may be needed to ensure the objectives of informed consent are met.

In the FDA Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (the “Guidance”),⁴⁶ “vulnerable populations” are defined as “Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.”⁴⁷

The Guidance states that “special attention should be paid to trials that may include vulnerable subjects,” and discusses various considerations for obtaining informed consent from members of this population.⁴⁸

⁴³ See, for e.g., NBAC Report at page xii; Opinion of the European Group on Ethics in Science and New Technologies to the European Commission, “Ethical Aspects of Clinical Research in Developing Countries” dated February 4, 2003; http://www.pfizer.com/responsibility/research_clinical_trials/global_clinical_trial_standards.jsp; <http://www.gsk.com/policies/GSK-on-clinical-trials-in-the-developing-world.pdf>.

⁴⁴ Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, page 1, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>.

⁴⁵ 21 CFR § 312.120.

⁴⁶ Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>.

⁴⁷ Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, at 1.61.

⁴⁸ Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, at 3.1.1.

Additional sources of guidance include: the NBAC Report,⁴⁹ the Report of the International Bioethics Committee of UNESCO On Consent, dated 2008,⁵⁰ and Ethical Challenges in study design and informed consent for health research in resource-poor settings issued by the WHO Special Programme for Research & Training in Tropical Diseases.⁵¹

In crafting an informed consent process for a study, the sponsor should address the following: (i) ensure that informed consent documentation is prepared in the appropriate native language(s); (ii) ensure that informed consent documentation is appropriately written for subjects who may be illiterate or have minimal reading or writing skills and that, as necessary, authorized unbiased persons serve as witnesses or parties who might further explain the Study to a subject; (iii) ensure that appropriate means of signifying consent are allowed and documented by the Study team (which may in some circumstances include oral assent or assent by fingerprint or other mark); (iv) ensure that even if community leaders or other family members may be involved in the consent process due to local cultural or religious norms, that the free-will of the subject to participate in the Study is confirmed; and (v) ensure that subjects understand and agree to proposed use of blood, urine or other samples.⁵²

D. Contractual Issues

The following are a few practical issues that may be encountered when contracting to conduct clinical trials in the developing world: (1) sites may request provision of equipment or other infrastructure resources — FCPA and local anti-corruption issues need to be considered; (2) in certain jurisdictions investigators may be reluctant to receive compensation from institutions, given administrative delays; (3) local ethics committees may require continued access of investigational product following trial; (4) some institutions and investigators carry no insurance whatsoever; (5) some institutions may not be established as legal entities.

⁴⁹ See Footnote 12.

⁵⁰ United Nations Educational, Scientific and Cultural Organization, Report of the International Bioethics Committee of UNESCO On Consent, 2008, available at <http://unesdoc.unesco.org/images/0017/001781/178124e.pdf>.

⁵¹ World Health Organization, Ethical Challenges in study design and informed consent for health research in resource-poor settings, available at http://apps.who.int/tdr/publications/tdr-research-publications/ethical-challenges-study-design/pdf/ethical_challenges.pdf.

⁵² Consideration should be given to whether any export, privacy or other considerations apply to the transport and analysis of such samples.

Part III:

Industry/Academia Relationships

The relationship between the life sciences industry and academia is a critical one to the development of breakthroughs in medicine. Industry finances basic and clinical research in academia through grant funding and direct payments pursuant to contracts. This section of the presentation will consider two topics that reflect both the strength and tensions of the relationship: industry funded investigator-initiated trials and contracting issues that arise between industry and academia in industry-sponsored agreements.

A. Industry-sponsored Clinical Trials: Contract Issues

Much has been written about tensions between industry and academia as it has surfaced around certain fundamental issues often heavily negotiated in clinical trial agreements: analysis and publication of clinical trial results; registration of clinical trials; intellectual property interests; financial support of clinical trials (payment of costs, indemnification for the institution and of subjects). In 2005, Harvard researchers published a study of certain clauses of clinical trial agreements between industry and academia and concluded that there is significant variation among academic institutions with respect to certain restrictive clauses such as publication and intellectual property and that greater sharing should occur among institutions to develop a consensus about standards.⁵³ Specifically, the researchers found disparity in what was acceptable regarding publication of data: while 85% of the institutions surveyed would not permit sponsors to revise manuscripts, there was considerable disagreement about whether sponsors would be permitted to insert their own statistical analysis (24% yes; 47% no and 29% unsure).⁵⁴ Equally split was language permitting sponsors to draft the manuscript (50% allowed, 40% disallowed, 10% uncertain) and permission for investigators to share data with third parties after the trial concluded (41% allowed, 34% disallowed). The researchers also identified conflicts involving the contracts that arose after the clinical trials had been completed. The most common dispute involved payment followed by intellectual property, and finally access to data.⁵⁵

There have been efforts to address these issues by developing a consensus about underlying principles and by creating templates for clinical trial agreements that are acceptable to industry and academia.

⁵³ Mello, M., Clarridge, B., Studdert, D., “Academic Medical Centers’ Standards for Clinical-Trial Agreements with Industry,” *N Engl. J. Med.*, 2005;352-2202-10.

⁵⁴ Mello, M. et. al., p. 2202

⁵⁵ *Ibid.*, p. 2207

Both academia and industry have set forth principles on these issues. Examples from academia include efforts by the Association of American Medical Colleges (AAMC) and the standards established by such bodies as the International Committee of Medical Journal Editors (ICJME). Industry principles have been formulated by PhRMA. Professional medical societies have also weighed in on the debate.⁵⁶

The ethical standards that have been generally articulated on behalf of academic institutions are evolving to encourage registration of clinical trials; the right by the investigators to access, review and publish data, albeit with due regard to the realities of a multi-center study within certain timing constraints but without respect to how the outcome influences the company's fortune; rejection of manipulations such as ghost writing and failure to disclose conflicts of interest.⁵⁷

PhRMA has set forth principles touching many of these same issues in its publications Principles on Conduct of Clinical Trials and Communication of Clinical Trial Sites which is available on its website.⁵⁸ Not all industry members of PhRMA have signed on to the Code but the principles are gaining greater acceptance.

Another factor that has influenced the debate is the regulation that affects the range of choices available to AMCs: most are tax exempt and some are public institutions. An issue that is important to AMCs but not to industry is the fact that commercial testing of pharmaceuticals or devices is regarded as "private use" under IRS regulations governing requirements for tax exempt bonds. If clinical trials sponsored by industry are conducted in a facility that has been constructed with tax exempt bonds, then during the time the bonds are outstanding, the facility may not be used (within certain limits) by entities for private business use.⁵⁹ This can be more or less an issue depending on how the facility has been financed and how the AMC keeps track of such use.⁶⁰ Another issue related to the tax exempt status or public status of an AMC is its perceived ability to place charitable assets either in the service of a commercial enterprise or at risk. This issue usually takes the form of a refusal to indemnify the commercial enterprise for any damages arising out of the trial regardless of fault.

⁵⁶ American Medical Association, "Ethical Guidelines Regarding Clinical Research"

⁵⁷ Ehringhaus, S., Korn, D., "Principles for Protecting Integrity in the Conduct and Reporting of Clinical Trials," Association of American Medical Colleges, January 6, 2006

⁵⁸ http://www.phrma.org/clinical_trials/

⁵⁹ See IRS Rev Proc 97-13 as modified by Rev Proc 2007-47 which provides a safe harbor for "basic research" that is defined as "any original investigation for the advancement of scientific knowledge not having a specific commercial objective. For example, product testing supporting the trade or business of a specific nongovernmental person is not treated as basic research."

⁶⁰ The newly revised Form 990, the tax return for non-profits has a new schedule that requires that the tax exempt filer provide much greater detail about private use of tax-exempt bond financed facilities.

Another strategy to find consensus between academia and industry is the effort to develop clinical trial templates that both sides can agree on. Several initiatives have been undertaken including an abortive effort by the AAMC,⁶¹ a private initiative known as MAGI,⁶² and one mounted by Duke Clinical Research Institute.⁶³ Although not a clinical trial template, a recent collaborative effort that was successfully sponsored by the National Cancer Institute (NCI) resulted in agreement (as at least a starting point) on the language of several contentious provisions including IP, publication, data, indemnity and subject injury.⁶⁴

The most successful clinical trial template developed that enjoys wide acceptance between industry and hospitals is used in the United Kingdom (UK) by the National Health Service (NHS) hospitals and the pharmaceutical industries. The template was developed by the UK Department of Health and the Association of the British Pharmaceutical Industry.⁶⁵ This comprehensive agreement is widely used and rarely negotiated in the UK. Perhaps one of the reasons for its success is that most hospitals in the UK are owned and operated by the NHS so wide adoption of the template once blessed by the Department of Health was assured. It is unlikely that such a situation would occur in the US outside of government created templates such as the Cooperative Research and Development Agreements and Clinical Trial Agreements developed by the US Department of Veteran's Affairs⁶⁶ or the NCI effort described earlier.

B. Support of Investigator-Initiated Clinical Trials

Investigator-initiated clinical trials are those where the investigator rather than the pharmaceutical or device company assumes the responsibilities of the sponsor of the clinical trial. Therefore, the investigator rather than a drug company designs the trial and oversees its conduct, and collects and analyzes the data. If the clinical trial involves an off-label use of a drug, the investigator is also responsible for securing an IND from the FDA.

Other differences between a trial that is investigator-initiated and sponsor-initiated are the facts that the trial is typically single site and the resulting data is owned by the investigator rather than the sponsor.

⁶¹ *Clinical Trial Contracts: A Discussion of Four Selected Provisions*, Association of American Medical Colleges, January 2004

⁶² <http://www.magiworld.org/>

⁶³ Contract Language for Clinical Research Agreements Between Academic Medical Centers, Duke Clinical Research Institute, Duke University

⁶⁴ *Proposed Standardized, Harmonized Clauses for Clinical Trial Agreements*, CEO Roundtable on Cancer, National Cancer Institute, August 27, 2008

⁶⁵ http://www.dh.gov.uk/en/Researchanddevelopment/A-Z/DH_4002073#_1

⁶⁶ http://www.index.va.gov/search/va/va_search.jsp?SQ=&TT=1&QT=clinical+trial+agreements&searchbtn=Search

Life science companies will often support investigator-initiated trials because they are interested in the results of the research which may point to new uses for a drug or device or possibly provide additional supportive data for a current indication. There are, however, some cautions. First, any payments to the investigator must be fair market value to avoid the implication that the payment is an attempt to induce the researcher who is often a physician to prescribe the drug and/or recommend the drug to others. Such conduct could violate the so-called Anti-kickback Statute, a civil and criminal statute that can carry onerous penalties.⁶⁷ Defining what is “fair market value,” while beyond the scope of this paper, needs to be carefully considered and attached to a realistic budget with hard, verifiable costs. Second, support of investigator initiated trials can expose the company to potential claims if the investigator does not conduct the trial in accordance with law and regulation and someone is damaged. Therefore, the company should be cautious in choosing which investigator to support.

⁶⁷ 42 U.S.C. §1320a-7b

Part IV:

Outsourcing Sponsor Responsibilities and the Evolving Roles of Academic Research Organizations/Contract Research Organizations/Site Management Organizations

I. Introduction

In today's global clinical trials market, the traditional lines between industry, academia and the various commercial organizations that support research are becoming blurred. Further, the interrelationships between these players are evolving and complex. Among other factors, the well publicized commercial pressures felt by big pharma to increase the productivity of their investigational product pipelines; the increasing movement by start up biotechs to a "virtual" company model;⁶⁸ and the increasing person power commitments and regulatory specialization required to conduct clinical trials globally have all contributed to these ground shifting changes in alliances among the key players.

At the same time, government, media and public scrutiny of actual and potential conflict of interest among industry and health care professionals (including academic researchers) has never been higher.

This chapter examines these market trends with a focus on the roles that contract research organizations ("CROs"), site management organizations ("SMOs") and academic research organizations ("AROs") are now playing in supporting global clinical research. Indeed, in certain cases, these entities are themselves assuming the profile of innovator development companies.

In examining these trends from the perspective of a life sciences "sponsor" company, we explore some of the potential regulatory, commercial and practical risks that one should consider in structuring and managing these relationships.

II. Discussion

A. Traditional CRO Role

Traditionally, pharmaceutical company sponsors utilized CROs as an outsourcing resource designed to fill narrowly defined gaps in personnel capacity or subject matter expertise. An example of the former might be where a sponsor required external monitors⁶⁹ to supplement its in-house contract research associate staff to support an unusually large multisite trial. An example of the latter would be where the

⁶⁸ "Early Stage Returns," Bruce L. Booth, *Nature Biotechnology*, 2006, 24;11;1335-1340

⁶⁹ A sponsor of a clinical trial is required to select a monitor, qualified by training and experience, to monitor the progress of the trial. 21 CFR 312.53(d).

sponsor company did not have biostatistical or medical writing services in-house to cover a particular therapeutic area relevant to the clinical trial. Under this model, the pharmaceutical company would contract for specified services on a fee for task performed basis, perhaps through an RFP process.

B. Traditional Academic Research Role

US based pharmaceutical companies have enjoyed a long and deep relationship with academic medical centers (“AMC”) in the conduct of clinical trials. The traditional form of this relationship has been where a physician/faculty member at the AMC serves as an “investigator”⁷⁰ for a clinical trial conducted at the AMC. In that scenario, the pharmaceutical company enters into a clinical trial agreement with the AMC and the investigator (or with an acknowledgment by the investigator), again with emphasis on a strict budget for specific services provided basis.⁷¹ In some cases, a key opinion leader serves as lead or coordinating investigator for a multi-site trial.

C. Changing Face of CRO Role

As its leading US trade association states, “The CRO industry is evolving into a full service model where CROs offer services from the earliest stages of development through clinical trials and post-approval research.”⁷² The global CRO market is estimated at US\$7.8 billion and is growing.⁷³

The impending patent cliffs faced by the pharmaceutical industry, as well as industry consolidation, together with the market forces noted previously, have all contributed to an increasing reliance on CRO’s to assist in the conduct of clinical trials. In response, we see CROs also consummating large scale transactions, increasing capacity, therapeutic focus, or breadth and geographic research, particularly in emerging markets such as Latin America, Asia and Central and Eastern Europe.

As example, in early 2009, PPD, Inc. acquired AbCRO, another CRO with operations in the Russia, Ukraine, Poland, Bulgaria and elsewhere in the prime Central and Eastern European market.⁷⁴ In

⁷⁰ An investigator is an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event the investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 21 CFR 312.3(b).

⁷¹ In part, the emphasis on defined fees for services are based upon the desire to avoid anti-kickback concerns. See e.g., OIG Compliance Program Guide for Pharmaceutical Manufacturers, 68 F.R. 86, May 5, 2003.

⁷² Source: Association of Clinical Research Organization – <http://www.acrohealth.org/industry-atagance.php>

⁷³ “Global Growth Remains Strong for CROs in 2008, Beyond,” *Centerwatch Monthly*, March 2008

⁷⁴ <http://investor.ppd.com/releasedetail.cfm?ReleaseID=378783>

contrast, also earlier this year, PPD announced the sale to Charles River Laboratories International Inc. of PPD's oncology focused subsidiary, Piedmont Research Center LLC in a US\$46 million deal.⁷⁵

These transactions are notable for their size and strategic focus, but there are other transactions which further represent a change in the character of CRO's core business model and their relationship with traditional innovator pharmaceutical companies.

For example, in 2008, Eli Lilly announced a series of transactions reflecting an aggressive programmatic outsourcing to CROs of its drug development program. First, it announced that Quintiles Transnational would be the outsource supporter of its clinical trial monitoring work in the US and that i3 would be the outsourcing supporter of most of the company's data management for clinical trials. These are but two examples of what industry observers have labeled a shift towards outsourcing to CROs functional, as opposed to transactional tasks.⁷⁶

More significant was Eli Lilly's announcement last year that it had sold its Greenfield, Indiana early stage drug development facility to Covance, another large CRO, for US\$50 million. As a companion to the sale, Covance signed a 10 year, US\$1.6 billion contract to provide to Eli Lilly drug development services for drug studies in Phases II-IV.⁷⁷ Such a transaction was a clear sign that a more partnership oriented CRO/industry model was afoot.

The evolution in CRO business models is not limited to US based companies. In China, domestic CROs have traditionally focused on relatively inexpensive areas such as biology and chemistry, with manufacturing of active pharmaceutical ingredients for generic drugs. Now, however, increasing numbers of China-based CROs are moving into more lucrative areas of drug development, such as pre clinical and clinical trials.⁷⁸ Also, most of the leading global pharmaceutical companies have established R&D centers and alliances with China based CROs to conduct drug discovery, translational medicine and clinical trials at centers such as the huge Shanghai Zhangjiang life sciences cluster.⁷⁹

Another example of novel partnering between industry and CROs is where pharma companies solicit outside investors, including venture or investment affiliates of CROs, to assist in financing the pharma companies' clinical trials. In that regard, these investors assume certain risk of outcome failure.⁸⁰ Such an

⁷⁵ *Boston Business Journal*, April 13, 2009; <http://investor.ppd.com/releasedetail.cfm?ReleaseID=375335>

⁷⁶ "Make a Match, Big Pharma is Finally Making a Commitment to Partner Based Outsourcing," Kenneth Getz, Rachel Zuckerman, David Zuckerman and Charles Piper, *Pharmaceutical Executive Magazine*, April 2009

⁷⁷ http://www.prnewswire.com/cgi-bin/micro_stories.pl?ACCT=916306&TICK=LLY&STORY=/www/story/08-06-2008/0004862818&EDATE=Aug+6,+2008

⁷⁸ "China's Drug Contractors are on a Fast Growth Track," *Reuters*, September 3, 2009

⁷⁹ "Unleashing the Dragon, the Sequel," *Pharmaceutical Executive Magazine*, September 2008

⁸⁰ "Drug Makers Explore External Financing for Research Efforts," *Wall Street Journal*, April 7, 2009

arrangement would be particularly of note if the main CRO entities are playing any role in servicing the clinical trial concerned.

It is important to note, however, that despite the growth in the CRO market, the past year's general economic downturn and more inward focus by a consolidated and consolidating pharmaceutical and biotech industry has resulted in some disappointing financial results or dramatic shifts in business focus by some of the big CRO players. For example, MDS recently announced it will sell the remainder of its CRO business, MDS Pharma Services.⁸¹ Also, an industry analyst reported that since Q1 2006, 6 of the top 7 publicly-traded CROs have seen a decline in net revenues and some have experienced a drop in stock value.⁸²

D. Changing Role of Academic Researchers

Although the life sciences industry continues to utilize academic research capabilities in the conventional way, through site by site engagements with investigators and AMCs, this is but one model. The proliferation of global trials, among other things, has led to a steady decline in the proportion of North American investigators conducting clinical trials. In 1990, the proportion of North America-based investigators conducting clinical trials was 96%. In 2007, its was 54%.⁸³

In addition to this general decline, US AMCs have experienced a loss of market share. In the US, the investigative market is made up of three primary segments. One is the part-time segment of physicians in private practice that derive a majority of its annual revenue from clinical practice. In 2007 this group surpassed AMCs (the second market segment) with a market share of 38%, as compared to 36%. The third segment consists of dedicated investigator sites that derive nearly 100% of their annual revenue from clinical trial grants. This group accounts for 26% of the market. Since 1998, AMCs are estimated to have lost 40% of its market share.⁸⁴

Despite this trend, academic KOLs and AMCs, of course, remain vital players in the clinical research market. A new model that has emerged is the growth of strong academic research organizations, which serve some of the same functions as CROs and SMOs.⁸⁵

⁸¹ <https://www.centerwatch.com/news-resources/clinical-trials-today/headline-details> - September 3, 2009

⁸² <https://www.outsourcing-pharma.com/clinical-development/CRO-growth-since-06-and-the-impact-of-the-downturn>

⁸³ "The Elusive Sponsor Site Relationship," Kenneth A. Getz, *Applied Clinical Trials*, February 2009.

⁸⁴ *Id.*

⁸⁵ Site management organizations are more typically affiliated with one or more investigators and many of them centralize patient recruitment, among other services.

In the US, two prime examples are Duke Clinical Research Institute, which promotes its organization as “enlisting” more than 5000 investigators in more than 63 countries to carry out scientific investigations.⁸⁶ Similarly, Harvard Clinical Research Institute is an academic research organization that “connects academia to industry” by working with a broad range of sponsors. Its website states that the Institute “meets industry standards and aggressive timelines and offers price competitive services that span the entire clinical trial process.” The services range from data safety monitoring board services, project management and “HCRI affiliated” academic physician providing assistance with study design.”⁸⁷

Even outside of the dedicated clinical research centers of AMCs, KOLs and AMC staff frequently provide assistance to pharma companies regarding protocol design, site selection, and other “sponsor” duties.

Despite the competition that may exist between CROs and the academic research community for access to industry sponsored or funded trials, there are also developing collaborations among them. For example, in 2008, Parexel announced an alliance with the Safe Implementation of Treatments in Strokes, a network of clinical sites specializing in stroke. Another example is Quintiles’ alliance with Med Star Research Institute, which is the centralized clinical research services center of Med Star Health, which includes a consortium of member AMCs.⁸⁸

E. Potential Risks to Sponsors of Evolving Outsourcing Arrangements/Recommendations

The evolving relationships with clinical research contractors/partners, as discussed above, present novel opportunities for collaboration, but they also present areas of risk and/or need for close management. The following are a few points for sponsors to keep in mind when documenting and structuring these relationships:

i. General Contractual Issues

1. Carefully define the contractor/partner. Given that certain AROs and CROs are part of large networks of affiliates, make sure its clear with whom you are contracting, and check the financial viability of, and insurance carried by, that party. In addition, if contracting with a parent level entity, ensure that it will be fully liable for all affiliates and, to the extent applicable, any subcontractors, such as labs.

⁸⁶ <https://www.dcri.duke.edu>

⁸⁷ Id.

⁸⁸ “CRO and AMC Collaboration,” Lisa Henderson, *Applied Clinical Trials*, February 2009

2. Identify key personnel. Given the increasing movement of personnel between projects or from CROs and AROs to industry, it is important to ensure that sponsor has right of selection over key personnel and their replacements. In some cases, departure of key personnel should carry penalties, such as right of termination.

3. Consider competition issues. Especially given the increasing consolidation and M&A activity in the CRO sector and the potential of wide-scale partnerships, it is important to consider at the outset of the selection process the relationship(s) that the contractor/partner has or may have in the future with sponsor's competitors. Such issues also should be addressed in contractual provisions.

4. Pricing/risk allocation. In the traditional fee for services model, CROs would request a termination fee in the event a trial is unexpectedly terminated, as a means of compensating the CRO for lost opportunity costs. In a "partnership" model, where the parties are forging an alliance across a therapeutic portfolio or otherwise, more risk-sharing may be appropriate (but regulatory concerns may exist with outcomes based payments).

ii. **Key Regulatory Considerations**

1. Define regulatory responsibilities of each party. In the traditional CRO/life science company contract under US laws, the life sciences company may elect to "transfer" its obligations as a "sponsor" to a CRO.⁸⁹

FDA regulations provide that a contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations ... applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a contract research organization to the extent it assumes one or more obligations of the sponsor.⁹⁰

It is therefore important to clarify in a services agreement or scope of work which obligations are being transferred to the CRO. We note that the FDA regulations do not provide similar language for AROs or SMOs, but to the extent the life sciences company

⁸⁹ Pursuant to 21 CFR 312.52(a), a sponsor may transfer its obligations under 21 CFR 312.50 (which obligations include, among other things, selection of investigators, maintaining control of investigational drug, monitoring the progress of all clinical investigations) to a CRO. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization.

⁹⁰ 21 CFR Part 312.52(b)

intends to transfer functionable “sponsor” duties to such entities, it should expressly provide so in the services agreement.

Further, for global trials, sponsors should be aware that in the EU and in other countries, there may not be a similar provision for regulatory “transfer” of sponsor obligations, though specific contractual obligations can be provided in a services agreement to provide as much protection as possible. As a related point, to the extent that the ARO or CRO will be involved with structuring or making payments to investigators, due diligence should be conducted to ensure that the ARO or CRO are familiar with and committed to compliance with FCPA and local regulations regarding payments to health care professionals.

Another similar regulatory issue is raised by the fact that the FDA regulations do not easily accommodate situations in which a CRO, ARO or SMO is potentially providing both “sponsor” services, such as monitoring and “investigator” services, such as providing in house investigators for clinical trials. We are increasingly seeing this scenario in small phase I studies conducted in the US In such cases, consideration should be given to having separate contracts and appropriate firewalls established among staff performing these separate functions.⁹¹

2. Supervisory Access Issues. In cases in which a CRO/ARO or SMO is providing sponsor access to one or more investigational sites, it is important to confirm that adequate contracts are in place to ensure appropriate supervision of staff at each site. From a practical standpoint, this can be particularly complicated, depending on who is the employer of the study team. Nevertheless, as FDA has recently made clear in guidance, “the staff involved directly in the conduct of a clinical investigation may include individuals who are not in the direct employ of the clinical investigator. For example, a site management organization may hire an investigator to conduct a study and provide the investigator with a study coordinator or nursing staff employed by the SMO. In this situation, the investigator should take steps to assure that the staff not under his direct employ are qualified to perform delegated tasks and have received adequate training ...”⁹²

⁹¹ Although FDA does provide for “sponsor-investigators,” the regulations expressly provide that this designation is for individual persons only. 21 CFR 312.3(b).

⁹² Draft Guidance for Industry, Protecting the Rights, Safety and Welfare of Study Subjects – Supervisory Responsibilities of Investigators, FDA, May 2007

In addition, the contract should also make clear that to the extent that the trial is being performed at a site controlled by a third party, the CRO/ARO/SMO have secured appropriate guarantees for compliance and access by sponsor for purposes of inspections.

3. Conflict of Interest. As discussed in Chapter 3, an overarching concern and area for further regulatory interpretation and, potentially, regulation, relates to the potential for conflicts of interest arising from these novel partnership arrangements. As one example, FDA's Financial Disclosure regulation at 21 CFR Part 54 only considers disclosures made regarding payments made by a sponsor to an investigator or his/her family, or other financial relationships between them. It does not address in any extensive manner the extent to which bias may be inherent to the relationships between investigators and non-sponsor CROs/SMOs or AROs, or between sponsors and CROs/SMOs or AROs. Nevertheless, issues involving investigator and institutional conflicts are being examined at a variety of levels and should be considered by a sponsor at the outset of and throughout the contractual relationship.

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