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LAWS AND ETHICS AFFECTING CLINICAL TRIALS IN AFRICA

MARK BARNES & NICK WALLACE

I. INTRODUCTION

In recent decades, clinical trials involving human subjects have become increasingly globalized as scientists and medical professionals conduct research in developing countries.¹ Some of this research seeks to study specific diseases that are rare in the United States, such as malaria, dengue fever and tuberculosis.² These studies can help address the lack of treatment options “available for the diseases that have the greatest impact in the developing world.”³ Other research may be motivated by the opportunity to secure U.S. Food and Drug Administration (“FDA”) approval of a pharmaceutical product, biological product, or medical device.⁴

For industry sponsors, conducting clinical trials abroad offers, in some cases, the possibility of significant savings through shorter trial time frames and lower costs per participant. Trials abroad can be completed more rapidly because recruiting human subjects in foreign countries has proven substantially easier than recruiting volunteers domestically.⁵ The duration of a clinical trial holds

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1. Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816, 816 (2009) (“Pharmaceutical and device companies have embraced globalization as a core component of their business models, especially in the realm of clinical trials.”); see, e.g. DANIEL R. LEVINSON, U.S. DEP’T OF HEALTH AND HUMAN SERVICES, OFFICE OF INSPECTOR GENERAL, CHALLENGES TO FDA’S ABILITY TO MONITOR AND INSPECT FOREIGN CLINICAL TRIALS i–ii (2010) (observing that many clinical trials for FDA-regulated drug products are performed outside the United States).

2. See REMIGIUS N. NWABUEZE, LEGAL AND ETHICAL REGULATION OF BIOMEDICAL RESEARCH IN DEVELOPING COUNTRIES 2–3 (2013); see, e.g., DNDI’S POLICIES, DRUGS FOR NEGLECTED DISEASES INITIATIVE, <http://www.dndi.org/about-dndi/dndi-policies> (last visited Sept. 17, 2016) (stating its mission to facilitate ways to promote more research and development for neglected diseases); Finnuala Kelleher, *The Pharmaceutical Industry’s Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nations*, 38 COLUM. J. L. & SOC. PROBS. 67 (2004) (stating that trial sponsors are attracted to developing countries for the prevalence of diseases that are rare in the United States).

3. *What We Do: Discovery & Translational Sciences Strategy Overview*, BILL & MELINDA GATES FOUNDATION, <http://www.gatesfoundation.org/What-We-Do/Global-Health/Discovery-and-Translational-Sciences> (last visited Sept. 17, 2017) (recognizing the need to “advance the goal of creating solutions that can be deployed, accepted, and sustained in the developing world” to help support preventative and curative therapies for diseases that are significantly left untreated in developing countries).

4. See Glickman et al., *supra* note 1 (stating that pharmaceutical companies seek to conduct clinical trials in developing countries because trials there are more cost-effective and the trials needed for FDA new drug approval can be completed more rapidly); see also NWABUEZE, *supra* note 2, at 4 (noting that pharmaceutical companies can bring their new drugs to market “cheaper and faster” by conducting their research in developing countries).

5. See Yevgenia Shtilman, *Pharmaceutical Drug Testing in the Former Soviet Union: Contract Research Organizations as Broker-Dealers in an Emerging Testing Ground for America’s Big Pharma*,

serious financial implications for study sponsors. In 2000, one estimate projected that a one-day delay in bringing a major drug to market could result in a loss of \$1.3 million in unrealized sales for a pharmaceutical company.⁶ In some cases, the overall costs of conducting clinical research abroad are significantly lower than the costs of conducting the same research domestically. Some reports from pharmaceutical sponsors suggest that a second-tier center in the United States is expected to charge more than ten times what a first-rate academic medical center in India charges per case report.⁷

Today, significant clinical research supporting FDA applications is conducted abroad. In 2008, 80 percent of marketing applications approved by the FDA for drugs or biologics relied on some data from foreign clinical trials.⁸ A 2007 study analyzed the industry-sponsored Phase III trials listed in the *ClinicalTrials.gov* registry and found that, for the 20 largest pharmaceutical companies, approximately one third of the trials were conducted outside of the United States and a majority of the study sites were located outside the United States (“ex-U.S.” sites).⁹ As of September 14, 2017, *ClinicalTrials.gov* showed 47 percent of registered studies as having a “non-U.S. only” location.¹⁰ Consequently, the legal and ethical implications of clinical trials conducted abroad affect a significant number of research participants. Between October 2007 and September 2008, trials conducted at 6,500 foreign research sites involved more than 200,000 subjects.¹¹

The ethical and legal challenges affecting clinical trials conducted in Africa are particularly pronounced, even though African countries host fewer clinical trial sites reported to the FDA than many other regions.¹² In many developing countries, laws, or the lack of enforcement of laws, may offer reduced protections

29 B.C. THIRD WORLD L.J. 425, 432–34 (2009) (describing domestic barriers, such as the lack of volunteers and stringent federal regulations, that delay the progression of clinical trials in the United States, motivating pharmaceutical companies to seek independent contractors who can help facilitate faster clinical trials in foreign countries with lighter regulatory frameworks).

6. See *id.* at 433.

7. See Glickman, *supra* note 1; see also Shtilman, *supra* note 5, at 441 (explaining how overseas clinical trials gain popularity by costing significantly less than trials in the United States).

8. See LEVINSON, *supra* note 1, at ii.

9. See Glickman, *supra* note 1; see also Shtilman, *supra* note 5, at 426, 431–32 (noting that both the need for large numbers of participants as well as insufficient American volunteers influence the pharmaceutical companies’ decision to conduct trials abroad).

10. See TRENDS, CHARTS, AND MAPS, <https://clinicaltrials.gov/ct2/resources/trends> (last visited Sept. 17, 2017).

11. LEVINSON, *supra* note 1, at 11; United States Senate, References, http://www.senate.gov/reference/glossary_term/fiscal_year.htm (last visited Sept. 17, 2017) (identifying the federal fiscal year as a period beginning October 1 and ending September 30).

12. See LEVINSON, *supra* note 1, at 12 (noting that the Office of the Inspector General (“OIG”) analyzed FDA marketing applications approved in 2008 and found that less than 10 percent of the foreign clinical trial subjects and foreign sites were located in the Africa and the Middle East region. The number of clinical trials conducted in Africa and not reported to the FDA is unknown).

to human subjects, and local regulatory bodies may lack the capacity to monitor clinical trials adequately.¹³ Clinical trials involving human subjects raise a unique set of ethical complications when carried out in developing countries. This article lays out the sources of law and ethical principles that apply when U.S. academic institutions and corporations sponsor or conduct clinical trials in African countries. Section II of this Article outlines laws that govern research conducted in Africa. In particular, Section II focuses on U.S. statutes and regulations that apply extraterritorially to research conducted abroad and notes certain gaps in the legal protections afforded to human subjects at ex-U.S. sites. Section III of this Article focuses on the specific application of ethical research principles to clinical research conducted in Africa, including to research conducted outside the parameters of legal protections for human subjects. This Section briefly outlines the evolution of ethical guidelines governing human subjects research and applies principles of ethical conduct to certain paradigms likely to emerge when foreign institutions and multi-national companies conduct clinical trials in Africa.

II. LAWS APPLICABLE TO CLINICAL TRIALS CONDUCTED IN AFRICA

Both foreign and U.S. law may apply when clinical trials are conducted at ex-U.S. sites by U.S.-based or U.S.-affiliated entities or researchers. The non-U.S. country where the trial site is found may have laws applicable to a range of relevant research and non-research activities. Additionally, certain U.S. statutes and regulations apply extraterritorially and regulate conduct at an ex-U.S. clinical research site if the research is funded by the U.S. government or if the data from the site are to be submitted to support a U.S. regulatory filing.¹⁴ Other U.S. laws apply to all activity, regardless of whether U.S. funding or regulatory approval is involved.¹⁵ Not infrequently, U.S. laws regulate a number of aspects of ex-U.S. clinical trials, including the site's protection of human subjects, the export of certain materials and data, payments made to officials of foreign governments (including medical staff and officials of government-affiliated hospitals), and registration of the ex-U.S. clinical trial. In addition to identifying certain research-related activities that are subject to U.S. or other national regulation, this Section identifies a category of certain ex-U.S. clinical trials for which no country's human subjects protection law may apply and specifies the

13. See Glickman, *supra* note 1, at 818 (noting further that regulatory bodies have limited information regarding clinical trials conducted in foreign countries and therefore are unable to serve as effective monitors of the quality of such research).

14. See, e.g., 21 C.F.R. § 312.120 (2008).

15. See, e.g., William Dubois, Note, *New Drug Research, the Extraterritorial Application of the FDA Regulations, and the Need for International Cooperation*, 36 VAND. J. TRANSNAT'L L. 161, 189-90 (2003).

circumstances in which certain sponsors and investigators have a heightened ethical duty to self-regulate to ensure that their research is conducted in conformity with the applicable ethical requirements.

A. Laws of the Country in Which the Clinical Trial Site is Located

Before beginning a program of ex-U.S. clinical trials, research sponsors and investigators must be aware of the legal requirements that pertain to their activities in the jurisdictions in which they conduct or sponsor clinical trials. Some countries in Africa have laws that govern the conduct of clinical trials specifically, and most have non-research-specific laws affecting the operations of clinical trials.¹⁶ For example, a host country may have laws regulating the drugs, devices or biotechnology used in the clinical trial; national and local taxation laws; labor and wage laws; immigration laws regulating work permits and business visas for the site's expatriate staff; professional licensure laws governing the site's doctors, nurses and pharmacists; privacy laws and data export laws; tissue and blood sample export control laws; and intellectual property laws.

As one example, South Africa has adopted detailed legal requirements for the protection of human research subjects and data privacy.¹⁷ These requirements are not identical to the U.S. human subjects and data privacy protections that apply extraterritorially.¹⁸ Clinical trials involving human research in South Africa must, among other requirements, register the research in the South African National Clinical Trials Register, submit the research proposal for ethics review and approval to a health research ethics committee registered in South Africa, and provide detailed information in order to obtain legally adequate informed consent.¹⁹

South African law protects the privacy of "personal information," which is broadly defined to include biometric information, medical history, demographic information, and contact information.²⁰ Because the law requires the "responsible party" to "take reasonably practicable steps to ensure that the data subject is aware of . . . the fact that . . . the responsible party intends to transfer the information to a third country," many sponsors of clinical trials in South Africa must notify the subject of their intent to transfer the data to one or more foreign countries for further analysis.²¹ Additionally, if the sponsor intends to submit the data

16. See, e.g., NATIONAL AGENCY FOR FOOD AND DRUG ADMINISTRATION AND CONTROL, NAFDAC GOOD CLINICAL PRACTICE GUIDELINES 2016, <http://www.nafdac.gov.ng/index.php/guidelines/cliinical-trials>.

17. See generally Protection of Personal Information Act 4 of 2013 (S. Afr.) (protecting "personal information processed by public and private bodies," including information of human test subjects).

18. See *infra* Part II.B.

19. See Government Notice (GN) R719/2014 (S. Afr.).

20. Protection of Personal Information Act 4 of 2013 §1 (S. Afr.).

21. *Id.* at § 18(1)(g).

to multiple foreign regulatory agencies to gain approval for marketing a drug, device or biologic product, the sponsor will likely wish to de-identify the personal information contained in the data to avoid the requirement to describe to the research subject “the level of protection afforded to the information by” the third countries to which the personal information is transferred.²²

Other countries in Africa may, however, lack robust legal regimes to protect human research subjects.²³ The Office for Human Research Protections (“OHRP”) of the U.S. Department of Health and Human Services (“DHHS”) maintains an International Compilation of Human Research Standards (“the Compilation”).²⁴ The Compilation catalogues more than 1,000 laws, regulations, and guidelines governing human subjects research in 126 countries.²⁵ As of the 2017 edition of the Compilation, OHRP identified only 25 African countries with laws specifically governing general human subjects research; research injury; clinical trial registries; drugs and devices; human biological materials; genetic research; or embryos, stem cells, and cloning.²⁶ Some scholars have noted that this absence of regulation may stem from an effort to attract the benefits of clinical research to countries where there is little access to medical research to benefit the population.²⁷

When conducting clinical trials in countries that lack laws specifically governing human subjects research, research sponsors and investigators may find themselves operating entirely outside the familiar legal frameworks in the U.S. that protect research subjects. U.S. laws protecting human subjects do not reach some purely private research conducted in other countries, as discussed below in Section II.B. When clinical trial sponsors and investigators operate outside clear legal regimes protecting human subjects, they have an ethical and moral duty to ensure that their conduct meets the requirements laid out in the guidelines for human subjects research, as discussed in Part III.

22. *Id.*

23. See Benjamin M. Meier, *International Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERKELEY J. INT’L L. 513, 532–33 (2002).

24. See OFF. FOR HUM. RES. PROTECTIONS, U.S. DEP’T OF HEALTH & HUM. SERV., INT’L COMPILATION OF HUM. RES. STANDARDS (2017).

25. *See id.*

26. *See id.* at 2, 157–66 (noting that the twenty-five identified countries with relevant laws are: Benin, Botswana, Burkina Faso, Cameroon, Côte-d’Ivoire, Democratic Republic of Congo, Ethiopia, Gambia, Ghana, Guinea, Kenya, Liberia, Malawi, Mozambique, Nigeria, Rwanda, Senegal, Sierra Leone, South Africa, Sudan, Tanzania, Tunisia, Uganda, Zambia, and Zimbabwe. Additionally, OHRP notes that it has consulted “in-country persons” to review the listings for accuracy and completeness, but the ongoing issuance of new standards prevents the Compilation from serving as an “exhaustive source of all current applicable laws.”).

27. *See Meier, supra* note 23.

B. United States Laws That Apply Extraterritorially

Some U.S. laws that protect human research subjects apply extraterritorially when the federal government funds or takes regulatory action based on data from a foreign clinical trial.²⁸ Other U.S. laws that do not involve the protection of human research subjects apply extraterritorially to clinical trials conducted outside the U.S. and regulate aspects of those trials, including the transfer of materials and data, payments to foreign officials, and registration of the trials. This Subsection analyzes the requirements of these laws as well as their applicability to various types of clinical trials.

1. The Common Rule

The Federal Policy for the Protection of Human Subjects, located at 45 C.F.R. part 46, applies extraterritorially, governing all research on human subjects that is “conducted, supported, or otherwise subject to regulation by the federal government outside the United States.”²⁹ The regulations at 45 C.F.R. part 46 contain four subparts.³⁰ Subpart A, known as the Common Rule, provides basic rules governing research involving human subjects. Additional subparts impose further requirements on human subjects research involving pregnant women,³¹ prisoners,³² and children as subjects.³³

Human subjects research that is covered by the Common Rule must be approved by an institutional review board (“IRB”), which has the authority to require modifications to be made or to disapprove covered research activities.³⁴ The Common Rule further requires that all covered research must secure “the legally effective informed consent of the subject or the subject’s legally authorized representative.”³⁵ Clinical trials in Africa that are covered by the Common Rule may face particular challenges in gaining adequate informed consent of research subjects, as discussed below in Subsection III.B.i.

28. See Jennifer S. Bard, *Closing the Gaps in Human Subject Research Law: Regulating Clinical Research Conducted Outside of the United States*, 21 ANNALS OF HEALTH L. (ASLME SPEC. ED.) 201, 202–3 (2012).

29. 45 C.F.R. § 46.101(a) (2015) (Specifically, the Common Rule applies to the agencies and departments that have taken “appropriate administrative action to make the policy applicable to such research.” Currently, the Common Rule has been “codified in separate regulations by 15 Federal departments and agencies,” with an additional three departments or agencies complying with the Common Rule, though they have not issued the Common Rule in regulations); see e.g., U.S. DEP’T OF HEALTH & HUM. SERVS., FED. POL’Y FOR THE PROTECTION OF HUM. SUBJECTS (‘COMMON RULE,’) <http://www.hhs.gov/ohrp/humansubjects/commonrule/>.

30. See 45 C.F.R. § 46 (2009).

31. See 45 C.F.R. §§ 46.201–07 (2009).

32. See 45 C.F.R. §§ 46.301–06 (1978).

33. See 45 C.F.R. §§ 46.401–09 (1997).

34. See 45 C.F.R. § 46.109 (2005).

35. 45 C.F.R. § 46.116 (2005).

Clinical trials in Africa are governed by the Common Rule's human subjects protections if the research falls under any of the three regulated categories.³⁶ Clinical trials that receive National Institutes of Health ("NIH") or Centers for Disease Control and Prevention ("CDC") funding, for example, are "supported" by a federal agency that follows the Common Rule and are subject to its human subjects protections.³⁷ Because the NIH and CDC play a significant role in funding new drug, vaccine and public health research, it is not uncommon for research carried out abroad to be subject to the Common Rule's requirements.

Clinical trial sponsors or investigators may apply for a discretionary waiver of the Common Rule's extraterritorial applicability.³⁸ When covered research takes place in a foreign country where human subjects protections differ from the Common Rule, a U.S. department or agency head may approve the substitution of the foreign procedures in lieu of the Common Rule's requirements.³⁹ However, the official may only approve such a substitution if the official determines that the policies afford protections that are at least equivalent to those provided in the Common Rule.⁴⁰ Because some countries in Africa lack legal protections for human research subjects, this discretionary waiver will only be available when clinical trials are conducted in the subset of countries with protections for human subjects, and then only if the country's protections are determined to be at least equivalent to those provided under the Common Rule.

2. Food & Drug Administration Regulations Governing Human Subjects Protections in Trials Seeking Marketing Approval of a Drug, Device or Biological Product

When clinical trials are conducted in Africa in order to generate data supporting a New Drug Application ("NDA"), a Premarket Approval Application ("PMA") for a medical device, or a Biologics License Application ("BLA"), the clinical trials must meet requirements imposed by the FDA.⁴¹ The FDA must approve an application for any new drug, medical device or biologic delivered

36. See *supra* note 1.

37. See NAT'L INST. OF HEALTH, CLINICAL R. POL'Y, <http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/research-involving-human-subjects> (last visited Sept. 18, 2017) (noting that the National Institutes of Health, as an agency of the United States Department of Health and Human Services follows the Common Rule); see also U.S. DEP'T OF HEALTH AND HUMAN SERV., "HUMAN RESEARCH PROTECTIONS" POL'Y (2010), <http://www.cdc.gov/od/science/integrity/docs/cdc-policy-human-research-protections.pdf> (last visited Sept. 18, 2017) (noting that the Common Rule is applicable to all research activities of the Centers for Disease Control and Prevention).

38. See *IRB Common Rule and HIPAA Waiver Approval*, RESEARCH DATA ASSISTANCE CENTER, <http://www.resdac.org/cms-data/request/materials/irb-common-rule-and-hipaa-waiver-approval> (last visited Sept. 18, 2017) (identifying the criteria and procedures for obtaining a waiver).

39. See 45 C.F.R. § 46.101(h) (2015).

40. See *id.*

41. See 21 C.F.R. § 314.2 (2015) (drugs); 21 C.F.R. § 814.1 (2015) (medical devices); 21 C.F.R. § 601.2 (2012) (biologics).

into interstate commerce in the United States.⁴² FDA requirements for foreign studies conducted to support a PMA are codified separately from the requirement for foreign studies conducted to support an NDA or BLA.⁴³ Substantively, however, the requirements are similar for the three applications.

The FDA allows applicants to submit as support for an NDA or BLA “a well-designed and well-conducted foreign clinical study not conducted under an Investigational New Drug Application (“IND”), if the following conditions are met: “The study was conducted in accordance with good clinical practice (“GCP”) . . . and; FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.”⁴⁴

Under FDA regulations, GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (“IEC”) and “obtaining and documenting the freely given informed consent of the subject.”⁴⁵ The FDA will only accept a foreign clinical study of a medical device not conducted under an Investigational Device Exemption (“IDE”) as support for a PMA if “the data are valid” and the research has been conducted “in conformance with the ‘Declaration of Helsinki’ or the laws and regulations of the country in which the research is conducted, whichever accords greater protection to human subjects.”⁴⁶

Foreign clinical trials generating data to support an NDA or BLA are subject to requirements to obtain approval by a review board and to obtain a subject’s informed consent under the FDA regulations.⁴⁷ Likewise, the Declaration of Helsinki, which contains the minimum requirements that a study must meet to be considered as support for a PMA, requires the submission of the research protocol to a “research ethics committee.”⁴⁸ Additionally, the Declaration requires

42. *See id.*

43. *See supra* note 1.

44. 21 C.F.R. § 312.120(a)(i)–(ii) (2015). Under this section, GCP is defined as 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 trial subjects are protected.” It includes review by an independent board and obtaining subjects’ informed consent; *see also* 21 C.F.R. § 312.120(b) (2015) (describing supporting information that the FDA requires of an NDA applicant submitting data from a foreign clinical study not conducted under an IND).

45. 21 C.F.R. § 312.120(a)(i) (2015); *see also* 21 C.F.R. § 50.20 (2015) (applying the informed consent requirement to foreign clinical trials involving human subjects used to generate data for FDA applications).

46. 21 C.F.R. § 814.15(b) (2015).

47. *See supra* note 1.

48. *See* World Medical Association, Inc., *WMA Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, 59 *WORLD MED. J.* 199, 200 (2013) (The Declaration explains that a “research protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the study”; such a committee must be “independent,” “transparent,” “qualified,” and free from any “undue influence” on behalf of the researcher).

that investigators obtain the informed consent of human subjects.⁴⁹ The particular challenges involved in obtaining informed consent of subjects in clinical trials conducted in Africa are discussed below in Subsection III.B.i.

4. *Privacy and Confidentiality Regulations*

The Health Insurance Portability and Accountability Act of 1996 and the regulations adopted thereunder (collectively, “HIPAA”) impose confidentiality requirements on protected health information (“PHI”) held by a “covered entity.”⁵⁰ Covered entities include (1) a health plan, (2) a health care clearinghouse, and (3) a health care provider, if that entity or person transmits any health information in electronic form in connection with a transaction covered by the subchapter.⁵¹ PHI is defined as “individually identifiable health information” that is transmitted by or maintained in electronic media or in any other form or medium.⁵²

Avoiding potential extraterritorial application of HIPAA has influenced the administration of international clinical trials. Some sponsors have faced concern that HIPAA might apply to the conduct of HIPAA-covered entities when they gather PHI abroad.⁵³ The HHS Secretary’s Advisory Committee on Human Research Protections (“SACHRP”) notes that some clinical research sponsors have “determined that these concerns can be eased by no longer relying on Covered Entities (such as academic research institutions or universities) to assist in the coordination of multi-national clinical trials.”⁵⁴ To reverse any regulatory bias against covered entities that could play a valuable role as investigators on foreign clinical trials, SACHRP recommends that “the Department give clear guidance in the near future on the scope of HIPAA’s application in the international context” and that the guidance restrict the extraterritorial application of HIPAA insofar as possible.⁵⁵ However, because the Department has not yet issued this guidance, commercial sponsors of clinical trials in Africa can, and often do, choose to directly contract with local, ex-U.S. hospitals and clinics to conduct trials, bypassing covered entity medical centers in the U.S. that, before HIPAA, might have acted as the data coordinating center or as the lead clinical trial site. Sponsors also often choose to rely on Contract Research Organizations or other

49. *See id.* at 200–01.

50. *See* 45 C.F.R. § 164.508(a) (2015).

51. *See* 45 C.F.R. § 160.102(a) (2015).

52. 45 C.F.R. § 160.103 (2015).

53. *See Secretary’s Advisory Committee on Human Research Protections: Appendix H*, U.S. DEP’T OF HEALTH & HUM. SERV. OFF. FOR HUM. RES. PROTECTIONS, <http://archive.hhs.gov/ohrp/sachrp/appendixh.html> (last updated Feb. 9, 2005).

54. *Id.*

55. *Id.*

entities that are not HIPAA covered entities when initiating clinical trials in Africa.

It should be noted that HIPAA is not the only source of a confidentiality requirement that applies extraterritorially. Even when HIPAA does not apply to foreign clinical trials, the Common Rule requires that an IRB consider whether the research plan includes adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.⁵⁶ Therefore, a clinical trial conducted at one or more sites in Africa that is not subject to HIPAA may still be subject to privacy and confidentiality requirements imposed through an IRB, if the clinical research is subject to FDA human subjects regulations.⁵⁷ As discussed above in Subsection II.B.ii, pharmaceutical clinical trials that generate research used to support a drug application to the FDA are subject to FDA regulations protecting human subjects, and therefore are already likely to face the imposition of confidentiality requirements on clinical trials conducted in Africa.

5. Export & Import Control Regulations

When U.S. entities conduct clinical trials in Africa, certain export control regulations may restrict their ability to convey some materials and technology outside the United States. The International Traffic in Arms Regulations (“ITAR”)⁵⁸ and Export Administration Regulations (“EAR”)⁵⁹ apply to all exports in clinical trials, regardless of whether the federal government has a role in funding or receiving data from the trials.

ITAR’s United States Munitions List designates the “articles, services, and related technical data” that are subject to controls as defense articles and services under the Arms Export Control Act.⁶⁰ The Munitions List designates numerous toxicological agents, including chemical agents, biological agents, and associated equipment, as defense articles.⁶¹ In order to export any of these agents and associated equipment for use in clinical trials, the sponsor must obtain the requisite licenses under ITAR.⁶²

56. See 45 U.S.C. § 46.111(a)(7) (2016).

57. See 45 C.F.R. § 46.101 (2016) (applying the privacy and confidentiality requirements of 45 C.F.R. § 46.111(a)(7) “to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research,” which includes the FDA).

58. See 22 C.F.R. § 120 *et seq.* (2015).

59. See 15 C.F.R. § 730 *et seq.* (2016).

60. See 22 C.F.R. § 121.1(a) (2015).

61. See 22 C.F.R. § 121.1 (2016) (Category XIV—Toxicological Agents, Including Chemical Agents, Biological Agents, and Associated Equipment); *see also* 22 C.F.R. § 120 *et seq.* (2016).

62. See 22 C.F.R. § 123.1 (2016) (requiring that “any person who intends to export or import temporarily a defense article must obtain the approval of the Directorate of Defense Trade Controls prior to the export or temporary import, unless the export or temporary import qualifies for an exemption under the provisions of this subchapter.”).

No African countries appear on the current list of countries to which the United States categorically refuses to grant a license for the export of defense articles and services.⁶³ However, the United States generally also will refuse to issue an export license under ITAR for exports to certain nations, such as when a United Nations embargo applies to a nation and a potential export is also contained on the Munitions List.⁶⁴ As of September 2017, countries in Africa subject to a policy of denials for the export of defense articles and services, except when a license may be issued on a case-by-case basis, include the Central African Republic, the Democratic Republic of Congo, Eritrea, Libya, Somalia, Sudan, and Zimbabwe.⁶⁵

The EAR regulates “‘dual-use’ item[s] . . . [having] civil applications as well as terrorism and military or weapons of mass destruction (WMD)-related applications.”⁶⁶ Relevant facts for determining the applicability of the EAR export prohibitions include the listing of an item on the Commerce Control List, the identity of a destination country, and the end-use.⁶⁷ Because the Commerce Control List contains various biological and chemical agents that have dual uses, those conducting clinical trials in Africa must ensure that exports of materials for use in their clinical trials are not prohibited under the EAR.

6. *Foreign Corrupt Practices Act*

Entities that operate in the U.S. must comply with the Foreign Corrupt Practices Act of 1977 (“FCPA”) when sponsoring or conducting clinical trials outside of the U.S.⁶⁸ The FCPA makes it unlawful for any person to offer, promise or pay “any money. . . [or] anything of value” to certain foreign persons in order to influence official acts or obtain business.⁶⁹

FCPA risks are especially relevant to sponsors and investigators of ex-U.S. clinical trials, as the former Assistant Attorney General for the Criminal Division of Department of Justice has noted a “significant risk” of FCPA violations in the

63. See 22 C.F.R. § 126.1(a), (c)(2)–(3) (1993).

64. See 22 C.F.R. § 126.1(c) (1993).

65. See 22 C.F.R. § 126.1(d)(2) (1993).

66. 15 C.F.R. § 730.3 (2013).

67. See 15 C.F.R. § 736.2(a) (1996).

68. See generally 15 U.S.C. § 78dd-1 (2010).

69. 15 U.S.C. § 78dd-1(a)(1)–(3) (2010) (individuals to whom such offers, promises or payments may not be made include: 1) “any foreign official for purposes of influencing any act or decision of such foreign official in his official capacity,” 2) “any foreign political party or official thereof or any candidate for foreign political office for purposes of—influencing any act or decision of such party, official, or candidate in its or his official capacity” in order to assist in “obtaining or retaining business for or with, or directing business to, any person,” and 3) any intermediary with the knowledge that “all or a portion of such money or thing of value will be offered, given, or promised, directly or indirectly, to any foreign official, to any foreign political party or official thereof, or to any candidate for foreign political office” for the prohibited purposes).

field.⁷⁰ In a 2009 speech, Assistant Attorney General Lanny Breuer stated that, “[i]n some foreign countries and under certain circumstances, nearly every aspect of the approval, manufacture, import, export, pricing, sale and marketing of a drug product may involve a ‘foreign official’” as defined in the FCPA.⁷¹

In Africa, sponsors of clinical trials, CROs and American lead investigators conducting a clinical trial may confront a number of scenarios that could give rise to FCPA liability as a result of having conferred “any money . . . [or] anything of value” to a foreign official in order to influence official acts or obtain business.⁷² While making an impermissible direct payment to a government official to approve an increased study enrollment, for example, would clearly violate the statute, possible liability may attach to many other activities surrounding a trial that are not so unambiguously prohibited. In many countries, hospitals hosting clinical trials are most often government-owned or government-controlled, and physicians and other staff administering a clinical trial are government or parastatal employees.⁷³ As government or parastatal employees, these medical professionals are regarded as “foreign officials” under the FCPA.⁷⁴

Payments to government officials (including physician-investigators) who are administering or conducting a trial do not become an impermissible payment made “to influence official acts or obtain business” if the payments are used to fund the trial and are calibrated to fair market value for the services performed.⁷⁵ However, the payments must not be intended to gain local regulatory approval to conduct the trial or to influence the exercise of any government official’s true discretionary authority.⁷⁶ Monetary payments are not the only transfers to foreign government employees that may implicate the FCPA. Authorship on papers, for example, when undeserved under applicable academic criteria, may be a thing “of value” under the FCPA, because authorship conveys professional

70. See Gardiner Harris & Natasha Singer, *U.S. Inquiry of Drug Makers is Widened*, N.Y. TIMES, Aug. 13, 2010, http://www.nytimes.com/2010/08/14/health/policy/14drug.html?_r=1.

71. *Id.* (further noting that the depth of involvement of foreign governments and officials in foreign health systems, and the competitive nature of the industry, creates risk for illegal payments that could corrupt the process of drug development, manufacture, import, export, and pricing).

72. 15 U.S.C. § 78dd-1(a)(3) (2010).

73. See B. Hanifin, M. Barnes, & N. Berg, *Corruption Risks in International Clinical Trials: Navigating Between Anti-Bribery Laws and Local Circumstances*, BLOOMBERG BNA MEDICAL RES. L. & POL’Y REPORT 1 (Jan. 6, 2016), <https://www.ropesgray.com/newsroom/news/2016/01/In-Bloomberg-BNA-Medical-Research-Law-Policy-Report-Litigators-Review-Corruption-Risks.aspx>.

74. See 15 U.S.C. § 78dd-1(f)(1)(a) (2010) (defining “foreign official” as “any officer or employee of a foreign government or any department, agency, or instrumentality thereof, or of a public international organization, or any person acting in an official capacity for or on behalf of any such government or department, agency, or instrumentality, or for or on behalf of any such public international organization.”).

75. See generally, 15 U.S.C. § 78dd-1 (2010) (providing an exception for payment(s) to foreign governments and officials for “routine governmental action” The fair market value of payments tends to support that *bona fide* services were purchased).

76. See *id.* (providing that any payment to a foreign government official is impermissible if the payment is for purposes of influencing the foreign official in his or her official capacity).

prestige and career opportunities. Therefore, in the allocation of any benefit, monetary or otherwise, clinical trial sponsors, CROs and lead investigators should assure that any benefits or payments are justifiable under FCPA standards.

In addition to the FCPA, multinational entities conducting clinical trials in Africa must also comply with the United Kingdom Bribery Act if they “carr[y] on a business, or part of a business, in any part of the United Kingdom.”⁷⁷ The scope of the United Kingdom Bribery Act extends to U.S.-based research sponsors that carry out research in Africa if they, for example, are registered to do business in the United Kingdom or sell pharmaceutical, medical device, or biological products there. Liability is triggered when a person “associated” with the covered commercial entity “bribes another person intending to obtain or retain business for [the entity] or to obtain or retain an advantage in the conduct of business for [the entity]” and the entity lacks “adequate procedures designed to prevent persons associated with [it] from undertaking such conduct.”⁷⁸ The Act broadly defines an associated person to include “a person who performs services for or on behalf of [the entity],” a standard which is determined “by reference to all the relevant circumstances and not merely by reference to the nature of the relationship between [the person] and [the entity].”⁷⁹ Consequently, all U.S.-based and local personnel at a sponsor’s trial site in Africa potentially could be determined to be “affiliated persons,” and therefore the sponsor must ensure that its procedures are adequate to prevent all its potential affiliates from engaging in bribery prohibited under the Act.

7. False Claims Act

The federal False Claims Act (“FCA”) provides that any person who “knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval” will be “liable to the United States Government for a civil penalty of not less than \$5,000 and not more than \$10,000 [as adjusted for inflation], plus three times the amount of damages which the Government sustains because of the act of that person.”⁸⁰

Academic institutions that receive funding from government agencies, such as NIH or CDC, to conduct research studies in Africa encounter several situations that could be characterized as having presented or having caused to be presented a false or fraudulent claim. For example, institutional grantees can risk FCA liability if project investigators charge to a grant costs that do not relate to the

77. Bribery Act 2010, c. 23 § 7 (U.K.).

78. *Id.*

79. *Id.* at § 8.

80. 31 U.S.C. § 3729 (2012).

specific objects of the grant, or if required procurement processes are not followed. Additionally, for example, institutional grantees may face liability under the FCA for excessive time and effort charges on federally funded grants to support personnel salaries.⁸¹

8. Registration on *ClinicalTrials.gov*

The Food and Drug Administration Act of 1997 instructed the NIH to create a database listing clinical trials of drugs that treat “serious or life-threatening conditions.”⁸² In 2000, the NIH released the *ClinicalTrials.gov* website.⁸³ The categories of clinical trials required to be registered on *ClinicalTrials.gov* were significantly expanded under the Food and Drug Administration Amendments Act of 2007 (“FDAAA”).⁸⁴ The FDAAA requires that all clinical trials of drugs, biologics and devices be registered.⁸⁵ Additionally, the FDAAA requires that summary results of registered trials of products approved, licensed or cleared by the FDA be posted on *ClinicalTrials.gov*.⁸⁶ Under the FDAAA, the registration requirement applies to any trial that is an “applicable clinical trial,” defined as “a controlled clinical investigation, other than a phase I clinical investigation” of a drug subject to NDA registration or a biologics license application.⁸⁷ Therefore, clinical trials conducted abroad must also be registered and listed on *ClinicalTrials.gov* if they are conducted as phase II or III trials in support of an NDA.

In a new rulemaking, NIH clarified that some entirely ex-U.S. clinical trials are not subject to registration. NIH issued a Notice of Proposed Rulemaking interpreting the provisions of the FDAAA on November 19, 2014 and issued a Final Rule on September 21, 2016.⁸⁸ The Final Rule implements the FDAAA’s mandated expanded registry and results bank and also clarifies, in the preamble, that a clinical investigation of a drug, device or biological product that is being conducted entirely outside of the U.S. (*i.e.*, a trial without any sites in the U.S. or in any territory of the U.S.) may or may not be an “applicable drug clinical

81. See, e.g., *Yale University to Pay \$7.6 Million to Resolve False Claims Act and Common Law Allegations*, U.S. DEP’T OF JUSTICE (Dec. 23, 2008), <https://oig.nasa.gov/press/pr2009-B.pdf>.

82. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 113, 111 Stat. 2295, 2311 (1997).

83. See U.S. NAT’L INST. OF HEALTH, *History, Policies, and Laws*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/about-site/history> (last updated July 2017) (providing a timeline of information relating to the expansion of the *ClinicalTrials.gov* website).

84. See Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 904 (2007) (codified at 42 U.S.C. 282).

85. See *id.*

86. See *id.*

87. *Id.*

88. See Clinical Trials Registration and Results Submission, 79 Fed. Reg. 69,466 (Nov. 19, 2014); see also Clinical Trials Registration and Results Submission, 81 Fed. Reg. 64,982 (Sept. 21, 2016).

trial” (defined to include biologics) or an “applicable device clinical trial” required to be reported on *ClinicalTrials.gov*.⁸⁹ Whether an exclusively ex-U.S. trial is an “applicable drug clinical trial” under the Final Rule is determined by whether the drug is subject to an NDA or to a biologics license application.⁹⁰ If the drug or biological product is “manufactured outside of the United States or its territories, the clinical investigation sites are all outside of the United States, and the clinical investigation is not being conducted under an IND, [then] the drug or biological product would not be considered to be subject” to an NDA or to biologics license application, thus the clinical investigation would not be an “applicable drug clinical trial” requiring registration on *ClinicalTrials.gov*.⁹¹ Likewise, if a clinical investigation for a device product is not conducted under an IDE and “is manufactured outside of the United States or its territories, and the clinical study sites are all outside of the United States and/or its territories” then the trial is not an applicable device clinical trial and is not subject to registration on *ClinicalTrials.gov*.⁹² The Final Rule clarifies for sponsors conducting exclusively ex-U.S. clinical trials for drugs not to be marketed within the U.S. that the related clinical trials are not required to be registered with the FDA.

Biomedical journals provide another significant professional impetus for both academics and industry sponsors to register clinical trials on *ClinicalTrials.gov*. The International Committee of Medical Journal Editors (“ICMJE”) requires all journals seeking its approval to enforce the ICMJE policy requiring “registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication.”⁹³ ICMJE specifically deems *ClinicalTrials.gov* to be an acceptable public trials registry, among others.⁹⁴

III. ETHICAL GUIDELINES FOR CLINICAL RESEARCH AND POTENTIAL ETHICAL ISSUES AFFECTING CLINICAL TRIALS IN AFRICA

In countries where human subjects research law is meager, non-existent or weakly enforced, a series of ethical guidelines nevertheless provide standards for research involving human subjects. Subsection A provides a brief overview of the history of the ethical principles applicable to clinical research in foreign countries. Subsection B applies one set of ethical principles, the *International Ethical Guidelines for Health-Related Research Involving Humans* to certain

89. 81 Fed. Reg. 64,982, 65,013, 65,015.

90. *See id.* at 65,015.

91. *Id.*

92. *Id.*

93. *Clinical Trial Registration*, INT’L COMM. OF MED. J. EDITORS, Jan. 29, 2016, <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>.

94. *See id.*

ethical challenges likely to arise when clinical trials are conducted by sponsors and investigators in Africa.

A. Sources of Ethical Principles

After World War II, the Nuremberg Code (“the Code”) was drafted in response to the medical experiments that Nazi doctors carried out on concentration camp prisoners.⁹⁵ The Code lays out principles of ethical experimentation on human subjects.⁹⁶ Officially, the Code was never adopted by the international community and, subsequently, questions emerged regarding “the applicability of its more stringent provisions when the research [was] clearly for the benefit of the patient.”⁹⁷ Subsequent ethical guidelines have emerged to clarify and expand upon the Code.⁹⁸

One subsequent ethical guideline, the Declaration of Helsinki (the “Declaration”), was promulgated by the World Medical Association in 1964 and is addressed primarily to physicians, although the Association encourages others involved in medical research involving human subjects to adopt the Declaration’s principles.⁹⁹ When a physician is involved in human subjects research, the Declaration provides that it is “the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research.”¹⁰⁰

In 1982, the Council for International Organizations of Medical Sciences (“CIOMS”) released the first version of its *International Ethical Guidelines for Health-Related Research Involving Humans* (the “Guidelines”).¹⁰¹ Most recently updated in 2016, these Guidelines aim to “provide internationally vetted ethical principles and detailed commentary on how universal ethical principles should be applied, with particular attention to conducting research in low-resource settings.”¹⁰² The Guidelines provide that, “[t]o ensure that people in low-

95. See Dawn Joyce Miller, Comment, *Research and Accountability: The Need for Uniform Regulation of International Pharmaceutical Drug Testing*, 13 PACE INT’L L. REV. 198, 198–99 (2001) (stating that “the Nuremberg trials resulted in the first enunciation of ethical principles for medical research involving human beings—the Nuremberg Code”).

96. See generally *The Nuremberg Code*, OFF. OF HIST. NAT’L INSTIT. OF HEALTH, <https://history.nih.gov/research/downloads/nuremberg.pdf> (last visited Sept. 18, 2017) (setting forth several principles including voluntary consent of human subjects and avoidance of unnecessary physical or mental suffering).

97. Miller, *supra* note 1, at 203.

98. See *id.* at 203 n.38, 205 (noting that the Declaration of Helsinki has expanded upon the Nuremberg Code’s protections).

99. See WORLD MED. ASS’N, *supra* note 48 at 199.

100. *Id.*

101. See *Int’l Ethical Guidelines for Health-Related Research Involving Humans*, COUNCIL FOR INT’L ORG. MED. SCI., <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf> (last modified 2016).

102. *Id.* at viii.

resource settings receive equitable benefit from their participation in health-related research . . . local social value [must] be created.”¹⁰³ Additionally, the Guidelines require that research in low-resource settings involve cooperation with government and other stakeholders “to make available as soon as possible any intervention or product developed, and knowledge generated . . . and to assist in building local research capacity,” including for example “training laboratory personnel” and “educating the public about the nature of research and the benefits resulting from a particular study.”¹⁰⁴

The pharmaceutical trade organization PhRMA has published its *Principles on Conduct of Clinical Trials*, which is voluntary for its members to adopt.¹⁰⁵ These principles require IRB review, the informed consent of human research study participants, and mandate that sponsors of trials in the developing world seek to collaborate with relevant parties, such as local health authorities and host governments, in order “to address issues associated with the conduct of the proposed study and its follow-up.”¹⁰⁶

B. Ethical Issues Affecting Clinical Trials in Africa

The emergence of ethical guidelines for human subjects research in the post-World War II era indicates the perennial nature of difficult ethical questions that inevitably arise in working with human research subjects. When research subjects are located in the developing world or emerging economies, applying the ethical guidelines often poses unique challenges. This section applies the *International Ethical Guidelines for Health-Related Research Involving Humans* to some difficult paradigms that may emerge in conducting clinical trials in Africa.

1. Obtaining Adequate Informed Consent

Assuring adequate informed consent poses serious challenges for sponsors and investigators in many African countries. Investigators seeking informed consent may need to navigate barriers including language, comprehension, and local cultural norms.¹⁰⁷ In some areas, “the use of local languages may facilitate the communication of information to potential participants” and allow the investigator to ensure the potential subjects’ comprehension.¹⁰⁸ Investigators working in such circumstances must take into account the competence and neutrality of

103. *Id.* at 3.

104. *Id.* at 3, 5.

105. See PRINCIPLES ON CONDUCT OF CLINICAL TRIALS: COMMUNICATION OF CLINICAL TRIAL RESULTS, PHRMA 2 (rev. ed. 2014), http://phrma.org/sites/default/files/pdf/042009_clinical_trial_principles_final_0.pdf.

106. *Id.* at 11.

107. See COUNCIL FOR INT’L ORG. MED. SCI., *supra* note 101, at 26, 34.

108. *Id.* at 35.

local translators to ensure that intended messages are being appropriately conveyed to research subjects.

Additionally, investigators in the developing world may face challenges in ensuring that the prospective subject has adequately understood the information provided. In countries with a low level of education among research subjects, investigators may have difficulty determining whether a person has understood the plan of research sufficient to give informed consent.¹⁰⁹ Commentary in the Guidelines recommends that the investigator should give each potential research subject the “opportunity to ask questions” and provide the potential subject answers before or during the research.¹¹⁰ Researchers also should use “evidence-based methods for imparting information to ensure comprehension.”¹¹¹

Finally, investigators must respect the customs of a community while simultaneously ensuring that adequate individual consent is obtained. For example, in some communities, the permission of a community leader, council of elders, or other designated authority may be expected before investigators approach individuals as potential human subjects.¹¹² For example, it has been reported that the African Malaria Network Trust has obtained the permission of community leaders to conduct trials in the village of Balonghin, Burkina Faso; two sites in Mali; a site in Gabon; and various communities in the town of Bagamoyo, Tanzania.¹¹³ However, the Guidelines note that individual consent must still be obtained, and a community leader’s consent cannot be used as a substitute.¹¹⁴

The potential difficulties in obtaining adequate informed consent in certain circumstances are highlighted by the Pfizer clinical trial of Trovan in Nigeria.¹¹⁵ In 1996, northern Nigeria experienced an epidemic of bacterial meningitis.¹¹⁶ During the outbreak, Pfizer sponsored a study of an experimental anti-meningitis drug, Trovan, on a group of 200 pediatric subjects.¹¹⁷ Eleven children died in the trial, five of whom had taken Trovan and six of whom had taken another older antibiotic used for comparison.¹¹⁸ The study proved contentious on multiple grounds, with a central issue being whether informed consent had been

109. See Meier, *supra* note 1, at 540.

110. COUNCIL FOR INT’L ORG. MED. SCI., *supra* note 101, at 34.

111. *Id.*

112. See *id.* at 35.

113. See Aceme Nyika et al., *Engaging Diverse Communities Participating in Clinical Trials: Case Examples from Across Africa*, 9 *MALARIA J.* 1–11 (2010).

114. See COUNCIL FOR INT’L ORG. MED. SCI., *supra* note 101, at 35.

115. See Donald G. McNeil, Jr., *Nigerians Receive First Payments for Children Who Died in 1996 Meningitis Trial*, N.Y. TIMES (Aug. 11, 2011), available at <http://www.ny-times.com/2011/08/12/world/africa/12nigeria.html>.

116. See *id.*

117. See *id.*

118. See *id.*

properly obtained from the children or their guardians.¹¹⁹ Plaintiffs in subsequent litigation alleged that the study had not appropriately implemented the treatment protocol requiring “researchers to offer or read the subjects documents requesting and facilitating their informed consent,” which researchers allegedly did not do “in either English or the subjects’ native language of Hausa.”¹²⁰

The Trovan clinical trial provides at least two lessons for investigators who seek to obtain informed consent when working in Africa. First, ensuring that local subjects are sufficiently informed so as to be able to give adequate consent is likely to require coordination with local parties who can explain the potential risks and rewards of trial participation in linguistically appropriate and culturally competent language.¹²¹ Although this was apparently done in the Trovan study, records of the informed consent process were generally lacking.¹²² Second, therefore, it is best to create a record of the informed consent of research subjects or their guardians, if only to avoid future disputes and litigation. When working with populations with high rates of illiteracy, written consent may be difficult to obtain, and alternative methods of documentation, such as audio or video recordings of statements of consent may be desirable, although investigators should also work with local partners to determine whether these technologies are likely to have a deterrent or coercive effect on potential subjects’ participation.¹²³

The HIVNET 012 Perinatal HIV Prevention Study, carried out in 1997 in Uganda, also illuminates the difficulties investigators face in obtaining adequate informed consent.¹²⁴ At the time of the study, “the standard of care for preventing mother-to-child transmission in both the United States and Europe” consisted of a three-part maternal-infant zidovudine regimen.¹²⁵ Due to a variety of factors, including “poor public health, clinical, and laboratory infrastructure and capacity [and] high rates of out-of-hospital delivery” the three-course regimen was

119. See *Abdullahi v. Pfizer, Inc.*, 562 F.3d 163, 169–70 (2d. Cir. 2009).

120. *Id.*

121. See, e.g., Donald J. Krogstad, et al., *Informed Consent in International Research: The Rationale for Different Approaches*, 83 AM. J. TROPICAL MED. & HYGIENE 743, 746 (2010) (recommending that community leaders participate in the consent process, where appropriate, to ensure participants understand the risks and benefits).

122. See Joe Stephens, *Panel Faults Pfizer in '96 Clinical Trial In Nigeria*, WASH. POST, May 7, 2006, available at <http://www.washingtonpost.com/wp-dyn/content/article/2006/05/06/AR2006050601338.html>.

123. See Maria Kuthning & Ferdinand Hundt, *Aspects of Vulnerable Patients and Informed Consent in Clinical Trials*, 11 GER. MED. SCI. 1, 9 (2013); see also Niranjana G. Kulkarni, *Audio-Video Recording of Informed Consent Process: Boon or Bane*, 5 PERSP. CLINICAL RES. 6 (2014).

124. See INST. OF MED. OF THE NAT'L ACADEMIES, REVIEW OF HIVNET 012 PERINATAL HIV PREVENTION STUDY 27 (2005).

125. *Id.*

impractical in Uganda.¹²⁶ The HIVNET 012 Study therefore tested a less intensive regimen, consisting of a shorter course of antiretroviral drugs, for its efficacy in preventing mother-to-child HIV transmission.¹²⁷

In a report affirming the validity of the study's questioned findings, the Institute of Medicine ("IOM") identified numerous ethical issues that the investigators had faced in obtaining adequate informed consent.¹²⁸ The report broadly noted that investigators "must tailor both the information and the way they convey it to the needs of participants," including "forms of documentation that are sensitive to local concerns," noting in particular that "in some settings, [there may be] a fear of signing documents."¹²⁹ These cultural differences challenge investigators to adapt standard informed consent practices to local circumstances.

One issue that the HIVNET 012 investigators confronted was whether a father's informed consent should be obtained.¹³⁰ The study's consent forms included a line for the father of the fetus or infant to sign if he was available.¹³¹ The investigators counseled study participants to involve fathers in the decision-making, but when participants "refused or were unable to involve fathers . . . the research team deemed those fathers 'unavailable.'"¹³² In its review of the study, the IOM found that obtaining informed consent from fathers was not required by U.S. federal regulations, which only require a father's consent when the research is solely of possible benefit and risk to the fetus, without any benefit or risk to the mother.¹³³ In the HIVNET 012 study, however, both maternal and fetal health were involved, so the fathers' consent was not required.¹³⁴ Moreover, the IOM report noted that requiring the father to be involved in the study posed "concerns about violating confidentiality by revealing the women's HIV status to the fathers, especially given the stigmatization of HIV-positive individuals."¹³⁵ This study therefore provides an example of the moral and legal risks involved in implementing an interventional drug study in a low-resource setting.

2. Informed Consent Implications in Project Wind-Up and Wind-Down

U.S. and E.U.-based staff can, without realizing, raise expectations for continued support, involvement or resources. Cultural differences may give rise to

126. *Id.* at 28.

127. *See id.* at 28–29.

128. *See id.* at 89.

129. *Id.*

130. *See id.* at 90.

131. *See id.*

132. *Id.*

133. *See id.* at 90–91.

134. INST. OF MED. OF THE NAT'L ACADEMIES, *supra* note 124, at 91 (noting that some medical benefits arguably did accrue to the pregnant women).

135. *Id.* at 90.

miscommunicated expectations such that research subjects may not realize that the foreign investigator and his or her foreign institution have not entered into a treatment relationship with them and that their actual relationship is different in character and duration from a treatment relationship.¹³⁶ To satisfy the duty to obtain informed consent, investigators working in circumstances where the nature of the research may be unclear have an ethical duty to ensure that they communicate to research subjects “how the research differs from routine medical care.”¹³⁷ Critically, for subjects who are unfamiliar with controlled trials, obtaining adequate informed consent requires “an explanation of features of the research design, e.g. randomization [and] double blinding. . . .”¹³⁸

3. Avoiding Undue Inducement When Subjects Lack Medical Alternatives

The comparative ease of recruiting study participants in African countries may, in some circumstances, raise concerns that a lack of medical treatment alternatives creates an undue pressure on research subjects to participate in a clinical trial.¹³⁹ In particular, some have noted the possibility that, “[i]n the absence of health care, virtually any offer of medical assistance (even in the guise of research) will be accepted as ‘better than nothing’ . . .”¹⁴⁰ For example, in Africa, participation in clinical trials was highly valued in the past because it was, for many, the only means of accessing treatment for HIV/AIDS.¹⁴¹

In clinical trials, health care that is essential to the safe conduct of the research, as well as medical services unrelated to the study, may be provided to research subjects. The Guidelines state that “[w]hen participants’ health needs during and after research cannot be met by the local health infrastructure or the participant’s pre-existing health insurance, the researcher and sponsor must make prior arrangements for adequate care for participants with local health authori-

136. See Nicholas A. Christakis, *The Ethical Design of an AIDS Vaccine Trial in Africa*, 18 HASTINGS CTR. REPORT 31, 35 (1988) (noting that “subjects with relatively little understanding of medical aspects of research participation . . . [may be] under the mistaken notion that they are being treated. . . .”).

137. COUNCIL FOR INT’L ORG. MED. SCI., *supra* note 101, at 103.

138. *Id.* at 105.

139. See Esther Chang, Note, *Fitting A Square Peg into a Round Hole?: Imposing Informed Consent and Post-Trial Obligations on United States Sponsored Clinical Trials in Developing Countries*, 11 S. CAL. INTERDISC. L. J. 339, 342, 353 (2002) (recognizing the relative ease in recruiting participants in African countries for certain studies and that participants with little access to care for life-threatening illnesses may face undue influence to enroll in a trial); see also Paul S. Appelbaum et al., *Voluntariness of Consent to Research: A Conceptual Model*, 39 HASTINGS CTR. REPORT 30, 30-31 (2009) (recognizing that issues of impaired voluntariness can arise where patients who otherwise lack access to medical care are invited to participate in clinical trials).

140. Meier, *supra* note 1, at 537 (citing George J. Annas & Michael A. Grodin, *Research Forum: Ethics and Studies of HIV, Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa*, 88 AM. J. PUB. HEALTH 560, 562 (1998)).

141. See NWABUEZE, *supra* note 2 at 2 (2013).

ties, members of the communities from which persons are drawn, or nongovernmental organizations such as health advocacy groups.”¹⁴² Additionally, the Guidelines note that addressing participants’ health needs requires researchers and sponsors to “make plans for . . . how care will be provided during the research when researchers discover conditions other than those under study.”¹⁴³

For clinical trials conducted in resource-poor settings in Africa, investigators must be aware of how the availability of health care services may affect the choices of research subjects.¹⁴⁴ The Guidelines note that providing medical services as a component of a clinical trial has the potential to run afoul of an ethical duty to avoid compensation so large that it creates an undue pressure to consent against the subject’s better judgment.¹⁴⁵ However, the Guidelines do not prohibit all research when there is merely a possibility that subjects will be induced to participate in a trial because it offers benefits relative to the routinely available medical care.¹⁴⁶ Noting that “the compensation that makes some people volunteer against their better judgment depends on their personal situation,” the Guidelines provide that “[r]esearch ethics committees must evaluate monetary and other forms of compensation in light of the traditions and socio-economic context of the particular culture and population in order to determine whether the average participant expected to enrol[l] in the study is likely to participate in the research against his or her better judgment because of the compensation offered.”¹⁴⁷ Therefore, in order to provide ethically sound financial and medical benefits to clinical trial participants in resource-poor settings in Africa, sponsors and investigators must take into account the potential for undue inducement, when the participants’ access to alternative sources of medical care is limited.

4. Ethical Issues in Identifying Human Subjects

When working in African countries, certain ethical challenges emerge related to the identification of research subjects. One set of challenges relates to the equity of the decision to locate such research in the country with populations and communities with limited resources.¹⁴⁸ An additional set of challenges

142. COUNCIL FOR INT’L ORG. MED. SCI., *supra* note 101, at 21.

143. *Id.*

144. See Ezekiel J. Emanuel et al., *What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research*, 189 J. INFECTIOUS DISEASES 930, 930 (2004) (“[While] limited health-care services . . . neither cause nor are necessary for exploitation, they increase the possibility of such exploitation.”).

145. See COUNCIL FOR INT’L ORG. MED. SCI., *supra* note 101, at 53 (“Compensation [broadly defined to include non-monetary forms such as free health services] must not be so large as to induce potential participants to consent to participate in the research against their better judgment (‘undue inducement’).”).

146. See *id.* at 53–54.

147. *Id.* at 54.

148. See *id.* at 2–5.

emerges when selecting research subjects from among the population of the developing country.

When working in populations with limited resources, the Guidelines require that the sponsor and investigator must make every effort to ensure that “the research is responsive to the health needs or priorities” of the population or community and that “any intervention or product developed, and knowledge generated” will be made available “for the population or community in which the research is carried out.”¹⁴⁹ First, responsiveness requires more than a determination that a studied disease is prevalent in the population, and includes further analysis into whether successful interventions are to be made available to the population, especially if the population may be unable to afford even a new drug that is cheaper than the standard treatment in other countries.¹⁵⁰ Second, “[p]ost-trial access plans are of particular concern” as a means of ensuring availability of products developed in “low-resource settings where governments lack the means or infrastructure to make such products widely available.”¹⁵¹ However, the Guidelines also provide that issues of post-trial availability in populations and communities should not be construed to preclude studies evaluating novel concepts, for example, in cases seeking to evaluate the efficacy of an experimental drug in treating a disease that occurs only in low-resource settings and “such research could not be carried out reasonably well in more developed communities.”¹⁵² In such instances, although there would not be a specific product that could be made available to the population or community at the end of the experimental trial even if the concept is found to be valid, the research may be ethically justifiable as “subsequent phases of research could result in a product that would be made reasonably available.”¹⁵³

Once a sponsor or sponsor-investigator determines that a clinical trial site will be located within a particular country, another set of ethical considerations apply to the selection of individual research subjects from among the population.¹⁵⁴ Ethical guidelines mandate that “[g]roups that are unlikely to benefit from any knowledge gained from the research should not bear a disproportionate share of the risks and burdens of research participation” and “[g]roups that are under-represented in medical research should be provided appropriate access to participate.”¹⁵⁵ Interpreting this provision, the Guidelines’ commentary provides that, “[w]hen burdens or benefits of research are to be apportioned unequally

149. *Id.* at 3.

150. See COUNCIL FOR INT’L ORG. OF MED. SCI., *supra* note 101, at 2–5.

151. *Id.* at 4–5.

152. *Id.* at 5.

153. *Id.* at 5.

154. See *id.* 7 (stating that “no group or class of persons [should] bear more than its fair share of the risks or burdens from research participation.”).

155. See COUNCIL FOR INT’L ORG. MED. SCI., *supra* note 101, at 7.

among individuals or groups, the criteria for unequal distribution should be scientifically and ethically justified rather than arbitrarily or conveniently chosen.”¹⁵⁶ To satisfy these ethical obligations, sponsors and investigators should be cognizant in their selection of particular ethnic or social groups within the country for possible study recruitment. Additionally, if there will be waiting lists for clinical trial enrollment, it is essential that any prioritization status to certain subjects be ethically justifiable. For example, a sound scientific reason may justify prioritizing subjects with particularly acute conditions, if relevant to the research being conducted. However, other potential criteria for participation, such as family relation to local clinical staff, should be avoided as not scientifically justifiable.

IV. CONCLUSION

Clinical trials conducted in Africa offer numerous potential benefits for studying diseases impacting public health, for pharmaceutical companies seeking to test the efficacy of new drugs, for local investigators seeking academic opportunities, and for local populations that may have lacked historical access to clinical trials or even to basic medical care. Conducting clinical trials in Africa, however, poses unique legal considerations that emerge from the complex framework of foreign and U.S. laws that may apply to foreign clinical trial sites. Additionally, clinical trials in Africa can present a number of ethically challenging situations with which sponsors and investigators may be unfamiliar. In navigating challenges such as obtaining informed consent in unfamiliar cultural and linguistic conditions, sponsors and investigators will find that the most essential ingredient to a successful research or service project in a developing country is having a competent and trustworthy local partner institution or set of investigators. Identifying such entities and persons contributes significantly to ethical and scientifically rigorous research in such projects.

156. *Id.*