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The Struggle of Regulating Clinical Trials in a Developing Nation: India's Experience

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Medical research is important to both human health and scientific advancement. Human subject research is necessary to assure that medicines are both safe and effective for the general public. Research on human beings is not something American citizens are unfamiliar with. However, unlike developing nations, many laws and regulations protect United States citizens who decide to volunteer for clinical trials. Although some developing nations, such as India, have made some progress by providing human rights protections for clinical trial participants, most of the legislation has been reactionary and ambiguous. In practice, the proposed bills leave vast amounts of discretion to the regulatory bodies in India.

This paper will begin with an overview of the legal framework which clinical trials must be conducted within in the United States, followed by an introduction to the barriers researchers face in obtaining truly informed consent from populations in developing nations due to challenges with literacy, culture and lack of access to health care. After a general introduction to these difficulties, we will explore the Indian experience. India will serve as the example of how research in developing nations is affected by regulatory guidelines and how research is impacted by local differences.

I. U.S. Regulations on Research with Human Subjects

Research¹ on human subjects² conducted within the United States is highly regulated, expensive, and is generally conducted over an extended period of time to

¹ “Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.” 45 C.F.R. 46.102(d) (2014).

ensure the safety of participants. Any research the government funds must comply with the Department of Health and Human Services' ("DHHS") "Common Rule,"³ and institutions⁴ must provide written assurances (contracts) of compliance.⁵ If the research is not federally funded the government also requires the sponsoring institution to commit to complying with the general principles in the Belmont Report.⁶

The "Common Rule" requires that Institutional Review Boards ("IRB") review research, in compliance with §46.101, §46.102, and §46.107 through §46.117.⁷

Research conducted in foreign countries is also covered by this policy,⁸ unless the Department or Agency Head⁹ deems the host country's regulations to be equivalent to U.S. regulations and approves the substitution of the foreign standards.¹⁰ The Agency Head has yet to make such a designation.

The Office for Human Research Protections ("OHRP") and the Food & Drug Administration ("FDA") oversee IRBs.¹¹ The "OHRP evaluates all written allegations or

² "Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains." 45 C.F.R. 46.102(f) (2014).

³ 45 C.F.R. 46.101(a)(1) (2015). N.B. The "Common Rule" only refers to subpart A of the regulation, since it is the only one that is common to all agencies.

⁴ "Institution means any public or private entity or agency (including federal, state, and other agencies)." 45 C.F.R. 46.102(b) (2015).

⁵ 45 C.F.R. 46.103 (2015).

⁶ The Belmont Report was created by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects* 4 (1979), available at <http://www.recerce.uab.es/ceeah/docs/Belmont%20Report.pdf>

⁷ *Id.* at 106; 45 C.F.R. 46.101(a)(2) (2015).

⁸ 45 C.F.R. 46.101(h) (2015).

⁹ "Department or agency head means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated." 45 C.F.R. 46.102(a) (2015)

¹⁰ *Id.*

¹¹ Carl H. Coleman, Jerry A. Menikoff, Jesse E. Goldner, Nancy N. Dubler. *The Ethics and Regulation of Research with Human Subjects*, 170 (2005).

indications of noncompliance with the HHS Regulations derived from any source. All compliance oversight evaluations are predicated on the HHS Regulations and the institution's Assurance of Compliance."¹² Noncompliance can result in anything from requiring an institution to develop corrective actions to OHRP recommending an institution or investigator be declared ineligible to participate in HHS supported research (government wide Debarment).¹³

The FDA was congressionally delegated the power to regulate the authorization of drugs, devices and biologics (also known as test articles) for marketing in the United States.¹⁴ The FDA participated in the International Conference on Harmonization ("ICH") – a tripartite effort between the United States, the European Union, and Japan – which formulated international standards for "Good Clinical Practice" ("GCP").¹⁵ The purpose of the ICH guidelines was to provide more uniformity of clinical data among regulatory agencies with respect to the conduct and design of clinical trials.^{16,17}

FDA regulations are triggered when clinical research involves one or more of the aforementioned test articles notwithstanding the study's source of funding.¹⁸ Although

¹² Memorandum from Director, OHRP, to OHRP Staff, Regarding Compliance Oversight Procedures (December 4, 2004).

¹³ Id.

¹⁴ See Supra Note 11 at 142 (2005).

¹⁵ See 62 Fed. Reg. 25, 692 (1997)

¹⁶ 62 Fed. Reg. 25, 692 (1997)

¹⁷ Id. However, despite being published in the federal register, 62 Fed. Reg. 25, 692 (1997), these are merely guidance and are not binding

¹⁸ Supra Note 16; See also National Bioethics Advisory Commission, Report on Ethical and Policy Issues in Research Involving Human Participants, 85-92 (2001) Although the OHRP enforces the four sub-parts (-A, -B, -C and -D) of the "Common Rule," (which includes additional protections for certain vulnerable research subjects) no sub-part specifically protects the economically or educationally disadvantaged research subjects. There are also no guidance materials aimed at helping IRBs in executing their duty to

the FDA does not have a division whose sole purpose is to ensure ethical human subject research, they have a separate enforcement unit, the Office for Good Clinical Practice (“OGCP”).¹⁹ The OGCP can impose sanctions for noncompliance with the good clinical practice standards.²⁰ “Good clinical practice (“GCP”) is a standard for the total research process: designing studies, conducting and monitoring them, recording data analyzing results, and reporting and submitting these results to support product applications to the FDA.”²¹ The OGCP is, in part, responsible for the broad purpose of ensuring studies involving human subjects is conducted in accordance with good clinical practice.²² Although the FDA regulations refer to “clinical investigations²³” and the DHHS regulations apply to “research,” one does not apply any more narrowly than the other. When a human subject is involved, both the Common Rule and the GCPs apply, since both the OHRP and the OGCP have respective jurisdiction over the study.

The FDA may approve a product for marketing in the U.S. pursuant to an Investigational New Drug Application (“IND”).²⁴ In order for the FDA to approve an

provide the “additional safeguards” for these research subject populations. The National Bioethics Advisory Commission’s¹⁸ 2001 Report on Ethical and Policy Issues in Research Involving Human Participants illustrates this gap where it states: [T]he sub-parts offer no definition of vulnerability and no analysis of the types of characteristics that render persons vulnerable... In addition, the regulations provide inadequate guidance about the types of safeguards that would be appropriate to protect against the risks associated with vulnerability.

¹⁹ Id.

²⁰ Id.

²¹ Id.

²² Id.

²³ 21 C.F.R. § 56.102 (c) provides: A “clinical investigation means any experiment that involves a test article and one or more human subjects.”

²⁴ INDs provide the FDA with information on the clinical trial protocol, the qualifications of trial personnel, and assurances that trials will protect subjects’ welfare, among other details. Department of Health and Human Services: Office of the Inspector General, Challenges to FDA’S Ability to Monitor and Inspect Foreign Clinical Trials, OEI-01-08-

IND that includes data from a foreign clinical trial the application must indicate that the research conforms to FDA requirements for investigator qualifications, good clinical practices and FDA inspections. Foreign studies can also be conducted pursuant to an IND. The number of INDs relying on clinical data of foreign trials continues to grow.²⁵ However, not all products marketed in the U.S. are the result of research conducted pursuant to an IND. This is because FDA regulations may also apply to foreign studies not conducted pursuant to an IND.²⁶ A non-IND study may be approved by the FDA so long as the “stud[y is] conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee (IEC).”²⁷

Therefore, three ways for clinical studies to be subject to federal regulation are: (1) the federal government is conducting or funding the study, (2) an institution has agreed to an assurance (contract) with the federal government confirming that it will comply with the Common Rule; or (3) the study involves a drug, biologic, or device, bringing it within the FDA’s jurisdiction.²⁸ Most research will inevitably fall within one

00510 (Jun. 2010), available at <http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf> (last visited March 28, 2015). FDA has 30 days to review the IND for safety to ensure that research subjects will not be subjected to unreasonable risk. 21 C.F.R. 312.42 (2014). A sponsor may begin its clinical trial 30 days after FDA receives an IND, provided that the agency does not place the study on clinical hold. 21 C.F.R. 312.40 and 312.42 (2014). Thereafter, FDA may choose to inspect a clinical trial while the trial is ongoing.

²⁵ Department of Health and Human Services: Office of the Inspector General, The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects, OIE-01-00-00190 (Sep. 2001), available at <https://oig.hhs.gov/oei/reports/oei-01-00-00190.pdf> (last visited March 28, 2015).

²⁶ 21 CFR part 312 (2008), available at <http://www.gpo.gov/fdsys/pkg/FR-2008-04-28/pdf/E8-9200.pdf#page=1>

²⁷ Id. The final rule replaced the requirement that non-IND studies be conducted in accordance with ethical principles in the Declaration of Helsinki (Declaration) issued by the World Medical Association (WMA), specifically the 1989 version (1989 Declaration).

²⁸ Supra Note 16

of these three rules, and in relation to drugs, is intended to ensure proper labeling and approvals. However, there are certain studies that fall outside of the aforementioned regulations. The National Bioethics Advisory Commission provided a list of research that could possibly escape federal regulations; these include research in the following settings: colleges, universities not receiving federal research funds; in vitro fertilization clinics; weight-loss or diet clinics; offices of some physicians and dentists, and psychotherapists.²⁹

In relation to research conducted pursuant to an IND, the OIG's 2010 report recognized that "[e]ighty percent of approved marketing applications for drugs and biologics contained data from foreign clinical trials[; and that more than] half of clinical trial subjects and sites were located outside the United States."³⁰ This, however, does not account for research not conducted pursuant to an IND. Therefore, it is likely that the actual percentage is higher than eighty percent.

Thus, the United States has implemented protection for human subjects to ensure consent is voluntarily given after the risks and benefits are explained. Unfortunately, these same protections either do not exist or are not enforced in developing nations.

II. Challenges to Informed Consent in Developing Countries

²⁹ See National Bioethics Advisory Commission, <https://bioethicsarchive.georgetown.edu/nbac/human/overvoll.pdf> (last visited March 28, 2015)

³⁰ Id.

²² Department of Health and Human Services: Office of the Inspector General, Challenges to FDA'S Ability to Monitor and Inspect Foreign Clinical Trials, OEI-01-08-00510 (Jun. 2010), available at <http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf> (last visited March 28, 2015). The DHHS Office of the Inspector General ("OIG") 2001 report explains that drug research under Investigational New Drug Applications ("IND") increased 16-fold between 1990 and 2000.

When the U.S. regulations described above are applied to developing nations, there are some innate difficulties in maximizing on the protections since there are some innate differences between the two types of populations.

First, citizens of developing countries are not as educated, if at all. Second, many developing nations are overwhelmingly influenced by culture and tradition. Third, and most importantly, there is a lack of access to health care in developing nations. These characteristics directly affect their perceptions of the risks and benefits of the research and their ability to give adequate informed consent.

The lack of education described above makes it difficult for developing nations to comply with the informed consent requirement. Although informed consent is the most basic requirement for clinical research, it is also the most complex. Generally, informed consent that meets the following four components is ethical: (1) disclosure of risks and potential benefits, (2) understanding of risks and benefits, (3) voluntariness and (4) competence of the participant.²¹

The need for autonomy and informed consent was recognized over a century ago, in the infamous Nuremberg Trials in Germany. These trials followed World War II and exposed the atrocities “committed by Nazi scientists and physicians under the guise of medical experimentation.”³¹ The Tribunal promulgated a set of ten principles, which have come to be known as the “Nuremberg Code,” providing the first set of international guidelines for research on human subjects.³²

³¹ Zulfiqar A. Bhutta, Ethics in International Health Research: A Perspective from the Developing World, Bulletin of the World Health Organization (2002).

³² Jacob Schuman, Beyond Nuremberg: A Critique of “Informed Consent” in Third World Human Subject Research, Journal of Law and Health Vol. 25:121 (2012).

The first principle expounded upon by the Tribunal is known as the most important one and it states: “the voluntary consent of the human subject is absolutely essential.”³³ It requires that:

[A] person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have **sufficient knowledge and comprehension** of the elements of the subject matter involved, **as to enable him to make an understanding and enlightened decision.**³⁴

The latter part of the requirement is problematic in developing nations since, as explained earlier, most populations are under-educated in developing nations. This makes full compliance with the informed consent nearly impracticable without extensive improvements narrowly tailored to the comprehension level of the population being researched.

The Ninth principle is also important because it gives the subject the right to withdraw from research at any point. Thus, once a participant has been involved long enough to truly understand the benefits and burdens of participating in the trial, she may withdraw, even if it's close to the conclusion of the trial. It states:

“during the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.”³⁵

This principle supports the first requirement that consent must be voluntary, since this principle ensures participation is voluntary all the way through to the end of the trial.

³³ "Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.

³⁴ Id.

³⁵ Id.

Before consent is even sought the eight other principles must also be satisfied.³⁶ Another important doctrine to clinical research on an international level is the Declaration of Helsinki (“DOH”). The DOH provides that, “Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.”³⁷ DOH additionally provides “[m]edical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.”³⁸

The influence that culture and tradition has on citizens of developing nations is another challenge to the direct application of U.S. regulations abroad. For example, some communities believe in family centered consent, where the family of the patient is supposed to receive the patient’s diagnosis and prognosis of a serious illness and decide whether to use life support or not.³⁹ In similar circumstances, it would be important for researchers to be aware of cultural conventions such as this when deciding whom to disclose the risks of entering the study. Clearly, not telling a subject of the risks would contravene the policy behind informed consent in the United States. This is why researchers and regulators face issues when attempting to implement and enforce U.S. regulations on developing nations. The principle of informed consent in these cultural contexts is an important challenge to the regulation of research in developing countries.

³⁶ Id.

³⁷ <http://www.wma.net/en/30publications/10policies/b3/> (last visited March 28, 2015)

³⁸ Id.

³⁹ See Supra Note 11, 366-67.

More specifically, it is impossible for U.S. regulations to merely use a one-size fits all approach, expecting consent to be genuinely informed. In the event that U.S. regulations are imported verbatim to developing countries like India, the opposite will likely occur and less and less people will participate in clinical trials. India's differences require that regulations be adapted to these challenges and tailored to their community's needs. This is true of most if not all developing nations.

The most significant difficulty is communities in developing nations often lack access to basic health care.⁴⁰ This directly affects the individual's perception of the benefits and risks of participation; and in turn, the adequacy of their informed consent. Many patients do not fully understand the risks associated with participating in a trial because the reality is that this is their only access to health care. This fact is exactly why *informed* consent is so important. Without providing adequate information to the person, they might believe they are assured a cure. Although participating in clinical research will provide people in developing countries with free health care, it is important that participants know the risks of adverse events or the possibility the test drug will have no effect. Thus, merely supplying a patient with a consent form without more follow-up and explanation will not likely inform the research subject of the risks associated with participating in the trial.

In today's clinical research environment, where sponsors are globalizing research and the subjects and sites are in widespread geographies with different cultures, education, and understandings of risk, it is increasingly important to ensure the

⁴⁰ Kristen Farrell, Human Experimentation in Developing Countries: Improving International Practices by Identifying Vulnerable Populations and Allocating Fair Benefits, 9 J. Health Care Policy 136 (2006).

protections are not only adequate, but also that the regulations are appropriate in the context of a developing country.

III. The Indian Experience

India is a perfect example of the different realities of conducting research on human subjects in developing countries, since it has been recognized as one of the most promising research hubs.⁴¹ The reasons U.S. pharmaceutical manufacturers outsource their research to India is its large (treatment naïve) patient population, data is usually compiled in English, and the approval process is significantly shorter and cheaper.⁴² “The average cost of Phase I/II/III trials in the United States is over \$20/50/100 million, respectively.”⁴³ Until recent developments that will be discussed further below, research in India cost nearly half what it does in the U.S. (50-60%) and was processed 75% faster than U.S. research.⁴⁴ Also, it used to only take researchers only 12 weeks to have a clinical trial approved in India.⁴⁵ Unsurprisingly, the number of registered clinical trials in India increased between 2007 and 2009 from 221 to 1,300, respectively.⁴⁶ However, the amount of research being conducted in India has steadily declined since 2010 for reasons that will be discussed herein.⁴⁷

⁴¹ Shiv Raman Dugal, Chairman, BoD, Institute of Clinical Research, New Dehli, “India: Clinical Research Hot-Spot” *available at* <http://www.biospectrumindia.com/biospecindia/news/157650/india-clinical-research-hot-spot> (last visited April 26, 2015).

⁴² Deepak Balakrishnan Nair, “Clinical Trial Regulation in India,” *available at* http://www.legalservicesindia.com/article/print.php?art_id=678 (last visited April 21, 2015).

⁴³ Id.

⁴⁴ Id.

⁴⁵ Id.

⁴⁶ Supra, Shiv Raman Dugal, “India: Clinical Research Hot-Spot.”

⁴⁷ Id.

Although India has made significant legislative progress, its legislation has still left many questions unanswered, providing a lot of uncertainty regarding what the future of research regulation in India will look like. The next section will highlight the improvements made in India as well as the gaps that need to be filled in order to provide research subjects with the fullest protections possible and a more predictable regulatory environment for research sponsors.

A. Challenges to Informed Consent in India: Education, Culture, and Economic Differences Impacting

Conducting trials in developing countries such as India raises additional concerns and complications that research sponsors must consider in depth. The three challenges to conducting ethical research in India are all related to the adequacy of informed consent.

One challenge to adequate informed consent in India is the low literacy level.⁴⁸ This distinct reality makes it difficult for researchers and their sponsors to use signed consent forms as evidence that the participant was informed (i.e., was competent and understood the risks) before signing up for the trial. Thus, some additional procedural safeguards are necessary to help protect both patient safety and researcher compliance with GCPs.

Another difficulty on obtaining informed consent is the overriding influence culture has on Indians. Certain topics may be culturally inappropriate for an investigator to ask directly^{49,50} and researchers may be reluctant to discuss particular topics with the

⁴⁸ *Supra* Deepak Balakrishnan Nair, “Clinical Trial Regulation in India”

⁴⁹ Inna Kassatkina, Stacy Liechti & Mark Opler, “Culture and language issues in global clinical trials” available at <http://www.multilingual.com> (last visited April 26, 2015).

research subject.⁵¹ More importantly, research participants are unlikely to answer questions honestly if asked.⁵² The sensitive nature of India's culture is illustrated by patients' fear of participation in clinical trials, because of the mandatory audiovisual recording of informed consent.⁵³ For cultural reasons, a patient might forego participating in a trial in order to avoid being recorded giving informed consent and potentially suffering from religious and/or social stigma; this is true, despite trials being their only hope for medical treatment or an improved quality of life because of the lack of health care in India.⁵⁴

Thus, it is extremely important for those designing trials and administering them to provide for cultural accommodations prior to executing a plan to research in India.⁵⁵ A researcher's failure to modify research protocols to be sensitive to India's cultural differences will likely "lead to deficient and unreliable [informed consent and] data as well as uncomfortable trials and patient participants."⁵⁶

The third and most significant hurdle is the economic disparity the Indian population is faced with. Most Indians suffer from poverty and do not have access to the most basic health care. This makes the target populations vulnerable to misunderstanding the benefits that are to be derived from participating in research. Many view it as their chance for a cure or a way to get access to care they never would have without signing up

⁵⁰ "For example, different relationships and rationales for taking medications and seeking medical services may create a perception of noncompliance — a term that fails to capture or address." *Id.*

⁵¹ *Id.*

⁵² *Id.*

⁵³ Madhur Singh, "Regulation Stifling Clinical Trials Sector, India Business Association Head Says" (September 3, 2014).

⁵⁴ *Id.*

⁵⁵ See *supra* Note 29.

⁵⁶ *Id.*

for a clinical trial. Although the latter is likely true, the former is usually wrong. Thus, there is a serious concern as to the comprehension of the participant and the informed consent that flows from the person understanding the risks and benefits associated with being part of a clinical trial.

These three challenges demonstrate how important it is that the regulation of clinical trials in India must be tailored to meet the unique needs of the Indian people; and “[i]t is incumbent on those designing trials, administering training, and providing ... support to consider potential problem areas prior to executing trial and to plan for contingencies and modifications.”⁵⁷ As mentioned earlier, India has made some significant progress in implementing legislation to better safeguard patient safety by requiring researches comply with regulations. The following sub-section goes through the different laws that have been proposed to address reported and litigated human rights violations.

B. Legislation Aimed at Addressing India’s Vulnerabilities

The legal framework regulating clinical research in India has grown more protective of its citizen’s safety much of which was instigated by horrific human rights violations and litigation. The regulations and rules created to reduce risks of Indian trial participants continues to be modified and improved to ensure the proper procedures are followed by researchers when conducting clinical research in India.

⁵⁷ Id.

Historically, clinical trials in India have been regulated under the rules and regulations in Schedule “Y” of the Drugs and Cosmetics Act of 1940 (“DC Act”).⁵⁸ In 2005 the legislature amended Schedule “Y” of the DC Act, which made it permissible for parallel global clinical trials as well as concomitant phase 2 and phase 3 trials.⁵⁹ The Drugs Controller General of India (the “DCGI”) is the government official who grants permission for new drugs to be administered to human subjects in clinical trials conducted in India.⁶⁰ In order for the DCGI to authorize a clinical trial, the proponent of the new medicine must submit an application that must include: (i) the study protocol, (ii) a draft of the Informed Consent form, (iii) a list of the proposed investigators, and (iv) background information regarding the medicine pursuant to Schedule Y of the Drugs and Cosmetics Rules.⁶¹ The Indian Council of Medical Research (“ICMR”) is a regulatory body in India that is responsible for the “formulation, coordination and promotion of biomedical research”⁶² and they must review and comment on all controversial medicines prior to the DCGI’s approval of same.⁶³

The procedure for obtaining market approval in India is as follows and depends on the status of the new medicine, which fall into three broad categories: (i) newly discovered drugs that are already approved/marketed in other countries; (ii) newly

⁵⁸ Schedule “Y” of the Drugs and Cosmetics Act of 1940 contains regulations relating to clinical trials, specifically, the requirements that need to be met in order to import, manufacture and market new drugs in India.

⁵⁹ Id.

⁶⁰ Id.

⁶¹ Id.

⁶² Indian Council of Medical Research, *available at* http://www.icmr.nic.in/About_Us/About_ICMR.html (last visited April 27, 2015)

⁶³ Proper Citation Needed – maybe resource #1 p. 2

discovered drugs that are not approved or marketed in other countries; (iii) new drugs discovered in India.⁶⁴

The ICMR also provides guidelines for biomedical research on human subjects.⁶⁵ ICMR Guidelines mandate Ethics Committees⁶⁶ (“EC”) at the institutional level.⁶⁷ ICMR Guidelines provide that the researcher should get approval from an appropriately constituted EC of the institution before submitting the proposal to DCGI.⁶⁸ Although the ICMR is not the focus of this paper, it is worth noting that the EC is the U.S. equivalent of an I.R.B. and plays the part of ethics regulator when it comes to clinical research involving human subjects. However, EC approval is not a required precondition for permission to conduct a clinical trial, as long as the applicant submits that they will not start the research without EC approval.

The ICMR Guidelines are meant to ensure that research on human subjects is safely conducted with the maximum benefit to mankind.⁶⁹ “This philosophical intent behind the ICMR [Guidelines] is virtually synonymous to the role of the [IRB], the C.F.R., and the Belmont principles combined...”⁷⁰ Despite the ICMR’s intent, its very

⁶⁴ *Supra* Deepak Balakrishnan Nair, “Clinical Trial Regulation in India,”

⁶⁵ Indian Council of Med. Research (ICMR), Ethical Guidelines for Biomedical Research on Human Participants 1 (2006), <http://www.icmr.nic.in/ethicalguidelines.pdf> [hereinafter ICMR Guidelines].

⁶⁶ Ethics committees are the custodians of the safety of research participants.

⁶⁷ *Id.*; Nisha Shah, “Trends in Biomaterials and Artificial Organs” available at <http://www.biomedsearch.com> (last visited April 27, 2015).

⁶⁸ *Id.*

⁶⁹ *Id.*

⁷⁰ Heather L. Mullins-Owens, Macey L. Henderson & Jason Henderson, Protecting a Vulnerable Population with Little Regulatory Framework: A Comparative Analysis of International Guidelines for Pediatric Research Ethics, 29 *J. Contemp. Health L. & Pol’y* 36 (2013). Available at <http://scholarship.law.edu/jchpl/vol29/iss1/5>

own 2002 Survey showed a lack of enforcement .⁷¹ India's difficulty with enforcing its ethical guidelines is also observed in the human rights violations committed by researchers within its legal framework.⁷²

The Supreme Court of India's ("the Court") January 2013 ruling suspended the power of India's regulatory authorities to approve clinical trials and gave the Indian Ministry of Health until September 24, 2014 to implement new regulations for alleged human rights violations.⁷³ The Public Interest organization that inspired the Court's ruling is Swathya Adhikar Manch (translated "Health Right Forum").⁷⁴ In their December 2012 petition they alleged that India's legal framework for approving clinical trials was completely inadequate.⁷⁵ Although the petition focused on a particular group of trials, it generally alleged that "more than 150,000 people are involved in at least 1,600 clinical trials and that during 2006-2011 at least 2,163 people have reportedly died in India while, or after, participating in such trials."⁷⁶

In accordance with the Court's ruling, the Ministry of Health and Family Welfare (the "Ministry") enacted new regulations on January 30, 2013 ("2013 Regulations"). The 2013 Regulations include many ambiguities that have caused much uncertainty. For

⁷¹ *Supra* Deepak Balakrishnan Nair, "Clinical Trial Regulation in India"

⁷² *Id.*

⁷³ *Id.*

⁷⁴ Mark Barnes, Minal M. Caron, Adarsh Varghese and Barbara E. Bierer, "India's Proposed Amendments to the Drug and Cosmetics Act: Compensation for Injuries to Clinical Trial Participants and the Criminalization of Clinical Research" (February 04, 2015).

⁷⁵ Writ Petition No. 33 of 2012, *available at* http://www.unethicalclinicaltrial.org/Awareness_Material.aspx (last visited May 8, 2015)

⁷⁶ *Id.* ¶ 8.

example, although the 2013 Regulations provide compensation for injury or death during a clinical trial, they do so in a vague manner.

For example, Section 1 of Rule 122-DAB provides injured subjects with the right to receive free medical management for as long as required without requiring that the injury be a result of or related to the clinical trial.⁷⁷ Conversely, Section 2 of Rule 122-DAB includes a relatedness requirement, which entitles research subjects to financial compensation beyond the medical expenses that must be paid by the “sponsor.”⁷⁸ Thus, regardless whether the injury is related to the clinical research, the participant would be entitled to free medical care. The regulations make it possible for any individual or institution involved at any stage of a clinical trial to be subject to the regulatory authority’s, yet to be declared, regulatory enforcement. Regardless of how well they define a “sponsor,” “investigator” or “clinical research organization,” the 2015 Reform Bill makes it possible for an academic institution or funding body to be responsible for compensating related and/or unrelated injuries.⁷⁹

In December of 2014, the Ministry of Health and Family Welfare published an amendment to the 2013 Regulations to limit sponsor liability to free medical management only for as long as necessary, or until it is proven that the injury is unrelated, whichever is shorter.⁸⁰ However, a clinical trial “related” injury is broad and includes everything

⁷⁷ Mark Barnes, Minal M. Caron, Adarsh Varghese and Barbara E. Bierer, “India's Proposed Amendments to the Drug and Cosmetics Act: Compensation for Injuries to Clinical Trial Participants and the Criminalization of Clinical Research” (February 04, 2015).

⁷⁸ Id.

⁷⁹ Id.

⁸⁰ See Drugs and Cosmetics (Sixth Amendment) Rules, 2014, Ministry of Health and Family Welfare (Dec. 12 2014) (emphasis added), available at <http://www.mohfw.gov.in/showfile.php?lid=3043> (last visited April 30, 2015)

from the use of placebo to the failure of the drug to have its intended therapeutic effect.⁸¹ In essence, the trial “sponsor,” could be responsible for having a control and providing placebo, or the drug not working as they had hoped. These compensable “injuries” are the kind someone not participating in the trial could suffer from by not seeking care and/or not taking medicine to treat themselves. Unfortunately, most citizens in developing countries have no other option because of the lack of basic health care in the first place. This in practice would equate to a guarantee of compensation for merely signing up for a trial – for better or for worse, you can make money by seeking compensation from a sponsor.

The Ministry enacted two related amendments, Rule 122-DAC and Rule 122-DD. Rule 122-DAC grants the Licensing Authority the power to grant permission to conduct a trial and to sanction sponsors for not complying with the applicable conditions.⁸² Rule 122-DD establishes the rules requiring Ethics Committees to register.⁸³

The most recent development in India is the 2015 proposed reform bill (“2015 Reform Bill”), which is set to amend the Drug and Cosmetic Act of 1940 (“D & C Act”). This 2015 Reform Bill leaves much to the imagination by including open-ended language providing unnamed Indian regulatory authorities with wide discretion to determine the

⁸¹ Id. (a) adverse effect of investigational product(s); (b) violation of the approved protocol ... by the Sponsor or his representative or the investigator; (c) failure of investigational product to provide intended therapeutic effect where, the standard care, though available, was not provided to the subject as per the clinical trial protocol; (d) use of placebo in a placebo-controlled trial where, the standard care, though available, was not provided to the subject as per the clinical trial protocol; (e) adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol; (f) for injury to a child in-utero because of the participation of parent in any clinical trial; [and] (g) any clinical trial procedures involved in the study.

⁸² See Rule 122-DAC §§(1)(f), (3)

⁸³ See Rule 122-DD §(1)

outer limits of clinical trial regulation in India. The most salient changes to India's regulatory environment are provisions providing (1) compensation for clinical trial injuries and (2) criminal penalties for (a) conducting trials without authorization or (b) violations of trial regulations.

In many provisions, the 2015 Reform Bill states "as may be prescribed," which in India is understood to mean that the provisions will be informed by rules that are issued pursuant to the statute. Therefore, the 2015 Reform Bill leaves issues to be prescribed later by India's regulatory authorities via the Drugs and Cosmetics Rules (i.e., Rule 122-DAB).⁸⁴ However, the Indian government has yet to draft proposed rules pursuant to the 2015 Reform Bill, making the future of research in India very uncertain.

With respect to compensation for clinical trial injuries, the 2015 Reform Bill represents causation in a broad and vague manner. The 2015 Reform Bill provides no guidance on the definition/standard of causation, nor does it explain how causation will be determined or enforced.⁸⁵ In fact, causation is phrased differently throughout - Chapter 1A: Section 4(B) states: "injury or death of a person *in the course of a clinical trial*," Section 4(C)(1) states: "injured or disabled *in a clinical trial*," and Section 4(C)(2)

⁸⁴ Section 4B with regard to "Determination regarding injury or death" states that "whether the injury or death of a person in the course of clinical trial, has been caused *due to* such clinical trial or not, shall be determined by such authority and in such manner as may be prescribed." The next section delineates how injured subjects will be compensated in the same manner: "Where a participant is injured or disabled in a clinical trial, the person or body permitted under Section 4A and the sponsor shall provide such medical treatment and compensation in such manner as may be provided." The provision that describes how participants who died similarly states: "Whether death of a participant is caused due to clinical trial, the person or a body permitted under section 4A and the sponsor shall provide to his legal heir, such compensation, in such a manner as *may be prescribed*."

⁸⁵ Section 4B - only states that causation "shall be determined by such authority and in such manner as may be prescribed."

states: “death ... *caused due to* clinical trial.⁸⁶ All of these iterations are different from Rule 122-DAB’s “related to” language and reveal the uncertainty surrounding the regulation of research in India. Also all parties involved in the trials will be subject to the prescriptions of the (non-proposed) regulations pursuant to the 2015 Reform Bill’s declaration that:

“No person, sponsor⁸⁷, clinical research organization or any other organization or investigator,⁸⁸ shall conduct any clinical trial⁸⁹ in respect of a new drug,⁹⁰ [or] investigational new drug⁹¹ ... in human participants except under, and in accordance with, the permission granted by the Central licensing Authority *in such form and manner as may be prescribed.*”⁹²

This discretionary legislation has deterred many pharmaceutical companies, medical institutions (American and Indian), and even the National Institutes of Health (NIH) from initiating trials in India and thwarted the amount of trials in India.⁹³ Although

⁸⁶ Id.

⁸⁷ The 2015 Reform Bill defines sponsor as “includ[ing] a person, a company or an institution responsible for the initiation, financing and management of a clinical trial.” §3(zc).

⁸⁸ The 2015 Reform Bill defines “investigator” as “a person permitted to conduct clinical trial by the Central Licensing Authority under section 4A.” §3(s).

⁸⁹ The 2015 Reform Bill defines “clinical trial,” with respect to drugs, as “any systematic study of new drug or investigational new drug ... in human participants to generate data for discovering or verifying its clinical, pharmacological ... or adverse effects with the objective of determining safety, efficacy, or tolerance of the drug.” §3(g)(i). Thus, device trials seem to be excluded from these proposed provisions.

⁹⁰ The 2015 Reform Bill defines “new drug” as “a drug ... which has not been used in the country to any significant extent under the specified conditions”; “a drug approved by the Central Licensing Authority for certain claims, which is proposed to be marketed with modified or new claims”; a “fixed dose combination of two or more drugs”; or vaccines and other products “intended to be used as drugs.” §3(x).

⁹¹ The 2015 Reform Bill defines “investigational new drug” as a “new chemical entity or substance which is under investigation in a clinical trial regarding its safety and efficacy.” §3(q).

⁹² Emphasis here.

⁹³ The amount of trials approved in India has dramatically declined from about Barbara Biere & Mark Barnes, Clinical trials, a lost opportunity for India, Financial Express, Nov. 3 2014, *available at*

an ethical directive regarding research on human subjects was needed, the resulting regulations have caused significant delays in clinical trials. India's shift towards strict regulation of clinical research (i.e., compensation guidelines for deaths and adverse events, mandatory audiovisual recording of informed consent and limiting the number of trials) is causing the number of trials in India to plummet, despite how India's population is ideal - since it has a large number of diverse, treatment naïve people with significant health problems and could benefit from the free, cutting-edge, health care trials provide.⁹⁴

Conversely, Section 4C's discretionary language gives India's regulatory authorities the flexibility to implement rules that would further limit drug research sponsor's liability to only injuries that are directly caused by the study drug or procedures. However, critics doubt India's regulatory authorities will make the changes necessary to effectuate such change since their amendments to rules in the past have only marginally improved the ambiguities.⁹⁵

The uncertainty is exacerbated by the criminal penalty provisions, since they similarly give deference to clinical trial regulations that have yet to be proposed.⁹⁶ Examples of the deferential language includes "prescribed under Section 4A" and "Section 4A and the rules made thereunder."⁹⁷ Although the 2015 Reform Bill has made some improvements by lowering criminal penalties compared to the amendments proposed in the 2013 Reform Bill, the ambiguities are proving to be a deterrent to

http://mrct.globalhealth.harvard.edu/files/mrct/files/ct_lost_opportunity1.pdf (last visited May 3, 2015); Yogendra

⁹⁴ Madhur Singh, "Regulation Stifling Clinical Trials Sector, India Business Association Head Says," Medical Research Law & Policy Report (August 21, 2014).

⁹⁵ Id.

⁹⁶ See Supra Note # 74.

⁹⁷ Section 4K of 2015 Reform Bill.

physicians.⁹⁸ For example, Section 4-O decreased the potential punishment based on the distinction between violations that cause adverse events versus those that do not, the latter would not include the possibility of imprisonment. One of the most notable differences between the 2013 draft amendments and the 2015 Reform Bill is the elimination of mandatory minimum prison sentences.⁹⁹

Both the civil and the criminal penalties associated with the proposed 2015 amendments of the Drug and Cosmetic Act of 1940 have added to physicians' hesitation to participate in clinical trials and will likely cause a significant reduction in the number of physician's participating in clinical trials in India. More importantly, the patients with serious and/or fatal diseases (i.e., cancer, AIDS, etc.) are being deprived from cutting-edge experimental medications, which they do not have access to otherwise. This is a stark contrast from 2005 to 2010, when the amount of trials increased year-to-year and was chipping away at India's triple threats of diseases - communicable diseases, non-communicable lifestyle related diseases and infectious diseases.¹⁰⁰

IV. Tackling India's Issues

Research is needed in India to help combat diseases that plague these populations. Relatedly, regulations are needed to ensure participants are treated ethically. This is no easy task considering all of the aforementioned challenges and this paper does not

⁹⁸ Sections 4ZA and 4ZE of the 2013 draft amendments resemble Sections 4K and 4-O of the 2015 Reform Bill, respectively.

⁹⁹ A comparison of 2013's draft amendments (4ZA and 4ZE) and the 2015 Reform Bill's (4L and 4-O) provisions is illustrative: A violation of Section 4ZA is subject to a term of imprisonment of no less than three (3) years. Whereas Section 4K establishes a maximum prison sentence of five years. Similarly, Section 4ZE sets forth higher penalties (a minimum term of two (2) years) than 4-O, which provides a maximum prison sentence.

¹⁰⁰ See Supra Note 72.

attempt to solve all of India's problems with one stroke a pen, but it is meant to provoke thoughts as to what can be done to effect progress towards a more robust and ethically sound research environment in India. The following paragraphs are three (3) proposed solutions to some of India's areas of regulatory opportunity.

First, India should legislate definitional causation regulations. Causation as it stands is overly broad and allows for compensation for "injuries" that a non-participant could endure. Enacting regulations that require a showing that "but for" the participant's participation, they would not have been injured will assure that they injured party receives compensation for injuries resulting from their participation. It also safeguards research sponsors from frivolous suits for injuries unrelated to the research.

Second, the regulations that are set to prescribe the rules for the criminal penalties provisions in the 2015 Reform Bill should, at least, require that culpability be determined based on *mens rea*. Without doing so, India's laws will punish unintentional research mistakes equally as those that are done intentionally. If India's would add degrees of culpability (increasing the punishment in direct response to the increased level of intent) to its regulations, it will likely retain more researchers. India would also do better by not holding individual doctor's culpable, unless they are grossly negligent or intentionally disobey the rules. The party that is generally able to bear the risk and the responsibility are the sponsors of research. Therefore, they should be the ones responsible for infractions, not Indian doctors. In light of research sponsors usually being institutions or corporations, India could implement agreements similar to those used by the U.S. justice

system (i.e., non-prosecution agreements¹⁰¹ and/or deferred prosecution agreements¹⁰²) instead of prison sentences. This has helped reduce the amount of violations in the U.S. and will likely help India too.

Third, India should either repeal its order requiring the audiovisual recording of participants providing informed consent and implement procedures that ensure information is provided in an understandable form. This could be accomplished by asking potential participants their last grade of completion and having pamphlets, made in India by Indians, explaining the risks and benefits of trial participation. The current audiovisual recording invades the person's privacy, which in India is a culturally sensitive matter for the reasons outlined above.

V. Conclusion

¹⁰¹ A Non-Prosecution Agreement is a: (1) Letter Agreement between the parties – not filed in court (Since nothing is filed in court, NPAs can be kept confidential if the government agrees). (2) Statement of Facts – the company is usually required to stipulate to the elements of a criminal violation. (3) Agreement – commitment to take certain steps to improve compliance with applicable laws and/or regulations. (4) Monetary penalties paid by the company. (5) Cooperation – non-public assistance with the government's investigation of others in the industry or company employees, etc. (6) The company agrees to face prosecution if it fails to satisfy the terms of the agreement, Available at https://oig.hhs.gov/fraud/medicaid-fraud-control-units-mfcu/policy_transmittals/90-1%20Definition%20of%20Convictions%20and%20Plea%20Negotiations.pdf (last visited May 8, 2015).

¹⁰² Id. A Deferred Prosecution Agreement includes: (1) Criminal Information and is filed in court. (2) Statement of Facts – public statement establishing the elements of a criminal violation, to which the company stipulates and agrees not to make any statements to the contrary. (3) Agreement – public commitment to take certain steps to improve compliance with applicable laws and/or regulations. (4) Monetary Penalties. (5) Cooperation – non-public assistance with the government's investigation of others in the industry or company employees, etc. (6) The company agrees to face prosecution if it fails to satisfy the terms of the agreement.

Ultimately, an independent expert group or committee should oversee all of these changes. This would ensure that participants and research sponsors are aware of the risks of clinical research in India and not deter either of them from participating in clinical trials in India. India is well on its way to becoming an example for other developing nations to emulate, but must not hastily respond to isolated incidents with reactionary law as it seems to have done with its previous amendments to the Drug and Cosmetic Act of 1940.

If the regulatory scheme remains as uncertain as it is now, it will definitely continue to dissuade drug research and development outsourcing to India. The people who suffer most from researchers pulling out of India are India's sick and poor people. Thus, it is in India's best interest to reconsider its 2015 Reform Bill and/or propose regulations that include changes such as those I have outlined in the preceding section; or draft more narrowly tailored regulations than it has in the past and not just import U.S. regulations, since India has unique vulnerabilities (educational, cultural and economic issues (i.e., lack of access to care)) compared to those of the United States.