

The Evolving Regulatory Landscape for Clinical Trials in India

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ABSTRACT

Since 2013, India has undergone a significant regulatory transformation in regard to clinical trials. Following controversial media coverage of deaths that were allegedly related to clinical trials, the Indian government attempted to bolster its regulatory framework by releasing a number of new and complex regulations that quickly made India an unpredictable jurisdiction in which to site and conduct clinical trials. This article describes the events and regulatory changes that have shaped India's clinical trial landscape over the past several years. The article ultimately concludes that many of the well-meaning requirements imposed on researchers and sponsors beginning in 2013 chilled the clinical trial environment, yet the requirements also brought appropriate attention to complex ethical issues. While many of the more stringent regulations have since been clarified or withdrawn through the Indian government's continuing reform efforts, the recent India experience demonstrates how regulatory uncertainty can deter advances in clinical research.

Over the past several years, India has undergone a significant transformation in its clinical trial activity and provides a useful case study in the revision and implementation of clinical trials regulations. By 2009, clinical trial research in India was experiencing significant growth. While the Drug Controller General of India (DCGI) granted only 65 approvals for clinical trials in 2008, it granted 391 in 2009 and 500 in 2010.¹ However, controversial media coverage of multiple deaths allegedly

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¹ *Post Stringent Norms, Clinical Trials in India Plummet*, HINDU (June 13, 2016), <http://www.thehindu.com/sci-tech/health/policy-and-issues/post-stringent-norms-clinical-trials-in-india->

related to clinical trials led the Indian government to release a number of new, and in some cases onerous, regulations between 2013 and 2015 in an effort to bolster its regulatory framework and protect trial participants. The new regulations quickly made India an unpredictable jurisdiction in which to site and conduct clinical trials.

Despite India's diverse patient pool, well-trained physician workforce, and relatively low health services costs, the government's new regulations and orders—and the uncertainty they created—led to a decline in the number of clinical trials approved by DCGI and a concomitant rapid deterioration of research infrastructure within India.² At the same time, the rapid changes and the debate surrounding them exposed a variable and often inadequate infrastructure for clinical research and led to major regulatory changes regarding difficult issues, including, most prominently, mandatory compensation for research-related injuries and deaths. While several of the new rules seem untenable in clinical research, over the past several years the Indian government has made an attempt to clarify and refine its revised clinical trials regulations. DCGI and other relevant regulatory bodies have begun using amendments and interpretations to scale back and clarify many of the earlier, most problematic rules and orders.

Additionally, India's Ministry of Health and Family Welfare (MoHFW) issued new draft rules in February 2018 (2018 Draft Rules), discussed further herein, addressing the full spectrum of clinical trials activities in an effort to improve the country's regulations. However, even if the 2018 Draft Rules are adopted, the rules likely will not allay all stakeholder concerns, as they do not clarify many of the provisions that have been widely debated over the past several years, and they do not fully address the chilling effects that the regulatory changes adopted beginning in 2013 have had on clinical trials activities in India. While India may yet be able to reclaim its status as a major hub for clinical research, stakeholders continue to grapple with the changing regulatory landscape, and the recent India experience demonstrates how regulatory uncertainty can deter advances in medical research and impede a population's voluntary access to experimental treatments.

plummet/article4639976.ece [https://perma.cc/PC26-JF5Y]. See also Shruti S. Bhide et al., *Assessment of Clinical Trials Registered at Clinical Trial Registry of India over Past Decade: An Audit*, 3 INT'L J. CLINICAL TRIALS 238, 240 (2016), <http://www.ijclinicaltrials.com/index.php/ijct/article/download/149/90> [https://perma.cc/8ZZS-V5H4] (stating that number of clinical trials from India registered on www.clinicaltrials.gov increased until 2010).

² See Y.K. Gupta & B. Dinesh Kumar, *Clinical Trials And Evolving Regulatory Science in India*, INDIAN J. PHARMACOLOGY 575, 575 (2014), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264069/> [https://perma.cc/TQB2-J8DT] (“This resulted in the sharp decline in the number of clinical trials (from 529 in 2010 to nearly 250 in 2012 to just over 100 in 2013) approved by DCGI.”); HINDU, *supra* note 1 (stating that following 500 clinical trials being approved by the DCGI in 2010, 325 were approved in 2011 and 262 were approved in 2012); Bhide et al., *supra* note 1, at 240 (showing a significant decline in the number of clinical trials from India registered on ClinicalTrials.gov since 2010). See also Aditi Tandon, *Clinical Trial Rules to Be Relaxed to Aid Research*, TRIBUNE (Jan. 17, 2016), <http://www.tribuneindia.com/news/nation/clinical-trial-rules-to-be-relaxed-to-aid-research/184473.html> [https://perma.cc/56XY-3ZEG] (quoting the Director General of the Indian Council of Medical Research, stating “after the new clinical trial guidelines . . . we witnessed a significant decline in the number of academic research trials for existing disease”); Thomson Reuters, *Overcoming Clinical Challenges in BRIC Markets: A White Paper*, 9 (Apr. 2014), http://bibliotecadigital.puc-campinas.edu.br/services/e-books/D_BRIC_nations_white_paper_final_201404.pdf (“Since 2010, the initiation of clinical trials in India has declined sharply. Sponsors such as Eli Lilly, AstraZeneca, Pfizer, and GSK have either pulled back or out completely, waiting for the regulatory landscape to stabilize.”).

This article describes the various events and regulatory changes that have shaped India's clinical trial landscape over the past several years. The article ultimately concludes that many of the well-meaning requirements imposed on researchers and sponsors beginning in 2013 have corroded the clinical trial environment, yet have also focused attention on complex ethical issues inherent in conducting advanced research among a comparatively indigent population. Many of the regulations or government orders have since been clarified or withdrawn, and the focus on training and education of investigators and ethics committee members, and on ethical conduct of clinical trials more generally, have arguably defined and improved the climate for human participant research. The impact of the proposed 2018 Draft Rules will still need to be assessed, if and in what form they are approved.

I. BACKGROUND: CLINICAL TRIAL RESEARCH IN INDIA

Issues with widespread drug alteration and fraud in the Indian market in the early 20th century led to the passage of India's Drugs and Cosmetic Act of 1940 and the Drugs and Cosmetics Rules of 1945, which regulate the import, manufacture, distribution, and sale of drugs and cosmetics in India.³ Those legislative measures established the Central Drugs Standard Control Organization ("CDSCO"), a division of the MoHFW.⁴ In 1988, the Indian government recognized, as other countries had, that the introduction of new drugs directly depends on the conduct and results of clinical trials and that trials using the local population are needed to assess the safety and efficacy of new medicinal products; as a result, the government established a set of guidelines and requirements for clinical trials, known as Schedule Y.⁵ The Indian Council of Medical Research ("ICMR"), an entity funded through the Indian government, subsequently issued the Ethical Guidelines for Biomedical Research on Human Subjects in 2000.⁶ In response to this increased clarity regarding legal requirements for human subjects research, India experienced a significant increase in the level of clinical trial activity taking place within the country, and the number of clinical trials peaked in 2010.⁷

India's regulatory landscape was soon dramatically altered as a result of two public interest litigation ("PIL") petitions that claimed violations of India's clinical trial regulations, and by the Indian government's response to the petitions and public opinion. In early 2010, the Indian media reported that several participants had died in a human papillomavirus ("HPV") vaccine study funded by the Bill and Melinda Gates Foundation ("BMGF") and managed in India by a U.S.-based international NGO,

³ See Mohammed Imran et al., *Clinical Research Regulation in India—History, Development, Initiatives, Challenges and Controversies: Still Long Way to Go*, 5 J. PHARM. BIOALLIED SCI. 2, 2–9 (2013), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3612334/> [<https://perma.cc/2X8Z-LMEV>].

⁴ *Id.*

⁵ See Drugs and Cosmetics Rules, 1945, Schedule Y, http://cdsco.nic.in/html/D&C_Rules_Schedule_Y.pdf [<https://perma.cc/HMU7-Y98J>]; Urmila M. Thatte & Padmaja A. Marathe, *Ethics Committees in India: Past, Present and Future*, 8 PERSP. CLINICAL RES. 22, 22–30 (2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5299801/> [<https://perma.cc/B69R-HKWS>].

⁶ Imran et al., *supra* note 3.

⁷ See *supra* notes 1–2.

Program for Appropriate Technology in Health (“PATH”).⁸ The trial involved vaccinating 13,000 girls ages 10–14 with Gardasil® and 10,000 with Cervarix®, both of which are recombinant HPV vaccines that had been approved by the U.S. FDA for the prevention of cervical cancer and cervical intraepithelial neoplasia.⁹ Scheduled to run until 2011, ICMR halted the study in early 2010 based on reports of safety and ethical violations in the trial.¹⁰ The Indian government then set up an inquiry committee to look into alleged irregularities in the conduct of the HPV studies.¹¹ Although the committee found inadequacies with respect to the documentation of informed consent, the government initiated no legal action against the researchers, their institutions, PATH, or BMGF at that time.¹²

Nearly concurrently, the U.S. Office for Human Research Protections (“OHRP”) in 2012 investigated a complaint and determined that subjects involved with long-running randomized cervical cancer trials in India funded by the U.S. National Cancer Institute (“NCI”) had not been provided with adequate information about trial participation.¹³ Beginning in 1998, trials funded by the NCI and BMGF that aimed to validate cervical cancer screening as a cost-effective prevention method reportedly compared cervical cancer death rates among 224,929 women who were offered cervical cancer screening to 138,624 women in a control group who were offered the

⁸ DEP’T OF HEALTH RES., MINISTRY OF HEALTH AND FAMILY WELFARE (INDIA), SEVENTY SECOND REPORT: ALLEGED IRREGULARITIES IN THE CONDUCT OF STUDIES USING HUMAN PAPILLOMA VIRUS (HPV) VACCINE BY PATH IN INDIA, at 1 (Aug. 30, 2013), <http://164.100.47.5/newcommittee/reports/EnglishCommittees/Committee%20on%20Health%20and%20Family%20Welfare/72.pdf> [https://perma.cc/ZGU8-YFVM] [hereinafter HPV Vaccine Report]. See also SAMA: RESOURCE GROUP FOR WOMEN AND HEALTH, MEMORANDUM TO THE HEALTH MINISTER ON WORLD HEALTH DAY OPPOSING HPV VACCINATIONS (Apr. 2010), <https://samawomenshealth.wordpress.com/2010/04/08/memorandum-to-the-health-minister-on-world-health-day-opposing-hpv-vaccinations/> [https://perma.cc/G9YJ-NSQ3]; L.J. Devon, *Bill Gates’ Philanthropy: 30,000 Indian Girls Used as Guinea Pigs to Test Cancer Vaccine*, NATURAL NEWS (Oct. 3, 2016), http://www.naturalnews.com/055513_Gates_Foundation_vaccine_experiments_human_guinea_pigs.html [https://perma.cc/SFE5-P4JK].

⁹ Sanjay Kumar & Declan Butler, *Calls in India for Legal Action Against US Charity*, NATURE (Sept. 9, 2013), <http://www.nature.com/news/calls-in-india-for-legal-action-against-us-charity-1.13700?referral=true> [https://perma.cc/JW8U-KAKB].

¹⁰ See A Nair, *Clinical Research: Regulatory Uncertainty Hits Drug Trials in India*, PHARMACEUTICAL JOURNAL (Mar. 12, 2015), <http://www.pharmaceutical-journal.com/news-and-analysis/features/clinical-research-regulatory-uncertainty-hits-drug-trials-in-india/20068063.article> [https://perma.cc/ACB2-HX7H]; Kumar, *supra* note 9.

¹¹ HPV Vaccine Report, *supra* note 8, at 9; Carolijn Terwindt, *Health Rights Litigation Pushes for Accountability in Clinical Trials in India*, 16 HEALTH & HUMAN RIGHTS J. 84, 87 (2014), <https://cdn2.sph.harvard.edu/wp-content/uploads/sites/13/2014/12/Terwindt-final1.pdf> [https://perma.cc/R4N7-H9ZK].

¹² See Terwindt, *supra* note 11, at 87. In terms of identified failings in the informed consent process, the committee reportedly found, for example, that school principals had signed the consent forms on behalf of the children. *Id.*

¹³ See Dep’t of Health & Hum. Servs., Division of Compliance Oversight, Letter on Human Research Protections Under Federalwide Assurance FWA-6143 (July 5, 2012), <http://archive.azcentral.com/ic/pdf/OHRP-letter-jul12.pdf> [https://perma.cc/H8T6-Q8XH]; Eric J. Suba, *US-Funded Measurements of Cervical Cancer Death Rates in India: Scientific and Ethical Concerns*, 11 INDIAN J. MED. ETHICS 167, 167–175 (2014), <https://www.ncbi.nlm.nih.gov/pubmed/25101547> [https://perma.cc/U33W-HNPD]. See also Rema Nagarajani, *Row Over Clinical Trial as 254 Indian Women Die*, TIMES OF INDIA (Apr. 21, 2014), <http://timesofindia.indiatimes.com/india/Row-over-clinical-trial-as-254-Indian-women-die/articleshow/34016785.cms> [https://perma.cc/G5ST-6ZYT]; Bob Ortega, *Ethical Questions Linger in Cervical Cancer Study*, USA TODAY (Aug. 31, 2013), <http://www.usatoday.com/story/news/nation/2013/08/31/ethical-questions-linger-in-cervical-cancer-study/2751705/> [https://perma.cc/TYD9-3ZJE].

usual standard of care, but no cancer screening.¹⁴ In an article in the Indian Journal of Medical Ethics, Dr. Eric Suba criticized the trials and, instead of concluding that cervical cancer screening was a compelling preventive measure that deserved government support, highlighted the fact that at least 254 women in the unscreened control and standard of care group died from cervical cancer.¹⁵ The article attracted media and advocacy group attention to trials in India and how the women involved with the trial were of low socioeconomic status and were residents of “Mumbai slums” and poor villages across India.¹⁶

In January 2012, the non-governmental organization Swasthya Adhikar Manch filed a PIL petition against the Indian government, alleging that inadequate government oversight of clinical trials had resulted in multiple participant deaths.¹⁷ Women’s health activists filed a second PIL petition relating to alleged inappropriate handling of the HPV trial by the Indian government, which was admitted for consideration by the Indian Supreme Court in January 2013.¹⁸

During the January 2013 consideration of the petitions, India’s Supreme Court members stated from the bench that the Indian government had fallen into a “deep slumber” and had not been ensuring that companies sponsoring research had complied with India’s clinical trials regulations.¹⁹ The court criticized CDSCO, asking for urgent action and ordering drug trials to be conducted under the supervision of the Health Secretary.²⁰ In addition, a report released by the Parliamentary Standing Committee on Health and Family Welfare on August 30, 2013 found that the study of the HPV vaccine had violated ethical norms, as informed consent had not been properly obtained from the parents or guardians of all study participants, many of whom were illiterate.²¹ Although the report concluded that participant deaths were likely not causally associated with the vaccine, as the deaths were from seemingly unrelated causes such as suicide, drowning, and malaria, the report still opined that those involved with the trial had failed to look into the deaths in a satisfactory manner and to maintain adequate study records. The report’s conclusions gave rise to significant

¹⁴ Suba, *supra* note 13, at 167.

¹⁵ *Id.* We note that other commentators sharply criticized Dr. Suba’s article, stating that he was “distorting facts and persistently disseminating biased and misleading views” and flagging “ethical concerns [that] are unsubstantiated by the evidence.” Rengaswamy Sankaranarayanan et al., *Response to Article Titled “US-Funded Measurements of Cervical Cancer Death Rates in India: Scientific and Ethical Concerns”* by Eric J Suba, 11 INDIAN J. MED. ETHICS 175, 175 (2014), <https://www.ncbi.nlm.nih.gov/pubmed/25101550> [<https://perma.cc/L589-F7YG>].

¹⁶ Nagarajani, *supra* note 13.

¹⁷ See *Swasthya Adhikar Manch v. Union of India* (UOI), W.P.(C) No. 33/2012 (India), <http://cdsco.nic.in/writereaddata/SC%20Order%2030th%20Sept%202013.pdf> [<https://perma.cc/D48U-2BA9>]; Barbara E. Bierer & Rebecca H. Li, *MRCT Center: India Regulatory Update*, The MRCT Center of Brigham and Women’s Hospital and Harvard (Mar. 9, 2016), <http://mrctcenter.org/wp-content/uploads/2016/03/GHRT-Webinar-India-2016-Mar-9s1.pdf> [<https://perma.cc/BP4Z-CX6E>].

¹⁸ Terwindt, *supra* note 11, at 88.

¹⁹ *Id.*; *Illegal Clinical Trials Creating ‘Havoc’: Supreme Court*, HINDU (Jan. 3, 2013), <http://www.thehindu.com/news/national/illegal-clinical-trials-creating-havoc-supreme-court/article4268671.ece> [<https://perma.cc/GB8Q-PDEP>].

²⁰ *Id.*

²¹ See HPV Vaccine Report, *supra* note 8 at 11. See also Kumar, *supra* note 9.

media attention on clinical trials in India and the related PIL petitions.²² In light of its order requiring clinical trials of new chemical entities to be “conducted strictly in accord with the procedure prescribed in Schedule ‘Y’ of Drugs & Cosmetics Act, 1940 under the direct supervision” of the MoHFW Secretary, the Supreme Court of India announced on September 30, 2013 the establishment by the MoHFW of “a system of supervision of clinical trials of new chemical entities by constituting Apex Committee and Technical Committee.”²³

II. FALLOUT FROM CLINICAL TRIAL-RELATED MEDIA ATTENTION: RESTRICTIVE 2013 REGULATIONS

Media coverage of the PATH-managed HPV vaccine study and the deaths associated with the cervical screening study conducted by the NCI and BMGF shone a bright light on clinical trials activity in India. Even though the media reports appear to have exaggerated or misrepresented the number and severity of participant injuries that were directly related to trial participation, the media attention and the Supreme Court’s call for urgent action led the Indian government to release a number of regulations imposing rigorous new requirements for conducting clinical trials in India.²⁴

As a first measure, India adopted sweeping compensation requirements for those injured during participation in a clinical trial. In January 2013, the MoHFW enacted Rule 122-DAB, entitled *Compensation in case of injury or death during clinical trial*.²⁵ For those suffering any injuries during a trial, even injuries *unrelated* to the trial, the original Section 1 stated that “[i]n the case of an injury *occurring* to the clinical trial subject, he or she shall be given free medical management *as long as required*.”²⁶ This broad provision required a sponsor to provide free medical care for any injuries that *occur* to the trial participant; it was not limited to injuries *caused by or resulting from* participation in the trial. The provision was also imposed irrespective of any fault or culpability for injuries on the part of the academic or industry sponsor. One year later, in 2014, the breadth of the provision was somewhat narrowed to require that medical management would be provided “as long as required *or* till such time it is established that the injury is not related to the clinical trial, whichever is earlier.”²⁷ Nevertheless, proving that an injury is not related to trial participation is an uncertain

²² See HPV Vaccine Report, *supra* note 8, at 6; Andrew Buncombe & Nina Lakhani, *Without Consent: How Drugs Companies Exploit Indian ‘Guinea Pigs,’* INDEPENDENT (Nov. 14, 2011), <http://www.independent.co.uk/news/world/asia/without-consent-how-drugs-companies-exploit-indian-guinea-pigs-6261919.html> [<https://perma.cc/U5TE-P8DN>]; Nair, *supra* note 10.

²³ See Swasthya Adhikar Manch, W.P.(C) No. 33/2012 (India).

²⁴ See Press Information Bureau, Gov’t of India, Press Release on Drug Trial Policy (Aug. 28, 2013), <http://pib.nic.in/newsite/erelease.aspx?relid=98830> [<https://perma.cc/CLA4-V9VH>].

²⁵ See Drugs and Cosmetics (First Amendment) Rules, 2013, 47 Gazette of India, pt. II sec 3(i), G.S.R. 53(E) (Jan. 30, 2013), [http://www.cdsc.nic.in/writereaddata/GSR%2053\(E\).pdf](http://www.cdsc.nic.in/writereaddata/GSR%2053(E).pdf) [<https://perma.cc/22CL-MCZZ>] [hereinafter G.S.R. 53(E)].

²⁶ *Id.* at 9 (emphasis added).

²⁷ This rule was amended in December 2014. See Drugs and Cosmetics (Sixth Amendment) Rules, 2014, 666 Gazette of India, pt. II sec 3(i), G.S.R. 889(E), at 5 (Dec. 12, 2014), [http://www.cdsc.nic.in/writereaddata/Notificationn%20on%20Compensation%20on%20clinical%20trial%20\(1\).pdf](http://www.cdsc.nic.in/writereaddata/Notificationn%20on%20Compensation%20on%20clinical%20trial%20(1).pdf) [<https://perma.cc/Y9WH-YBSS>] (emphasis added) [hereinafter G.S.R. 889(E)].

and difficult endeavor. Further, under Section 2 of Rule 122-DAB, for injuries “related to” the clinical trial, “such subject shall also be entitled for financial compensation . . . over and above any expenses incurred on the medical management of the subject.”²⁸ Thus, even after reform in 2014, Rule 122-DAB entitled a clinical trial participant to have his or her medical costs covered by the sponsor for any injury received during the clinical trial, even injuries entirely unrelated to the participant’s participation in the trial or use of the investigational agent, for “as long as required” or until it is established that the injury is not related to the clinical trial, and to additional “financial compensation” if the injury is “related to the clinical trial.”

Although compensation for clinical trial participants who suffer injuries “related to the clinical trial” seems reasonable on its face, the first iteration of Section 5 of Rule 122-DAB provided a surprisingly broad list of circumstances under which an injury to a clinical trial participant may be considered “clinical trial related.”²⁹ Such circumstances included many risks that are attendant to any clinical trials participation, including adverse effect of the investigational product, “failure of investigational product to provide intended therapeutic effect,” and “use of placebo in a placebo-controlled trial.”³⁰ The breadth of these provisions is striking. Considering “adverse effect of the investigational product” to be a compensable trial-related injury fails to acknowledge that the purpose behind phase I-III clinical trials is to assess the safety and efficacy of an investigational drug. It is antithetical to the goal of a clinical trial to require compensation for injuries stemming from an adverse effect of the investigational product when the risks are ever-present and when study participants have been fully informed and have consented to the risks after receiving appropriate risk and benefit information during the informed consent process. The “adverse effect of the investigational product” provision also does not accommodate the reality of trials of “high risk, high reward” therapies, such as cancer treatment, in which there is a high risk of adverse effect of the investigational product, yet the trial participant—after being informed of all these risks—chooses to proceed given the significant potential benefits. Trial-related adverse events cannot be known in advance, which is why proper protections are in place, including institutional review board (IRB) or ethics committee (EC) review and approval and the informed consent process. These “related to” provisions, therefore, fail to acknowledge that all interventional trials of an investigational drug necessarily carry the risk that the product may not perform as expected or that patients receiving the standard of care or placebo arm may receive less effective care. In fact, clinical research could reach no reliable scientific conclusions without such results.

In December 2014, these provisions were narrowed, such that “failure” of the investigational product thereafter would only be considered grounds for compensation “where, the standard care, though available, was not provided to the subject as per the clinical trial protocol.”³¹ The new iteration of the list of “related to” circumstances

²⁸ G.S.R. 53(E), *supra* note 25, at 9.

²⁹ *Id.*

³⁰ *Id.*

³¹ See G.S.R. 889(E), *supra* note 27, at 5. The full list is as follows: (i) adverse effect of investigational product(s); (ii) violation of the approved protocol, scientific misconduct, or negligence by the Sponsor or his representative or the investigator; (iii) 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; (iv) use of placebo in a placebo-controlled trial where, the standard care, though available, was

nevertheless retained “adverse effect of investigational product.” Therefore, the “related to” provisions still failed to recognize that the primary goal of an investigational trial is to compare the safety and efficacy of the investigational product to the standard of care. In addition, the Indian government amended the provision to require compensation for any injury due to the “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.”³² The revision offered no clarity, however, as to the meaning of “standard” and “available,” both of which are of crucial importance in applying this standard. Second, the provision is particularly confusing in light of how these concepts are traditionally understood in clinical trials. On the one hand, when standard of care for treating serious illness is reasonably available, it is generally considered unethical for a study design to include placebo, but this provision of the Indian regulations was not limited to serious illnesses. On the other hand, for conditions that do not pose a serious threat to an individual’s health, the use of placebo may be appropriate because it allows a more rapid and definitive proof of efficacy (or lack of efficacy) of the comparator agent. Thus, the placebo provision, even as amended, does not capture the salient issues, or reflect the complexities, surrounding the use of placebos in trials.

CDSCO has issued an order stating that “compensation in case of injury or death discerned at a later stage should be paid to the trial participant/his/her nominee as the case may be, if any drug-related anomaly is discerned at a later stage and accepted to be drug related.”³³ While reasonably aimed at better protecting Indian clinical trial subjects, this change has the consequence of extending sponsor and researcher anxiety about compensation well into the future. Under this provision, if a sponsor fails to provide proper medical management and/or compensation to the subject, DCGI may suspend or cancel the trial, and/or “restrict the Sponsor including his representative(s) [from] conduct[ing] any further clinical trials” in India or “take any other action deemed fit.”³⁴ Although the Indian MoHFW later clarified that compensation need not be paid for injury or death due to “totally *proven* unrelated causes,”³⁵ even as amended the compensation provisions still suffer from the issues raised above and lack clarity

not provided to the subject as per the clinical trial protocol; (v) adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol; (vi) for injury to a child in-utero because of the participation of parent in any clinical trial; [and] (vii) any clinical trial procedures involved in the study.

³² *Id.*

³³ CENT. DRUGS STANDARD CONTROL ORG., 12-01/14-DC Pt. 47, ORDER ON CLINICAL TRIAL—COMPENSATION IN CASE OF INJURY OR DEATH DISCERNED AT A LATER STAGE (July 3, 2014), <http://www.cdsc0.nic.in/writereaddata/oo4.pdf> [<https://perma.cc/3EQV-CX9H>]. One example of such drug-related injury compensation can be seen with those who suffered deformities due to use of Thalidomide, a drug prescribed to pregnant women to combat morning sickness that resulted in thousands of children being born with severe disabilities. Some individuals affected were able to receive compensation from distributors through the Thalidomide Trust. See generally Angus Crawford, *Were more babies affected?*, BBC NEWS (Oct. 14, 2013), <http://www.bbc.com/news/health-24472269> [<https://perma.cc/SM32-JHHZ>].

³⁴ G.S.R. 53(E), *supra* note 25, at 10.

³⁵ See MINISTRY OF HEALTH & FAM. WELFARE, ACTIONS ON THE RECOMMENDATIONS OF PROF. RANJIT ROY CHAUDHURY EXPERT COMMITTEE TO FORMULATE POLICY AND GUIDELINES FOR APPROVAL OF NEW DRUGS, CLINICAL TRIALS AND BANNING OF DRUGS, 7 (Nov. 6, 2013), http://www.cdsc0.nic.in/writereaddata/Action_RR_Choudhury_Committee_06.11.2013.pdf [<https://perma.cc/BAS2-BSK4>] (emphasis added).

as to what is considered “standard care” or “available.” It would be preferable if the rules were to address what is meant by standard care, such as providing that “standard care” is not considered “available” unless the participant would have sought and reasonably would have been expected to receive the standard treatment but for his or her enrollment in the trial.³⁶

In its rules mandating compensation for injuries sustained by participants, the Indian Government has essentially embraced a principle of no-fault liability whereby participants stand to receive compensation without having the burden of proving that their injuries stemmed from negligence or willful noncompliance of the investigator, sponsor, or contract research organization. The rules create an inversion of general legal concepts relating to liability and causation where the onus is typically on the participant to prove any injury suffered was directly caused by the negligence or reckless acts of another. Some have praised the Indian government’s approach, explaining how “it enables participants to receive compensation in situations where negligence cannot be proved” which is “of critical importance especially in clinical trials where the injuries sustained are often independent of any negligent act.”³⁷ Another argument for such an approach is that the certainty of compensation calculations actually favors research sponsors; this compensation system, with its well-defined payment formulae, is “favorable for the sponsor/investigator[,] as the amount payable can be calculated on the basis of certain parameters such as age, salary, previous medical history etc.,” instead of the unpredictability associated with damages calculations typically seen in the United States under a negligence theory in a tort action.³⁸

Nevertheless, a no-fault approach assigns financial liability to sponsors irrespective of fault or culpability, holding them responsible for many potential adverse outcomes of a trial, even in the absence of negligence or error and despite the myriad risks about which individuals are informed prior to the trial. These broad provisions and potentially higher compensation costs have made academic institutions and pharmaceutical companies hesitant to site clinical trials in India. Not only are such provisions a financial risk concern for trial sponsors, but they are also an ethical concern from an undue inducement standpoint, as the potential opportunity to receive mandatory compensation in a number of different situations might arguably cloud an individual’s decision-making when choosing whether or not to participate in a trial.³⁹

The 2013 regulatory changes also added a number of requirements for ECs—the Indian equivalent of IRBs or research ethics committees under U.S. and EU law. First, effective February 2013, ECs were required to be registered with the Indian

³⁶ This standard continues to be heightened in the global North, such that a treatment, even if not available in the community, might be considered standard and given to patients who become known to investigators. See Ruth Macklin, *Standard of Care: An Evolution in Ethical Thinking*, 372 LANCET 284, 284 (2008), [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(08\)61098-3/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)61098-3/fulltext) (discussing those arguing that “when a proven intervention exists anywhere in the world, it should be provided to the control group, even if that intervention would not be available outside the clinical trial in the developing country”).

³⁷ Renuka Munshi & Urmila Thatte, *Compensation for Research Related Injury*, PERSP. CLINICAL RES. 61, 61–69 (2013), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3601709/> [<https://perma.cc/F5VF-8XFC>].

³⁸ *Id.*

³⁹ *See id.*

government.⁴⁰ Following the required registration, CDSCO released specific rules for serious adverse event (“SAE”) reporting.⁴¹ Specifically, G.S.R. 53(E) sets forth detailed timeframes and obligations on the sponsor, investigator, and EC regarding reporting obligations for SAEs in clinical trials.⁴² Perhaps most importantly, in the case of an SAE occurring to the clinical trial subject, including death, the EC must formulate and submit an SAE report along with “its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative” within 30 days of the occurrence of the SAE.⁴³ The sponsor and the investigator are required to send their reports on SAEs to the central licensing authority, chairperson of the EC and head of the institution, all on a compressed timeframe. This has proven difficult to implement, as investigators may have difficulty meeting their reporting deadline given the possibility of delay between the occurrence of the adverse event and when the investigator becomes aware of the event, which in turn would hinder the EC’s ability to make such a report within the prescribed 30-day period. It would be more reasonable to expect such reports to be due within 30 days of discovery—rather than occurrence—of the SAE.

Other CDSCO rules instituted around the same time were intended to strengthen India’s clinical trial regulatory structure but made commencing and conducting clinical trials more complex. For example, rules required that no investigator could conduct more than three trials at any time and that only multispecialty hospitals having at least 50 beds and adequate emergency facilities and ECs could be considered as eligible to be trial sites.⁴⁴ The latter provision ignores the fact that trials studying many conditions (e.g., psoriasis, vaccine prevention studies) do not require in-patient facilities and may take place in a variety of locations, without requiring hospital facilities at all.

As part of the Indian government’s effort to improve clinical trials regulation, the government empaneled an expert committee chaired by Dr. Ranjit Roy Chaudhury (the “Chaudhury Expert Committee”), an *éminence grise* of allopathic medicine in India. In July 2013, the Chaudhury Expert Committee released a report laying out numerous recommendations for improving clinical trials in India.⁴⁵ In November

⁴⁰ See Drugs and Cosmetics (Third Amendment) Rules, 2013, 65 Gazette of India, pt. II sec. 3(i), G.S.R. 72(E), 8 (Aug. 2, 2013), [http://cdsco.nic.in/writereaddata/G.S.R.%2072\(E\)%20dated%2008.02.2013.pdf](http://cdsco.nic.in/writereaddata/G.S.R.%2072(E)%20dated%2008.02.2013.pdf) [<https://perma.cc/B6EA-LFQG>]. Prior to reviewing and approving a clinical trial protocol, an ethics committee must register with the Licensing Authority.

⁴¹ G.S.R. 53(E), *supra* note 25 at 10–11. “A serious adverse event is an untoward medical occurrence during clinical trial that is associated with death, in patient hospitalization (in case the study was being conducted on out-patient), prolongation of hospitalisation (in case the study was being conducted on in-patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening,” *id.* at 12.

⁴² *Id.* at 8–17.

⁴³ G.S.R. 889(E), *supra* note 27, at 6.

⁴⁴ CENT. DRUGS STANDARD CONTROL ORG., 12-01/14-DC Pt. 74, ORDER LIMITING NUMBER OF CLINICAL TRIALS AN INVESTIGATOR CAN UNDERTAKE AT A TIME (July 3, 2014), <http://www.cdsco.nic.in/writereaddata/officer%20order%202.pdf> [<https://perma.cc/32J4-M4HY>]; CENT. DRUGS STANDARD CONTROL ORG., MINUTES OF 15TH TECHNICAL COMMITTEE MEETING HELD ON 04.06.2014 (June 4, 2014), [http://www.cdsco.nic.in/writereaddata/15th_TC_Meeting__04%2006%202014\(1\).pdf](http://www.cdsco.nic.in/writereaddata/15th_TC_Meeting__04%2006%202014(1).pdf) [<https://perma.cc/78SZ-QUTF>].

⁴⁵ See RANJIT ROY CHAUDHURY ET AL., CENT. DRUGS STANDARD CONTROL ORG., REPORT OF PROF. RANJIT ROY CHAUDHURY EXPERT COMMITTEE 2–6 (2013), <http://www.cdsco.nic.in/>

2013, the MoHFW responded to the committee's suggestions, adopting some but rejecting others.⁴⁶ One of the Committee's suggestions included accreditation requirements for all institutional entities in the clinical trial enterprise, including the investigator, EC, and study site. MoHFW agreed with the Chaudhury Expert Committee recommendation and issued a statement that it would adopt and implement mandatory accreditation of ECs, investigators and research sites.⁴⁷ The National Accreditation Board for Hospitals and Healthcare Providers ("NABH") was given the mandate and funds to establish accreditation standards and has since developed standards for accreditation of the investigator, EC, and trial site.⁴⁸ In November 2016, the MoHFW released an order approving mandatory accreditation of ECs effective January 1, 2018, and the NABH subsequently announced it had begun accepting applications from ECs for accreditation.⁴⁹ Under the NABH standards, EC accreditation involves the development of standard operating procedures and an on-site assessment, among several other requirements. As one Indian commenter noted, the process likely will prove "long, arduous, and demanding," and importantly, it is unclear "whether such process improvements . . . can translate into benefits for subjects – high quality of care, subject safety, respect and protection of rights and welfare of the subjects."⁵⁰ The Indian government's clinical trial rules went beyond what is required in almost all other jurisdictions: EC accreditation in many other countries, including the United States, is voluntary.

The Chaudhury Expert Committee's report also endorsed another new requirement for those conducting clinical trials: audio–video ("AV") recording of the informed consent process. Draft rules for AV recording were initially proposed in a MoHFW notification released in June 2013.⁵¹ The proposal had also been supported by the Honorable Supreme Court of India, which, in response to the Swasthya Adhikar Manch PIL, issued an order requiring AV recording of the informed consent process

writereaddata/Report_of_Dr_Ranjit_Roy.pdf [https://perma.cc/4HB9-WXWG] [hereinafter, Report of Chaudhury Committee].

⁴⁶ See MINISTRY OF HEALTH & FAM. WELFARE, *supra* note 35, at 1–15.

⁴⁷ *Id.* at 1.

⁴⁸ See NAT'L ACCREDITATION BD. FOR HOSP. & HEALTHCARE PROVIDERS, ACCREDITATION STANDARDS FOR CLINICAL TRIAL IN INDIA 4–5 (2015), <http://www.cdsc.nic.in/writereaddata/finalAccreditation%20Standards.pdf> [https://perma.cc/5TRC-3QD7].

⁴⁹ See R.G. SINGH, MINISTRY OF HEALTH & FAM. WELFARE, 12-01/14-DC Pt. 47, ORDER REGARDING ACCREDITATION OF ETHICS COMMITTEES (Nov. 28, 2016), http://www.nabh.co/Announcement/Accreditation_ECApproval.pdf [https://perma.cc/TC5G-H45G]; NAT'L ACCREDITATION BD. FOR HOSP. & HEALTHCARE PROVIDERS, NOTICE <http://www.nabh.co/Announcement/CTNotice.pdf> [https://perma.cc/82LA-9DYA].

⁵⁰ Arun Bhatt, *Ethics Committees: Challenge of Evidence-Based Accreditation*, 8 PERSP. CLINICAL RES. 105, 105–106 (2017). See also NAT'L ACCREDITATION BD. FOR HOSP. & HEALTHCARE PROVIDERS, INFORMATION BROCHURE FOR ETHICS COMMITTEE ACCREDITATION PROGRAM (2016), http://www.nabh.co/Ct_Brochure.aspx [https://perma.cc/4JQS-T4ZX].

⁵¹ Drugs and Cosmetics (Second Amendment) Rules, 2013, 279 Gazette of India pt. II sec. 3(i), G.S.R. 364(E), 2 (June 7, 2013), <http://www.cdsc.nic.in/writereaddata/GSR%20364Ejune13.pdf> [https://perma.cc/N6ZH-DVKN]. See also CENT. DRUGS STANDARD CONTROL ORG., DRAFT GUIDELINES ON AUDIO-VISUAL RECORDING OF INFORMED CONSENT PROCESS IN CLINICAL TRIAL 4 (Jan. 9, 2014), http://www.cdsc.nic.in/writereaddata/Guidance_for_AV%20Recording_09.January.14.pdf [https://perma.cc/2A2L-8DRK]; G.N. SINGH, CENT. DRUGS STANDARD CONTROL ORG., GCT/20/SC/Clin./2013, ORDER (Nov. 19, 2013), <http://cdsc.nic.in/writereaddata/Office%20Order%20dated%2019.11.2013.pdf> [https://perma.cc/A2XY-RCGS].

for the five clinical trials that had been approved by DCGI from January through August of 2013.⁵² In November 2013, the MoHFW finalized the AV requirement for all clinical trials by releasing an order directing “all the sponsors/investigators/institutes/organizations and other stakeholders involved in conduct of clinical trials . . . to adhere to the [] requirement of audio-visual recording of informed consent process of trial subjects.”⁵³

Requiring AV recording of informed consent was intended to protect research participants, but it also raised a myriad of practical, cultural, and privacy concerns, which hindered participants from enrolling in studies. One of the primary obstacles to complying with the AV recording requirement was infrastructure. AV recordings require proper equipment and adequate space to accommodate those involved in the consent process. The requirement also resulted in “lack of participation for religious, cultural or social reasons that [led] to a reluctance to be recorded on video.”⁵⁴ For example, in rural parts of India, women often wear headscarves and avoid eye contact with men, and were often reportedly uncomfortable with being filmed on camera.⁵⁵ Additionally, one study of individuals in rural South India found that “[a]ll the study subjects who gave verbal consent also gave written informed consent. However . . . almost one-third (34%) refused to give consent for A-V recording.”⁵⁶ There were also privacy and confidentiality concerns, as the regulations did not specify who would be allowed to view the consent recordings. The regulations failed to address the increased obligations and security concerns associated with storing and safely maintaining these recordings; “The investigators will have to strengthen the governance at the site to ensure that there is no theft . . . [and] will have to assure the participants by explaining what this information will be used for and how it will be stored.”⁵⁷ The rules also did not specify for how long investigators must maintain such recordings or whether and to what extent sponsors may also be responsible for maintaining such recordings.

CDSCO addressed some of these concerns in its January 2014 guidelines, explaining how “the Investigator must safeguard the confidentiality of trial data, which might lead to the identification of the individual subjects” and that “[i]n order to maintain the confidentiality, the videographer should be engaged as part of the study team.”⁵⁸ Nevertheless, these guidelines, while helpful, do not address many of the other practical, cultural, and security-related concerns.

In July 2015 CDSCO recognized these difficulties and significantly reduced and narrowed the mandate. The new CDSCO rule provided that an AV recording of the informed consent session must be maintained by the investigator “in case of *vulnerable*

⁵² SINGH, *supra* note 51.

⁵³ *Id.* at 2.

⁵⁴ Gagandeep Kang, *Video Informed Consent*, 376 N. ENGL. J. MED., 856, 864 (2017), <https://www.nejm.org/doi/pdf/10.1056/NEJMra1603773>.

⁵⁵ Niranjana G. Kulkarni et al., *Audio-Video Recording of Informed Consent Process: Boon or Bane*, 5 PERSP. CLINICAL RES. 6, 6–10 (2014).

⁵⁶ Ramesh Chand Chauhan et al., *Consent for Audio-Video Recording of Informed Consent Process in Rural South India*, 6 PERSP. CLINICAL RES. 159, 159–162 (2015).

⁵⁷ Kulkarni et al., *supra* note 55.

⁵⁸ CENT. DRUGS STANDARD CONTROL ORG., *supra* note 51, at 8.

subjects in clinical trials of New Chemical Entity or New Molecular Entity.”⁵⁹ The new rule scaled back the burden of the provision by limiting its application only to trials of new chemical or molecular entities. Also, the revised regulation permits audio recording alone, without video recording, to satisfy the requirement for trials related to human immunodeficiency virus and leprosy, presumably to reduce the possibility of confidentiality breaches regarding those sensitive conditions.⁶⁰

The CDSCO revision nevertheless requires further explanation as to which patients will be considered “vulnerable” and therefore for whose informed consent the AV recording requirement remains applicable. Although the new rule appeared to narrow the scope of the AV requirements, the rule would still be applicable in most instances if vulnerability is defined broadly to include characteristics—such as relative indigence—that apply to a large proportion of the Indian population. Indeed, under the current regulations, a section on ECs under Schedule Y provides the following examples of vulnerable subjects: “members of a group with hierarchical structure (e.g. prisoners armed forces personnel, staff and students of medical, nursing and pharmacy academic institutions), patients with incurable diseases, unemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or others incapable of personally giving consent.”⁶¹ It is unclear whether the approach to “vulnerable subjects” in this EC-related section would be adopted in the context of the AV requirements. If it were, the breadth of this list and the inclusion of unemployed and impoverished individuals might sweep in a large portion of the Indian population, depending on how “impoverished” and other terms are defined and interpreted.

The Indian government has been working continuously to address these ambiguities. The ICMR even recently released revised ethical guidelines that offer some additional helpful insight into which groups might be considered “vulnerable.”⁶² Specifically, ICMR’s 2017 Ethical Guidelines describe certain “[c]haracteristics that make individuals vulnerable,” such as “legal status – children; clinical conditions – cognitive impairment, unconsciousness; or situational conditions – including but not limited to being economically or socially disadvantaged”⁶³ Neither the aforementioned provisions in Schedule Y nor these guidelines have shed much light

⁵⁹ Drugs and Cosmetics (Fifth Amendment) Rules, 2015, 489 Gazette of India, pt. II sec. 3(i), G.S.R. 611(E), 3 (July 31, 2015) (emphasis added), <http://www.cdscsco.nic.in/writereaddata/Gazette%20Notification%2031%20July%202015.pdf> [<https://perma.cc/72X3-Q2AY>].

⁶⁰ *Id.*

⁶¹ Drugs and Cosmetics Rules, 1945, Schedule Y, 506-07, http://cdscsco.nic.in/html/D&C_Rules_Schedule_Y.pdf [<https://perma.cc/HMU7-Y98J>].

⁶² See generally INDIAN COUNCIL OF MED. RESEARCH, NATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL AND HEALTH RESEARCH INVOLVING HUMAN PARTICIPANTS (Oct. 2017) (emphasis added), https://icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf [<https://perma.cc/U5T4-64US>]; Draft Medical Device Rules, 724 Gazette of India 145, 218 (Oct. 17, 2016) (explaining that, for trials of medical devices, “vulnerable subjects” means “members of a group with hierarchical structure (e.g. prisoners, armed forces personnel, staff and students of medical, nursing and pharmacy academicians institutions), patients with incurable diseases, unemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or others in capable of personally giving consent.”) (finalized as Medical Devices Rules, 2017, 70 Gazette of India 143 (Jan. 31, 2017), <http://www.cdscsco.nic.in/writereaddata/Medical%20Device%20Rule%20gsr78E.pdf> [<https://perma.cc/EHE4-HRBH>]).

⁶³ INDIAN COUNCIL OF MED. RESEARCH, *supra* note 62, at 10–11.

on the parameters of impoverished or “economically or socially disadvantaged” status, or how those characteristics would be assessed. Nevertheless, these provisions coupled with India’s demographics, including estimates that one in five Indians are poor and 80 percent live in rural areas,⁶⁴ suggest that many Indian trial participants would be considered economically or socially disadvantaged, and hence vulnerable, thereby triggering the stringent AV informed consent requirements for many participants in trials for new molecular or chemical entities.

The Chaudhury Expert Committee also recommended that the government promulgate a “strong provision for ancillary care to cater for patients suffering from any other illness during the trial,” even if unrelated to the trial itself.⁶⁵ Consequently, on July 3, 2014, CDSCO issued an order that sponsors must provide “ancillary care . . . to the clinical trial subject for brief illness in the same hospital/trial site, wherever required.”⁶⁶ Yet that order defines neither “ancillary care” nor “brief illness” and could benefit from further clarification. Under the provision as written, the academic or industry sponsor automatically is responsible to provide care for trial participants for any “brief illness,” regardless of relatedness to the trial. The provision has not only increased uncertainty regarding the obligation of a sponsor to provide care for trial participants outside of the treatment set forth in the protocol, but also has created the possibility that individuals with serious preexisting medical conditions may enroll in trials in order to receive free medical care. This incentive for trial enrollment could predictably result in adverse selection in the subject population and trigger the ethical problem of “undue influence” over potential subjects who may otherwise struggle to afford necessary care relating to their illnesses. In sum, the “ancillary care” provision likely discourages sponsors from siting clinical trials in India and may unduly incentivize persons to seek to enroll in trials.

The Indian Parliament subsequently became active in proposing strict legislation regarding clinical trials issues. In an effort to address perceived gaps in the Indian clinical trials regulatory regime, a new comprehensive regulatory reform bill—the Drugs and Cosmetics Amendment Bill 2013 (the “2013 bill”)—was introduced in Parliament in August 2013, but ultimately was not enacted.⁶⁷ Section 4ZE of the 2013 bill provided that any clinical researcher (including the institution, sponsor, or investigator) who fails to conduct a clinical trial in accordance with “the conditions of permission” imposed by the Central Licensing Authority may be punished with a minimum of two years imprisonment and a fine in the amount of Rs. 5 lakhs.⁶⁸ In addition, section 4ZG of the 2013 bill provided that any researcher who fails to compensate a subject suffering a trial-related injury “shall be punishable with

⁶⁴ *India’s Poverty Profile*, WORLD BANK (May 27, 2016), <http://www.worldbank.org/en/news/infographic/2016/05/27/india-s-poverty-profile> [<https://perma.cc/3ZRT-L6JP>].

⁶⁵ Report of Chaudhury Committee, *supra* note 45, at 3.

⁶⁶ G.N. SINGH, CENT. DRUGS STANDARD CONTROL ORG., 12-01/14-CD Pt. 47, ORDER REGARDING PROVIDING ANCILLARY CARE TO THE CLINICAL TRIAL SUBJECTS (July 3, 2014), <http://www.cdsc.nic.in/writereaddata/oo5.pdf> [<https://perma.cc/QE6S-42VT>].

⁶⁷ The Drugs and Cosmetics (Amendment) Act Bill, 2013, No. LVIII, 2013 (India), <http://www.prsindia.org/uploads/media/Drugs%20and%20Cosmetics/drugs%20and%20cosmetics%20bill.pdf> [<https://perma.cc/47HM-7TZP>].

⁶⁸ *Id.* at 13. See also Mark Barnes et al., *Clinical Trial Research Is No Crime*, HINDU BUSINESSLINE (Dec. 1, 2014), <http://www.thehindubusinessline.com/opinion/clinical-trial-research-is-no-crime/article6652150.ece> [<https://perma.cc/YA8N-L4XH>].

imprisonment which may extend to two years and with fine which shall not be less than twice the amount of the compensation.”⁶⁹ Given the uncertain scope of these harsh penalties, the provisions were met with resistance. During his 2013 deposition for Parliament’s Committee on Health and Family Welfare, Dilip G. Shah, then-secretary general of the Indian Pharmaceutical Alliance, expressed concern that the penalties would stunt the siting of clinical trials in India and were “without adequate safeguards and prone to abuse.”⁷⁰ By June 2016, the Indian government decided to withdraw the 2013 proposed bill.⁷¹

On December 31, 2014, India’s new Bharatiya Janata Party government released a new proposed bill to amend the Drugs and Cosmetics Act of 1940 (the “2015 reform bill”).⁷² Instead of clarifying the subject injury compensation requirements, however, the bill delegated the resolution of those issues to the proper regulatory authority, including the power to define “injury . . . in the course of a clinical trial” and the power to determine the compensation provisions for such injuries.⁷³ In addition, the 2015 reform bill was similar to the 2013 bill in that it set forth criminal penalties for those who conduct trials without proper authorization to do so or those who conduct trials in violation of the clinical trial regulations.⁷⁴ Specifically, Section 4K essentially created criminal liability for conducting a clinical trial without permission.⁷⁵ Also, under Section 4-O “[w]hoever, himself or by any other person on his behalf, conducts clinical trials with any new drug . . . in contravention of the conditions of permission issued under section 4A and rules made thereunder” that causes adverse effects on participants shall be punishable with imprisonment and/or a fine.⁷⁶ While these proposed criminal provisions suggested an intent to make more rigorous India’s clinical trials regulatory protections, they nevertheless are troubling, as they reflect a lack of understanding “that the conditions, requirements and conduct of clinical trials are enormously complex, and that strict adherence to all conditions of a protocol is almost never possible.”⁷⁷ Importantly, however, neither the 2013 bill nor the 2015 reform bill was enacted.

⁶⁹ The Drugs and Cosmetics (Amendment) Act Bill, 2013, *supra* note 67, at 14.

⁷⁰ Barnes et al., *supra* note 68.

⁷¹ See *The Drugs and Cosmetics (Amendment) Bill, 2013*, PRS LEGISLATIVE RESEARCH, <http://www.prsindia.org/billtrack/the-drugs-and-cosmetics-amendment-bill-2007-2903/> [<https://perma.cc/AH8K-H3CM>]; *Cabinet Withdraws Drugs & Cosmetics (Amendment) Bill 2013, To Bring New Draft*, HINDUSTAN TIMES (June 22, 2016, 19:13 IST), <http://www.hindustantimes.com/india-news/cabinet-withdraws-drugs-cosmetics-amendment-bill-2013-to-bring-new-draft/story-wssy9Lfw2m2NZNRfQzYDyL.html> [<https://perma.cc/QKW8-F9BS>].

⁷² See Draft Drugs and Cosmetics (Amendment) Bill, 2015 (Dec. 31, 2014), [http://www.cdsc0.nic.in/writereaddata/D&%20C%20AMMENDMENT%20BILL\(1\).pdf](http://www.cdsc0.nic.in/writereaddata/D&%20C%20AMMENDMENT%20BILL(1).pdf) [<https://perma.cc/LQ57-YSML>]. See also Mark Barnes et al., *India’s Proposed Amendments to the Drug and Cosmetics Act: Compensation for Injuries to Clinical Trial Participants and the Criminalization of Clinical Research*, 9 LIFE SCI. LAW & INDUS. REP. 117, 7 (2015), BNA 1935–7257.

⁷³ Draft Drugs and Cosmetics (Amendment) Bill, 2015, *supra* note 72, at 7. See also Barnes et al., *supra* note 72, at 4.

⁷⁴ See Draft Drugs and Cosmetics (Amendment) Bill, 2015, *supra* note 72, at 10.

⁷⁵ *Id.* (“Whoever himself, or by any other person on his behalf, conducts clinical trial of . . . any new drug . . . in contravention of section 4A and the rules made thereunder, shall be punishable with imprisonment which may extend to three years or fine which may extend to five lakh rupees or both.”).

⁷⁶ *Id.* at 11.

⁷⁷ Barnes et al., *supra* note 72, at 7.

III. EFFECT OF NEW REGULATIONS

According to some observers, the series of stringent regulations and proposed bills since 2013 has hindered meaningful clinical trials of new therapeutic agents. As the President of the Indian Society for Clinical Research stated in a 2016 article, these “hasty regulatory reforms . . . have posed a challenge to conducting clinical [research] in the country.”⁷⁸ The well-intentioned, yet largely unproductive, regulation-making affected much of the human subjects research infrastructure in India. It led to a significant reduction in clinical trial activity by leading industry sponsors and other organizations, including, for a time, the U.S. National Institutes of Health (“NIH”).⁷⁹ In response to India’s new regulations, the NIH placed several ongoing clinical trials on hold in 2013.⁸⁰ In addition, NIH elected to forego starting or funding major new drug and medical device trials in India.⁸¹ In so doing, NIH issued a public statement: “Because of the uncertainties posed by the new requirements, NIH and some grantees have suspended new patient enrolment for some of its ongoing interventional trials. Some NIH-funded trials and other planned activities have been postponed pending clarification of the new regulations.”⁸²

The aggregated regulatory changes and the proposed Parliamentary bill’s criminalization of deviations from trial protocols led to a precipitous decline in the number of clinical trials approved in India.⁸³ As a 2013 article in *The Hindu* reported, “[c]linical trials of drugs in India have seen a drastic fall this year after toughened norms were introduced following Supreme Court directives,” and how, consequently,

⁷⁸ Melissa Fassbender, *Trust Needed to Bring Back Clinical Trials to India, Says ISCR President*, OUTSOURCINGPHARMA.COM (Jan. 21, 2016), <http://www.outsourcing-pharma.com/Clinical-Development/Trust-needed-to-bring-back-clinical-trials-to-India> [https://perma.cc/WC9J-UW4B].

⁷⁹ See Press Information Bureau, *supra* note 24 (“The National Institutes of Health (NIH), have raised concerns about how these new requirements will be implemented, particularly the specific provision related to compensation. NIH have suspended enrolment of participants in 35 interventional trials in India.”). Biogen Idec also suspended trials for six months to assess the impact of these changes. *Overcoming Clinical Challenges in BRIC Markets: A White Paper*, *supra* note 2, at 9. See also Chirang Shah et al., *Regulatory Approval in India: An Updated Review*, APPLIEDCLINICALTRIALS.COM (May 4, 2016), <http://www.appliedclinicaltrials.com/regulatory-approval-india-updated-review> [https://perma.cc/RS9N-MPEY] (“Because of these changes to the regulatory framework, many multinationals withdrew their clinical studies from India. This resulted in a standstill for the entire clinical research industry in India.”).

⁸⁰ See Sara Reardon, *NIH Makes Wary Return to India*, NATURE (Feb. 11, 2014), <http://www.nature.com/news/nih-makes-wary-return-to-india-1.14699>; [https://perma.cc/9D7U-8R4N]; *American Research Centre Stops Clinical Trials in India*, FIRSTPOST (July 28, 2013), <http://www.firstpost.com/world/american-research-centre-stops-clinical-trials-in-india-991725.html>; [https://perma.cc/WSY7-QWL6]; Press Information Bureau, *supra* note 24.

⁸¹ Barbara Bierer & Mark Barnes, *Clinical Trials, A Lost Opportunity for India*, FINANCIAL EXPRESS (Nov. 3, 2014), <http://www.financialexpress.com/archive/clinical-trials-a-lost-opportunity-for-india/1303767/>. [https://perma.cc/TB4K-85KK].

⁸² Andrew Buncombe, *“A Heaven for Clinical Trials, a Hell for India”: Court Orders Government to Regulate Drugs Testing by International Pharmaceutical Companies*, INDEPENDENT (Sept. 30, 2013), <http://www.independent.co.uk/news/world/asia/a-heaven-for-clinical-trials-a-hell-for-india-court-orders-government-to-regulate-drugs-testing-by-8849461.html> [https://perma.cc/6EDX-EPQV].

⁸³ See *Reconsidering India as a Clinical Trial Location: Revised Regulations Warrant a Fresh Look*, PHARM-OLAM INTERNATIONAL, 6 (2016), https://cdn2.hubspot.net/hubfs/4238150/PharmOlam_March2018/PDF/pharm-olam_india_clinical_trials_white_paper_1.pdf?t=1539471111921 [https://perma.cc/M9EL-RV62].

“there has also been a significant reduction in the number of sponsoring pharma firms applying for such approvals.”⁸⁴ Additionally, following the flurry of new rules and orders, many Indian-owned, India-based contract research organizations (“CROs”) ceased operations in India. Max India, for example, announced the sale of its clinical research business to a Canadian CRO, stating that the regulatory challenges had made it difficult to scale up the business.⁸⁵ Reports also suggest that due to these regulatory revisions, multinational pharmaceutical companies generally reduced their presence and activity in India.⁸⁶

It is difficult to avoid the conclusion that some of the harsher regulatory reforms harmed the clinical enterprise throughout India, resulting in fewer trials of new, experimental therapeutic products and shutting off the availability of experimental products to persons in India, who would have accessed them through a clinical trial. Declining pharmaceutical investment in India would be regrettable in light of India’s enormous potential as a location for clinical trials and, more importantly, because it would hinder the Indian population’s access to novel, innovative investigational therapies that may meet unmet medical needs. Promoting and bolstering clinical trials activity in India would also be a boon to the Indian economy, spurring many jobs such as those in research, clinical data management, biostatistics, and IT services.⁸⁷

These trends may now begin to be reversed or at least stabilize, as some regulatory reforms have been scaled back or implemented in a less severe way than originally feared. Reports indicate that since 2013, the number of clinical trials approved by DCGI has increased.⁸⁸ Since 2015, Phase IV trials have increased, perhaps reflecting a lower risk of compensable injury in post-marketing studies.⁸⁹ Some sources suggest that CRO presence in India is also rebounding. For example, in September 2017, Quanticate expanded its presence in India by opening a new office in Bangalore and announcing plans to increase its workforce in order to meet increased demand in India.⁹⁰ Further, as a result of ongoing efforts on the part of the government to clarify

⁸⁴ HINDU, *supra* note 1.

⁸⁵ Nair, *supra* note 10. The article also states that “[m]any CROs say that conducting clinical trials in India is now difficult and cumbersome, and have not gone ahead with trials despite getting government approval.” *Id.*

⁸⁶ Datamonitor Healthcare, *Indian Pharmaceutical Market*, PHARMA INTELLIGENCE, 2 (2013), https://pharmaintelligence.informa.com/~/_/media/Informa-Shop-Window/Pharma/Files/PDFs/whitepapers/Indian-Pharmaceutical-Market-White-paper_11-2016.pdf. This white paper further suggests that the “use of compulsory licenses for patented drugs is further contributing to the loss of faith in the Indian patent system among Western manufacturers.” *Id.* at 3.

⁸⁷ See, e.g., *Global Pharma Looks to India: Prospects for Growth*, PRICEWATERHOUSECOOPERS 1, 5, <https://www.pwc.com/gx/en/pharma-life-sciences/pdf/global-pharma-looks-to-india-final.pdf> [<https://perma.cc/732H-9JRW>].

⁸⁸ Jyoti Shelar, *After a Lull of Five Years, Clinical Trials on the Rise in India*, HINDU (June 2, 2018), <https://www.thehindu.com/news/national/after-a-lull-of-five-years-clinical-trials-on-the-rise-in-india/article24069487.ece> (“There is a gradual revival in the number of clinical trials being done in India. From an all-time low of 17 clinical trials approved by the Drug Controller General of India (DCGI) in 2013, the number has slowly increased to 97 in 2017, a more than 400% jump in five years.”).

⁸⁹ Mathini Ilancheran, *Measuring the Impact of Reforms on India’s Clinical Trial Environment*, CLINICAL LEADER (Oct. 12, 2017), <https://www.clinicalleader.com/doc/measuring-the-impact-of-reforms-on-india-s-clinical-trial-environment-0001>. [<https://perma.cc/3J99-TLC9>].

⁹⁰ See *UK CRO Quanticate Doubles its Footprint in India*, PHARMATIMES (Sept. 27, 2017), http://www.pharmatimes.com/news/uk_cro_quanticate_doubles_its_footprint_in_india_1206470. [<https://perma.cc/4V5P-KLBQ>].

requirements, many industry observers remain optimistic regarding India's future as a center for clinical research.⁹¹

IV. MORE RECENT CLARIFICATIONS OF STRINGENT REGULATIONS

Given the adverse effects of revised regulations on India's clinical trial enterprise, the Indian government appears to now be clarifying many of the new requirements, presumably to correct excessive regulations and thereby reinvigorate clinical research. For example, in an effort to decrease administrative burden and speed up review of proposed research in India, India launched an online submission system for permission to conduct clinical trials in 2015.⁹² Moreover, evidence suggests that certain regulations have not been enforced strictly as written, with governmental authorities instead showing flexibility in the implementation and enforcement of the rules. Specifically, despite the ambiguity and potential breadth of the compensation provisions, governmental authorities in India have stated in public fora that compensation, in practice, has only been afforded to a clinical trial subject when the SAE or death has been determined to be causally related to the investigational drug—which is a much more rigorous standard than what is reflected in the current revised regulation.⁹³ Moreover, the aforementioned ICMR 2017 Ethical Guidelines provide additional guidance regarding India's clinical trials rules, including specifying that with respect to the compensation provisions, “[m]edical management should be free if the harm is *related* to the research” and that “[c]ompensation should be given to any participant *when the injury is related to the research.*”⁹⁴ This suggests a more strict causation standard for compensation than is set forth in the applicable national regulations. The 2017 ICMR guidelines are evidence of efforts by the Indian

⁹¹ See e.g., Amita Bhavé & Suresh Menon, *Regulatory Environment for Clinical Research: Recent Past and Expected Future*, 8 PERSP. CLINICAL RES. 14, 11-16 (2017), <http://www.picronline.org/article.asp?issn=2229-3485;year=2017;volume=8;issue=1;spage=11;epage=16;aulast=Bhave> (“Indian regulations have been evolving positively in the recent past and are expected to be much more conducive for clinical research facilitating faster approval timelines, increased transparency while fully ensuring patient safety. This will help bring newer innovative medicines to Indian patients at an earliest.”); Sanil Manavalan & Catherine Sinfield, *Conducting Clinical Trials in India: Opportunities and Challenges*, CLINICAL LEADER (Aug. 8, 2017), <https://www.clinicalleader.com/doc/conducting-clinical-trials-in-india-opportunities-and-challenges-0001> (“More checks and balances have been put in place for certification of sites, ethics committees, and limiting the number of concurrent trials by a principal investigator. Central Drug Standards Control Office (CDSCO) has also issued GCPs inspection checklist recently in August 2016 and is helpful for sponsors and sites. Overall, this translates into better quality trials and cleaner data than what existed prior to the overhaul, the evolving process positively supports clinical research in India while appropriately balancing patient safety.”) [<https://perma.cc/7SNC-8BE9>].

⁹² See CENT. DRUGS STANDARD CONTROL ORG., 04-01/2012-Misc.-159, NOTICE REGARDING IT ENABLED SYSTEM FOR ONLINE SUBMISSION OF APPLICATIONS OF CLINICAL TRIAL-REG. (Sept. 9, 2015), <http://www.cdsc.nic.in/writereaddata/latestNotice%20for%20website%20OCTAMS.pdf> [<https://perma.cc/WK99-9B99>].

⁹³ Bierer, *supra* note 17 (“Verbal reports from governmental authorities have assured us that compensation has only been awarded when SAEs and death have been determined to be causally related to investigational drug.”).

⁹⁴ INDIAN COUNCIL OF MED. RESEARCH, *supra* note 62 (emphasis added). See also *id.* at 81 (“Provision of free treatment and compensation for any study-related injury must be ensured for the trial participant. The EC must determine the compensation amount after the investigator has described the relatedness.”).

government to clarify and remedy some of the harsher regulatory changes imposed beginning in 2013.

Another example of easing of regulatory requirements came in November 2015, when CDSCO released a regulatory circular allowing ECs to approve requests for new clinical trial sites and new investigators to be added to a clinical trial without CDSCO's approval as long as the ECs conduct "due diligence" on new sites and investigators.⁹⁵ ECs must still inform DCGI of additions or deletions of sites and investigators, and DCGI may object to any such additions or deletions, but clinical trial sponsors are no longer required to obtain a "no objection" certificate from DCGI each time they add a site or investigator to a study.⁹⁶ The government has scaled back requirements for trials that have an "academic/research" purpose and are not conducted in preparation for a regulatory submission; beginning in October 2015, permission from DCGI is no longer required for "clinical trials for academic/research purposes that are non-regulatory in nature . . . provided that, the trials were approved by the respective Ethics Committee and they are not for regulatory submissions (i.e., if the trial are not for claiming permission of New Drug for marketing as per Drugs and Cosmetics Rules)."⁹⁷

Other changes were made in August 2016 in an effort to ease regulatory hurdles to conducting clinical trials. Specifically, in August 2016, CDSCO released an order removing the prohibition on investigators conducting more than three trials at a time, stating: "[the] Ethics Committee after examining the risk and complexity involved in the trial being conducted/proposed shall decide about how many trials an investigator can undertake."⁹⁸ At the same time, CDSCO released an order effectively eliminating the requirement that trials be conducted only at sites with more than 50 hospital beds, requiring instead that the EC must decide whether the trial site is suitable.⁹⁹

As described above, in June 2016 the Indian government withdrew the previously discussed Drugs and Cosmetics (Amendment) Bill, 2013.¹⁰⁰ Additionally, CDSCO released a notice stating that the MoHFW plans to "re-visit the Drugs and Cosmetics Act, 1940 and Rules, 1945 to match up with the current regulatory requirements related to safety, efficacy and quality of drugs, medical devices and cosmetics."¹⁰¹ The

⁹⁵ CENT. DRUGS STANDARD CONTROL ORG., 12-01/14-DC Pt. 47, CIRCULAR REGARDING REQUIREMENT OF NOC FROM DCGI FOR ADDITION OF NEW CLINICAL TRIAL SITE OR INVESTIGATOR (Nov. 10, 2015), <http://www.cdscn.org.in/writereaddata/NOC%20for%20DCGI.pdf> [<https://perma.cc/8D4M-ZADY>].

⁹⁶ *Id.*

⁹⁷ CENT. DRUGS STANDARD CONTROL ORG., 12-01/14-DC Pt. 47, CIRCULAR REGARDING REQUIREMENT OF PERMISSION FOR CONDUCT OF CLINICAL TRIALS FOR ACADEMIC/RESEARCH PURPOSES THAT ARE NON-REGULATORY IN NATURE (Nov. 10, 2015), <http://www.cdscn.org.in/writereaddata/Requirement%20of%20permission%20for%20conductd.pdf> [<https://perma.cc/E75Y-5BUA>].

⁹⁸ CENT. DRUGS STANDARD CONTROL ORG., 12-01/14-DC Pt. 47, CIRCULAR REGARDING RESTRICTION OF CONDUCTING THREE CLINICAL TRIALS PER INVESTIGATOR (Aug. 2, 2016), <http://www.cdscn.org.in/writereaddata/restricion%20of%20conducting%20three.pdf> [<https://perma.cc/G8PG-SJ9N>].

⁹⁹ CENT. DRUGS STANDARD CONTROL ORG., 12-01/14-DC Pt. 47, CIRCULAR REGARDING REQUIREMENT OF 50 BEDDED SITE FOR CLINICAL TRIAL (Aug. 2, 2016), <http://www.cdscn.org.in/writereaddata/requirement%20of%2050%20bedded%20.pdf> [<https://perma.cc/66GK-URF8>].

¹⁰⁰ See *Cabinet Withdraws Drugs & Cosmetics (Amendment) Bill 2013, To Bring New Draft*, *supra* note 71.

¹⁰¹ CENT. DRUGS STANDARD CONTROL ORG., D-21013/63/2016-DC, NOTICE REGARDING REVISIT OF DRUGS AND COSMETICS ACT 1940 AND RULES 1945 (June 6, 2016), http://www.cdscn.org.in/writereaddata/Noticedatede06_6_2016.pdf [<https://perma.cc/K6EE-98R8>]. See CENT. DRUGS STANDARD

government has suggested that it plans to draft a fresh law, although its timeframe for doing so is presently unclear. It is also unclear what effect, if any, this has on the draft 2015 bill, which—unlike the 2013 bill—remains available on CDSCO's website.¹⁰²

On January 31, 2017, the Indian government released rules relating to the regulation of medical devices, including provisions relating to clinical investigations of such devices.¹⁰³ The rules demonstrate additional strides the Indian government has taken to further clarify its regulatory framework. Previously, medical devices simply had been regulated as drugs under the Drugs and Cosmetics Rules, 1945, while other devices largely went unregulated.¹⁰⁴

In September 2017, the Technical Committee headed by Dr. Jagdish Prasad, the Director General of Health Services, made an additional effort to promote ethical clinical trials activity in India and bolster the market for India-based CROs and hospitals by announcing that companies would be required to include Indian patients in global clinical trials in order to market in India a new drug developed outside of the country.¹⁰⁵ The Technical Committee stated that “[a]ny firm intending to market a new drug which is being developed outside the country, should include Indian patients in the Global Clinical Trial.”¹⁰⁶ Although it is unclear what the overall effect of this change will be, it nevertheless demonstrates the government's continued focus on ensuring the safety and efficacy of drugs marketed in India. Further, the change will require pharmaceutical companies wishing to market their products in India to conduct clinical trials in India, which presumably will lead to an increase in the volume of clinical trials activity in the country.

Finally, the 2018 Draft Rules described above consolidate and clarify many of the previously discussed notices and orders released over the years, yet also include disconcerting compensation-related provisions.¹⁰⁷ Of particular concern is the fact that the 2018 Draft Rules not only preserve the requirement that the sponsor compensate trial participants for all injuries deemed “related to” a clinical trial under a broad list,

CONTROL ORG., ACTS AND RULES, <http://www.cdsc0.nic.in/forms/contentpage1.aspx?lid=1888> [<https://perma.cc/C26C-4DAV>] (last updated Jan. 19, 2017).

¹⁰²See CDSCO, *Acts and Rules*, <https://cdsc0.gov.in/opencms/opencms/en/Acts-Rules/index.html> [<https://perma.cc/C26C-4DAV>] (last updated Jan. 19, 2017).

¹⁰³See Medical Device Rules, 2017, 70 Gazette of India, pt. II sec. 3(i), G.S.R. 781(E) (Jan. 31, 2017), [http://www.cdsc0.nic.in/writereaddata/Medical%20Device%20Rule%20gsr78E\(1\).pdf](http://www.cdsc0.nic.in/writereaddata/Medical%20Device%20Rule%20gsr78E(1).pdf) [<https://perma.cc/7PNQ-S45L>]. Chapter VII covers clinical investigations of medical devices and clinical performance evaluations of new in vitro diagnostic devices. *Id.* at 157.

¹⁰⁴See Bhavik Narsana & Minhaz Lokhandwala, *India: The Medical Devices Rules – An Analysis*, MONDAQ.COM (Sept. 11, 2017), <http://www.mondaq.com/india/x/627736/Life+Sciences+Biotechnology/The+Medical+Devices+Rules+An+Analysis>. [<https://perma.cc/AP9H-MSU3>].

¹⁰⁵CENT. DRUGS STANDARD CONTROL ORG., MINUTES OF 42ND TECHNICAL COMMITTEE MEETING HELD ON 25.09.2017 (June 25, 2017), http://www.cdsc0.nic.in/writereaddata/technical%20committee%2042%2025_9_2017.pdf, [<https://perma.cc/XZL5-TB45>]; Sushmi Deyl, *To Market New Drugs in India, Global Trials Must Include Indians*, TIMES OF INDIA (Oct. 11, 2017), <https://timesofindia.indiatimes.com/india/to-market-new-drugs-in-india-global-trials-must-include-indians/articleshow/61029119.cms>; [<https://perma.cc/6J7T-CJTD>].

¹⁰⁶CENT. DRUGS STANDARD CONTROL ORG., *supra* note 105, at 2.

¹⁰⁷See Draft New Drugs and Clinical Trials Rules, 2018 (2017), <http://www.cdsc0.nic.in/writereaddata/Draft%20CT%20Rules%20sent%20for%20Publication.pdf> [<https://perma.cc/4NE2-8UYF>]. Seeking to speed up the trial application process, the 2018 Draft Rules also provide that an application to conduct a clinical trial of a new drug that was either discovered in India or will be manufactured and marketed in India must be processed within 45 days. *Id.* at Ch. VI, Section 23.

but the 2018 Draft Rules also would increase the burden on sponsors, even in excess of the existing regulations. Under the 2018 Draft Rules, for example, if a research subject dies or suffers a permanent disability during a trial, and if the EC finds the injury to be “related to” the trial under the broad existing definition of “related to”, then (1) the EC must determine in its opinion the compensation to be paid based on the formulae the government have developed (which are based on certain factors such as age of the subject) and (2) the trial sponsor, within 15 days of the EC’s determination, must pay an interim compensation of 60 percent of the full compensation.¹⁰⁸ More concerning still is an explanatory footnote to the rules explaining that interim compensation would be irrevocable, meaning even if it is later determined that the death or injury was *not* related to the clinical trial, the interim compensation must stand and is not reimbursable to the sponsor: “For removal of doubt it is hereby declared that the amount paid as an interim compensation as referred to in sub-rule (1) to the trial subject or its legal heir, as the case may be, shall not be recoverable irrespective of the cause of the death or permanent disability during the clinical trial.”¹⁰⁹ Under the proposal, the sponsor is automatically assessed at least 60 percent of total compensation if the EC determines that a research participant’s death or permanent disability is indeed related to the trial.

The 2018 Draft Rules also generally preserve the broad list of circumstances deemed “related to” a clinical trial, which are much broader than would be determined through longstanding methods of assessing causality of injuries in clinical trials.¹¹⁰ The 2018 Draft Rules’ version of this list misses the mark in the same way as its predecessor currently still in effect: by holding sponsors responsible for injuries irrespective of fault, and by failing to acknowledge that the purpose of conducting clinical trials, in part, is to determine adverse events and safety of the investigational product. These rules are not only onerous, by requiring the sponsor or person who has obtained permission to pay interim compensation irrespective of whether the injury indeed is related to the trial or due to fault, but are also complicated, which alone could deter the siting of clinical trials in India.

In regard to medical management of trial participants, sponsors would be, under these Draft Rules, financially responsible for all participants’ other non-trial related illnesses: “Where the trial subject is suffering from any other illness during participation in clinical trial or bioavailability and bioequivalence study, the sponsor shall provide necessary medical management and ancillary care.”¹¹¹ The extreme breadth and unworkability of such a provision is best illustrated by an example. Pursuant to the rule as written, if a participant in a trial for an experimental new kind of eye drop has cancer, the sponsor of the trial would be responsible for providing “medical management and ancillary care” in connection with the participant’s cancer, leaving the sponsor exposed to high, unpredictable costs that are completely unrelated to the treatment being provided pursuant to the protocol. Once again, these proposed measures—though undoubtedly intended to benefit clinical trial participants—go beyond what other countries’ regulatory regimes typically demand of trial sponsors, and full implementation of the proposed provisions would likely continue to deter the

¹⁰⁸*Id.* at Ch. VI, Section 39.

¹⁰⁹*Id.*

¹¹⁰*Id.* at Ch. VI, Section 41.

¹¹¹*Id.*

siting of clinical trials in India. The 2018 Draft Rules have been published for public objections and suggestions and are expected to be finalized after review of the comments and suggestions received from the stakeholders. One can hope that the final rules will roll back some of the provisions of these 2018 Draft Rules that put extraordinary burden on the sponsors.

V. CONCLUSION

After extensive national media attention following multiple deaths of participants allegedly related to participation in clinical trials, India took aggressive regulatory measures in order to address perceived risks for clinical trial participants. India has made important strides in developing a robust regulatory framework around clinical trials, the central focus of which is the protection of Indian clinical trial participants. While other countries mandate clinical trials insurance, India became one of few countries to mandate compensation for research-related injury, and specifically one of the only countries to provide compensation for economic losses.¹¹² The Indian government also has taken steps to make sure ECs are properly formed, trained and operated through accreditation. These and other initiatives, including the desire to compensate and make whole, individuals who are injured in connection with clinical trials, are all commendable.

These measures were intended to bolster and strengthen India's clinical trial regulatory system and protect human subjects, but many of the regulatory changes exceeded clinical trials regulations in other countries and lacked definition, clarity, and compelling public policy rationale. In injury compensation, for example, assuring compensation to participants who are injured during a trial but whose injuries were not directly caused by participation in the trial may appear to vindicate important social justice values, but it also disincentivizes sponsors and trial funders from initiating trials in the country. Although many of these regulatory requirements recently have been clarified and scaled back, this regulatory experience has threatened the increasingly robust system surrounding, and enormous potential of, clinical research in India. More recent efforts to clarify and mitigate the harsher aspects of India's clinical trials regulations, however, suggest that India retains great promise as a site for clinical research of new, significant medicinal products, due, among other factors, to the diversity of its people, its relatively low labor and capital costs, and a corps of well-trained physicians working in a set of modern medical centers. The Indian government's recent clarifications, reversals, and revisions of a number of its new rules have spurred optimism about the clinical research climate in India, even as

¹¹²See Munshi, *supra* note 37 at 66-67 ("In the USA, it is not mandatory by law for sponsors and Institutions to provide either free medical care or compensation for research related injuries to trial participants The Association of the British Pharmaceutical Industry (ABPI) guidelines . . . have been modified and adopted by many other countries such as South Africa, Australia and New Zealand. Unfortunately, these guidelines clearly state that there is 'no legal commitment' to pay compensation for research related injuries."). See also George Rugare Chingarande & Keymanthri Moodley, *Disparate Compensation Policies for Research Related Injury in an Era of Multinational Trials: A Case Study of Brazil, Russia, India, China and South Africa*, BMC MED. ETHICS. 2018, 10, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5816510/> [<https://perma.cc/KH5J-V423>] (discussing how "Brazil, India and South Africa have regulations that cover both medical treatment and financial compensation over and above the medical expenses," but that "[o]nly India provides for the compensation of economic losses . . . [o]f the five countries under comparison India has by far the most comprehensive and most stringent regulations.").

the episode provides an important global lesson in how significant changes in a regulatory regime can profoundly affect clinical research activity.¹¹³ During the media attention in 2013 and 2014, it was often said that, “there is no smoke without fire”—meaning the reported problems of clinical trial injuries in India must point to an underlying problem with how trials have been regulated. In the recent clarifications and proposed revisions of the regulations, the Indian government continues to seek to strike a balance between the safety of its population and the scientific requirements and needs for clinical research in India. Although that balance has not yet been struck in a fully sustainable and satisfactory way, the ongoing regulatory efforts and continued responsiveness of the Indian government give some reason for optimism about the future of India as a robust center of clinical research.

¹¹³See e.g., *Reconsidering India as a Clinical Trial Location: Revised Regulations Warrant a Fresh Look*, *supra* note 83 at 11 (stating that India as a destination for clinical trials deserves a “fresh look” in light of the easing of many requirements); Arun Bhatt, *Future of Indian Clinical Trials: Moving Forward from Hyped Potential to Human Protection*, 8 PERSP. CLINICAL RES. 2, 2-4 (2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5299800/> [<https://perma.cc/J4WK-SAXY>] (“As the Indian clinical trial environment became unattractive, the regulators amended some of the stringent regulatory requirements in 2015. And now, there is optimism among the stakeholders about prospects of growth of clinical trials.”).

November 27, 2018

Post-Submission Update:

The Evolving Regulatory Landscape for Clinical Trials in India

Following submission of this article to the Food and Drug Law Journal, there have been several developments related to India's 2018 draft clinical trials rules. As discussed in Section IV of the article, India's Ministry of Health and Family Welfare issued draft 2018 clinical trials rules on February 1, 2018, which were open to a 45-day comment period. On September 12, 2018, the Supreme Court of India issued an order at a hearing for a case brought by Swasthya Adhikar Manch, the activist group that has previously challenged regulatory oversight of clinical trials in India, including one of the petitions that contributed to the prolific rulemaking beginning in 2013.¹ In the order, the Supreme Court found that none of the petitioners who had brought the case for Swasthya Adhikar Manch had filed comments to the draft rules. With the comment period having closed without input from these interested parties, the Indian government agreed to re-open the comment period for 30 additional days.

On November 14, 2018, the Central Drugs Standard Control Organization (CDSCO) released a notice stating that per the Supreme Court's order, the comment period for the 2018 draft rules will be reopened and a hearing held on November 22, 2018 for the petitioners and other interested parties to submit and discuss their comments.²

Finally, while unconfirmed, sources indicate that the controversial compensation provision requiring sponsors to pay 60 percent of compensation in case of death or permanent disability upfront, even where it is later established that the death or disability was unrelated to the clinical trial, may be eliminated in light of serious opposition from industry and organizations, including the World Health Organization.³ India's clinical trial regulations continue to be in a state of flux, and should be monitored.

Mark Barnes, Jamie Flaherty, Minal Caron, Alishan Naqvee, Barbara Bierer

¹ See *Swasthya Adhikar Manch v. Union of India (UOI)*, W.P.(C) No. 33/2012 (India) (Sept. 12, 2018), https://www.sci.gov.in/supremecourt/2012/1056/1056_2012_Order_12-Sep-2018.pdf.

² See Notice, No. 04-07/2012, CDSCO (Nov. 14, 2018),

https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MjExMQ.

³ See e.g., Deepak Patel, *Govt May Ease Compensation Clause in Clinical Trial Rules*, Indian Express (Nov. 26, 2018), <https://indianexpress.com/article/business/govt-may-ease-compensation-clause-in-clinical-trial-rules-5464128/> (“‘There is a serious opposition to this provision of clinical trial rules by industry and even the WHO (World Health Organisation). In the final version, we may remove this clause as it can prove to be too onerous for companies and sponsor organisations that run various clinical trials in India,’ said a senior government official on the condition of anonymity.”); Dilsher Dhillon, *India's government may scrap an important compensation rule for human subjects in clinical trials in a bid to placate pharma companies*, Business Insider India (Nov. 26, 2018), <https://www.businessinsider.in/indias-government-may-scrap-an-important-compensation-rule-for-human-subjects-in-clinical-trials-in-a-bid-to-placate-pharma-companies/articleshow/66806673.cms>.