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India's Proposed Amendments to the Drug and Cosmetics Act: Compensation for Injuries to Clinical Trial Participants and the Criminalization of Clinical Research




By Mark Barnes, Minal M. Caron, Adarsh Varghese and Barbara E. Bierer

On Dec. 31, 2014, India's new Bharatiya Janata Party (BJP) government of Prime Minister Narendra Modi released a draft of a new bill that would amend the Drugs and Cosmetics Act of 1940, and invited public comments on the draft until Jan. 19, 2015. The bill represents the BJP government's version of significant reforms to the authority of the Indian drug and device regulatory agency and, in some important respects, differs from a comparable reform bill that was offered by the Congress Party government in 2013. The draft legislation would broaden the scope of regulatory authority to include medical devices and addresses the marketing approval process for the medical device industry. More significantly for universities, research institutions and drug and device companies considering siting clinical trials in India, the draft bill adds a new chapter on clinical trials, which could, if adopted and dependent upon implementing regulations, ameliorate but potentially complicate the sponsoring of clinical trials in India. That proposed chapter on clinical trials addresses the circumstances in which a clinical trial participant would be compensated for an injury and who must provide such compensation—issues that have been the subject of a vigorous and contentious debate in India over the past two years. The chapter on clinical trials also sets forth certain criminal penalties for those involved in clinical research who violate clinical trial regulations and conditions of clinical trial approvals.

Mark Barnes, JD, LLM, and Barbara Bierer, MD, are the Harvard faculty co-chairs of the Multi-Regional Clinical Trials Center at Harvard University (Harvard MRCT), where Adarsh Varghese, LL.B., BCL, an LLM candidate at Harvard Law School, serves as a research associate. Mr. Barnes and Minal Caron, JD, are attorneys at Ropes & Gray LLP, Boston.

In this article, we will describe the specific controversy regarding regulations, adopted in January 2013 (and amended in December 2014), mandating that sponsors provide compensation for injuries to participants in clinical trials. We will then identify how the 2015 reform bill could change the terms and operation of those compensation regulations profoundly, and thus have a significant impact on the willingness of all clinical trial stakeholders to conduct clinical trials in India. We also describe herein the criminal penalty sections in the 2015 reform bill that, if enacted, likely would have a substantial chilling effect on the willingness of physicians to conduct clinical trials. As part of our analysis of both the compensation issues and the criminal penalty issues, we will note how the 2015 BJP reform bill compares to the 2013 Congress Party reform bill that was introduced but never enacted.

I. Introduction and Background

The draft legislation introduced by the BJP government tracks the regulatory developments that have dramatically changed the clinical trial environment in India over the past several years. Until early 2013, India had been emerging as a favored destination for clinical trials, due to its large and diverse population, its significant public health problems, the availability of reliable

clinical practice human resources and sites and the relatively low cost of conducting trials.[1] However, the last few years have seen public perception of clinical trial practice in India shift toward distrust. To a large degree, this has been driven by media reports of allegedly inappropriate clinical trial practices, together with concerns that citizens of India are enrolling in clinical trials without fully informed consent and that once enrolled, they face a serious risk of suffering uncompensated injuries or death caused by trial procedures and test agents.[2]

In early 2011, the standing committee formed by the Indian Parliament to report on the regulatory authority responsible for overseeing clinical trials (Central Drugs Standard Control Organization/Drugs Controller General of India, or CDSCO/DCGI) indicated that the legal heirs of subjects who died while enrolled in a clinical trial were not adequately compensated. Capturing this sentiment, the public interest group Swasthya Adhikar Manch (translated, ''Health Right Forum'') filed a petition before the Supreme Court of India against the Ministry of Health and Family Welfare (Ministry) in December 2012, alleging that the framework for approving and regulating clinical trials in India was wholly inadequate.[3] The petition focused on a particular set of clinical trials but also generally alleged that ''at the all India level, 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.''[4] In January 2013, as a ruling in that lawsuit, the Supreme Court suspended the power of the India regulatory authorities to approve clinical trials due to what the Court found to be inadequate oversight of such trials. In response to the court ruling, the Ministry of Health and Family Welfare (the parent agency of CDSCO/DCGI) in January 2013 issued new regulations, as described in more detail below, related to oversight of clinical trials and compensation for injuries to trial participants. These regulations provide for a broad and uncertain scope of liability that arguably reaches all the stakeholders involved in the operation of a clinical trial—from the institutions running the trials, to major and minor financial supporters of the trials, to the investigators conducting the trials.

The breadth and uncertainty of the regulations has led to a predictable but dramatic decrease in the number of significant clinical trials of new drugs in India, as sponsors and investigators have decided that the large and uncertain future costs and liabilities associated with conducting future trials are too onerous to bear. Many major pharmaceutical companies, American medical institutions, leading Indian medical institutions, and the National Institutes of Health (NIH) have elected to forgo starting or funding major drug trials in India.[5] Accordingly, although the exact numbers are difficult to ascertain, new clinical trial approvals in India have declined precipitously over the last two years.[6] Many academic, government and industry sponsors will not consider placing new clinical trials in India until and unless the uncertainties caused by the January 2013 regulations have been resolved. Importantly, the BJP government's 2015 proposed reform bill addresses these compensation issues, but in ways whose ultimate effects remain unclear.

The 2015 reform bill is in the form of a proposed amendment to the statute itself (*i.e.*, the Drugs and Cosmetics Act, 1940), while the previous Congress Party 2013 reform bill would have introduced changes by way of amendments to the rules issued under the statute (Drugs and Cosmetics Rule, 1945). Amendments to the statute must go through a parliamentary process, while the government in power can amend rules on its own. Therefore, even if the 2015 reform bill is passed in its proposed form by the Indian Parliament, the government would then need to issue relevant rules to define in detail how the statute will be implemented. The BJP government appears to have recognized this and has called for comments on the changes that would need to be made to the current rules, noting that ''amendment to the Drugs and Cosmetics Rules, 1945 *is also required* with proposed amendments in Drug and Cosmetics Act, 1940.''[7] While this therefore presents the government with an opportunity to do away with Rule 122-DAB or alter it significantly, the draft legislation does not by its terms solve most of the issues related to uncertainty and vagueness that plague the 2013 compensation regulations. That uncertainty will persist until the accompanying relevant and specific regulations have been issued.

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[1] *See* Barbara Bierer & Mark Barnes, *Clinical trials, a lost opportunity for India*, Financial Express, Nov. 3, 2014, *available at* http://mrct.globalhealth.harvard.edu/files/mrct/files/ct_lost_opportunity1.pdf; Yogendra K. Gupta et al., *Compensation for Clinical Trial-Related Injury and Death in India: Challenges and the Way Forward*, Drug Safety 37:12, at 1 (Oct. 7, 2014).

[2] *See* Gupta et al., *supra* note 1, at 1 (''Isolated cases of alleged incorrectly conducted trials not conforming to the principles of ethics, coupled with unbalanced media reporting have generated debate from public to parliament regarding clinical trials in the country''); N. V. Ramamurthy, *Inept media trials of clinical trials*, Perspectives in Clinical Research, Apr-Jun 2012; at 47, *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3371547 (''Possibly by unintended misrepresentation, or mostly out of ignorance of the nuances involved in the clinical trials process, the media has done more harm than good, and got away with it. On the other side, the industry has been reluctant to engage with the media in a meaningful dialog for too long now.'').

[3] Writ Petition No. 33 of 2012, *available at* http://www.unethicalclinicaltrial.org/Awarness_Material.aspx.

[4] *Id.* ¶ 8.

[5] Numbers of new trials approved in India appear to have declined from about 500 in 2012 to about 70 in 2013, with 150 anticipated for 2014. Bierer & Barnes, *supra* note 1. Other sources have cited other figures for the decline in the number of recent clinical trial approvals in India, but those estimates also indicate a significant downward trend in the number of new trials. *See* Gupta et al., *supra* note 1, at 2 (noting ''the sharp drop in the number of clinical trials (from 529 in 2010 to 253 in 2012 to 107 in 2013) approved by the Drug Controller General'').

[6] *See* Mark Barnes & Barbara Bierer, *Clinical trial regulation in India: Science or social justice?* Express Pharma, Nov. 25, 2014, *available at* http://www.financialexpress.com/article/pharma/management-pharma/ct-regulation-in-india-science-or-social-justice/12495/.

[7] *See:* http://mohfw.nic.in/index1.php?lang=1&level=1&sublinkid=4929&lid=3034 (emphasis added).

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II. Injury Compensation Provisions[8]

A. 2013 Regulations

On Jan. 30, 2013, the Ministry enacted Rule 122-DAB: ''Compensation in case of injury or death during clinical trial.'' Section 1 provides 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.'' The breadth of this provision is made apparent when comparing Section 1 against Section 2, which states: ''In case the injury . . . is *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.''[9,10] Thus, under Rule 122-DAB, a clinical trial participant is entitled to have his or her medical costs covered for any injury received during the clinical trial for ''as long as required,'' regardless of whether the injury is related to the trial, as well as additional ''financial compensation'' if the injury is related to the clinical trial. Such expenses related to medical management and financial compensation must be borne by the ''sponsor'' of the clinical trial, a term that is not adequately defined in the relevant regulations and therefore could potentially reach even funders of a clinical trial, as well as academic institutions that are initiating a trial without external sponsorship.[11] Recently, on Dec. 12, 2014, an amendment to the January 2013 regulations was published that somewhat limits the exposure of the sponsor, specifically stating ''free medical management shall be given as long as required *or till such time it is established that the injury is not related to the clinical trial, whichever is earlier*.''[12] As discussed further below, however, the determination of ''relatedness'' to the clinical trial is poorly defined, making it extremely difficult for any sponsor to prove ''that is injury is not related to the clinical trial.''[13]

At first impression, the requirement that compensation be paid to clinical trial participants who suffer injuries ''related to the clinical trial'' sounds like a reasonable, even-handed approach to protect the rights of participants. However, Section 5 of Rule 122-DAB provides an illustrative list of circumstances under which an injury to a clinical trial participant must be considered ''clinical trial related.''[14] The list is strikingly broad by any definition, covering any injury that is ''due to'':

(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.[15]

As with the other important terms in Rule 122-DAB, there remains significant ambiguity as to what shall be considered an injury due to, for example, the ''use of placebo'' or a ''failure of investigational product to provide intended therapeutic effect.'' Generally, however, it is apparent that ''clinical trial related injury or death'' under Section 5 of Rule 122-DAB encompasses almost all adverse events that could occur to subjects in clini-

[8] Some of the editorial commentary provided in this and the following section was first made in comments that the authors filed with the Indian government on Jan. 12, 2015. *See* Letter from Barnes et al. to Dr. Shailendra Kumar, Department of Health and Family Welfare, (Jan. 11, 2015) (on file with author), *available at* http://mrct.globalhealth.harvard.edu/file/326696. That commentary focused on particular provisions of the 2015 draft legislation that the authors believe should be revised before the bill is introduced to the Indian Parliament.

[9] Emphasis added.

[10] Section 3 extends the same type of compensation available in Section 2 to ''clinical trial related death'': ''In the case of clinical trial related death of the subject, his/her nominee(s) would be entitled to financial compensation . . . over and above any expenses incurred on the medical management of such subject.''

[11] Rule 122-DAB, § (4) (''The expenses on medical management and financial compensation in the case of clinical trial injury or death of the trial subject shall be borne by the sponsor of the trial.'').

[12] *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.

[13] The Dec. 12, 2014, amendment also adds a subsection to Section 2 of Rule 122-DAB: ''(2A) [I]n case, there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages of the subject.'' *See* Drugs and Cosmetics (Sixth Amendment) Rules, 2012, *supra* note 12. This new language does not, however, reduce the breadth and uncertainty of the ''related to'' provision.

[14] The full introductory statement preceding the list of ''reasons'' in Section 5 is as follows: ''Any injury or death of the subject occurring in clinical trial due to following reasons shall be considered as clinical trial related injury or death and the subject or his/her nominee(s), as the case may be, are entitled for financial compensation for such injury or death: . . . .'' Responding to a barrage of criticism since the January 2013 issuance of these compensation regulations, the Ministry on Dec. 12, 2014, published an amended definition of trial-related injury, by which the following words were appended to the criteria in subsections (c) and (d): ''where, the standard care, though available, was not provided to the subject as per the clinical trial protocol.'' *See* Drugs and Cosmetics (Sixth Amendment) Rules, 2014, *supra* note 12. Even these amended definitions, however, have been severely criticized as overly broad. For example, in any clinical trial using an experimental agent, all ''standard care'' will not have been provided to every subject. *See* Letter from Barnes et al. to Hon. Secretary Lov Varma, Department of Health and Family Welfare, (June 18, 2014) (on file with author), *available at* http://mrct.globalhealth.harvard.edu/files/mrct/files/2014-06-18_comments_from_harvard_mrct_to_draft_rules_to_amend_the_drugs_and_cosmetics_rules.pdf.

[15] This list incorporates the changes that were made as part of the Dec. 12, 2014, amendment to Section 5 of Rule 122-DAB, as described above, *supra*, at notes 12, 14 and accompanying text.

cal trials, independent of conventional legal, scientific and clinical understandings of causation.

In February 2013, the Ministry also enacted two related amendments of comparatively lesser importance. Rule 122-DAC sets out the Licensing Authority's ability to ''issue permission for conduct of clinical trial,'' as well as its ability to use sanctions or other measures if the clinical trial sponsor or investigator ''fails to comply'' with the applicable conditions, which include the failure to provide ''complete medical management and compensation in the case of trial related injury or death in accordance with rule 122-DAB.''[16] Rule 122-DD sets out rules related to the registration and operation of Ethics Committees, the entities tasked with ''review[ing] and accord[ing] its approval to a clinical trial protocol.''[17]

B. 2015 Proposed Reform Bill: Compensation for Clinical Trial Injuries

It remains to be seen whether the 2015 reform bill would change the essence of Rule 122-DAB.[18] Instead, the 2015 proposed reform bill appears to build and modify that framework, primarily by requiring that the relevant regulatory authority develop new rules—instead of simply rehashing the rules in Rule 122-DAB—prescribing how a clinical trial should be conducted and when an injury is ''due to'' a clinical trial and therefore compensable. The making of prudent new rules to implement the bill, if it is adopted, will therefore be critical, as explained below.

The 2015 bill would add a new chapter to the Drug and Cosmetics Act, 1940—Chapter 1A, entitled ''Clinical Trials.'' Section 4A of that chapter leaves no question that all parties involved in carrying out a clinical trial—regardless of the precise definition of ''sponsor'' or ''investigator''—will be subject to the regulatory authority's ''prescriptions'':

> No person, sponsor,[19] clinical research organisation or any other organisation or investigator,[20] shall conduct any clinical trial[21] in respect of a new drug,[22] [or] investigational new drug[23] . . . 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*.[24]

The ''as may be prescribed'' authority plays an important role in interpreting the remaining sections of Chapter 1A, because these sections refer to ''permitted'' entities and conduct under the Section 4A rulemaking authority.[25]

Chapter 1A addresses compensation for ''injury or death of a person in the course of a clinical trial''[26] as well as the criminal penalties that may apply for certain violations of clinical trial regulations.[27] A common theme throughout these sections is that the legislation delegates most of the important issues to ''be prescribed'' by the proper regulatory authority, in particular the power to define ''injury . . . in the course of a clinical trial'' and the power to determine the compensation provisions for such injuries. Section 4B, ''Determination regarding injury or death,'' states that ''[w]hether 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.''[28] The next section delegates the decisions about responsibility for how injured participants will be compensated in the same fashion: ''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.''[29] The provision for participants who have died is essentially the same: ''Where 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 manner as may be prescribed.''[30] Typically in Indian law and practice, the use of ''as may be pre-

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[16] *See* Rule 122-DAC, §§ (1)(f), (3).

[17] *See* Rule 122-DD, § (1).

[18] After the 2013 amendments were issued, draft legislation was introduced (later in 2013) and draft rules were published (in April 2014) that would have amended Rule 122-DAB. We discuss the 2013 draft legislation below. For commentary on the April 2014 draft rules, see Letter from Barnes et al. to Hon. Secretary Lov Varma, *supra* note 13 (''Draft Rules to Amend the Drugs and Cosmetics Rules (1945): Comments and Recommendations of the Multi-Regional Clinical Trials Center at Harvard University (6-18-15)''). Although those proposed amendments to the compensation rules were somehow intended to reduce the breadth and reach of the January 2013 regulations, they are replete with their own ambiguities, and would continue to require compensation for almost all injuries that occur to participants in trials, regardless of any direct causal link between the injury and the experimental agent or method used in the trial.

[19] The 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).

[20] The bill defines ''investigator'' as ''a person permitted to conduct clinical trial by the Central Licensing Authority under section 4A.'' § 3(s).

[21] The 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). Device trials therefore appear to be excluded from these proposed provisions. Whether the exclusion of device trials was intentional or a drafting error will be clarified when the final bill is presented.

[22] The 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).

[23] The 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).

[24] Emphasis added.

[25] *See, e.g.*, § 4(C)(1) (''the person or a body permitted under section 4A and the sponsor shall provide . . .''); 4-O (''Whoever . . . conducts clinical trials . . . in contravention of the conditions of permission issued under section 4A and rules made thereunder'').

[26] *See* Chapter 1A, §§ 4B, 4C.

[27] *See id.* §§ 4K, 4-O.

[28] Emphasis added.

[29] *Id.* § 4C(1)

[30] The causation language in the two subsections is different—''participant is injured or disabled *in* a clinical trial'' in § 4C(1), as compared to ''death of a participant is caused *due to* clinical trial'' in § 4C(2). We discuss this difference in the following section, but we ultimately assume that this is simply a drafting mistake and that both provisions are referring to situations in which the injury/death was ''caused by''

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scribed'' in a statute signals that the relevant provisions would be ''prescribed'' in the rules that are issued pursuant to the statute (here, the Drugs and Cosmetics Rules, 1945). Therefore, if the 2015 reform bill is adopted, it is obviously important to see how the implementing rules will be amended, including Rule 122-DAB. The BJP government has not yet produced a draft of the proposed amended implementing rules but at this point has simply invited comments on what changes need to be made to the existing rules.

C. Analysis[31]

As noted above, the ''injury . . . related to the clinical trial'' language in Rule 122-DAB sweeps in almost all injuries that could conceivably occur to a clinical trial participant during his or her participation, regardless of whether such injuries stem from that participation. The current draft bill is actually more problematic than Rule 122-DAB with respect to compensation, because the proposed bill only sets out that causation ''shall be determined by such authority and in such manner as may be prescribed.''[32] Such language sheds no light on how causation will be defined, determined and enforced. The draft bill provides no hint of a definition or standard for causation, nor is it even clear which regulatory ''authority'' in Section 4B is being referred to as the entity that will be tasked with prescribing regulations. Indeed, by issuing only proposed amendments to the statute without issuing corresponding draft rules as well, the BJP government has only added to an already confused situation. Further confusing is that Chapter 1A uses three different phrasings with respect to causation—''injury or death of a person *in the course of* a clinical trial'' (Section 4B), ''injured or disabled *in* a clinical trial'' (Section 4C(1)) and ''death . . . *caused due to* clinical trial'' (Section 4C(2)),[33] all of which are different from the ''related to'' language in the existing Rule 122-DAB. Although all three iterations in the 2015 draft bill express the same ''injury related to'' concept,[34] the differences are illustrative of just how much uncertainty exists surrounding how the government will handle causation, if and when new or revised compensation regulations are issued pursuant to the 2015 bill.

The open-ended provisions of Chapter 1A in the draft bill alternately, however, can be viewed as a potential fresh slate. The draft bill improves upon Rule 122-DAB by avoiding any provision analogous to § 2(i)(1), which essentially requires a sponsor or other party to pay for medical costs of any injury that a clinical trial participant suffers regardless of any ''relation'' to the trial. Regarding ''related to'' causation, whereas Rule 122-DAB, § (2)(i)(5), is unmistakable in its breadth, enactment of the 2015 draft bill as written would provide the regulatory agency responsible for implementing its open-ended ''in such manner as may be prescribed'' authority in a way that could address the concerns of the legal, scientific and research communities regarding causation.

The Indian government is well aware of these concerns, as nonpartisan groups including the Indian Society for Clinical Research and the Multi-Regional Clinical Trials Center at Harvard University (Harvard MRCT) have advocated for objective definitions related to injury compensation that are clearly understandable to all stakeholders in the clinical research process and for causality determinations that are legally and scientifically sound. Harvard MRCT has proposed, for example, that the government could effect such principles by appointing Expert Committees that make expedited causality assessments and undertake such assessments according to scientific principles (as opposed to the broad laundry list of ''causes'' in Rule 122-DAB § 2(i)(5)).[35] Such an expedited assessment would ensure that a research participant injured ''due to'' the trial receives immediate medical care and compensation, while at the same time ensuring that sponsors and those conducting the trial would not be liable for injuries not caused by the trial itself.

Although reasons for optimism exist, there are even stronger reasons to remain cautious in projecting the direction in which the Indian regulatory authorities may proceed. First, the recent past—with its enactment of Rule 122-DAB and the problematic amendments adopted in December 2014, which provide only marginal improvements to those regulations[36]—does not provide

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the clinical trial (in large part, because the Section 4C is titled ''Medical treatment and compensation for injury or death *due to* clinical trial.'').

[31] Here, we are comparing Rule 122-DAB with the 2015 draft legislation. However, there were similar provisions in the 2013 Congress Party draft legislation that was never adopted. *See* The Drug and Cosmetics (Amendment) Bill, 2013, Chapter 1B. The provisions in the 2013 draft legislation regarding injury compensation are nearly identical to those in the 2015 reform bill. Chapter 1B of the 2013 bill, Section 4P, sets out that ''No *person* shall initiate or conduct any clinical trial . . . except under, and in accordance with, the permission granted . . . .'' The emphasis highlights the only meaningful difference between the 2013 and 2015 drafts; the scope of persons who are subject to the ''permission'' of the regulatory authority has increased in breadth, from ''no person'' in 2013 to ''no person, sponsor, clinical research organisation or any other organisation or investigator'' in 2015. Thus, more clinical trial stakeholders are expressly subject to the government's rulemaking authority under the 2015 proposed reform bill.

With respect to the determination regarding injury or death section, Section 4Q of the 2013 reform bill contains identical causation language to Section 4B of the 2015 bill, instructing the proper authority to determine whether the injury or death was ''caused *due* to the clinical trial.'' Finally, the 2013 draft uses more precise language and a narrower class of liable persons in its ''Medical treatment and compensation for injury due to clinical trial section.'' This section applies when a person is ''injured *as a result of his participation* in a clinical trial,'' as opposed to ''injured or disabled *in* a clinical trial'' in the 2015 version. Further, the 2013 draft notes compensation ''shall be provided by the person conducting the clinical trial,'' instead of ''the person or body permitted under section 4A and the sponsor'' in the 2015 version, mirroring the difference between Section 4P of the 2013 draft and Section 4A of the 2015 draft that is noted above. *Compare* Chapter 1B, § 4R(1) of the 2013 bill, *with* Chapter 1A, § 4(C)(1) of the 2015 bill.

[32] § 4B.

[33] Emphasis added.

[34] If our interpretation is correct—that there are no actual differences in meaning between the three different versions—the alignment of these terms could very likely be revised once the government has reviewed the public commentary on the draft.

[35] *See supra* note 8.

[36] These very modest ''improvements'' to Rule 122-DAB are the addition of language to limit the exposure of the sponsor for medical management costs unrelated to the clinical trial in Section 1, to differentiate between permanent and ''non-permanent'' injuries and the corresponding ''quantum of com-

any comfort that causation will be handled appropriately in a second iteration pursuant to this 2015 reform bill. Additionally, in July 2013 the expert committee commissioned by Indian regulatory authorities and chaired by the eminent Dr. Ranjit Roy Chaudhury released a report providing recommendations for improving clinical trials in India. In its report, one of the committee's recommendations was the following: ''In *totally proven unrelated cases*, e.g. building collapse, drowning, road accident, etc. . . . compensation may not be payable. In all other cases of death or injury/disability, compensation should be paid to the participant or his legal heirs.''[37] While the committee's exclusion of obviously unrelated causes was welcome, its recommendation nevertheless continued to assume an overly broad definition of causation of injury. Traditional legal concepts require proof to demonstrate that any particular potential cause—in this case, clinical trial participation—actually causes an injury, in large part because it is often not possible to ''prove'' that one thing is ''not related to'' another—a general principle that holds particularly true with respect to the practice of medicine. Further, a ''totally unproven cases'' standard poses an adverse selection problem: it would incentivize persons with serious preexisting medical conditions to enroll in clinical trials in order to capitalize on the reasonable probability of receiving free care (unrelated to the clinical trial) for their unrelated illness, a further cost that would add to the burden that is discouraging organizations and industry from conducting clinical trials in India.

It would be more straightforward, logical and fair if the current Rule 122-DAB or the reissuance of that Rule pursuant to the 2015 draft bill were to require an affirmative demonstration of causation. Such proof need not be onerous, and any concern about placing an unduly heavy burden of proof on the side of the injured participant could be addressed through the government's proper use of its wide ''prescriptive'' mandate in the draft bill to select competent and unbiased judges of causation. Suitable and impartial judges could be trained in the scientific principles of causation, enforcing the rights of participants who often will have less access to legal resources than other clinical trial stakeholders, while also providing certainty to the other stakeholders that the expenses of conducting such trials will not include a risk of paying for every conceivable medical issue that could arise for any participant, regardless of causation.

Another question under the 2015 draft bill is which persons and organizations would be exposed to potential liability under revised injury compensation provisions. Section 4A sets out that ''[n]o *person, sponsor, clinical research organisation or any other organisation or investigator* . . . shall conduct any clinical trial'' except in accordance with the permission granted and rules prescribed under Chapter 1A. Section 4C, ''Medical treatment and compensation for injury or death due to trial,'' instructs that where there is a predicate injury, ''the *person or body permitted under section 4A and the sponsor* shall provide such medical treatment and compensation in such manner as may be prescribed.''[38] The breadth of actors listed in Section 4A would mean that essentially any person who contributes any funding or support or plays any role in a clinical trial could be regulated and held accountable under Section 4A and therefore subject to the risk of liability under Section 4C. This would broaden potential liability from ''sponsors'' alone, to include research institutions and researchers themselves. Further, the language also suggests that the ''sponsor'' *will* be liable, a term which also is defined broadly: ''a person, a company or an institution responsible for the initiation, financing and management of a clinical trial.''[39] As with the causation provisions, however, the ''shall provide . . . compensation as may be prescribed'' language in Section 4C gives the regulatory authority wide discretion to implement responsible rules regarding liability.

Optimally, the responsibility for providing medical care and compensation to participants who are injured as a direct result of their enrollment and participation in a clinical trial should be determined according to the actual culpability of the various parties. Therefore, for example, a sponsor should be responsible for the cost of care if the injury has been caused directly by the study drug, but the investigator or clinical site would be responsible if the injury stemmed from negligent and inappropriate administration of the drug contrary to the approved research protocol. Legal and financial responsibility should, in short, follow culpable behavior, and Section 4C provides the flexibility for Indian authorities to institute such a regime – assuming that any implementing rules would embrace not only an appropriate definition of causation, but also an assignation of liability to the person or entity whose action actually was the cause of the injury, as opposed to invariably assigning liability to the ''sponsor,'' as is now the case under Rule 122-DAB. Otherwise, the uncertainty regarding liability for compensation and the consequent disincentive to conduct clinical research will only be exacerbated.

III. Criminal Penalty Provisions

A. 2015 Proposed Reform Bill and Comparison to 2013 Proposed Reform Bill

The 2015 BJP reform bill, like the previous Congress Party 2013 reform bill, contains significant criminal penalties for those who conduct trials without proper authorization to do so, or who conduct trials in violation of clinical trial regulations. The criminal penalty provisions of the 2015 reform bill contain the same deference to regulations for clinical trial conduct that would be ''prescribed under Section 4A.''

For example, Rule 4K, ''Penalty for conducting clinical trial . . . without permission,'' states that: ''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.''

pensation'' in Section 2A and the slight qualifications to the illustrative list of ''clinical trial related'' injuries in Section 5. *See supra* notes 12-14.

[37] *Report of the Prof. Ranjit Roy Chaudhury Expert Committee to Formulate Policy and Guidelines for Approval of New Drugs, Clinical Trials and Banning of Drugs* at 81 (July 2013), *available at* http://www.indiaenvironmentportal.org.in/files/file/clinical%20trials1.pdf.

[38] Emphasis added in both sentences.

[39] § 3(zc).

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Rule 4-O, ''Penalty for violation of conditions of permission,'' sets forth that ''[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'' shall be punishable; violators ''shall be punishable'' with imprisonment which may extend to one year and/or a fine which may extend to three lakh rupees if the violation ''causes adverse affects on the body of participants,'' or with only a fine if the violation ''does not cause any adverse affect.''[40]

These criminal penalty provisions in the 2015 reform bill improve upon the 2013 bill's provision,[41] to some extent, by lowering the criminal penalties. The class of persons is described identically in both draft bills,[42] as is the type of ''violation'' that triggers criminal liability.[43] The criminal penalties, however, are substantially greater in the 2013 draft, and contain mandatory minimums, which are not part of the 2015 draft.[44] Further, the 2013 bill provides for substantially increased penalties if a violation of Section 4ZA or 4ZE ''caused grievous hurt to or death or hurt of any trial participant,'' a mechanism that is wholly absent in the 2015 bill.[45] In fact, Section 4-O of the 2015 bill differentiates between violations that cause adverse effects and those that do not, and this differentiation serves to *decrease* the possible penalty if the violation has caused no adverse effect, by eliminating imprisonment as a possible sentence.

B. Analysis

In contrast to the uncertain, open-ended provisions regarding compensation in the 2015 draft bill that leave much to be determined through implementing regulations, the criminalization provisions of Chapter 1A are very specific in one particular respect: the maximum penalties that apply (to violations of the yet-to-be-promulgated rules) under Chapter 1A are firmly laid out. The problem with these sections, including the significant chilling effect on clinical trials that likely would follow, is the uncertainty surrounding which persons and entities may be subject to such multiple-year prison sentences.

Under Section 4-O, there is an utter lack of differentiation among levels of culpability: ''Whoever himself, or by any other person on his behalf, *conducts clinical trials . . . in contravention of* section 4A and the rules made thereunder . . . shall be punishable with imprisonment for a term which may exceed one year.''[46] In other words, the criminal penalty for violating ''conditions of permission'' does not distinguish intentional violations of conditions made in bad faith from less culpable violations, such as inadvertent mistakes, genuine misinterpretations, good faith deviations from narrow protocols and other mistakes that may occur in the normal course of conducting clinical trials and practicing medicine. This is extremely troubling. Such language, criminalizing the conduct of clinical trial investigators, does not comprehend 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, given the vicissitudes of the lives and conditions of participants; the unpredictable nature of actual health care delivery; and the fact that clinical treatment of patients enrolled in trials remains one of a physician/investigator's art and skill. For example, an investigator may vary from conditions of an approved protocol in order to accommodate the health circumstances of a participant who has a previously undiscovered transient health condition unrelated to the clinical trial and, based upon the discovery of that condition, the investigator deems it best for the patient to defer or avoid altogether a clinical procedure required by the protocol. Conducting a clinical trial is not, as these criminalization proposals seem to assume, mere rigid adherence to rules, regardless of circumstance. At most, good faith mistakes in understanding a protocol, in the normal course of providing treatment to patients, should result in additional training and education, not prison.

Section 4K creates criminal liability for ''whoever himself, or by any other person on his behalf, conducts'' a clinical trial ''without permission.''[47] Section 4K therefore appears to be referring to the situation in which an individual physician-investigator conducts a clinical trial without having obtained adequate approval. Although less troubling than the specter of liability in Section 4-O, there are situations in which the need for approval of a clinical study may be less than clear (*e.g.*, a clinical study examining the effects of decreasing the number of cycles of approved chemotherapeutic regimens from six to four, a study of the effect of common off-label uses of an approved drug) and in which there has been a true misunderstanding by the physician-investigator as to the regulatory approval that should have been obtained. It would be unfair to apply criminal penalties strictly in such cases, but this ambiguity is not contemplated by the current proposed language of Section 4K.

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[40] §§ 4-O(a)-(b).

[41] Sections 4ZA and 4ZE of the 2013 draft resemble Sections 4K and 4-O of the 2015 draft, respectively.

[42] ''Whoever, himself or by any persons on his behalf . . . .''

[43] E.g., ''in contravention of conditions of permission issued under section [4P/4A] and the rules made thereunder'' in Sections 4ZE and 4-O.

[44] Violations of Section 4ZA are subject to a term of imprisonment that would ''not be less than three years [and] may extend to five years and with fine which may extend to ten lakh rupees,'' as compared to Section 4K of the 2015 draft which sets out a *maximum* sentence of five years and ten lakh rupees. Similarly, Section 4ZE sets out higher penalties than Section 4-O of the 2015 draft: a minimum term of imprisonment of two years and a minimum fine of five lakh rupees, compared to a maximum sentence and fine of one year and three lakh rupees in the 2015 bill.

[45] These 2013 ''grievous hurt or death'' enhancements are substantial: a *minimum* term of imprisonment of five years, a ten-year maximum term, and a minimum fine of twenty lakh rupees under Section 4ZA, and a three-year minimum term, seven-year maximum term, and ten lakh rupee minimum fine under Section 4ZE.

[46] § 4-O(a) (emphasis added). Subsection (a) deals with violations ''which cause[] adverse effects.''

[47] The actual text of Section 4K sets penalties for ''whoever himself, or by any other person on his behalf, conducts clinical trial . . . in contravention of section 4A and *the rules made thereunder*.'' However, Section 4-O deals with violations of ''rules'' under section 4A. Given that the title of 4K reads ''Penalty for conducting clinical trial . . . without permission,'' the intent appears to be that Section 4K is to apply *only* in cases where a clinical trial is conducted without obtaining permission to conduct that trial. We assume that this section deals only with the ''without permission'' context and do not discuss this issue further.

In both criminal penalty sections,[48] another troubling point is the absence of procedural safeguards available to protect the rights of those who may be accused and prosecuted. The draft bill is silent on protections, such as appeal procedures and guarantees that the parties adjudicating whether there was a criminal violation in the first instance will have the proper expertise to understand all of the complexities of clinical trials and health care delivery. Without such safeguards, the general uncertainty surrounding these criminal penalty provisions is only exacerbated.

A related point of concern is that, as with the compensation provisions, which persons or entities may be found liable under the criminal penalty sections is not clear. Sections 4K and 4-O use the same language, extending liability to ''[w]hoever, himself or by any other person on his behalf, conducts clinical trials.'' This seems to imply that only the investigator and his team of caretakers can be held liable under this section, as opposed to sponsors and other stakeholders, but there is no further guidance in Chapter 1A to define ''whoever, himself or by any other person on his behalf,'' or to confirm that the penalty sections apply only to individuals and not sponsors or other stakeholders.

Given the looming threat of multiple-year prison sentences and the utter lack of clarity over who may be subject to such sentences, what types of conduct they may be imposed for and the procedures by which they would be adjudicated, the overall specter of criminal punishment in Sections 4K and 4-O could readily be predicted to have a chilling effect on the willingness of all physicians, except perhaps the least scrupulous, to participate in clinical research activities. This chilling effect will be to the detriment of patients with serious or fatal conditions who could benefit from access to cutting-edge experimental therapies, as in oncology, and to the detriment of the development of science and research in India generally. Except in the most carefully defined and egregious circumstances (such as intentional, malicious violation of an approved protocol), criminalization of research is unwise public policy. There are many ways—through training, education, monitoring and oversight—to assure appropriate conduct of clinical research, but the specter of criminalization contained in the 2015 bill is not the answer.

[48] Sections 4L and 4P provide enhanced penalties for being ''again convicted'' under Sections 4K and 4-O; we do not separately discuss these sections.

IV. Conclusion

The draft 2015 legislation could influence the willingness of clinical trial stakeholders to conduct trials in India in some profound ways, as compared to the current 2013 regulations that are now in effect. The key issues in the draft legislation are the injury compensation provisions and the criminal penalty provisions. The criminal penalty provisions of the 2015 bill are troubling, as described above. The possibility of multiple-year prison sentences, as well as substantial uncertainty over which persons involved in a clinical trial could be subject to such penalties and what types of conduct they would be imposed for, almost certainly would reduce the willingness of physicians to conduct such trials.

In regard to rules regarding compensation for clinical trial injuries, the 2015 draft bill contains incremental improvements over the 2013 proposed legislation, but the major problems that have led to the decline in clinical trial activity in India over the past several years would not be quickly or immediately resolved by the language in the 2015 bill. Perhaps some of the flaws in the 2013 compensation regulations would be addressed upon the government's consideration of, and incorporation of, various public comments to the draft bill. If not, and if a version of the bill is enacted similar to its current form, the government entities tasked with carrying out the open-ended regulatory mandate in the bill will have fundamental decisions to make about how clinical trials should be regulated. For example, the regulatory authorities would have the authority, under the draft bill, to break away from the existing framework under Rule 122-DAB and craft an injury compensation policy that is even-handed and well-defined, and to promulgate ''rules of permission'' of clinical trials that do not leave well-meaning clinical trial investigators subject to the threat of criminal liability for exercising their discretion on behalf of participant-patients. Further, the regulatory authorities could ensure that determinations regarding compensation and culpability are adjudicated in a procedurally sound fashion, by a neutral body that has the proper expertise to make accurate decisions on an expedited basis. Until such developments are formally enacted, however, the willingness of academic institutions, industry and physicians to conduct cutting-edge clinical trials in India appears likely to remain quite diminished.

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