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India Releases New Draft Rules Reinforcing Compensation Requirements for Injuries 'Related To' Clinical Trials

By Jamie Flaherty, Mark Barnes, Sarah White, and Barbara Bierer

I. Introduction

On Feb. 1, 2018, India's Ministry of Health and Family Welfare (the ''Ministry''), in supersession of India's Drugs and Cosmetics Rules, 1945, issued new draft rules pertaining to clinical trials, entitled ''New Drugs and Clinical Trials Rules, 2018.'' (*See generally* New Drugs and Clinical Trials Rules, 2018, Ministry of Health and Family Welfare, G.S.R. 104(E) (Feb. 1, 2018) (hereinafter, the ''2018 Draft Rules'')).

The 2018 Draft Rules—the Indian government's most recent attempt to bolster and clarify its clinical trials regulatory regime—come in the wake of significant changes in the regulation of clinical trials, which began in 2013. If adopted, these Draft Rules would preserve provisions relating to compensation and other controversial requirements that have been widely debated by academic and industry stakeholders over the past several years. For research institutions and pharmaceutical companies considering siting clinical trials in India, the 2018 Draft Rules leave unremedied the onerous rules that have been implemented since 2013, and, if adopted in final form, would tend to prolong India's status as a location that many may continue to regard as unsuitable for conducting clinical research.

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Following controversy several years ago surrounding deaths reportedly related to clinical trial participation in India, the Indian government, between 2013 and 2015, released a number of well-intentioned, yet ultimately ambiguous and burdensome, rules pertaining to clinical trials. (*See, e.g.*, 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*, 09 LSLR 117 at 7 (Jan. 23, 2015)). Unsurprisingly, these sweeping regulatory changes had a chilling effect on the willingness of physicians, academic institutions, and industry sponsors to conduct clinical trials in India, with the U.S. National Institutes of Health, for example, for a time suspending funding for major interventional trials in India. (*See* Press Release, *Drug Trial Policy*, Press Information Bureau, Gov't of India (Aug. 28, 2013)).

Over time, however, the Indian government has scaled back many regulatory requirements and made important strides in clarifying and refining its clinical trial regulations. The 2018 Draft Rules aim to improve the transparency and predictability of India's clinical trials-related regulatory framework, and consolidate and clarify the myriad notices, orders, and other regulatory notifications issued by the Central Drugs Standard Control Organization (''CDSCO'') over the past few years. Included in these Draft Rules are definitions for relevant terms, as well forms for entities to use in connection with the application process for clinical trials approvals. The 2018 Draft Rules outline the roles and responsibilities of the sponsor, investigator, and ethics committee at various stages of the clinical trials process, and apply to all sponsors (including both academic and industry sponsors for regulated trials). Since a regulatory amendment in 2015, however, permission from the Indian Central Licensing Authority, the Drugs Controller General of India (''DCGI''), has not been required for ''clinical trials for academic/research pur-

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poses 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[s] are not for claiming permission of New Drug for marketing as per Drugs and Cosmetics Rules).'' (Circular No. 12-01/14-DC (Pt. 47), CDSCO (Oct. 11, 2015)). The 2018 Draft Rules include a section describing this exception for these academic clinical trials. (*See* 2018 Draft Rules, Section 28).

The Draft Rules also clarify, and provide mechanisms to expedite, the application process for new clinical trials, including by limiting the processing time to 45 days for an application to conduct a clinical trial of a new drug that was either discovered in India or that will be manufactured and marketed in India. Although these rules include many helpful provisions and represent an important step toward clarifying India's clinical trials regulations, the 2018 Draft Rules require further clarification and do not fully address the chilling effects that the regulatory changes adopted beginning in 2013 have had on clinical trials activities in India.

II. Injury Compensation and Medical Management Provisions

One of the most significant regulatory changes has related to injury compensation for clinical trial participants. In 2013, the Indian government enacted a rule requiring sponsors to compensate clinical trial participants for trial-related injuries. (*See* Drugs and Cosmetics (First Amendment) Rules, 2013, Ministry of Health and Family Welfare, G.S.R. 53(E) (Jan. 30, 2013); Drugs and Cosmetics (Sixth Amendment) Rules, 2014, Ministry of Health and Family Welfare, G.S.R. 889(E) (Dec. 12, 2014)). These rules established that an injury or death, if occurring during a trial or study, must be considered related to the trial, such that almost all adverse events that could occur to clinical trial participants would be considered ''related to'' the trial and thus compensable, although the rules also provided for a process by which the application of these criteria is undertaken by ethics committees and DCGI itself. (Drugs and Cosmetics (Sixth Amendment) Rules, 2014, Ministry of Health and Family Welfare, G.S.R. 889(E) (Dec. 12, 2014)).

The 2018 Draft Rules—the latest proposed iteration of these compensation-related provisions—largely preserve this broad list of circumstances/injuries that might be deemed ''related to'' (*i.e.*, caused by) trial participation. (2018 Draft Rules, Section 41(5)). Yet the purpose of any investigational trial is to evaluate how an investigational product compares in efficacy and safety to the standard of care, with one of the treatment groups predictably faring worse or better than the other. Under one provision in the 2018 Draft Rules, an injury ''related to'' a trial would include ″[n]ot providing the required standard care, though available to the subject as per clinical trial protocol in the placebo controlled trial.'' First, clarity is needed as to the meaning here of ''standard'' and ''available,'' both of which would be of crucial importance in applying this standard. Second and moreover, however, this provision is particularly confusing in light of how such 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. 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 drug. A regulatory approach more effective than what has been proposed in the 2018 Draft Rules would be simply to prohibit the use of placebos when (1) the condition under investigation is serious or life-threatening and (2) some local standard of care is available.

Another injury deemed by these Draft Rules as ''related to'' a clinical trial would be the ''adverse effect of the investigational product.'' This provision of the Draft Rules—like its predecessor version now in effect—fails to acknowledge that the purpose of conducting clinical trials is to determine adverse events and safety of the investigational product. It is antithetical to the very goal of a clinical trial to require compensation for injuries stemming from an adverse effect of the investigational product, when such risks are ever-present and when study participants have been fully informed of these risks but consent to endure them after receiving appropriate risk and benefit information during the informed consent process. This provision in particular 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.

Indeed, the 2018 Draft Rules not only preserve the requirements that the sponsor compensate trial participants for all injuries during trials, regardless of fault or actual causation, but also would increase sponsor burdens, even in excess of the existing regulations. Specifically, under Section 39 of the 2018 Draft Rules, if a research subject dies or suffers a permanent disability during a trial and if the Ethics Committee (″EC″) finds the injury to be ''related to'' the trial under the loose standards of the existing regulations, the trial sponsor, within 15 days of the EC's determination, must pay an interim compensation of 60 percent of the full compensation that would be awarded in the event that a final determination is made that the injury is ''related to'' the trial and therefore compensable. (*Id.* at Section 39.) A footnote to the rules explains that this interim compensation is irrevocable, meaning even if it is later determined that the death or injury was *not* related to the clinical trial, this 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.'' (*Id.*) Therefore, under this proposal, the sponsor would be automatically assessed at least 60 percent of total compensation if the EC determines that a research participant's death or permanent disability is related to the trial, regardless of the ultimate determination of the government authorities in this regard.

The 2018 Draft Rules also would continue the sponsor's obligation to provide free medical management for injuries suffered by clinical trial participants during the trial for ''as long as required as per the opinion of investigator and the Ethics Committee,'' regardless of

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whether the injury that necessitates such medical management is related to the clinical trial. (*Id.* at Section 41). In essence, under the Draft Rules, sponsors are 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.'' (*Id.*). Unlike the 2014 order establishing this ''ancillary care'' requirement, this sponsor obligation is not limited to medical treatment ''for brief illness'' but rather extends to the entire duration of the participation in the trial. (*See* Order, File No. 12-01/14-CD (Pt. 47), CDSCO (March 7, 2014)). Further, the proposed rules do not define ''ancillary care'' or what might be considered ''necessary medical management.'' This provision not only would increase uncertainty regarding the obligation of a sponsor to provide care for trial participants outside of the treatment set forth in the protocol, but also leaves the door open for individuals with serious preexisting medical conditions to enroll in trials in order to receive free medical care. For these reasons, this provision, if implemented, likely would continue to dissuade sponsors from being willing to locate clinical trials in India due to the unpredictable potentially high costs. Further, this guarantee of medical care for all medical conditions would offer perverse incentives for persons to enroll in trials, and potentially lead to undue inducement of trial participants, who, facing the prospect of free medical care and management and compensation, may be unable to weigh rationally the costs and benefits of clinical trial participation.

The 2018 Draft Rules indicate that the burden of providing compensation or free medical management pursuant to these provisions is that of ''the sponsor *or* of the person who has obtained permission [to initiate a new clinical trial] from the Central Licensing Authority,'' instead of the sponsor alone. (2018 Draft Rules, Section 40, 41 (emphasis added).) This more nuanced provision is helpful because it provides that the burden may not fall solely on the sponsor, but instead may be the responsibility of another party that has obtained permission or has been contracted to conduct the trial, such as a contract research organization (''CRO''). Also, the Draft Rules contain a broad definition of ''sponsor,'' which includes ''a company or an institution or an organization responsible for initiation and management of a clinical trial.'' Although the Draft Rules do not explicitly address how the responsible entity would be determined, it appears that the interested parties (*e.g.*, sponsor, CRO) would be able to allocate responsibility among and between themselves in a way that more closely reflects the actual responsibilities of the various parties involved in conducting the trial, as opposed to the entire obligation automatically falling solely on the sponsor. The 2018 Draft Rules do not address—but should address—explicitly the mechanism by which such responsibility should be apportioned (i.e., through contract) and in the absence of such agreement, provide a default entity that would be deemed responsible; otherwise, it would be unclear whether the responsible party would be the sponsor or the person who obtained permission to conduct the trial. The Draft Rules also, ideally, would not limit the potential responsible parties to the sponsor or person who obtained permission to conduct the study, which, according to the proposed definitions, would include a study sponsor or CRO, but not a study site or investigator. It would be preferable if the Draft Rules in any final form were to clarify what apportionment of responsibility is permissible, and to preserve the ability of parties to apportion responsibility among themselves, including sponsor, investigator, institution, and their contractors or agents.

III. Audio-Visual Consent

The 2018 Draft Rules maintain the requirement within the current Schedule Y of the Drugs and Cosmetics Rules that the investigator must maintain an ''audio-video recording of the informed consent process in case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and his understanding on such consent.'' (*Id.* at Section 1(g)). The Draft Rules also include the same exception as that contained in the existing Schedule Y, requiring an audio recording only for cases ''of clinical trial of anti-HIV and anti-leprosy drugs'' and ''vulnerable subjects.'' (*Id.*). Notably, the Ministry does not define ''vulnerable subjects'' in these Draft Rules. Another section of the Draft Rules on ECs preserves the broadly defined categories of such subjects contained in existing regulations: ''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 other incapable of personally giving consent.'' (*Id.* at Third Schedule). Given the breadth of this list, many Indian trial participants likely would be considered ''vulnerable,'' thus triggering the audio-visual recording requirement.

Requiring audio-visual recording of informed consent, while intended to protect research participants, nevertheless has raised myriad practical and cultural concerns, and may even deter participants from enrolling in studies, due to personal and religious objections to the recording itself. In addition, this provision raises privacy and confidentiality concerns, as the rules do not specify who may view the consent recordings and do not address the increased burden and obligations associated with storing and safely maintaining these recordings.

IV. Application Process

The 2018 Draft Rules touch upon other facets of clinical trials activities, including the application process for trial approval. Specifically, the Draft Rules, in an effort to speed up the trial application and approval process for those interested in siting trials in India, 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 Section 23).

V. Post-Trial Access

Another provision of the 2018 Draft Rules would require sponsors to provide post-trial access to a drug at no cost to the trial participant if (1) the investigator has recommended such post-trial access for an individual

after completion of a trial, (2) the trial relates to an indication for which no alternative therapy is available and the drug has been found beneficial to the subject by the investigator, (3) the EC has approved the continued access, (4) the subject consents to post-trial use of the investigational drug, and (5) the investigator has certified and the trial subject declares in writing that for such post-trial use the ''sponsor shall have no liability for post-trial use of investigational new drug or new drug''—i.e., sponsor will not be found to have financial liability for injuries resulting from continued use of the study drug. (*Id.*). In case of agreement of the investigator, research participant, and EC, the sponsor appears to be required to continue to provide the experimental drug, on a free basis; however, with these provisions, the Ministry has failed to address the complexity and subtlety of post-trial access. For example, after a phase I or phase II study, a sponsor may decide not to continue to a phase III study, and therefore may not even have the institutional capacity to continue to provide an experimental drug, even if that drug has been deemed needed by the participant, his or her physician, and the EC. This provision as drafted would also presumably require the sponsor to provide the former trial participant with a lifetime of free experimental drugs, especially in the case of a drug treating a chronic condition. Although the Indian Council of Medical Research's 2006 guidance provides that for post-trial access the ''sponsoring agency should provide the drug to the patient till [sic] it is marketed in the country and thereafter at a reduced rate for the participants whenever possible,'' this would seem unworkable in situations in which the sponsor does not move forward with marketing the drug. If an experimental drug has shown significant safety concerns and/or poor efficacy and the sponsor therefore understandably decides to abandon further development of the drug, it would seem unwise, unfair and grossly inefficient for the sponsor to be required by law to continue to provide that drug.

VI. Conclusion

With its diverse patient pool, highly skilled medical workforce, and relatively low costs of health services, India has enormous potential as a location for clinical trials. That potential, however, has been limited by regulatory changes that have shaped India's clinical trial landscape over the past several years. The 2018 Draft Rules are the most recent step taken by the Indian government to clarify its evolving regulatory approach. Yet the 2018 Draft Rules would preserve—and in some cases, exacerbate—provisions that have been widely criticized. Adoption and implementation of these proposed rules in India would likely continue to deter academic institutions, industry sponsors, and physicians from planning and siting clinical trials in India.

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