Post-Submission Update: The Evolving Regulatory Landscape for Clinical Trials in India

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I. INTRODUCTION

Following submission of this article to the *Food and Drug Law Journal*, there have been further developments related to India's 2018 draft clinical trials rules ("2018 Draft Rules"). In the Fall of 2018, the Supreme Court of India issued an order reopening the period for comment to the 2018 Draft Rules,[1] and the Central Drugs Standard Control Organization ("CDSCO") then re-opened the comment period.[2] Following these procedural developments, and specifically referencing the Supreme Court's desire that "new clinical trial rules [ ] be finalized urgently," India's Ministry of Health and Family Welfare ("MoHFW") released, via notification dated March 19, 2019, final new clinical trials rules, entitled the "New Drugs and Clinical Trials Rules, 2019" ("2019 Rules").[3] As with the 2018 Draft Rules, these finalized rules consolidate and clarify the myriad notices, orders, and other regulatory notifications issued by the CDSCO over the past few years and reflect ongoing efforts to improving India's clinical trials regulatory framework.

II. COMPENSATION AND MEDICAL MANAGEMENT

The 2019 Rules reflect several key changes from the proposed 2018 Draft Rules; as our article described the 2018 Draft Rules, we have drafted this update to describe briefly some of these changes. One of the most significant changes is the elimination of the sixty percent interim participant (subject) injury compensation requirement. The 2018 Draft Rules proposed that if an ethics committee determined that a participant's injury of death or permanent disability was related to a clinical trial, then the ethics committee would assess the compensation amount owed to the participant due to such injury, and the sponsor would then be required immediately to pay an interim

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[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] New Drugs and Clinical Trials Rules, 2019, MINISTRY OF HEALTH & FAM. WELFARE, Notification, G.S.R. 227(E), (March 19, 2019), https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NDI2MQ== [hereinafter the "2019 Rules"].

compensation payment of sixty percent of that full amount.[4] This interim payment would have been irrevocable even if it were later found that the injury had been unrelated to the clinical trial. Critically, the 2019 Rules have eliminated completely this onerous—and in our view, unfair—irrevocable compensation payment requirement.

The 2019 Rules generally preserve changes proposed in the 2018 Draft Rules whereby compensation for injury would ultimately be determined by the Drug Controller General of India ("DCGI") based on recommendations from an expert committee, as opposed to an ethics committee. The 2018 Draft Rules proposed compensation for death or permanent disability to be determined by the DCGI based on recommendations from an expert committee; however, for serious adverse events ("SAEs") other than death and permanent disability, research ethics committees were tasked with determining causation and compensation, despite such committees generally lacking expertise for making such determinations.[5] Most importantly, the 2019 Rules contemplate expert committee and DCGI involvement in compensation determinations for both categories, rather than relying in any way on research ethics committees to make such a causation determination. SAEs of death are now to be reviewed by an expert committee, which makes its recommendations to the DCGI, with DCGI ultimately determining the relatedness and quantum of compensation.[6] Similarly, SAEs of permanent disability or other injury will be reviewed by the DCGI or an expert committee, with DCGI ultimately responsible for deciding the amount of injury compensation.[7] A sponsor or its representative that obtained permission to conduct the study has 30 days to compensate the injured participant. In sum, the rules now provide that these complex assessments of relatedness and compensation will be determined by the better-resourced DCGI, with assistance from expert committees—a marked improvement from the former approach that layered these burdens onto research ethics committees.

In addition, the 2019 Rules have finalized the inclusion at the Seventh Schedule of the helpful compensation formulae that had been developed by the MoHFW (based on certain factors, such as age, seriousness, and severity of the disease; presence of co-morbidity; and duration of disease of the participant at the time of the enrollment), which introduces clarity and defines the limit of financial liability on the part of the sponsor for certain injuries.[8]

The 2019 Rules—like the 2018 Draft Rules—preserve the broad list of circumstances described in the article that are deemed "related to" a clinical trial, which could continue to deter the siting of clinical trials in India given their greater reach as compared to conventional standards of causality.[9] However, the 2019 Rules helpfully reintroduce an element of relatedness with respect to the provision of medical management to study participants. The 2018 Draft Rules had proposed that the sponsor

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[4] *See* Ch. VI, Rule 39, Draft New Drugs and Clinical Trials Rules, 2018 (2017), http://www.cdsco.nic.in/writereaddata/Draft%20CT%20Rules%20sent%20for%20Publication.pdf [hereinafter "2018 Draft Rules"].

[5] *Id.* at Ch. VI, Rule 42.

[6] 2019 Rules, Ch. VI, Rule 42(2)(v).

[7] *Id.* at Rule 42(3)(iv).

[8] *Id.* at Seventh Schedule.

[9] *Id.* at Ch. VI, Rule 41.

would be required to provide free medical management for as long as required based on the opinion of the investigator and the ethics committee, regardless of whether the condition requiring medical management was related to the study. Importantly, the 2019 Rules provide that such medical management is required "per the opinion of [the] investigator *or till such time it is established that the injury is not related to the clinical trial* . . . as the case may be, whichever is earlier."[10] While this nevertheless introduces the ambiguity and difficulty that is attendant to proving a negative, it nevertheless reintroduces the concept of relatedness with respect to the obligation to provide free medical management. The 2019 Rules also have eliminated the problematic provision that we cite in our article: "where the trial subject is suffering from any other illness during participation in clinical trial . . . the sponsor shall provide necessary medical management and ancillary care."[11] As we described, this rule would have imposed unworkable demands on sponsors to provide care for any other illness that might afflict a study participant.

III. AUDIO-VISUAL RECORDING OF INFORMED CONSENT

The 2019 Rules retain the requirement previously set forth in a CDSCO rule 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," but requiring audio recording only for cases "of clinical trial of anti-HIV and anti-leprosy drugs" and "vulnerable subjects."[12] As we noted in our article, while intended to protect research participants, this requirement nevertheless has raised significant cultural and logistical concerns.

IV. POST-TRIAL ACCESS

The 2019 Rules finalize certain post-access requirements, requiring 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 ethics committee has approved the continued access; (4) the subject or legal heir 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."[13]

Although the rule appears to allow the investigator to declare to the participant that the sponsor shall have no liability for post-trial use of the drug, this requirement nevertheless may prove otherwise unworkable in certain circumstances. For example, after a Phase I or Phase II study, a sponsor may decide not to continue to a Phase III study for a multitude of reasons, and thus may not wish to provide such study drug,

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[10] *Id.* at Rule 40(1)(emphasis added).

[11] 2018 Draft Rules, Ch. VI, Rule 41.

[12] 2019 Rules, Third Schedule, Rule 2(g).

[13] *Id.* at Ch. V, Rule 27.

and, moreover, may not have the institutional capacity to continue to provide an experimental drug if it is no longer produced. Nevertheless, this requirement exemplifies the regulatory changes India has implemented over the past five years: well-intentioned and thought-provoking, yet also broad and potentially problematic in terms of the incentives that international clinical trial sponsors may have to conduct studies in India.

V. NEW DEFINITIONS

In an important step towards increased clarity, the 2019 Rules include a definition for "academic clinical trial," where results are intended to be used only for "academic or research purposes."[14] As we noted in the article, the Indian government has provided that permission is not needed to conduct an academic clinical trial in India (provided use of the drug is for research purposes, the study has undergone ethics committee review, and observations are not required to be submitted to DCGI or for promotional purposes).[15]

The 2019 Rules also provide a term for orphan drugs, now defined as drugs intended to treat conditions that affect not more than 500,000 persons in India, and contemplate fee waivers for applications to conduct clinical trials for such drugs in India.[16]

VI. EXPEDITED APPLICATION REVIEW & FLEXIBILITY IN APPLICATION REQUIREMENTS; PRE-AND POST-SUBMISSION MEETINGS

The 2019 Rules set forth timing parameters for review of clinical trial applications. Specifically, the Indian government has ninety days to review and make a decision on an application to conduct a clinical trial.[17] The rules expedite the application process for new clinical trials as part of development in India by limiting the processing time to thirty days for 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.[18] If applicants do not receive notice of rejection or communication of deficiency within thirty days, then permission to conduct the trial will be deemed to have been granted.[19] The Rules thus promote efficiency, with such "deemed approval" likely encouraging local drug development.

Sponsors will no longer need to conduct a clinical trial testing for safety and efficacy in the Indian population; the 2019 Rules provide that for a new imported drug, a new local clinical trial is not required if (1) the new drug is already approved and marketed

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[14] *Id.* at Ch. I, Rule 2 (defining 'academic clinical trial' as "a clinical trial of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a trial are intended to be used only for academic or research purposes and not for seeking approval of the Central Licencing Authority or regulatory authority of any country for marketing or commercial purpose").

[15] *Id.* at Ch. V, Rule 28.

[16] *Id.* at Ch. I, Rule 2(x); Sixth Schedule.

[17] *Id.* at Ch. V, Rule 22.

[18] *Id.* at Ch. V, Rule 23.

[19] *Id.*

outside of India in certain countries and if no unexpected SAEs have been reported; (2) the DCGI has already granted permission to conduct a global clinical trial for the new drug, which is ongoing in India and has been approved in the meantime in certain other countries; (3) there is no evidence of relevant differences in the Indian population that would affect the safety and efficacy of the new drug; and (4) the applicant commits to conduct a Phase IV trial in India (though this may be waived in unmet medical, life-threatening, or serious medical condition situations).[20]

In order to preserve flexibility and in anticipation of different possible scenarios, the 2019 Rules contemplate situations for a new drug where relaxation, abbreviations, omission, or deferment of data may be considered.[21] For example, depending on the nature of the new drugs to be imported or clinical trial to be undertaken, requirements in terms of clinical data may differ, including depending on the specific phase of the trial to be conducted.[22] For drugs intended to be used in life-threatening or serious disease conditions or rare diseases, and for drugs intended "to be used in the diseases of special relevance to Indian scenario or unmet medical need in India, disaster or special defense use," the following mechanisms may be used to expedite the development and approval process:[23]

> a. An accelerated approval process where there is a prima facie case of the product having meaningful therapeutic benefit over existing treatment, whereby approval may be based on data generated in a clinical trial using a surrogate endpoint, and may include post-approval data submission requirements; or[24]
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> b. A "quick or expeditious review process," where the sponsor or its designee may apply to the licensing authority if evidence for safety and efficacy have been established, even if the drug has not completed all clinical trial phases if certain conditions are met, or in time of war or disaster where a fulsome clinical trial may not be possible.[25]

Once approved, the 2019 Rules set forth several conditions on the permission to conduct a clinical trial.[26] One such requirement is the electronic submission via India's SUGAM online portal every six months of a status report as to whether the clinical trial is ongoing, completed or terminated.[27]

In addition, the Second Schedule of the 2019 Rules addresses requirements associated with proposed new claims for an already approved drug, providing that any data or information required to get permission to import or manufacture a drug will depend on the regulatory status of the drug for the new claim in another country, though new data may be necessary to substantiate the new claims.[28]

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[20] *Id.* at Ch. X, Rule 75.

[21] *Id.* at Second Schedule, Rule 1(2).

[22] *Id.* at Rule 1(2)(i).

[23] *Id.* at Rule 1(2)(ii).

[24] *Id.* at Rule 1(2)(A).

[25] *Id.* at Rule 1(2)(B).

[26] *Id.* at Ch. 5, Rule 25.

[27] *Id.* at Rule 25(viii).

[28] *Id.* at Second Schedule, Rule 1(3).

The 2019 Rules provide the opportunity for sponsors and other stakeholders to get clarity on applicable regulations through pre- and/or post-submission meetings: "Any person who intends to make an application for grant of licence or permission for import or manufacture of new drugs or to conduct clinical trial may request, by making an application in writing, a pre-submission meeting with the Central Licencing Authority or any other officer authorised by the Central Licencing Authority for seeking guidance about the requirements of law and procedure of such licence or permission of manufacturing process, clinical trial and other requirements."[29]

VII. PENALTIES FOR NON-COMPLIANCE; RIGHT TO APPEAL

The 2019 Rules contemplate penalties for non-compliance with the Rules, but generally grant the aggrieved party a right to appeal. For example, if a sponsor or other entity to whom permission to conduct a clinical trial has been granted fails to comply with the Rules, the DCGI may issue a warning, reject the results of the trial, suspend or cancel the permission, or debar the investigator or the sponsor from conducting clinical trials in the future.[30] However, the aggrieved party then has sixty days to appeal such action.[31]

VIII. CONCLUSION

In conclusion, while certain requirements under India's clinical trials regulatory framework might be in need of further clarification, we perceive these rules as a favorable development and evidence that India continues to raise and address important ethical and legal questions in the clinical trials space by continually fine-tuning its clinical trial regulatory framework.

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[29] *Id.* at Ch. XIII, Rule 98. *See also* Rule 99 for post-submission meetings.

[30] *Id.* at Ch. V, Rule 30.

[31] *Id.*